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INVESTIGATOR GUIDE

Castle Institutional Review Board

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1. Introduction:

This Investigator Guide sets forth expectations, and provides helpful information, for Investigators who are conducting studies approved by Castle IRB. Castle IRB views itself as a partner in the research process and seeks to provide guidance on human subjects research protection matters throughout the research life cycle. Working together, we can best protect research participants.

2. Mission Statement:

The mission of Castle IRB is to protect the rights and welfare of human participants in gene and cell therapy clinical trials while providing efficient, compliant IRB review of research. Using our portfolio of expertise, we strive to be the leading IRB partner in advancing safe, ethical and compliant gene and cell therapy clinical trials to accelerate the next evolution in advanced therapies.

3. Services Offered:

With organizational components that include a registered Institutional Review Board (IRB), Castle IRB provides the following services:

- Initial and ongoing IRB review of research for acceptability under Department of Health and Human Services regulations at 45 CFR 46, Food and Drug Administration regulations at 21 CFR parts 50, 56, 312, 600, and 812, and the International Conference on Harmonization "Guidance for Industry – E6 Good Clinical Practice" (ICH GCP) as applicable.
- Determinations that research meets the criteria for Exemption from IRB Review, with or without Limited IRB Review, in accordance with 45 CFR 46.104 and/or 21 CFR 56.104.
- Determinations that research does not require IRB review per federal regulations, and review of Generic Materials, such as generic recruitment materials, for alignment with IRB requirements.
- Clinical (non-research) uses of Humanitarian Use Devices (HUD).
- Translations/verifications (via 3rd party vendor) of study documents.
- IRB review of human gene transfer experiments compliant with Section III-C of the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Modules *(NIH Guidelines)*.

Fees for Castle IRB review services are set forth in a Castle IRB Fee Schedule and provided to current and prospective clients upon request. Fees and Payment Terms are included in Agreements with clients. Castle IRB may amend or update the Fee Schedule from time to time in its sole discretion. Castle IRB will use reasonable efforts to provide clients with no less than thirty (30) days prior notice to any change to the Fee Schedule. Fees are not impacted by IRB review determination outcomes and vice versa.

4. Guiding Ethical Principles:

Castle IRB is committed to ensuring that research is designed and conducted in accordance with the core ethical principles in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research:

- Respect for persons (principles of informed consent: individuals should be treated as autonomous agents with the right to make decisions for themselves, and those with diminished autonomy (e.g., minors, prisoners, persons with cognitive impairment) are entitled to additional protections).

- Beneficence (research must be designed and implemented so as to maximize the possible benefits and minimize possible harms to research participants).
- Justice (fairness in inclusion and exclusion: the possible benefits and burdens of the research should be equitably distributed among potential research participants).

For clinical trials subject to ICH GCP, Castle IRB will also ensure that studies shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

5. Regulations:

Castle IRB reviews and oversees research in compliance with the following federal regulations, when applicable:

- **Department of Health and Human Services (DHHS) at 45 CFR 46** if the research has federal funding or when otherwise required, such as when required by the Federalwide Assurance (FWA) of an institution relying on our IRB review services, including Subpart B for research involving pregnant women, fetuses, or neonates; Subpart C for research involving prisoners; Subpart D for research involving children; and Subpart E regarding registration of IRBs.
- **Food and Drug Administration (FDA) at 21 CFR 50; 56; 312; 600; and 812** as they apply to clinical investigations and other research involving products regulated by FDA.
- **Health Insurance Portability and Accountability Act (HIPAA):** on behalf of conduct sites/relying institutions who are covered entities, Castle IRB can review the following in accordance with the HIPAA Privacy Rule:
  - Waivers or alterations of authorization for use and disclosure of Protected Health Information (PHI).
  - Written authorizations for use or disclosure of PHI.
- When research is supported by other federal agencies, such as the Department of Defense, additional applicable agency regulatory requirements will be followed.

Castle IRB has an IRB Organization number issued by the Office for Human Research Protections (OHRP)/FDA: IORG0010151, and Castle IRB's registration number is IRB00012054. As Castle IRB does not currently conduct research, it does not hold an FWA.

Castle IRB will adhere to state and local laws, including international laws or regulations when applicable, and will confirm that Sponsor/CRO and Investigator Site Submitters are knowledgeable of such applicable local laws and regulations.
Should a submitter choose to submit a research study for Castle IRB review that falls outside of the scope of regulations specified above ("voluntary review"), Castle IRB will apply FDA regulations at 21 CFR 50 and 56 to the review unless the state in which the research will take place requires DHHS regulations be used. In such cases, DHHS regulations at 45 CFR 46 will be used instead. Other requests to use DHHS regulations rather than FDA regulations, or in addition, can be approved by the Director of IRB Operations.

6. Associated Guidelines:

Castle IRB complies with the International Conference on Harmonization Good Clinical Practice Guidelines (ICH GCP) to the extent required by sponsors, but generally only to the extent that they are compatible with FDA regulations in place for clinical investigations Castle IRB will ensure that studies subject to ICH GCP shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice and applicable regulatory requirements.

Castle IRB complies with Section III-C of the *NIH Guidelines,* which currently require that research subject to the *NIH Guidelines* not be initiated until applicable institutional and regulatory authorization(s) and approvals [including IRB approval] have been obtained. Should the *NIH Guidelines* be revised to include additional requirements for IRB review, such requirements will be adopted by Castle IRB.

7. Human Subjects Research:

In determining what is human subjects research requiring IRB review, Castle IRB uses the definitions provided by DHHS and FDA regulations and applies them to activities subject to their respective jurisdictions. Castle IRB Analysts and managerial staff (e.g., Director of IRB Operations) can make determinations of whether a study constitutes human subjects research requiring IRB review prior to formal submission of an IRB Application to Castle IRB, or once a submission is made. Similarly, Castle IRB can make determinations of whether a particular institution or investigator is "engaged" in the conduct of human subjects research, and uses the OHRP Guidance, "Engagement of Institutions in Human Subjects Research" to do so (see "Not Human Subjects Research Determinations" section of this Guidance for more details). Notifications of such determinations and related information on submission expectations will be put in writing to the study sponsor and/or investigator and kept in IRB records.

The following definitions will be used to consider whether activities are human subjects research requiring IRB review as applicable (per the "Regulations" section of this Guidance):

Research (DHHS 45 CFR 46.102(l)): A systematic investigation including research development, testing and evaluations, designed to develop or contribute to generalizable knowledge.

- Systematic Investigation: an activity that involves a prospective plan and involves data collection and analysis to answer a question.
- Generalizable: knowledge that may be transferred or extrapolated to a broader population or situation than from which it was initially derived.

For activities subject to DHHS regulations, the following activities are not considered research:

- Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.
- Public health surveillance activities conducted by a public health authority, limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance.
    - Including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority.
    - Including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products.
    - Including those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
- Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
- Authorized operational activities (as determined by the relevant federal agency) in support of intelligence, homeland security, defense, or other national security missions.

Research (FDA): Any experiment that involves a test article and one or more human subjects and that is either subject to requirements for prior submission to the FDA under section 505(i) or 520(g) of the Act, or is not subject to requirements for prior submission to the FDA under these sections of the Act, but the results of which are intended to be submitted

later to, or held for inspection by, the FDA as part of an application for research or marketing permit. The terms "research," "clinical research," "clinical study," "study," and "clinical investigations" are deemed to be synonymous for purposes of this part (21 CFR 50.3(c) and 21 CFR 56.102(c)).

Human Subject (DHHS 45 CFR46.102(e)): A living individual about whom an investigator conducting research obtains (1) information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens, or (2) obtains, uses, studies, analyzes, or generates private identifiable information or identifiable biospecimens.

- Intervention includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulation of the subject or the subject's environment that are performed for research purposes.
- Interaction includes communication or interpersonal contact between investigator and subject.
- Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., medical record).

Human Subject (FDA): An individual who is or becomes a participant in research, either as a recipient of a test article or as a control. A subject may be either a healthy individual or a patient (21 CFR 50.3(g) and 21 CFR 56.102(e)). For clinical investigations involving medical devices, the results of which are intended to be submitted later to, or held for inspection, by the Food and Drug Administration as part of an application for a research or marketing permit, human subject also means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.

Additional federal agency definitions for human subjects research are used when applicable.

8. Submissions of New Studies to Castle IRB:

Castle IRB uses an online portal system for most submissions for IRB review. Links to the Castle IRB portal system, forms, and submission instructions are available to clients on the Castle IRB website. Forms and instructions inform submitters of the information that must be provided for IRB review. This is true for new protocol submissions, as well as ongoing review of research. Castle IRB review is only initiated upon proper submission of forms and requested information.

Submitters can choose one of two ways of working with the Castle IRB team: working the materials up with a Castle IRB team member on a web conference call or completing the submission independently. Regardless of the method chosen, before the study materials can be advanced for IRB review, Castle IRB staff will ensure the following prior to accepting the submission for review:

- Completeness: is all necessary information provided, and are all necessary documents (e.g., IRB Application, Sponsor's Protocol, Investigator's Brochure, etc.) included in the submission
- Ancillary reviews: is a status and information provided for:
    - Institutional Biosafety Committee review (for studies involving administration of recombinant or synthetic nucleic acid molecules or DNA or RNA-derived from this technology)
    - Radiation Safety Committee review (for studies involving the investigational use of ionizing radiation/radioactive materials)
    - Conflicts of Interest (COI) review (review of COI management plans for acceptance when an investigator COI has been identified)

- Training Verification: Castle IRB requires that Principal Investigators and other team members have and maintain training in human research protections, taken within the past three years. This requirement may be met by completing training through the CITI Program, which Castle makes available at no charge (see Castle IRB Website for registration information), or a comparable training as determined by Castle IRB, and can include:
    - NIH Training on Protecting Human Research Participants
    - GCP Training
    - ACRP Certified Clinical Investigator Training or *ACRP certification (e.g., CCRC, CCRA, CPI)*
    - CenterWatch: Protecting Study Volunteers in Research
    - DIA Certified Investigator (CCI)
    - SOCRA Clinical Research Professional (CCRP)
    - Tri-Council Policy Statement Online Training (TCPS)
    - Seminar, online, or institutional training specific to HSR protections. If modules/content of training are available, key content areas for consideration of acceptance include:
        - Ethical Principles, such as The Belmont Report and/or Declaration of Helsinki
        - DHHS or FDA Regulations and/or IRB Requirements
        - FDA Regulated Research/Good Clinical Practice
        - Informed Consent, privacy and confidentiality
        - Privacy/Confidentiality/Research Records-GCP
- Documentation of PI training must be submitted with IRB Initial Reviews unless such documentation is already on file at Castle IRB, and the PI is obligated to verify and provide assurance that other research team members are in compliance.
- Submissions that do not comply with the Castle IRB training requirements at time of initial submission will be accepted for review but must demonstrate compliance as a condition for receiving IRB Approval.
- Clinical trial sponsors typically require, and Castle IRB strongly encourages that Principal Investigators and other clinical research team members complete training in Good Clinical Practice (GCP) every three years, which is required by the NIH if conducting an NIH-sponsored clinical trial. A GCP course is also available through Castle IRB's CITI subscription.
- Reliance Agreement (IRB Authorization Agreement) is in place between Castle IRB and the conduct site Institution relying on Castle IRB for IRB services, when required.

New protocols may be submitted for a single site or for a multi-site protocol that will be conducted at various sites, in which case site applications will also be submitted for each Principal Investigator relying on Castle IRB for IRB review and oversight. Castle IRB will verify that considerations above are in place for the master protocol as well as each conduct Site/Investigator(s).

<u>Submission Requirements</u>

New Protocol Submissions [Multisite Initial Protocol Application if submitting the master protocol and related materials without a conduct site; Single Site Application if submitting the protocol and a conduct site] and Site Applications [for sites proposing to conduct already approved protocols in multi-site review scenarios] must include at least the following documents, though specific instructions on what to submit will be specified in Castle IRB Forms. Note: this does not apply to exempt applications.

- A Castle IRB Application (called an xForm in the online portal system).

- A research protocol or document outlining the study's design, including information about purposes of the research, the scientific or scholarly rationale, methodology, the procedures to be performed, including those already being done for diagnostic or treatment purposes, anticipated risks and benefits, subject selection criteria, plans for obtaining informed consent or justification for a waiver or alteration of consent or documentation of consent, data analysis plans, data safety and monitoring plans, privacy and confidentiality measures, and other key information as instructed by Castle IRB. This is typically a sponsor's protocol. When following DHHS regulations, this must include the complete DHHS-approved protocol when one exists. Should no protocol exist, Investigators can use Appendix A "Protocol Template" of this Guidance to design one.
- Informed consent forms, assent forms, and/or other consent materials. When following DHHS regulations, this must include the DHHS-approved sample consent document when one exists.
- Test article information, such as an Investigator's Brochure, package insert, device manual or other device documentation, and IND or IDE number information, as applicable.
- For Site Applications, the CV, licensure, certifications, suspensions/disbarment, human subjects research training documentation for the Principal Investigator and the qualifications, capacity, and any suspensions/FDA Form 483s of the research site.
- Recruitment materials, study instruments, and other materials to be used in the conduct of the study as instructed by Castle IRB.
- Information regarding the status of any applicable ancillary reviews. This includes financial conflict of interest disclosure for all investigators and their immediate family members, and sharing of the institution's management plan, if applicable.

Reviews of New Protocols [multisite or single site] will be at a convened IRB meeting unless it is determined that the Submission qualifies for review under Expedited Review categories at 21 CFR 56.110, 45 CFR 46.110 or does not constitute human subjects research requiring IRB review. See "Full Board Review" section of this Guidance for additional details. Reviews of Site Applications will typically be conducted via Expedited Review, as amendments to active protocols, unless is it determined that the change is more than minor. See "Expedited Review" section of this Guidance for additional details.

Additional Multi-Center Study Considerations

Submissions for multi-center studies (studies with the same research protocol taking place at multiple, unaffiliated locations, also referred to as multi-site), and studies being conducted at multiple affiliated sites within a research network, are first submitted as master protocols using the Castle IRB Multisite Initial Protocol Application.. Additional sites will be submitted for IRB review using Site Applications; each site will need to submit a distinct Site Application for initial review. Site Applications can be submitted by the Sponsor, the Contract Research Organization (CRO) on behalf of the sponsor, or by the Site(s) directly.

Submission of the master protocol shall include at least the Castle IRB Application, research protocol, test article information (e.g., Investigator's Brochure), and study-level consent materials (with placeholders for Investigator and site-specific information). Available patient-facing documents, such as participant instructions, subject diaries, and recruitment materials should also be submitted if applicable. While the master protocol review is underway, additional Site Applications may be prepared and submitted for review; however, no Site Application can be approved prior to the master protocol and master consent documents being approved. Castle IRB advises sponsors/CROs/coordinating centers to ensure that sites use the Castle IRB approved master consent documents when adding site-specific customizations to consent materials. If the site requires only standard information be added to consent document(s), as provided in the

Castle IRB Application (e.g., Investigator name/contact information, payment information), Castle IRB staff can insert language as part of the IRB approval process.

Approval of a master protocol alone does not allow a research study to proceed; for research to be conducted, both the master protocol plus an Investigator/Conduct Site institution's Site Application must receive Castle IRB approval. This requirement will be communicated to Sponsors and CROs in determination letters from Castle IRB.

Criteria for IRB Review

New protocols are reviewed for alignment with guiding ethical principles, and compliance with applicable regulations, guidelines, state and local laws as outlined in the "Criteria for IRB Approval of Research" section of this Guidance. For studies that present no more than minimal risk to research participants, this will include consideration of whether the study only involves procedures that fall under Expedited Review Categories at 45 CFR 46.110 and 21 CFR 56.110, as applicable. See "Expedited Review" section of this Guidance for additional details.

When an investigator is responsible for the overall conduct of a study, such as serving as the lead researcher of a multi-site study, the IRB requests and evaluates information about the management of information that is relevant to the protection of participants, such as unanticipated problems involving risks to participants or others, interim results, and protocol modifications.

9. Types of IRB Review:

9.1 Full Board Review:

Human Research studies that are more than minimal risk, and/or minimal risk human research studies that are not eligible for expedited review per federal regulations at 21 CFR 56.110, 45 CFR 46.110, or Exempt determination per 21 CFR 56.104, 45 CFR 46.104, are reviewed by the convened IRB. Ongoing submissions for those studies, including amendments that are more than minor changes to research, continuing reviews, and certain reports of protocol deviations, unanticipated problems, and noncompliance, further described below, are also reviewed by the convened IRB.

Submissions determined by Castle IRB staff to require review at a convened IRB meeting will be placed on a future meeting agenda according to IRB meeting dates, associated deadlines, and availability of the necessary expertise. There are no limits to the number of protocols placed on an agenda as meetings are held at a frequency that enables reasonable meeting duration (e.g., 2 hours or less). Meeting dates and deadlines are maintained by Castle IRB and the schedule adjusted as needed in response to anticipated workload. Castle IRB staff can place Submissions on a later meeting in cases of exceptional volume, and typically placement is based on a first come, first served basis.

Castle IRB conducts convened meetings on Wednesdays with an ability to hold additional meetings on an as needed basis. Submission deadlines are on Monday of the prior week. Submitters typically receive determination letters within 48 hours of Castle IRB meetings.

9.2 Expedited Review:

Minimal risk research studies that qualify for expedited review in accordance with regulations at 21 CFR 56.110, 45 CFR 46.110 can be reviewed via expedited review procedures by a designated member of the Castle IRB committee. In addition, for multi-site studies in which Castle IRB has reviewed the master protocol to be conducted at each site, submissions made to add new sites to the master protocol will also typically be reviewed via expedited review

procedures. Expedited submissions are reviewed upon receipt and determination letters are typically issued in one week for initial reviews, and two to three business days once the submission is accepted for Site Applications and on-going reviews.

Initial Reviews

To qualify for expedited review via 21 CFR 56.110, 45 CFR 46.110, the research must meet the following criteria:

- Research activities present no more than minimal risk to human subjects.
    - The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal. Additionally, the expedited review procedure may not be used for classified research involving human subjects.
- Research activities involve only procedures listed in one or more of the following Expedited Review Categories.
    - The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects. The categories in this list apply regardless of the age of subjects, except as noted.

Expedited Review Categories:

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
   (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
   (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
   (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
   (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means.
   Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted

prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject=s privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

New Site Applications

For multi-site studies in which Castle IRB has reviewed the master protocol to be conducted at each site, submissions made to add new sites to the master protocol will also be reviewed via expedited review procedures, with some exceptions. Examples of scenarios that would be considered more than minor changes and reviewed by the convened IRB include:

- Sites that request changes to consent documents that materially impact the understandability, meaning, or adequacy of previously approved required or additional elements of consent.
- Sites that request changes to the protocol design that materially increase risk, decrease benefit or decrease the scientific merit of the study (see examples in the paragraph below).
- Sites with local considerations, including plans for the consent process, plans to manage participant privacy and confidentiality, Site or Investigator qualifications, or other considerations (such as distinct cultural qualities or vulnerable populations) related to the criteria for approval that materially increase risk or decrease benefit of the study, or are unable to be assessed for adequacy given the knowledge and professional judgment of the Expedited reviewer.

Amendments to Active Studies

For any active (IRB-approved) studies, regardless of whether originally reviewed under expedited review categories or by the convened IRB, minor modifications that would not materially increase risk, decrease benefit, or decrease the scientific merit of the study are also eligible for expedited review.

Examples of minor modifications include:

- Changes to improve the clarity of study materials or to correct errors.
- Addition or deletion of study sites, with some exceptions.
- Narrowing the range of inclusion criteria or expanding the range of exclusion criteria.
- Addition of research activities that meet expedited criteria under 21 CFR 56.110 or 45 CFR 46.110.
- Removal of procedures such as biological sample collections as long as it does not impact safety evaluations or alter the study's ability to meet its primary objectives.

Examples of more than minor modifications which may require review by the convened IRB (for studies that were initially full board) include:

- A new consent/assent form or extensive changes to currently approved consent forms.
- A 20% or greater increase in blood volume.
- A 20% or greater increase in the number of subjects to be enrolled.
- Increase or decrease in the dosage of study drug.
- Increase or decrease in the duration of exposure to study drug.
- Addition of new (or changes to existing) procedures or tests intended to improve monitoring for, or reduce the risk of, side effects/adverse reactions.
- Dropping of a test intended to monitor safety.
- Changes that affect the risk/benefit ratio of the study or specifically indicate a more than minor increased risk to participants.
- Adding a vulnerable population (not for studies initially reviewed via Expedited Review).
- Changes that significantly affect the scope of the investigation (e.g., adding/removing an arm or cohort, significant alteration to the hypothesis or research design).

Continuing Review of Active Studies

Continuing Review of research previously approved under expedited review can be reviewed using expedited review procedures unless research activities have changed such that the research no longer qualifies for expedited review. Continuing Review of research previously approved by the convened IRB can be reviewed using expedited review procedures under certain conditions (see "Continuing Reviews" section of this Guide for details).

9.3 Not Human Subjects Research Determinations:

Sponsors or investigators needing a determination of whether a project constitutes human subjects research requiring IRB approval will submit information requested by Castle IRB for such a determination. Castle IRB will utilize definitions provided by federal regulations as described above in this Investigator Guide.

Requests for consideration of whether activities are human subjects research subject to IRB review and approval should be submitted to irbteam@castleirb.com. Requests should contain full details of the proposed project as well as justification for why the requestor believes the study does not require IRB review. Included in the request should be:

- A full description of the project aims and activities
- Determination of whether the project meets the definition of research with explanation of key

considerations
- Determination of whether the project meets the definition of human subject with explanation of key considerations

Notifications of official Castle IRB determinations and related information or submission expectations will be put in writing to the requestor and kept in IRB records. The typical turnaround time for a determination is 24-48 hours.

9.4 Exempt Human Subject Research:

Submission Requirements

Exempt Review Determination Submissions must include at least the following documents, though specific instructions on what to submit will be specified in the Castle IRB Exempt review application:

- A Castle IRB Exempt Determination Application specifying which exempt category(ies) apply to the research.
- A research protocol or study summary, which includes the study design, aims, and associated tasks/procedures.
- Informed consent/assent forms or participant information scripts/materials used to seek participant permission to take part in the research, for studies involving interactions with participants.
- Human subjects research training documentation for the Principal Investigator.
- Recruitment materials, study instruments, and other materials to be used in the conduct of the study as instructed by the Exempt Application.
- Information regarding the status of any applicable ancillary reviews. This includes financial conflict of interest disclosure for all investigators and their immediate family members, and sharing of the institution's management plan, if applicable.
- HIPAA materials, if applicable.

Criteria for IRB Review

- Exempt submissions are reviewed for alignment with guiding ethical principles in the Belmont Report and to ensure all parts of the research fall under one or more exempt categories of review based on the applicable regulations (DHHS regulations at 45 CFR 46.104 or FDA regulations at 21 CFR 56.104). If the review is a voluntary review (meaning neither set of regulations apply, but the submitter of the exempt determination application requests IRB review), exempt regulations at 45 CFR 46.104 will be applied.
- In addition, exempt submissions are reviewed to ensure compliance with the following:
    - The research must present no more than minimal risk to subjects.
    - The selection of subjects is equitable and recruitment materials are acceptable.
    - If the study will be recording identifiable information, adequate provisions are in place to maintain confidentiality of the data.
    - As appropriate, adequate provisions are in place to maintain the privacy interests of participants.
- If the researcher will be interacting with participants, there is a consent/assent form, information sheet, script or explanation that discloses adequate information for participants to make a voluntary decision regarding whether to participate in the research. Elements should be presented in a language that participants will understand, in a manner that allows adequate time to make a decision in an environment free from coercion or undue influence, and should include the following elements:
    - The activity involves research and the purpose of the research.
    - Description of the procedures and expected duration.

    - If a benign, behavioral intervention involving deception, that participants will be unaware or misled regarding the nature or purposes of the research.
    - Statement of risks and benefits, if any.
    - Payment information, if applicable.
    - Statement that participation is voluntary.
    - Name and contact information of the researcher and Castle IRB.
    - Provisions in place to maintain privacy and confidentiality.
    - Other key information a reasonable person would expect to be disclosed.
    - Statement of financial interests, if any exist.
- If the study enrolls minors, there generally should be a plan to obtain permission from parents/children. Note: Under the Family Educational Rights and Privacy Act (FERPA, 34 CFR Part 99), schools must have written permission from the parent or eligible student in order to release information from a student's education record.
- The research does not involve a test article regulated by the FDA, unless the research meets the criteria for exemption described in 21 CFR 56.104(d).
- The research does not involve prisoners, except for research aimed at involving a broader subject population that only incidentally includes prisoners.

Study contacts listed on Exempt Determination Applications will be notified of IRB determinations upon completion of review including whether the study was determined to be Exempt or requires further IRB review.

Ongoing Review of Exempt Research

Exempt research is not required to undergo continuing review. Further, minor modifications to exempt studies do not require review and approval unless the modification may change the study's eligibility for exemption.

Substantive modifications that have the potential to change the nature of the research and, therefore, the study's eligibility for exemption, require review and approval prior to implementation of the modification.

Castle IRB will send periodic (e.g., annual) status inquiries to primary contacts of Exempt applications to determine whether the project is ongoing or can be closed. Studies can be closed when interactions or interventions with study participants are complete, data collection is complete, and analysis of identifiable data is complete. There is no closure form or IRB review required for exempt study closures; they are handled administratively by Castle IRB staff.

9.5 Generic Materials

Submission Requirements

Generic Materials are submitted outside of a protocol submission; the submitter requests IRB review to ensure that materials will meet IRB requirements in place for such material. Generic Material review requests are submitted to irbteam@castleirb.com with the materials requiring review.

Types of Generic Materials can include, but are not limited to:

- Materials unrelated to a specific study, intended for broader use (e.g., short form template consents)
- General interest flyers/recruitment materials/scripts to join the database of participants for study centers (e.g., Phase 1 study centers)

- Generic material for an upcoming study (can name the condition/type of study, but not specific study)
- For studies not subject to DHHS regulations/not requiring an FDA IND/IDE application ("Voluntary Reviews") ONLY: pre-screening scripts (with a restriction that no participants will be enrolled or undergo study procedures prior to submission/approval of a study protocol and obtaining participants informed consent as approved by the IRB).

Criteria for IRB Review

Generic Materials are assigned to an IRB Chair or Designated Member for review via the Reviewer Checklist for Generic Materials. Reviewers verify that material align with IRB requirements in place for such a document (e.g., requirements in place for recruitment materials). When approved, documents can receive an IRB Review Date, but will not be given an IRB *Approval* stamp.

9.6 Humanitarian Use Devices (HUD)

Submission Requirements

Review of an HUD submission must include at least the following documents, when available. While not all HUD submissions will contain these materials, it is the responsibility of the physician submitting the application to ensure that it is complete, with all documents provided by the device manufacturer.

- A Castle IRB HUD Application.
- Letter from FDA to the HDE holder, which indicates that an application for the HUD has been reviewed and approved by the FDA, including date of HUD designated HDE number.
- Patient Information Packet
- Informed Consent materials (Consents, Assents)
- Device manual(s) and or Instructions for Use (IFU)
- Product labeling
- Documentation of the responsible physician's certified training to use the HUD
- Curriculum vitae (CV) for the responsible physician

Criteria for IRB Review

Submissions for HUD use will be verified by Castle IRB Staff to not be testing safety or effectiveness of the device, and that the use of the HUD is in alignment with clinical (non-research) purposes. The responsible physician or appropriately authorized designee will obtain and document informed consent from each patient or legally authorized representative prior to the use of the HUD if required by Castle IRB as determined in the initial, convened meeting. The FDA does not require informed consent for the clinical use of a HUD; however, the institution at which the HUD will be used, or an IRB may require that informed consent be obtained. Castle IRB does not require informed consent for the clinical use of a HUD, however, Castle IRB does expect the treating physician to provide patients with information from the HDE holder's Patient Information Packet when practicable.

Initial Reviews of HUD

Initial review of a HUD will be completed by a convened IRB. Specific requirements for informed consent and the determination whether future continuing review may be completed via expedited review procedures will be voted on at this meeting.

Ongoing Review of HUD

Continuing review may occur using expedited review procedures if the HUD is not being used in the course of a research study and the IRB has determined continuing review can be conducted via expedited review. Continuing review of a HUD must include the following documents, when available:

- Humanitarian Use Device Continuing Review Form
- Most recent Medical Device Reporting (MDR) summary as provided by the sponsor submitted to the FDA.
- Any uses that were off-label or emergency use.
- Any adverse events or unanticipated problems involving risk to patients or others that are possibly related to the use of the HUD.

Emergency Use of a HUD

Further information regarding emergency use is outlined in section 22.3, "Emergency Use, Planned Emergency Research, and Expanded Access".

10. Ongoing Submissions to Castle IRB:

Investigators are expected to conduct research exactly as approved by the IRB, and in accordance with ethical principles, federal regulations, state and local laws, related guidelines, professional standards, institutional requirements and Castle IRB policies. Once IRB and other ancillary approvals are in place, and a study begins, there are events that must be reported to study sponsors, institutional officials, and Castle IRB to ensure the ongoing safety of participants and to satisfy regulatory requirements.

The types of events include the following, and are further described in this section:

- Amendments (changes in research): any proposed changes in research or study materials, prior to implementing changes except to remove apparent, immediate hazards to research participants. This includes changes in the investigative team's conflicts of interest and licensure.
- Continuing Review/Progress Reports: periodic (typically annual) review of study progress to ensure it is safe to continue.
- Reportable Events: events related to safety or compliance, including protocol deviations, noncompliance, unanticipated problems, participant complaints, breaches in privacy or confidentiality, and study or enrollment halts due to subject safety concerns or loss of resources needed to conduct the trial safely.
- Closures: closing of IRB oversight, which could include early termination of studies.

10.1 Amendments

Any changes to the study or study materials including consent forms must be submitted to, reviewed, and approved by the IRB prior to implementing the changes except when necessary to implement sooner to eliminate apparent immediate hazards to research participants. As such, Amendments should be submitted to the IRB in advance. If modifications must be made to remove apparent immediate hazards to participants, an Amendment must still be submitted to the IRB promptly (e.g., within 5 days of implementing the change). In addition to reviewing the changes for acceptability, the IRB will determine whether the early adoption of such changes was consistent with ensuring the participants' continued rights, safety, and welfare.

Submission Requirements

Castle IRB considers Amendments to include any changes in research, which could be occurring at a single site level, or across all studies in a multi-site study. All Amendments must be submitted on the Castle Amendment Form which summarizes the request for changes and plans for reconsenting participants. Additional items to submit may depend on the type of change (see sections below). Note: to optimize IRB review of Amendments, new versions of materials should be tracked "redlined" to show proposed modifications from previously approved versions. Castle IRB Amendment Guidance [Castle Guidance 020] is used to determine which changes require prior IRB approval in Human Factors research utilizing iterative design methodology

Protocol Amendments:

Amendments must include at least the following though specific instructions on what to submit is specified in the Castle IRB Amendment form:

- Completed Amendment form that summarizes requested changes, provides an explanation for requesting changes, and provides an opinion of whether requested changes pose additional risks to participants.
- Clean and Redlined version of Research Protocol and Summary of Changes, if available
- Clean and Redlined version of product information (e.g., Investigator's Brochure) if applicable
- Clean and Redlined version of Consent Materials, if impacted. Plans for obtaining additional consent from research participants and an explanation for such plans, as applicable.
- Clean and Redlined version of participant-facing materials (study instruments, subject diaries, recruitment materials etc.), if impacted
- For multi-site research, Sponsors/CROs may submit on behalf of all sites, and the master template consent document(s) alone should be submitted. Castle IRB staff will incorporate site specific customizations into new versions once approved.

Product Information Changes:

- Completed Amendment form
- Clean and Redlined version of product information (e.g., Investigator's Brochure)
- Clean and Redlined version of Research Protocol, consent materials, etc. if impacted
- For multi-site research, Sponsors/CROs may submit on behalf of all sites. If applicable, the master template consent document(s) alone should be submitted. Castle IRB staff will incorporate site specific customizations into new versions once approved.

Consent Document and Study Material Changes:

- Completed Amendment form with proposed plans to reconsent enrolled participants, if applicable
- Clean and Redlined version of Consent Document(s)
- Clean and Redlined version (if revising existing materials) of participant-facing materials (study instruments, subject diaries, recruitment materials etc.)
- For multi-site research, Sponsors/CROs may submit on behalf of all sites, and the master template consent document(s) alone should be submitted. Castle IRB staff will incorporate site specific customizations into new versions once approved.

Change to Investigators, Sites, or Local Site Information:

- Completed Amendment form with revisions included, including change of PI, changes to research team member financial conflict of interest information, site locations, participant payment information, and/or inclusion of a

new vulnerable population including a need to add non-English speaking populations and need for translated consent/study materials
    - Note, updates are not required to this form to provide new medical license expiry information, clinicaltrials.gov numbers, or minor fluctuations in staff that do not potentially impact the rights, safety or welfare of participants. Questions about whether local changes require this form can be sent to irbteam@castleirb.com
- For changes to the Principal Investigator or Site Location(s), for PI changes, the new PI's license information, CV, certifications, suspensions/disbarment, human subjects research training documentation; for Site changes, the qualifications, capacity, and any suspensions/FDA Form 483s of the research site.
    - Castle IRB expects the Investigators, Institution, and Sponsor/CRO to ensure a safe transition of study oversight and operations
- Clean and Redlined version of Consent Document(s) and other patient-facing materials, if impacted

Criteria for IRB Review

Amendments to studies initially reviewed by the convened IRB will be conducted at a convened meeting unless changes consist of only minor modifications which qualify for Expedited review.

Amendments are reviewed for continued alignment with guiding ethical principles, and continued compliance with applicable regulations. In addition, the IRB reviews to ensure that:

- Changes to the protocol are adequately explained and justified.
- New findings that may relate to subject well-being or willingness to continue participation have been provided to subjects or will be upon IRB approval.
- The Site and Investigator still appear to have adequate resources and infrastructure to conduct the study safely.

10.2 Continuing Reviews

Certain research approved by the IRB is subject to continuing review. This includes:

- Research studies initially approved by the convened IRB (not under an Expedited Category of Review).
- Research studies approved under Expedited Categories of Review if subject to FDA regulations.
- Research studies approved under Expedited Categories of Review that are not subject to FDA regulations, but the IRB required continuing review (with justification provided in IRB records), or research subject to DHHS regulations meets criteria for expedited categories 8b and 9, in accordance with guidance in OHRP 2018 Requirements FAQs.

Studies that are subject to DHHS regulations, and not FDA regulations, are not required to undergo continuing review if the research meets one or more categories of research that quality for Expedited Review at 45.CFR.46.110, or when research has progressed to the point that it involves only one or both of the following:

- Data analysis, including analysis of identifiable private information or specimens, or
- Accessing follow-up clinical data from procedures that participants would undergo as part of clinical care.

Active studies not subject to continuing review will be prompted to provide Progress Reports on an annual basis to allow Castle IRB to maintain oversight until the study is officially closed with Castle IRB via a Closure Form. Progress Reports are reviewed and acknowledged by Castle IRB Staff.

Active studies subject to continuing review requirements require submission for continuing review unless the study meets the criteria for study closure (see "Concluding IRB Oversight" section of this Guidance for more details).

Submissions for continuing review must be made far enough in advance, no less than 30 days in advance of expiry, to allow for IRB review prior to the expiration date of current IRB approval. Expiration dates will be listed in the IRB approval letter; IRB approval expires at 11:59 P.M. (Central Time, United States)on the expiration date listed. While the IRB sends courtesy reminders in advance of the expiration date to prompt submission for continuing review, Investigators are expected to track expiration dates and submit independently of such reminders. Any lapse in IRB approval will result in a halt of research activities with the exception of continuation of activities that are in the best interest of the safety and wellbeing of research participants.

Submission Requirements

Continuing Review Submissions must include at least the following though specific instructions on what to submit will be provided on the Castle IRB Continuing Review Form:

- Completed Continuing Review form with all requested information, including number of participants accrued, a summary of activities including any withdrawals, complaints, and unanticipated problems experienced in the prior approval period (reportable events must be accompanied by a Castle IRB Reportable Events Form).
- Updated human subjects protection training documentation (showing completion in the prior 3 years), if applicable. While IRB review of a continuing review can proceed with out of date human subjects protection training, a condition for full approval will be to provide documentation that the Investigator is back in compliance with training requirements.
- Assurances that only IRB approved study materials, including informed consent forms are being used in study conduct, along with any newly proposed consent documents (those with changes must be submitted on a separate Castle IRB Amendment Form.
- Any new information that would impact the IRB's consideration of prior determinations of risks and benefits and other approval criteria, including any changes to the approval status of test articles.
- Information related to the data and safety monitoring plan.

Continuing Reviews can be submitted for a single site. .For multi-center studies, a Continuing Review Form must be submitted on behalf of the study overall, as well as for each site individually. For studies requesting changes with the Continuing Review, changes must be submitted separately via an Amendment Form.

Criteria for IRB Review

Generally, if a protocol was approved at a convened meeting of the IRB at initial review, the continuing review will be reviewed at a convened meeting. However, if research initially did not qualify for Expedited review, the IRB may review the study under Expedited Review if at least one of the following apply:

- The IRB designates the protocol as minimal risk and determines it to qualify for future Expedited review under Category 9 of 21 CFR 56.110; 45 CFR 46.110.
- The protocol now meets the general categories for expedited review (e.g., if expedited categories or the protocol changes such that the study now meets expedited review criteria).
- For FDA regulated research, the protocol meets the criteria for expedited review under categories 8a, 8b, or 8c of 21 CFR 56.110.
- For DHHS regulated research, the protocol meets the criteria for expedited review under category 8b of 45 CFR 46.110 or category A or B of 45 CFR 46.109(f)(1)(iii).

Once the Continuing Review Submission is reviewed to determine Expedited versus convened IRB review and assigned, the IRB reviews to ensure continued alignment with guiding ethical principles, and continued compliance with applicable regulations. The IRB also ensures that current IRB approved study materials including informed consent forms are being used in the conduct of the study.

In addition, the IRB reviews to ensure that:

- Any new risk or other relevant information has been considered and risks are still minimized and reasonable in relation to anticipated benefits.
- The informed consent document being used is the currently approved version(s) and contains any new risk or other information that could affect a participant's willingness to participate/continue.
- If open to accrual, the consent process still appears acceptable (no subject complaints or other concerns have been raised that suggest modifications to the process are needed).
- There are no known local considerations that prevent ongoing conduct of the study (changes to the investigator's or institution's qualifications, commitments or resources; changes to applicable laws; or local complaints or concerns about the study).
- Investigator's human subjects protection training is current (taken within prior three years)
- Research progress is acceptable (enrollment numbers as expected or justified; protocol deviations are explained and reasonable in nature or number; no material changes have occurred since previous IRB review).

The IRB sometimes seeks verification from sources other than the Principal Investigator that no material changes have occurred during the IRB approval period of a study that would impact the IRB's determinations.

Criteria for external verification include:

- Complex studies with exceptionally high risks to participants.
- Novel research with a high degree of uncertainty regarding the risks involved.
- Studies run by Principal Investigators who have previously failed to comply with federal regulation or IRB requirements or by PIs who are suspected to be noncompliant or have gotten previous participant complaints.
- Studies in which the IRB has discovered new information about a study from sources other than the Principal Investigator in the past.

Sources for external verification may include:

- Available literature related to the research.
- Institutional assurance (e.g., verification from the Investigator's Institution).
- Ancillary Review assurance (e.g., Institutional Biosafety Committee records).
- Research participants.
- Study sponsors or CROs.
- IRB consultants.

The IRB may become aware of new information that it determines should be provided to participants as it may impact their willingness to continue in the study or may otherwise be important to their rights and wellbeing. This information can be provided to participants via letter, addendum consent or modified consent as deemed appropriate by the PI and approved by the IRB. This information will also be considered by the IRB to ensure that all regulatory criteria for approval are still met, and the study can continue being conducted as designed.

10.3 Reportable Events

During the conduct of a research study, unanticipated events may occur, and new information may become available that must be promptly reported to Castle IRB. Reportable Events may occur at a single site but could impact other sites in a multi-center study.

Castle IRB requires the following events to be reported within seven (7) calendar days once known to the research team, even if only preliminary information is available:

- Adverse events that meet the definition of an unanticipated problem involving risk to participants or others (see "Unanticipated Problems" section of this Guidance for definition)
- Unanticipated Adverse Drug or Device Effects (see "Unanticipated Problems" section of this Guidance for definition)
- New information that indicates there are new or increased risks to participants or others or decreased benefits of the research. For studies subject to ICH-GCP Guidelines this includes new information or changes that significantly impact or adversely affect the conduct of the clinical trial
- Death of a research participant that is related or possibly related to the research
- Data security breaches that placed participants or others at greater risk of harm
- Changes made to remove apparent, immediate hazards to participants without prior approval of the IRB
- Protocol deviations that placed one or more participants at increased harm or have the potential to occur again (see "Protocol Deviations" section of this Guidance for definition)
- Allegations or findings of noncompliance
- Participant complaints that were not addressed by the research team or indicate an increase in risk
- Incarceration of an active study participant or a participant has become a ward of the state
- Audits, inspections, or inquiries by a federal agency
- Suspension or premature termination by the sponsor, investigator, or institution
- State medical board or federal agency action (e.g., Form FDA 483, FDA Warning Letter, medical license action)
- Other information the sponsor/CRO has mandated the research team to report to the IRB

<u>Submission Requirements</u>

Use Castle IRB's Reportable Events Form to submit reportable events and information to Castle IRB. Submissions must include at least the following, though specific instructions on what to submit is provided in the Reportable Events Form:

- Details of the event and changes, if any, that were implemented to remove any apparent, immediate hazards to participants, with justification for such actions.
- Root cause of the reportable event, including the Principal Investigator's explanation for why the event occurred and what will be done to ensure that it does not recur.
- Plans, if any, for amending the protocol or study materials.
- Plans, if any, for notifying current participants when the information may relate to participants' willingness to continue in the study.
- An assessment of whether the event meets the criteria of an Unanticipated Problem involving risks to subjects and others.

If you are unsure if the event you have identified requires reporting, please contact Castle IRB for assistance. Reportable Events may be submitted for a single site, and for multi-center studies, on behalf of all or some sites.

Criteria for IRB Review

Reportable Event submissions are first reviewed by Castle IRB Staff, and the IRB Chair as needed, to determine whether the event was indeed reportable, and whether the event potentially meets the definition of an Unanticipated Problem or serious and continuing noncompliance. Submissions deemed unnecessary to report will be returned to the investigator or Acknowledged. Protocol deviations and noncompliance reports that are determined to potentially constitute serious or continuing noncompliance will be assigned to the convened IRB for review. Events that are deemed to potentially constitute Unanticipated Problems or unanticipated device effects will be assigned to the convened IRB for review, unless assessed to involve no more than minimal risk to participants or others, in which case expedited review procedures can be used.

Unanticipated Problems: Unanticipated Problems (UP) are defined as any accident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of the nature, severity, or frequency.
- Related, or possibly related to the subject's participation in the research.
- Places participant or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

UPs can also include unanticipated device effects, defined as any serious adverse effect on health, 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 protocol, or any unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The IRB will review the Report to determine whether the event constitutes an Unanticipated Problem, reportable to Federal Agencies and Institutional Officials. The IRB will consider the changes implemented or planned in response to ensure protection of the safety, welfare and rights of research participants and others, including adequacy of information being provided to participants that may relate to subject well-being or willingness to continue participation. In addition, the IRB reviews to ensure the study will have continued alignment with guiding ethical principles, and continued compliance with applicable regulations. Finally, Unanticipated Problems are reviewed to determine whether there is evidence of Noncompliance, such as a failure to adhere to the IRB approved protocol, and to determine whether a suspension in whole or in part is warranted.

Possible IRB actions resulting from reviews of an Unanticipated Problem include:

- Verify that changes implemented to remove apparent, immediate hazards to participants were made appropriately, and in accordance with federal regulations and IRB policies.
- Review proposed changes in accordance with IRB policies for Amendments.
- Request additional changes to the protocol or study materials as needed to protect human participants and others, and/or to keep the study in alignment with ethical principles, federal, state, or local regulations, ICH-GCP as applicable, or other sponsor or agency requirements, as applicable.
- Verify that plans for notification/additional consent from participants (future, current, past) are adequate and appropriate, and request modifications as needed.
- Suspend enrollment of new participants, if needed for safety.
- Suspend continuation of current participants, if needed for safety.
- Consider whether the IRB should seek information from sources other than the Principal Investigator, such as from the conduct site(s) affected by the event.
- Consider whether the UP is potentially serious or continuing noncompliance.

- Consider whether IRB approval of the study should be suspended or terminated.
    - In such cases, the IRB must consider impact on the rights and welfare of enrolled participants and whether participants in active intervention or inactive (those who withdrew or completed participation) should be informed of the suspension/termination of IRB approval.
- Require continuing review more frequently than annually.
- Ensure that any related reporting requirements are understood by all responsible parties.
- Require audit or monitoring of the research or consent process.

Protocol Deviations: A protocol deviation is defined as a departure from the IRB approved protocol, including use of study materials not approved by the IRB, if the deviation increased the risk of harm to participants, adversely affected a participant's rights, safety or welfare, or adversely affected the integrity of the data or research. This includes but is not limited to:

- A study visit with safety labs was missed, placing the participant at increased risk.
- A wrong dose was given to a study participant.
- Consent was obtained using the wrong version of the document, with outdated content.
- Study instruments were not consistently completed for a large percentage of study participants.

Possible IRB actions resulting from reviews of a Protocol Deviation determined not to be serious or continuing noncompliance include:

- Verify that any changes implemented to remove apparent, immediate hazards to participants were made appropriately, and in accordance with federal regulations and IRB policies.
- Require changes to the protocol or study materials as needed to protect human participants and others, and/or to keep the study in alignment with ethical principles, federal, state, or local regulations, ICH-GCP as applicable, or other sponsor or agency requirements, as applicable.
- Verify that plans for additional consent from participants are adequate and appropriate, and request modifications as needed.
- Consider whether the IRB should seek information from sources other than the Principal Investigator (e.g., from the Institution or research participants) to ensure full understanding of events, including performing or requiring an investigation.
- Consider whether the deviation constitutes an Unanticipated Problem.
- Accept or request changes to the investigator's corrective action plans and determine whether corrective action plans require verification or monitoring.
- Suspend enrollment of new participants, if needed for safety.
- Suspend continuation of current participants, if needed for safety.
- Suspend IRB approval of the study.
    - In such cases, the IRB must consider impact on the rights and welfare of enrolled participants and whether participants in active intervention or inactive (those who withdrew or completed participation) should be informed of the suspension of IRB approval.
- Issue correspondence to the Investigator that summarizes the incident of noncompliance, relevant regulations/policy expectations, and potential outcomes should there be recurrence in the future.
- Require additional education in human subjects research protections, Good Clinical Practice, the protocol, federal regulations, IRB policies or other.
- Require audit or monitoring of the research or consent process or require continuing review more than annually.

IRB Determinations and actions will be promptly communicated to investigators and other parties (including Institutional Officials) in accordance with the terms of the Reliance Agreement in place between Castle IRB and the Conduct Site/Relying Institution.

10.4 Protocol Exceptions

A protocol exception is when an investigator plans to intentionally change or alter a protocol for one participant, including enrollment exceptions. Such requests must be submitted to Castle IRB for review and approval prior to implementation, using the Reportable Events Form.

11. Criteria for IRB Approval of Research:

The IRB shall review and approve or disapprove individual applications involving human subjects research as required by and in compliance with federal regulations at 21 CFR 50, 56 and 45 CFR 46. This shall include all new research applications, ongoing review (continuing review) of existing research applications, changes to approved research (amendments), reportable events including Unanticipated Problems to Subjects and Others and Protocol Deviations.

IRB Review and Approval Criteria

To be approved by the IRB, initially and on an ongoing basis, the IRB must determine that all Submissions demonstrate that the research meets the following criteria, as applicable:

- **Department of Health and Human Services (DHHS) at 45 CFR 46** if the research has federal funding or when otherwise required, such as when required by the FWA of an institution relying on Castle IRB review services, including Subpart B for research involving pregnant women, fetuses, or neonates; Subpart C for research involving prisoners; and Subpart D for research involving children.
- **Food and Drug Administration (FDA) at 21 CFR 50; 56; 312; 600; and 812** as they apply to clinical investigations and other research involving products regulated by FDA.
- **Health Insurance Portability and Accountability Act (HIPAA):** on behalf of conduct sites/relying institutions who are covered entities, Castle IRB can review the following in accordance with the HIPAA Privacy Rule:
  - Waivers or alterations of authorization for use and disclosure of Protected Health Information (PHI).
  - Written authorizations for use or disclosure of PHI.
- **Federal Agency Requirements** when research is supported by other federal agencies, such as the Department of Defense.
- **International Conference on Harmonization Good Clinical Practice E6 (ICH GCP)** guidelines to the extent required by sponsors, but generally only to the extent that they are compatible with FDA regulations.
- **NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules *(NIH Guidelines)*:** Castle IRB assures that research subject to the *NIH Guidelines* has complied, or intends to comply, with the requirement for Institutional Biosafety Committee (IBC) review and approval.
- **State and local laws:** Conduct Site Investigators are asked to disclose and document knowledge of any relevant local laws, including any state, local, and international laws that apply to the research. Castle IRB will confirm that Investigators are knowledgeable of such applicable laws and regulations.

See “Study Design Considerations” for additional information regarding criteria for IRB approval.

12. IRB Determinations and Investigator Notifications:

Based on IRB review, the IRB shall make one of the following determinations for Submissions reviewed:

- APPROVED – The research is approved by the IRB as is; no changes are required.
- CONTINGENTLY APPROVED – Certain conditions must be met before the Submission may be approved.
- DEFERRED/TABLED – The IRB requires more information before making a final determination.
- DISAPPROVED – The IRB Committee does NOT approve the Submission. This determination can only be made by the convened IRB, not when conducting Expedited Review procedures.
- ACKNOWLEDGED – Generally used for review of reportable information in active research, not Initial Reviews, Amendments, or Continuing Reviews.

The IRB shall notify the PI and submission contact(s) of the IRB's determination.

Research subject to IRB approval (e.g., research that is deemed human subjects research, and not exempt from IRB review) cannot commence until the application is Approved by the IRB. Additional approvals may also apply. For example, if a master protocol was submitted, but not a conduct site and investigator, sites/investigators will need to be approved prior to the research being conducted at each site. In addition, ancillary approvals, such as Institutional Biosafety Committee (IBC) approval, must be in place when applicable.

In cases where a submission is Approved, the IRB shall provide an Approval Letter to the PI and submission contact(s) with specifics about the study and its approval including the expiration date of approval, and for site approvals, a summary of PI responsibilities while conducting the study. Castle IRB staff will list and/or provide IRB approved study materials for use in the study l. Consent document(s) and other participant-facing materials will be given IRB approval information in the header or footer. Only these versions should be used in the conduct of the study. Investigators are expected to conduct research according to the IRB approved protocol and use only the IRB approved study materials. Any changes to the study or study materials will require an Amendment request to be submitted to the IRB prior to implementation unless the change is being made to remove apparent immediate hazards to study participants. Castle IRB Amendment Guidance [Castle Guidance 020] is used to determine which modifications require prior IRB approval in Human Factors research utilizing iterative design methodology.

If research is Contingently Approved, the IRB shall clearly define the changes that must be made before the research can be fully Approved. Castle IRB staff are available to work with the submission contact(s) to assure these conditions have been met and are appropriately documented. The IRB Chair, a Designee of the IRB Committee or IRB Staff may determine when the conditions established by the IRB have been adequately addressed and the proposed research may be fully Approved.

If research is Deferred or Tabled, the IRB shall clearly define the conditions that must be met before the research may be re-evaluated. Castle IRB staff shall follow up with the submission contact(s) to assure appropriate information or documentation has been provided. When possible, the response will return to the original IRB Reviewer or Committee that tabled the review for further consideration and review.

If research is Disapproved at a convened IRB meeting, a main basis for disapproval will be provided to the submission contact(s) who will have the option to appeal for reconsideration.

If a Submission is Acknowledged, the IRB shall provide an Acknowledgement letter to the submission contact(s) along with any required actions or recommendations.

Requests for Modifications/Additional Information

Submission contact(s) are frequently contacted following an IRB review with a request for additional information. Generally, these communications are made via documented correspondence (determination letter, e-mail, or electronic IRB system); however, other communication methods (e.g. telephone) may be used when the information needed is minimal (e.g. insertion of a word in an informed consent document to clarify the text). The IRB may request that submission contact(s) attend a subsequent IRB meeting to provide further information.

Review of Responses

When the IRB requires modifications to research to secure full Approval, the response will be reviewed to verify that the conditions for approval have been satisfied. The IRB requests this information be provided at the earliest opportunity and will send reminders to prompt for a response. A Submission may be administratively withdrawn by Castle IRB staff if a timely response is not received. The submission contact(s) will be notified of such expectations and actions. See "Appeal of IRB Determinations" section of this Guidance for details on how to submit an appeal.

13. Principal Investigator Responsibilities:

The Principal Investigator (PI) is ultimately responsible for assuring compliance with Castle IRB and institutional policies and procedures, federal regulations, and state and local laws for the oversight of the research. The following are PI responsibilities, and are not all inclusive:

- Design and conduct research in accordance with ethical principles, federal regulations, state and local laws, related guidelines, professional standards, institutional requirements and Castle IRB policies. For human gene transfer clinical trials, this includes compliance with the *NIH Guidelines*, when applicable.
- Design studies as otherwise outlined in the "Study Design Considerations" section of this Guidance.
- Ensure that there are adequate resources to carry out the research safely. This includes but is not limited to having sufficient time to personally lead the study, having sufficient levels of qualified research team members, ensuring there is sufficient space and the necessary equipment to conduct the study, and ensuring all study stuff maintain credentials and privileges needed to conduct the research. Consider halting research if resources become unavailable.
- Ensure proper submission of all required sponsor and IRB paperwork and forms (see Initial and Ongoing Submission sections of this Guidance for details). Keep track of all Submission deadlines and IRB approval expiration dates to ensure there are no lapses in IRB approval for active studies.
- Report any conflicts of interest that may impact objectivity in research conduct and abide by requirements for financial disclosure and any associated management plans
- Ensure that ancillary approvals, such as Radiation Safety Committee, Institutional Biosafety Committee, and Pharmacy approvals, among others, are in place if required prior to convening the research and maintained throughout the life of the study.
- Provide (directly or through the study's Contract Research Organization) attestation or other written statement that agreements with study sponsors:
    - Indicate who will provide care in cases of research-related injury and who is responsible to pay for it.
    - Obligate study sponsors to promptly (no longer than within 30 days) report to the site or investigator any findings (including those from study monitors) that could affect the safety of participants, influence the conduct of the study, or alter the IRB's approval to continue the study. The site or investigator must

then promptly (no longer than within 30 days, and within reporting timeframes specified in this Investigator Guide) forward this information to Castle IRB.
    - Obligate study sponsors to promptly (specify timeframe in the agreement) provide routine and urgent data and safety monitoring reports to the site or investigator, and the site or investigator will then promptly (no longer than within 30 days, and within reporting timeframes specified in this Investigator Guide) forward to Castle IRB.
    - Obligate study sponsors to notify the site or investigator of findings from a closed study that directly affect participant safety, and specify a time frame for reporting (e.g., two years), that is appropriate for each individual study. The site or investigator will then promptly forward this information to Castle IRB.
- Maintain training in human subjects research protections, good clinical practice, and related topics as applicable, and ensure that other study team members maintain required training.
- Maintain expertise in the study protocol and ensure all study team members maintain understanding to ensure the research is conducted in accordance with the IRB approved protocol and with current, IRB approved study materials including informed consent forms.
- Oversee all study procedures and delegate tasks to study personnel according to their credentials, capabilities and capacity. Provide ongoing supervision and correct issues in real time. Implement, abide by and oversee corrective and preventive actions where indicated.
- Submit any proposed changes in research or study materials to the IRB prior to implementing them except to remove apparent, immediate hazards to research participants. In case of the latter, prompt submission (5 business days post implementation) to the IRB is still required.
- Submit for Continuing Review or Study Closure far enough in advance of the protocol approval period expiration date to allow for IRB review and approval to avoid lapses in IRB approval, and discontinue research activities except to remove apparent, immediate hazards to research participants should a lapse in approval occur.
- Submit other events, including Unanticipated Problems and Noncompliance, to the IRB in accordance with the Reportable Events Form.
- Report directly to study sponsor/funding agency for any adverse events, compliance concerns, participant data and/or other required information as defined by the Sponsor or protocol.
- Use fair and equitable recruitment practices in research and avoid practices that place participants at risk for coercion or undue influence.
- Obtain the legally effective informed consent of participants or their Legally Authorized Representatives as required by the IRB; ensure participant understandability both initially and as the study progresses.
- Ensure that the rights, safety and welfare of research participants guide all actions throughout the conduct of the study. Provide additional protections for participants who may be vulnerable to coercion or undue influence, when possible, to minimize risks.
- Ensure research participant questions, requests for information, and concerns are addressed swiftly and completely; inform the IRB, study sponsor, and other parties as appropriate, when assistance is needed to address participant complaints or concerns.
- Protect participant privacy and confidentiality in accordance with the IRB approved protocol and federal, state and local laws, including HIPAA and Certificates of Confidentiality (COC) for NIH-funded studies or other research covered by a COC.
- Maintain study records as approved by the IRB, and in accordance with sponsor, regulatory, and/or other requirements; have records available for audit or inspection by the sponsor, Castle IRB, their institution, regulatory agencies or other authorities.

The FDA Guidance for Industry "Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects" includes additional responsibilities for PIs conducting clinical investigations of drugs, including biological products, under 21 CFR part 312 and of medical devices under 21 CFR part 812, such as:

- Ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan, and applicable regulations.
- Protecting the rights, safety, and welfare of subjects under the investigator's care.
- Controlling drugs, biological products, and devices under investigation (21 CFR 312.60, 21 CFR 812.100).
- Principal Investigators commit themselves to personally conduct or supervise the investigation; thus, the investigator should have sufficient time to properly conduct and supervise the clinical trial, including ensuring tasks are appropriately delegated, and that research team members are properly trained, initially and on an ongoing basis.

Investigators of clinical trials subject to ICH-GCP Guidelines have additional responsibilities including, but not limited to:

- The Investigator provides evidence of his or her qualifications through up-to-date curriculum vitae or other relevant documentation requested by the sponsor, the IRB or EC, or the regulatory authority.
- The Investigator is familiar with the appropriate use of the investigational product, as described in the protocol, in the current investigator brochure, in the product information, and in other information sources provided by the sponsor.
- The Investigator maintains a list of appropriately qualified persons to whom they have delegated significant clinical trial-related duties.
- A qualified physician (or dentist, when appropriate), who is PI or a co-researcher for the clinical trial, is responsible for all clinical trial-related medical or dental decisions.
- During and following a participant's participation in a clinical trial, the Investigator ensures that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the clinical trial. Investigators inform participants when medical care is needed for other illnesses of which the Investigators become aware.
- The Investigator follows the clinical trial's randomization procedures, if any, and ensures that the code is broken only in accordance with the protocol. If the clinical trial is blinded, the Investigator promptly documents and explains to the sponsor any premature unblinding.
- The Investigator informs the participant's primary physician about the participant's participation in the clinical trial if the participant has a primary physician and if the participant agrees to the primary physician being informed.
- Investigators and research staff provide all the disclosures and follow the requirements pertaining to consent covered by ICH-GCP.
- The Investigator reports all serious adverse events (SAEs) to the sponsor except for those SAEs that the protocol or other document (e.g., investigator's brochure) identifies as not needing immediate reporting. The Investigator follows regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authority and the IRB.
- The Investigator reports adverse events or laboratory abnormalities identified in the protocol as critical to safety evaluations to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
- For reported deaths, the Investigator supplies the sponsor and IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).

- The Investigator provides written reports to the sponsor, the IRB, and, where applicable, the organization on any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.
- Although a participant is not obliged to give his or her reasons for withdrawing prematurely from a clinical trial, the Investigator makes a reasonable effort to ascertain the reason, while fully respecting the participant's rights.
- The Investigator ensures the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.
- If the Investigator terminates or suspends a clinical trial without prior agreement of the sponsor, the Investigator informs the organization, sponsor, and the IRB.
- If the IRB terminates or suspends approval of the clinical trial, the Investigator promptly notifies the sponsor.
- Upon completion of the clinical trial, the Investigator informs the organization, the IRB with a summary of the trial's outcome, and the regulatory authority with any reports required.

Investigators should be aware of the full spectrum of duties required by ICH-GCP.

13.1 Co-PI Responsibilities:

Castle IRB allows one co-Principal Investigator (Co-PI) to be named to a study. A Co-PI has responsibilities similar to that of a PI. While the PI has ultimate responsibility for the conduct of a study, the Co-PI is also obligated to ensure the study is conducted in compliance with applicable laws, regulations, and IRB policy governing the conduct of the research. The Castle IRB application will ask for any special details on roles played by the PI/Co-PI (e.g., scientific oversight versus administrative/overall oversight).

14. Other Research Team Member Responsibilities:

All other members of the research team are responsible for protecting research participants and may perform tasks as delegated by the Principal Investigator, but they are not primarily responsible for the research study.

Other responsibilities include:

- Conduct research in accordance with ethical principles, federal regulations, state and local laws, related guidelines, professional standards, institutional requirements and Castle IRB policies.
- Assist in proper submission of all required sponsor and IRB paperwork and forms.
- Report any conflicts of interest that may impact objectivity in research conduct and abide by any requirements for financial disclosure and any associated management plans.
- Submit any proposed changes in research or study materials to the IRB prior to implementing them except to remove apparent, immediate hazards to research participants. In case of the latter, prompt submission (5 business days post implementation) to the IRB is still required.
- Maintain expertise in the study protocol and ensure the research is conducted in accordance with the IRB approved protocol and with current, IRB approved study materials including informed consent forms.
- Maintain training in human subjects research protections and complete specific protocol training. Investigators who conduct clinical trials should also complete and maintain training in good clinical practice (GCP).
- Obtain the legally effective informed consent of participants or their Legally Authorized Representatives as required by the IRB; ensure participant understandability both initially and as the study progresses.
- Ensure that the rights, safety and welfare of research participants guide all actions throughout the conduct of the study. Provide additional protections for participants who may be vulnerable to coercion or undue influence, when possible, to minimize risks.

- Ensure research participant questions, requests for information, and concerns are addressed swiftly and completely; inform the IRB, study sponsor, and other parties as appropriate, when assistance is needed to address participant complaints or concerns.
- Protect participant privacy and confidentiality in accordance with the IRB approved protocol and federal, state and local laws, including HIPAA.
- Maintain study records as approved by the IRB, and in accordance with sponsor, regulatory, and/or other requirements; have records available for audit or inspection by the sponsor, Castle IRB, institution, regulatory agencies or other authorities.

15. Financial Conflicts of Interest:

A financial conflict of interest of an investigator or other research team member can be broadly defined as an interest that competes with the investigator or other research team member's obligation to protect the rights and welfare of research participants or preserve the integrity of the research.

Principal Investigators and research team members responsible for the design, conduct, or reporting of research must disclose significant financial interests related to the research initially and throughout the life of the study. A financial conflict of interest related to the research means financial interest in the sponsor, product, or service being tested. Castle IRB requires disclosure of financial interests related to the sponsor, product, or service being tested when a research team member or their immediate family member (spouse, domestic partner, or dependent child) has any of the following:

- Excess of $5,000 in aggregate annual remuneration (including salary, consulting fees, honoraria, paid speaking fees/authorship, etc.)
- Compensation related to the research such that the payment amount is affected by study outcomes, including proprietary interests (patents, licensing agreements, royalty payments, etc.)
- Equity interest (stock, stock options, or other ownership interests) in the sponsor, product or service being tested, or any governance or executive relationship with sponsor entities.

As stated in "Principal Investigator Responsibilities" and "Other Research Team Member Responsibilities" sections above, researchers are responsible for reporting any conflicts of interest that may impact objectivity in research conduct and abide by any associated management plans. Information about researcher financial conflicts of interest is collected on Castle IRB submission forms and is expected to be updated in real time (i.e. 5 business days upon it changing) via an Amendment to Castle IRB.

Institutions who rely on Castle IRB for IRB review and oversight services are obligated to maintain policies and procedures to manage or eliminate investigator and organizational conflicts of interest (COI). Such policies and procedures shall address the primary components of COI disclosure, evaluation and management, monitoring and enforcement, record retention, and reporting and education that meet the laws, regulations, codes, or other requirements to which the research and institution is bound.
Institutional management plans are to be shared on Castle IRB submission forms and are expected to be updated in real time. Castle IRB has the final authority to decide whether the interest and its management, if any, allows the research to be approved. Castle IRB can determine that additional methods for managing conflicts of interest must be put in place to obtain IRB approval, but cannot remove components from management plans put in place by the Institution.

Castle IRB will provide evaluation and management of investigator COIs at sites that do not have an internal process. Examples of ways Castle IRB may require management of COIs include reducing or eliminating the financial interest, restricting the conflicted research team member from all or certain duties, such as recruitment, obtaining consent, or collecting or reporting study data, requiring disclosure of the conflict to study team members and to prospective participants in the consent form, and/or requiring an independent research monitor.

Investigators may refer to the following Federal Guidelines for conflicts of interest in research: DHHS Guidance "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection" and FDA Guidance "Financial Disclosure by Clinical Investigators".

To further ensure that financial conflicts of interest do not compromise the quality or integrity of research, Castle IRB maintains policies and procedures to ensure that no IRB staff, member or consultant takes place in the review of research for which they have a conflict of interest except to provide information requested by the IRB. Further, organizational conflicts of interest for Castle IRB, its parent company Sabai Global, and senior officials are disclosed, reviewed by outside legal counsel, and managed.

16. Study Design Considerations:

As outlined in the "Principal Investigator Responsibilities" section, Investigators must design studies with protection of the rights, safety and welfare of research participants as a primary concern. In addition, studies should be:

- Consistent with sound study design and designed in accordance with standards of the discipline so that research will most likely develop or contribute to generalizable knowledge.
- Designed in accordance with ethical principles, federal regulations, state and local laws, related guidelines, institutional requirements and Castle IRB policies. For human gene transfer clinical trials, this includes compliance with the *NIH Guidelines*, when applicable, and for drug studies, it may include ICH-GCP Guidelines.
- Pursued only after feasibility assessments are conducted to ensure that there will be access to the necessary number of participants to answer research questions, sufficient numbers of qualified staff, sufficient time available for the PI to lead and oversee the study, and sufficient space and equipment to conduct the study safely.
- Designed in a manner that minimizes risks to participants. Studies should have sound rationale for chosen procedures and study populations and include a risk-potential benefit analysis.
- Designed with plans for monitoring the data for the safety of participants. Such monitoring may be done in real time for individual participants, with aggregate reviews taking place at certain time points. Consideration should also be given to the qualifications and independence of the individual(s) assessing the data.

Templates are widely available for Investigators looking to design clinical trial protocols. Castle IRB recommends making use of such templates when suitable for their study. Castle IRB also recommends Investigators designing cellular and gene therapy clinical trials to refer to applicable FDA Guidance: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances for unique considerations of this cutting-edge research. Community engagement in the design of research is also strongly recommended (see "Community Engagement" section of this Guidance for more information).

Castle IRB has included a basic Protocol Template as Appendix A of this Guidance. Prompts therein will assist Investigators with generating a protocol with the necessary information that Castle IRB will need to have to assess whether research meets regulatory criteria for approval to proceed.

16.1 Risks

Protocols are expected to outline reasonably foreseeable risks of the research, the measures put in place to minimize risks, potential benefits of the research, and reasonably available alternatives so that Castle IRB can make the necessary determinations regarding risks and benefits at 45 CFR 46.111(a)(1) and (2); 21 CFR 56.111(a)(1) and (2).

In order to approve research, the IRB must find that:

- Risks to participants are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose participants to risk.
- Risks to participants are minimized, when appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes.
- Risks to participants are reasonable in relationship to the potential benefits, if any, to participants, and the importance of the knowledge that may be expected to result.
- Risks are minimized by ensuring the following is in place to protect participants:
    - Adequate time for the researchers to conduct and complete the research.
    - Adequate capacity and availability of the PI to supervise the study.
    - Adequate number of qualified staff.
    - Adequate facilities.
    - Access to a population that will allow recruitment of the necessary number of participants.
    - Availability of medical or psychosocial resources that participants may need as a consequence of participating in the research.

Researchers should not commence a research study without adequate resources to protect participants and should stop a research study if resources become unavailable.

16.2 Data and Safety Monitoring

In order to approve research, the IRB must find that when appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects (45 CFR 46.111 (a)(6); 21 CFR 56.111 (a)(6).

The IRB might consider provisions such as:

- What safety information will be collected, including serious adverse events.
- How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).
- The frequency of data collection, including when safety data collection starts.
- The frequency of review of cumulative safety data, which might need to occur after a specific number of participants have been enrolled, at specific time points, or upon recognition of harms.
- Whether a data monitoring committee is proposed, including the committee composition, independence from the sponsor, and plans for reporting data monitoring committee findings to the IRB and the sponsor.

FDA Guidelines for cellular and gene therapies have advised that for early phase trials, all AEs should be captured, even if the investigational product is an add-on to known toxic therapies [per FDA Guidance, attribution of individual AEs to the product, study procedures, or other causes can be unreliable]. Early phase studies may have a medical monitor and study Investigators assessing safety data and events, as opposed to later phase studies who employ Data and Safety Monitoring Boards to assess aggregate data at certain time points or frequencies throughout the study. FDA guidelines generally recommend a monitoring committee in addition to a medical monitor for human gene transfer trials. Castle IRB will consider plans proposed to monitor study data, if any, to ensure they are adequate to protect the safety of study participants.

Other sections of this policy that address regulatory criteria for approval include:

- "Informed Consent"
- "Vulnerable Subjects, Additional Considerations and Protections"
- "Recruitment and Compensation"
- "Privacy and Confidentiality"

16.3 PI Oversight

Principal Investigators are ultimately responsible for the conduct of the research. In addition to ensuring that adequate resources are in place to conduct the study safely, the PI is responsible for oversight of the study and study staff, including ensuring that research staff are qualified by training and experience for their research roles. Research team members must have knowledge of applicable laws, regulations, codes, guidance, professional standards, IRB and Institutional policies and procedures, and sponsor requirements regarding the research and protection of research participants, initially and throughout the life of the study.

When researchers delegate responsibilities to study team members, they should ensure that individuals are properly trained, credentialed, and available to perform such duties. Documentation of delegations, such as a delegation log, should be kept with study records to demonstrate who can perform certain functions, especially obtaining informed consent from research participants. Selection of and delegation to research team members is the responsibility of the PI; Castle IRB does not request names of research team members on the IRB Application. Rather, the amount of research staffing by role is requested on IRB Applications, along with whether those roles have been delegated the duty of obtaining consent.

The PI is expected to regularly meet with research team members on study progress, and to provide ongoing supervision. PIs should address any issues in study conduct or with study staff promptly. Due to the importance of the PI role, students and trainees are typically not allowed to serve alone in the PI role; rather, a more experienced Investigator will likely be required to serve as PI, or at least jointly as a co-Investigator. Gene and cell therapy clinical trials will almost certainly require a licensed physician to serve as PI.

Investigators must also ensure that study records are kept in accordance with applicable requirements, including complete and accurate case histories and informed consent documents for research participants. ICH-GCP requires that Investigators ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor. Data must also be kept securely, in accordance with IRB and sponsor requirements, and retained typically no less than three years post study closure, though records subject to HIPAA and FDA market approvals are often required to be retained for much longer periods. Investigators must be knowledgeable of and abide by all applicable study record requirements.

16.4 NIH Genomic Data Sharing Policy

Studies that are subject to the NIH Genomic Data Sharing (GDS) Policy have additional protocol design considerations and NIH certification requirements. Though the investigator's institution is responsible for providing the required certification to the NIH (each site or lead site for multi-site studies, as agreed upon by the institutions), as part of it's review of the research, Castle IRB will verify the following:

- The protocol for the collection of genomic and phenotypic data is consistent with 45 CFR Part 46.
- Data submission and subsequent data sharing for research purposes are not inconsistent with the informed consent of study participants from whom the data were obtained.

- Consideration was given to risks to individual participants and their families associated with data submitted to NIH-designated data repositories and subsequent sharing.
- To the extent relevant and possible, consideration was given to risks to groups or populations associated with submitting data to NIH-designated data repositories and subsequent sharing.
- The investigator's plan for de-identifying datasets is consistent with the standards outlined in the GDS Policy.

Investigators should ensure that the protocol accurately and completely describes data collection, data sharing, and de-identification plans including what data will be submitted to NIH repositories, and further ensure that information provided in the informed consent materials is consistent with the protocol. Assessment of risks to individuals and potential group harms should be considered in the protocol and reflected in risk minimization plans described in the protocol to enable Castle IRB's verification. Consent language must disclose data collection, data sharing, and data de-identification plans, including details for submission of data to NIH repositories and potential future uses. Castle IRB team members may assist investigators by providing example consent language if desired.

17. Informed Consent:

In accordance with ethical principles, and as required by federal regulations, legally effective informed consent, and HIPAA Authorization when applicable, must be sought from each potential research participant or the participant's Legally Authorized Representative (LAR) prior to taking part in non-exempt human subjects research unless an exception applies or a waiver has been granted by an IRB.

It is the Sponsor/CRO and investigator's responsibility to develop informed consent materials and outline the proposed consent process in the Submission for IRB review, and for the IRB to ensure alignment with ethical principles and compliance with federal regulations, local laws, and IRB policies.

17.1 The Consent Process

The consent process should be viewed as an ongoing process of the investigator informing participants of the purposes and procedures of the research, the risks and benefits associated, and other pertinent information to enable participants to make a fully informed decision whether to participate. To achieve its purpose, the consent process must be culturally and linguistically appropriate for the population being enrolled. Setting and timing of the consent process are also critical to facilitating the participant's understanding and to ensure privacy is protected.

To meet regulatory requirements for informed consent, the consent process must have all of the following attributes:

- Informed consent of the prospective participant or the participant's LAR will be obtained unless the requirement for consent has been waived or altered by the IRB.
- The circumstances of the consent process will provide the prospective participant or LAR sufficient opportunity to ask questions and consider whether to participate.
- The circumstances of the consent process will minimize the possibility of coercion or undue influence.
- The information provided during the consent process will be presented in language understandable to the participant or the participant's LAR.
- The information being communicated during the consent process will be free of exculpatory language through which the participant or LAR is made to waive or appear to waive any legal rights or to release (or appear to release) the Investigator, Sponsor, or the Conduct Site or its agents from liability for negligence.

- For DHHS-regulated research:
  - The prospective participant or LAR must be provided with the information that a reasonable person would want to have to make an informed decision about whether to participate, and an opportunity to discuss that information.
  - Except for broad consent obtained in accordance with relevant regulations,
    - Informed consent must begin with a concise (i.e. one page or less) and focused presentation of the key information that is most likely to assist a prospective participant or LAR in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension. Castle IRB requests the following points, as they pertain to the proposed study, be addressed as part of the key information presentation:
      - The fact that consent is being sought for research and that participation is voluntary.
      - The purposes of the research, the expected duration of the prospective subject's participation, and the procedures to be followed in the research.
      - The reasonably foreseeable risks or discomforts to the prospective subject, focusing on the most likely and most serious.
      - The benefits to the prospective subject or to others that may reasonably be expected from the research.
      - Appropriate alternative procedures or courses of treatments, if any, that might be advantageous to the prospective subject.
    - Informed consent as a whole must present information in sufficient detail relating to the research and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective participant or LAR's understanding of the reasons why one might or might not want to participate.

17.2 Elements of Informed Consent

To meet the regulatory requirements for informed consent, consent materials must have all the following required basic elements, and additional elements and disclosures as applicable or as determined by the IRB.

<u>Required (Basic) Elements (21 CFR 50; 45 CFR 46):</u>

- A statement that the study involves research, explanation of the purposes of the research, expected duration of participation, description of the procedures to be followed, and identification of any procedures that are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others that may reasonably be expected from the research.
- Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject, including consideration of possible risks and benefits of the alternatives.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
- For research involving greater than minimal risk, an explanation about whether:
  - Medical treatments are available if injury occurs and, if so, what they consist of or where further information can be obtained.
  - Compensation is available if injury occurs and, if so, an explanation as to what it consists of or where further information can be obtained.
- Explanation of whom to contact for answers to pertinent questions about the research and the subject's rights and whom to contact in the event of a research-related injury to the subject.

- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- For research regulated by FDA:
  - A statement that informs the subject of the possibility that FDA may inspect the records.
  - For applicable clinical trials, the following statement notifying the subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not identify you. At most, the website will include a summary of the results. You can search this website at any time."
  - The consent document does not give the participant the option of removing their previously collected data (should the participant choose to withdraw from the study).
- For research regulated by DHHS, one of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:
  - A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
  - A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.
- For research subject to ICH-GCP:
  - A description of the IRB, its role, and that the research was approved by an IRB.
  - The probability of random assignment, if applicable.
  - Any participant responsibilities.
  - Any reasonably foreseeable risks to an embryo, fetus, or nursing infant, if any.
  - A statement that there is no intended clinical benefit to the participant, when applicable.
  - A statement that monitors, auditors, the IRB and regulatory authorities will be granted access to the participant's medical records for verification of clinical trial procedures and data, without violating the confidentiality of the participant, to the extent permitted by applicable laws and regulations and a statement that by signing a written informed consent document, the participant or LAR is authorizing such access.
  - A statement that if the results of the trial are published, the participant's identity will remain confidential.
  - Disclosure that the researcher will inform the participant's primary physician about participation in the study if the participant agrees to such notification.

Castle IRB may also require that additional elements or information be given to the prospective participants or their LAR when, in the IRB's judgment, the information would meaningfully add to the protection of the rights and welfare of the research subject. For example, Castle IRB requires that human gene transfer clinical trial consent forms specify that the study agent contains, or consists of, recombinant DNA or has been genetically modified, and information about the Genetic Information Nondiscrimination Act (GINA), when genetic testing is part of the study. In addition, Castle IRB considers whether it is appropriate to include any implications for future clinical trial participation, as gene therapy clinical trials often exclude persons who have previously undergone other gene therapies or who have previously been exposed to viruses involved in the gene therapy under study.

Additional Elements

Additional Elements of Informed Consent could include:

- A statement that the particular treatment or procedure may involve risks to the participant (or to the embryo or fetus, if the participant is or may become pregnant) that are currently unforeseeable.
- Anticipated circumstances under which participation may be terminated by the Investigator without regard to the participant's consent.
- If the research is covered by a Certificate of Confidentiality (COC), protections and limitations of the COC.
- Any additional costs to the participant that may result from participation in the research.
- Amount, timing, and methods of payments for participation.
- Consequences of a participant's decision to withdraw from the research and procedures for termination of participation.
- A statement that significant new findings developed during the course of the research that may affect the participant's willingness to continue participation will be provided.
- Approximate number of participants involved in the study.
- A statement that the participant's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the participant will or will not share in the profit.
- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to participants, and if so, under what conditions.
- For research involving biospecimens, whether the research will (if known) or might include genome sequencing.
- A disclosure of the Investigator or Conduct Site's conflict of interest with the research, should any such conflicts exist.

For DHHS-regulated research, if broad consent is being utilized, the investigator and the IRB must ensure such consent includes required elements at 45 CFR 46.116(d). To allow the use of Broad Consent, the IRB must also determine that the study is limited to the storage, maintenance, and secondary research use of identifiable private information and identifiable specimens (collected for either research studies other than the proposed research, or non-research purposes); the study has undergone limited IRB review and meets requirements for exempt Category 7 or Category 8 [note: at present, Castle IRB does not provide Exempt review under categories 7 or 8]; investigators must provide all required disclosures for broad consent to each participant or participant's LAR; if there is a change made for research purposes in the way the identifiable private information or specimens are stored or maintained, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data.

Importantly, these informed consent requirements are not intended to preempt any applicable federal, state or local laws (including tribal law) that require additional information be disclosed in order for informed consent to be legally effective. Further, nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state or local law (including tribal law).

17.3 Short Form Consent for Non-English-Speaking Participants

In circumstances where it was unanticipated that the prospective participant providing consent does not speak or understand English, and there is inadequate time to prepare and submit translated consent materials for IRB approval, a short form consent process can be used as an alternative to the process outlined above. In such cases:

- A short form consent document is prepared in the language that the prospective participant or LAR can understand.
- The short form consent document states that the required basic and appropriate additional elements of consent have been presented orally to the prospective participant or LAR.

    - For DHHS regulated research, this includes 1) a statement that the key information required by 45 CFR 46.116(a)(5)(i) was first presented to the prospective participant or LAR, before other information, if any, was provided, and 2) required disclosures when the research involves private identifiable information or identifiable biospecimens.
- A written summary of required consent elements is used for the oral presentation of information. This can be the English IRB-approved consent form.
- There will be a witness present for the consent process who is conversant in both languages. The witness should not be a member of the research team.
- Documentation of the consent process and a copy of signed documentation is handled in accordance with the following:
    - Prospective participant or LAR signs the short form consent document.
    - Person obtaining consent signs a copy of the written summary that was presented orally.
    - The witness should sign both the short form consent document and the written summary.
    - The prospective participant or LAR receives a signed copy of the short form consent document and written summary.

17.4 Consent Addendum for New Information

When participants need to be informed about new risks, or changes in the risks or benefits of study participation, an addendum consent which focuses on the new information may be more appropriate than a modified version of the full informed consent document. This includes scenarios in which Investigators are informing enrolled participants about significant new information or findings that may have a bearing on study participants' willingness to continue participation in the study.

17.5 Obtaining Consent

According to Federal Regulations, the "Investigator" must obtain the legally effective informed consent of the participant or the participant's LAR. However, it is not always possible or practicable for the Principal Investigator (PI) to obtain informed consent from each participant. Although the PI is always legally responsible for the informed consent process and for establishing the necessary content of the informed consent form and discussion, it is often reasonable for the PI to identify qualified individuals on the research team that can be delegated to obtain participant informed consent.

When assigning responsibility for obtaining consent to research team members, the PI should carefully consider the qualifications of the team members, including their understanding of protocol procedures and risks, and ability to explain complicated information effectively. Novice researchers designated to obtain consent should be appropriately supervised and mentored. Delegations should also be documented in writing.

<u>Circumstances When Obtaining Consent May Not be Delegated</u>

In some instances, the IRB may limit the duty of obtaining consent to the PI and physician members of the research team. This may be necessary to comply with local laws, or the IRB may require it for research involving highly complicated study designs and serious medical conditions.

If the IRB has determined a study as one where obtaining consent cannot be delegated by the PI, this determination may be appealed by the Investigator. The decision to grant an appeal will be made at the sole discretion of the IRB. Appeals should include:

- Why the designee is qualified to obtain consent.
- Why it is not practicable for the PI and Physician study team members to obtain consent.
- How the participant will be given the option to speak with the PI or physician study team member ***before*** making his/her decision to participate in the research.

17.6 Who May Provide Research Consent: State and Local Laws

When determining who may consent to participate in a research study, the PI must follow the general provisions and regulations set forth by state and local laws. Specifically, many state and local laws define when a person is at the age of majority and consent for themselves, when a minor can consent for themselves, who can provide consent for a ward of the state, and when persons can consent for adults who lack the capacity to provide consent for themselves (i.e., Legally Authorized Representatives (LAR)).

Castle IRB will ask for the Investigator and Conduct Site Institution to disclose and document knowledge of relevant state and local laws impacting informed consent.

17.7 Assent in Research Involving Minors

When minors cannot legally give consent, informed consent must be obtained from parents ("parental permission"), or a legally appointed guardian (an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care and/or research). However, in DHHS-regulated research with minors, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition. For minors who are wards of the state, state and local laws will be followed in determining who is able to provide consent on behalf of the child/children to be enrolled.

The IRB shall also determine whether adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. When deemed capable, the IRB also determines whether assent must be documented, and if so, how.

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

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be assented or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement in circumstances in which consent may be waived in accordance with 21 CFR 50.55; 45 CFR 46.116.

If the research study involves minors who will continue to undergo research interventions (including the collection of identifiable private information) after they become adults, the IRB Submission should address a mechanism (e.g., addendum informed consent document with copy of originally signed consent form attached; new consent form) whereby direct consent for continued participation in the research study will be obtained from these individuals at the time they reach adult status.

17.8 Witness to the Consent Process

Some research may be required to have a witness observe the process of obtaining research participant consent, such as research involving a short form consent process.

ICH Guidance (ICH GCP 4.8.9) for impartial witness is as follows: If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

Importantly, the witness should not be the person to discuss or obtain consent or otherwise be a member of the research team. Prior to participation in the trial, the participant or the participant's LAR should receive a copy of the signed and dated written consent document and any other written information provided to the participants.

17.9 IRB Observance of Consent Process

Federal Regulations give IRBs the authority to observe or have a third party observe the consent process. As such, Castle IRB may observe or ask the Conduct Site to observe the consent process to provide additional protections to research participants (e.g., in studies involving adults with diminished decision-making capacity or studies with complex interventions). Observation can be performed by agents of Castle IRB or by third party individuals authorized by Castle IRB, such as officials at the Conduct Site/Relying Institution.

17.10 Documentation of Consent

Sponsors/CROs and Investigators are responsible for submitting consent materials meeting regulatory requirements for IRB review and approval. In addition to other required elements of consent, considerations must be made for including the necessary signature lines to document participant or LAR consent. Signature lines for the person obtaining consent are also typically required. For participants, printed name and signature lines for Adult subjects may be sufficient, or lines may be needed for Guardian(s)/LARs (i.e., for research involving minors or adults unable to provide consent for themselves), and for other research (e.g., when a short form consent process is used), printed name and signature lines may be needed for a witness to the consent process.

Only the IRB approved informed consent documents may be used in the conduct of research. If Informed Consent is to be documented in written form, along with an approval letter, the PI will receive access to the IRB-approved consent form for the study which will contain the IRB's approval stamp showing the IRB approval date. Investigators should take caution to use the correct, current and IRB-approved version when obtaining and documenting consent.

<u>Signature and Recordkeeping Requirements</u>

Federal regulations require written documentation of informed consent unless the research meets the criteria for waiver of documentation.

When documenting informed consent:

- The participant or LAR should sign, date and initial all necessary sections of the consent document only after all questions are answered and s/he agrees to take part.
- The person who is obtaining the participant's informed consent must also sign and date the consent form at the same time as the participant. Studies in which the consent process occurs remotely (e.g., school-based research in which consent forms are sent home to parents) may have alternative procedures if approved by the IRB.

- When following ICH-GCP (E6)(R2) guidelines, prior to the participant's participation in the trial, the written consent document should be signed and personally dated by the participant or their LAR, and signed and personally dated by the person who conducted the informed consent discussion.
- A copy of the signed consent document is to be given to the participant or LAR in accordance with DHHS regulations, FDA regulations, and ICH-GCP (E6).
- Electronic signatures may be used to document consent, in compliance with 21 CFR 11 and applicable FDA Guidance when applicable. Electronic versions of consent forms (when used to meet documentation requirements) must also be available in hard copy for review and retention by potential participants.

Castle IRB does not require a LAR to provide consent for participants who are capable of consenting, but physically incapable of signing the form (e.g., due to paralysis, or persons who cannot read or write); however, consent must still be obtained in accordance with applicable state and local laws.

Waiver of Written (Signed) Consent

The IRB may waive the requirement to obtain a signed consent form for some or all subjects if it finds that either:

- The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context, or
- For studies not subject to FDA regulations:
    - The only record linking the subject and the research would be the informed consent document and the principal risk would be potential harm resulting from a breach of confidentiality; each participant or LAR will be asked whether the participant/LAR wants documentation linking the participant with the research, and the participant/LAR's wishes will govern, or
    - If the participant or LAR is a member of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

When written (signed) consent is waived, the elements of consent must still be presented to participants. Castle IRB typically requires information be provided in a written (or electronic) format, though for some research, a verbal script may be permitted. In such cases, the information provided must still contain required elements of informed consent. Castle IRB must review and approve the written description of the information that will be provided to participants in cases when the IRB considers waiving the requirement to obtain written documentation of the consent process.

17.11 E-Consent

Researchers who will be obtaining consent electronically, meaning the signatures will be obtained in an electronic format, such as on the internet, or a device such as a tablet or smart phone, must ensure that signatures are obtained in compliance with FDA 21 Part 11 when applicable.

17.12 Waiver or Alteration of Consent

In limited circumstances described below, the IRB can approve a waiver or alteration of some or all of the elements of informed consent. It is the Investigator's responsibility to provide necessary justification for a waiver of consent in the IRB Submission, and for the IRB to ensure all requirements are met. Such determinations are recorded in the protocol file and/or meeting minutes.

The IRB can alter the elements of informed consent, or waive requirements for informed consent, for research (including DHHS-regulated research involving public benefit or service programs conducted by or subject to the approval of state or local officials) that meets all of the following criteria:

- The research involves no more than minimal risk to subjects.

- The waiver or alteration will not adversely affect the rights and welfare of subjects.
- The research could not practicably be carried out without the waiver or alteration.
- Whenever appropriate, subjects will be provided with additional pertinent information after participation.
- For DHHS-regulated research, if the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

The IRB may waive the requirement for parental consent if it determines that the research study is designated for conditions or for a subject population (e.g., neglected or abused children) for which parental or guardian permission is not a reasonable requirement to protect the subjects per 45 CFR 46.408.

For DHHS-regulated research, the following also apply:

- Consent requirements can be waived if the research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
    - Public benefit or service programs;
    - Procedures for obtaining benefits or services under those programs;
    - Possible changes in or alternatives to those programs or procedures; or
    - Possible changes in methods or levels of payment for benefits or services under those programs; and
    - The research could not practicably be carried out without the waiver or alteration.
- If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.
- An IRB may approve a consent procedure that omits some, or alters some or all, of the elements of informed consent set forth in 45 CFR 46.116(b) and (c) provided the IRB satisfies the requirements of 45 CFR 46.116(e)(3). An IRB may not omit or alter any of the requirements described in 45 CFR 46.116(a). If a broad consent procedure is used, an IRB may not omit or alter any of the elements required under 45 CFR 46.116 (d).

For FDA-regulated research, the following scenarios may also apply:

- The IRB can waive the informed consent process in clinical investigations of in vitro diagnostic devices when it can be determined that all of the following are true:
    - The investigation meets the IDE exemption criteria at 21 CFR 812(c)(3).
    - The study uses leftover specimens (i.e., remnants of specimens collected for routine clinical care or analysis that would have been discarded or specimens that were previously collected for other research or clinical purposes).
    - The specimens are not individually identifiable such that the investigators associated with the study, including the sponsor, cannot readily ascertain the identity of subjects (including through clinical information that may accompany the specimen).
    - The individuals caring for the patients are different from, and do not share information about the patient with, those conducting the investigation.
    - Specimen providers and recipients have systems to prevent the release of personal information.
- The IRB can approve a waiver of the requirements for informed consent for nonexempt research in life-threatening situations in which it is not possible to obtain informed consent from subjects or their legally authorized representatives.

17.13 Waiver of Consent for Determining Eligibility

For DHHS-regulated research, as allowed by 45 CFR 46.116(g), the IRB can approve plans for the investigator to obtain information or biospecimens for the purpose of screening, recruiting, or determining eligibility of prospective subjects without the informed consent of the prospective subject or LAR if:

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

17.14 Special Considerations in Informed Consent

The circumstances of the consent process must provide potential participants or their LAR sufficient opportunity to consider whether to participate and minimize the possibility of coercion or undue influence. When some or all of the participants may be more vulnerable to coercion or undue influence, such as children (including wards of the state), prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards are included to protect the rights and welfare of these participants.

Additional requirements for obtaining informed consent (or assent) in specific populations are described in the "Vulnerable Subjects, Additional Considerations and Protections" section of this Investigator Guide.

17.15 Participant Transfers

Participants transferring to an investigator and conduct site from another conduct site will require re-consent prior to continuing procedures. Additional considerations may apply; thus, investigators are encouraged to work with Castle IRB in these scenarios prior to conducting research procedures.

17.16 Participant Withdrawals

When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remains part of the study database and may not be removed, and the consent document cannot give the participant the option of having data removed.

Castle IRB must provide approval if an investigator wants to continue data collection after a participant withdraws from an interventional study. If approved, the investigator may ask the participant or their guardians/LAR whether they wish to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the participant distinguishes between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review and address the maintenance of privacy and confidentiality of the participant's information. The researcher must obtain the participant's consent for this limited participation in the study, assuming this situation was not described in the original consent document, and Castle IRB must approve the consent document.

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

Although a participant is not obligated to give his or her reasons for withdrawing prematurely from a clinical trial, when following ICH-GCP Guidelines in particular, the Investigator makes a reasonable effort to ascertain the reason, while fully respecting the participant's rights.

17.17 Posting of Clinical Trial Consent Forms

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

If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal website (e.g. confidential commercial information), such Federal department or agency may permit or require redactions to the information posted.

18. Authorization to Use or Disclose Protected Health Information:

To use or disclose PHI, researchers must obtain an authorization signed by the research participants or their guardians/LAR, or a waiver of authorization as detailed below.

On behalf of conduct sites/relying institutions who are covered entities, Castle IRB can review the following in accordance with the HIPAA Privacy Rule:

- Waivers or alterations of authorization for use and disclosure of Protected Health Information (PHI).
- Written authorizations for use or disclosure of PHI.

18.1 Required Elements of HIPAA Authorization

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

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

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

    - The covered entity will not condition treatment, payment, enrollment, or eligibility for benefits on whether the individual signs the authorization when the prohibition on conditioning of authorizations applies; or
    - The consequences to the individual of a refusal to sign the authorization (i.e., inability to take part in the research).
- The potential for information disclosed pursuant to the authorization to be subject to redisclosure by the recipient and no longer be protected.
- The authorization must be written in plain language.
- The individual must be provided with a copy of the signed authorization.

18.2 Waiver of Authorization for Use and Disclosure of PHI

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

- Documentation that a waiver of the research participants' authorizations for use/disclosure of PHI has been approved by the IRB; or
- Where researchers represent:
    - That the research is only for purposes of preparing a research protocol or similar uses preparatory to research.
    - That he or she will not remove any PHI from the covered entity and
    - That PHI is necessary for the research purpose; or
- To disclose PHI of decedents, where the researcher represents that the use or disclosure of PHI is:
    - Solely for research on the PHI of decedents,
    - Necessary for the research, and
    - Documentation of the death of the individuals about whom PHI is sought and provided.

To request a waiver of the research participants' authorization under 45 CFR 164.512(i)(2)(ii), the researcher must justify that the use or disclosure of PHI involves no more than a minimal risk to the privacy of individuals based on the presence of:

- An adequate plan to protect PHI from improper use or disclosure;
- An adequate plan to destroy identifiers at the earliest opportunity absent a health or research justification or legal requirement to retain them;
- Adequate written assurances that the PHI will not be used or disclosed to a third party except as required by law, for authorized oversight of the research study, or for other research uses and disclosures permitted by the Privacy Rule.

In addition, the research could not practicably be conducted without the waiver or alteration, and the research could not practicably be conducted without access to and use of PHI.

19. Vulnerable Subjects, Additional Considerations and Protections:

Federal regulations stipulate that for a study to receive IRB approval when all or some of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects. ICH GCP also considers the following persons to be vulnerable: students, veterans, terminally ill participants, and ethnic minority groups. Thus, research involving potentially vulnerable populations shall include additional protections when deemed necessary to minimize risks of a study in relation to anticipated benefits.

Federal regulations set forth specific protections for pregnant women, neonates and fetuses, prisoners, and children that must be followed; however, special considerations may also be necessary for other potentially vulnerable populations, including adults with diminished decision-making capacity who are unable to provide fully informed consent. IRB Submissions must identify inclusion of vulnerable populations and describe the additional safeguards included in the protocol to protect the rights and welfare of participants for IRB review and consideration. Examples of additional safeguards could include strategies to minimize the possibility of participants being coerced or unduly influenced to participate in research.

When reviewing research involving vulnerable populations, the IRB applies additional federal regulations as well as state and local laws applicable to the population. For example, regulations define children (minors) as persons who have not attained the legal age for consent to treatment or procedures involved in the research under applicable law of the jurisdiction in which the research will be conducted. As such, state and local law must be applied to research involving minors. State laws also apply to research involving LARs who provide consent on behalf of adults unable to provide consent for themselves, and for studies involving Wards of the State.

The IRB reviews the research to assess adequacy of additional safeguards in place to protect the rights and welfare of participants. For minimal risk research, it may be determined that no additional protections are warranted.

19.1 Research Involving Minors

For research involving minors (persons who have not attained the legal age for consent to treatment or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted), the IRB must determine whether research falls under one of the allowable categories:

- (**21 CFR 50.51; 45 CFR 46.404**) Research that does not involve greater than minimal risk may be approved if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.
- (**21 CFR 50.52; 45 CFR 46.405**) Research involving greater than minimal risk, but presenting the prospect of direct benefit to an individual participant, or a monitoring procedure that is likely to contribute to the participant's well-being may be approved if the IRB finds that:
  - The risk is justified by the anticipated benefit to the participant;
  - The relationship of anticipated benefit to risk is at least as favorable as that presented by available alternative approaches; and
  - Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.
- (**21 CFR 50.53; 45 CFR 46.406**) Research involving greater than minimal risk presented by an intervention or procedure that does not hold out prospect of direct benefit to individual participants, or by a monitoring procedure which is not likely to contribute to the well-being of the participants, but likely to yield generalizable knowledge about the participant's disorder or condition may be approved only if the IRB finds that:
  - The risk represents a minor increase over minimal risk;
  - The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations;
  - The intervention or procedure is likely to yield generalizable knowledge about the participant's disorder or condition which is of vital importance for the understanding or amelioration of the participant's disorder or condition; and
  - Adequate provisions are made for soliciting assent of the children or permission of their parents or guardians.
- (**21 CFR 50.54; 45 CFR 46.407**) Research that is not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children may be approved if the IRB and the Secretary of Health and Human Services (DHHS), after consultation with a panel of experts in

pertinent disciplines and following an opportunity for public review and comment, find that the research in fact satisfies one of the above three categories; or satisfies all of the following requirements:

- The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children;
- The research will be conducted in accordance with sound ethical principles; and
- Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.
- Note: if the research study is not federally-funded or subject to FDA regulation, Castle IRB will request review by a panel of pediatric experts to determine the applicability of approval under Section 45 CFR 46.407.

Children who are wards of the state or any other agency, institution, or entity can be included in research approved under 21 CFR 50.53/21 CFR 50.54; 45 CFR 46.406/45 CFR 46.407 only if such research is:

- Related to their status as wards; or
- Conducted in schools, camps, hospitals, institutions or similar settings in which the majority of children involved as participants are not wards (21 CFR 50.56; 45 CFR 46.409).

In such research, an advocate will be appointed for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. Additional state and local laws often apply and shall also be observed.

- One individual may serve as an advocate for more than one ward.
- The advocate will be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role of advocate or member of the IRB) with the research, the investigator(s), or the guardian organization (21 CFR 50.56; 45 CFR 46.409).

19.2 Research Involving Prisoners

Prisoners are a specially designated vulnerable population with additional protections and regulations set forth in Subpart C of the DHHS regulations. A prisoner means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing (45 CFR 46.303(c)).

Research involving prisoners that is federally funded, conducted in a federal prison, or deemed more than minimal risk will be reviewed by a convened IRB committee which includes at least one member who is a prisoner or a prisoner representative with appropriate background and experience to serve in that capacity. Modifications to studies initially reviewed by the convened IRB that involve more than minor changes must be reviewed using the same procedures as initial review. Modifications that involve only minor changes can be reviewed using expedited review procedures if a determination is made that the changes involve no more than minimal risk for the prison population being studied and the prisoner representative concurs. Continuing reviews must use the same procedures used for initial review, including the prisoner representative responsibilities with one exception: if no participants have been enrolled, the research may receive continuing review using Expedited review procedures under the corresponding expedited category #8.

Studies involving interactions with prisoners can be reviewed via expedited review procedures if a determination is made that the research involves no greater than minimal risk for the prison population being studied and the prisoner representative concurs with this determination. For research that does not involve interaction with prisoners (e.g., existing data or record review) to be reviewed by expedited review, a determination must be made that the research

involves no greater than minimal risk for the prison population being studied, but in this scenario, prisoner representative concurrence and review is not required. Review of modifications and continuing review must use the same procedures as initial review.

The IRB will approve research involving prisoners only if it finds and documents that:

- The research falls under one or more of the following categories:
  - The possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk* and no more than inconvenience to the subjects;
  - Prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
  - Conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary of Health and Human Services has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or
  - Practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary of Health and Human Services has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of the intent to approve such research.
  - In addition to allowable categories of research on prisoners in Subpart C, epidemiological research is also allowable when the research meets the following criteria: a) the sole purposes of the research are to describe the prevalence or incidence of a disease by identifying all cases or to study potential risk factor associations for a disease; b) the research presents no more than minimal risk and no more than inconvenience to the prisoner-participant; and c) prisoners are not a particular focus of the research.

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

If a study utilizing prisoners as research participants is federally funded, Castle IRB will send a letter to the Office for Human Research Protections (OHRP) indicating it has approved a study that will include prisoners, the category the study fits into as well as how the study satisfies the six criteria noted under the regulations. A research study is not permitted to commence for DHHS supported research until written approval is received from OHRP on behalf of the DHHS Secretary under the provisions of 45 CFR 46.306(a)(2).

If a subject becomes a prisoner after enrollment in a research study the investigator should notify the IRB immediately. If the study had not previously been reviewed under Subpart C (if applicable) or equivalent protections, either the prisoner-subject must be withdrawn from study participation; or the IRB must, at the earliest opportunity, re-review the research protocol and consent form in accordance with the listed requirements. The IRB will first confirm that the participant meets the definition of a prisoner, according to DHHS guidelines. If the participant is determined to be a prisoner, the IRB can either (a) approve the involvement of the prisoner-subject in the research or (b) determine that this subject must be withdrawn from the research. Before terminating the enrollment of the involved participant, the IRB should consider the risks (health and safety) associated with termination. If the subject-prisoner is withdrawn from study participation, s/he must be fully informed of the reason for such action, and if treatment is involved, involved parties should aim to keep the participant on the study intervention under an alternative mechanism (expanded access, off-label use, etc.). If the participant cannot be terminated due to health or safety reasons, keep the participant enrolled and review the research under Subpart C. If some requirements of Subpart C cannot be met, but if it is in the best interests of the participant to remain in the study, inform OHRP of the determination along with the justification.

If a participant is incarcerated temporarily while enrolled in a study, if the temporary incarceration has no effect on the study, keep the participant enrolled. If the temporary incarceration has an effect on the study, handle according to the same guidance above.

19.3 Research involving Pregnant Women, Neonates and Fetuses

For all federally-funded and greater than minimal risk research involving pregnant women, fetuses, or neonates, the IRB will approve the conduct of the research only if it finds that the research meets the regulatory criteria for approval addressed under the federal regulations at 45 CFR 46 Subpart B (45 CFR 46.204, "Research involving pregnant women or fetuses prior to delivery"; 45 CFR 46.205, "Research involving neonates"; 45 CFR 46.206, "Research involving, after delivery, the placenta, the dead fetus, or fetal material"). For research that does not meet the criteria for approval addressed under 45 CFR 46.204, "Research involving pregnant women or fetuses prior to delivery"; 45 CFR 46.205, "Research involving fetuses after delivery"; or 45 CFR 46.206, "Research involving, after delivery, the placenta, the dead fetus, or fetal material," the IRB must find that:

- The research presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women or fetuses; and
- The research, if federally supported, will be submitted for review and approval by the Secretary, DHHS, in accordance with the provisions of 45 CFR 46.207, “Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women or fetuses”. If the research study is not federally-supported, the IRB will use a review by a panel of obstetrician/ gynecology experts (2 members with expertise in the area who are not currently IRB members) and an ethicist to recommend whether to approve the study as research that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women or fetuses.

For research without federal funding that is deemed not greater than minimal risk, 45 CFR 46 Subpart B will be used as a guide, but determinations will primarily be made by assuring that risks to the fetus are not greater than minimal and regulatory criteria for approval at 21 CFR 56.111 are met. The IRB may require additional protections in consideration of protocol specific risks to the pregnant woman or fetus.

Regarding consent:

- For research involving pregnant women or the fetus prior to delivery, the documented, written informed consent of the pregnant women or her authorized representative will be obtained in accordance with the provisions of 45 CFR 46.204; unless the IRB grants either a waiver of informed consent or a waiver of the requirement to document informed consent in accordance with applicable regulations.
- For research involving neonates of uncertain viability, the documented, written informed consent of either parent or the authorized representative of either parent will be obtained in accordance with the provisions of 45 CFR 46.205; unless the IRB grants either a waiver of informed consent or a waiver of the requirement to document informed consent in accordance with applicable regulations.
- For research involving nonviable neonates (i.e., neonates determined to be unable, after delivery, to survive to the point of independently maintaining heartbeat and respiration), the documented, written informed consent of both parents will be obtained in accordance with the provisions of 45 CFR 46.205.
    - If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the IRB may approve the research based on the consent of one parent. (Note: the consent of the father need not be obtained if the pregnancy resulted from rape or incest.)
    - Note: the IRB may <u>not</u> grant approval for authorized representative (i.e., proxy) consent or a waiver of the requirement to obtain consent for research involving nonviable neonates.

19.4 Adults with Diminished Capacity to Provide Consent

Diminished decision-making capacity comprises a broad range of conditions. Examples include healthy individuals in shock (temporary decisional impairment), those born with severe intellectual disabilities (permanent decisional impairment), individuals with age-related dementia (progressive decisional impairment), individuals with mental illnesses such as schizophrenia (fluctuating capacity), and individuals under the influence of certain drugs (temporary and/or fluctuating capacity). Generally, all adults should be presumed capable of providing informed consent unless there is specific evidence that an individual's condition/disability would impair reasoning or judgment, or other indication that the individual is unable to understand and choose whether or not to participate in research.

Adults unable to provide informed consent may not be the subjects of research when the research can be performed with other appropriate subjects.

The IRB can approve studies involving adults unable to provide informed consent if the proposed research involves interventions or procedures that:

- Do not involve greater than minimal risk.
- Involve greater than minimal risk but presents the prospect of direct benefit to the individual participants.
    - The risk is justified by the anticipated benefit to the participant.
    - Comparison of the risk to the anticipated benefit is at least as favorable as that presented by available alternative approaches.
- Involves greater than minimal risk and no prospect of direct benefit to the individual participants, but is likely to yield generalizable knowledge about the participant's disorder or condition.
    - The risk presents a reasonable increase (e.g., minor) over minimal risk.
    - The research involves experiences that are reasonably equivalent to those in the participant's actual (or expected) medical, dental, psychological, social, or educational situations.
    - The research is likely to yield generalizable knowledge about the participant's disorder or condition that is of critical importance for the understanding or improvement of the disorder/condition.

For research subject to ICH Guidance (ICH GCP 4.8.13, 4.8.14), additional considerations apply. Except as described below, in accordance with ICH-GCP 4.8.14, a non-therapeutic trial (i.e., a trial in which there is no anticipated direct

clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form. Non-therapeutic trials may be conducted in subjects with consent of a LAR provided the following conditions are met:

- The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.
- The foreseeable risks to the subjects are low.
- The negative impact on the subject's well-being is minimized and low.
- The trial is not prohibited by law.
- The approval of the IRB is expressly sought on the inclusion of such subjects.
- Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended.
- Subjects should be closely monitored and should be withdrawn if they appear to be unduly distressed.

If a participant is deemed incapable of providing informed consent and a LAR is needed, investigators should refer to state and local laws to assist in determining who can serve as LAR. The LAR should be informed of his/her role and obligation to protect the rights and welfare of the participant including that his/her obligation as a surrogate decision maker is to try to determine what the participant would decide if the participant were able to make such decisions or, if the participant's wishes cannot be determined, what is in the participant's best interests.

For participants with fluctuating decision-making capacity or those with decreasing capacity to give consent, a re-consent or re-assent process, with or without a LAR, may be necessary. If such a process is necessary, clear procedures for obtaining re-consent or re-assent must be fully described in the IRB Application.

For participants in which there is a predicted loss of decision-making capacity (e.g. before the administration of anesthesia) advance informed consent is an option. When advance informed consent is obtained, investigators and the participant should be aware of the individual who will serve as his or her LAR if capacity to consent is lost during the course of the research.

An adult unable to provide informed consent to participate in research may be able to assent to participation. The IRB is responsible for determining when the assent of some or all such adults is required in proposed research and the appropriate method for documenting the adult's assent (if any), as described below.

Assent to participate in research by an adult with diminished decision-making capacity (for whom a LAR will provide informed consent) is to be obtained when, in the judgment of the IRB, the adult is capable of providing assent. In determining whether proposed participants are capable of providing assent, the IRBs will take into account the condition and psychological/emotional states of the adults involved.

The assent of adults with diminished decision-making capacity to participate in research is to be obtained, except in any of the following circumstances:

- The adults are not capable of providing assent based on condition or psychological/emotional state
- The capability of some or all of the adults is so limited that they cannot reasonably be assented
- The criteria for waiver (or alteration) of informed consent applies.

The IRBs may determine that the assent of some or all of the adults is not required. If assent is not a requirement of some adults, the IRB will indicate which adults (e.g., individuals with severe dementia) are not required to assent.

Assent processes are to include the key elements of informed consent and are to be provided in language appropriate for an adult with diminished decision-making capacity, based on the nature of the study and the

expected ability of the prospective participant(s) to understand the purpose and the procedures involved in the research.

Although some individuals may not have the capacity to provide consent or assent, these individuals may resist participating in a research study approved by their LARs. Under no circumstances may participants be forced or coerced to participate. The study must include clear and appropriate procedures for respecting dissent.

19.5 Educationally Disadvantaged

Persons who are educationally disadvantaged, such as illiterate persons, may be in a vulnerable position when trying to determine whether or not to take place in research or when providing written consent. As such, Castle IRB will determine whether special considerations should be given to ensure their rights and welfare are protected in research.

Illiterate persons who understand English may have the consent document read to them and may make their mark to demonstrate consent in accordance with local law. In this case, a witness signature should be obtained, especially when required by state and local laws or ICH Guidelines (see "Witness to the Consent Process" section of this Guidance).

19.6 Economically Disadvantaged

Persons who are economically disadvantaged may be more influenced by payment incentives or compensation than those who are not. As such, Castle IRB will determine whether special considerations should be given to ensure their rights and welfare are protected, and that the potential for undue influence is mitigated. For example, payment for research should be prorated and not subject to completion of the research. Further, Castle IRB will ensure that research advertisements and consent documents do not include offers of "free care".

19.7 Students or Employees

Persons who are students or employees of Investigators conducting research are vulnerable to coercion, as they may believe that harm or disadvantage could come to them if they choose not to take part in a study for which they are otherwise eligible. As such, Castle IRB will consider whether additional safeguards, such as prohibiting the Investigator from directly recruiting or enrolling their students or employees, are prudent to mitigate such risks. In addition, more robust privacy and confidentiality measures may need to be employed.

19.8 Terminally Ill

Persons who are facing life threatening disease with limited options for treatment may be more susceptible to participating in research than those with more numerous alternatives for care. As such, Castle IRB will consider whether additional safeguards are needed for the consent process, including consent documents, to minimize undue influence to participate in research. For example, special attention may be given to ensuring the consent form and process do not give the impression of false hope or only hope and include the alternative of supportive/palliative care.

19.9 International and Multicultural Considerations

Human research subject to DHHS or FDA regulations conducted outside the United States must conform to the same ethical and regulatory standards to which research conducted in the United States is held, as well as applicable local laws and norms of the host country, which may include additional IRB approval in the host country.

When research is supported by a US federal agency, if an international institution or site is considered to be "Engaged" in research (according to the OHRP Guidance, "Engagement of Institutions in Human Subjects Research"), the international institution must obtain and maintain compliance with an FWA from the US DHHS. The site also

must receive approval for the research from an IRB familiar with the local research context and registered with the Office of Human Research Protections of DHHS or obtain DHHS approval as an equivalent host country entity.

Submissions with international considerations should address, but are not limited to the following:

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

During review, Castle IRB will:

- Ensure that equivalent protections are provided to participants enrolled in research in another country, and;
- Make determinations and decisions based on laws and knowledge of the country in which the research will be conducted, such as:
    - If there are laws or guidance related to human research subject protections.
    - If there are other laws that will need to be factored into the research.
    - If the local or government has their own required approvals.
- Consider whether a Consultant reviewer is needed to make any of the determinations above.

If investigational drugs or devices will be used at the foreign site, the foreign site must agree to abide by ICH GCP which provides a consistent set of definitions and requirements for record-keeping, adverse event reporting and all other aspects of clinical trial conduct.

20. Privacy and Confidentiality:

Federal regulations (21 CFR 56.111; 45 CFR 46.111) require that where appropriate, research involving human subjects include adequate provisions to protect the privacy interests of participants and to maintain the confidentiality of data. This includes Exempt studies requiring Limited IRB Review.

Researchers are expected to plan for the appropriate protection of participant privacy and confidentiality of participant data collected in research, to specify those plans in study protocols and IRB Submissions, and to abide by IRB determinations and follow the plans as approved by the IRB. Unless consent has been waived, researchers must explain the provisions for privacy confidentiality in the informed consent form and process.

20.1 Participant Privacy

The IRB assesses privacy information during the review process. Consideration is given to time and place of recruitment, consent discussions, and the procedures of the research; study population considerations; information to be collected; and how and with whom it is shared.

To approve research, Castle IRB must determine that, when appropriate, there are adequate provisions to protect the privacy interests of participants, from recruitment through all phases of research. Such provisions could include:

- The conditions under which information is collected (e.g., physical locations, telephone contact, mail, or email solicitations) afford protections against interactions with participants being witnessed, overheard, inadvertently intercepted, or viewed.
- Information being collected is limited to the minimum amount necessary to accomplish the research purposes.
- Identifiable information is shared with the minimum number of persons necessary to accomplish the research purposes.
- Information about adolescents and teenagers can be collected aside from a parent or guardian.
- Additional protections are in place for potentially vulnerable populations, where knowledge of research participation (e.g., prisoners, certain cultures) or interception of data (e.g., illegal immigrant status) could especially harm participants.

20.2 Confidentiality Considerations

The IRB assesses confidentiality provisions during the review process. IRB review considers the study population involved, the sensitive nature of data, the ability to identify data, and how and with whom data are shared.

Confidentiality considerations include:

- Provisions for maintaining the confidentiality of data are necessary for most research studies. However, in some types of research, such as oral history research, individuals may wish to be acknowledged for their participation.
- Studies with greater risk of harm require more robust provisions. Risk elevates as data are more sensitive, more identifiable, and/or as data are shared with greater numbers of individuals or externally.
- Keeping the identities of participants confidential may be as important as (or more important than) keeping the data obtained about them confidential (e.g., studies involving stigmatizing or illegal information). Additional measures to safeguard confidentiality may be considered in such cases, such as a waiver of documentation of consent or a requirement to obtain a certificate of confidentiality.

20.3 Protected Health Information (PHI)

Research conducted at a covered entity involving PHI must also follow the requirements of the Health Insurance Portability and Accountability Act (HIPAA).

20.4 Certificates of Confidentiality

Certificates of Confidentiality (COC) protect the privacy of research participants by prohibiting disclosure of identifiable, sensitive research information unless the participant provides consent or other conditions apply. NIH-funded studies that involve identifiable, sensitive information are automatically covered by a COC upon award, and researchers can request a COC from NIH for other (non NIH-funded) studies. Issuance of COCs for such requests is at the discretion of the NIH. More information is available on the NIH website.

For the purposes of the NIH Policy for issuing COCs, “identifiable, sensitive information” means information about an individual that is gathered or used during biomedical, behavioral, clinical or other research, where the following may

occur:

- An individual is identified; or
- For which there is at least a very small risk, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

Examples of NIH-funded research automatically covered by a certificate of confidentiality include:

- Biomedical, behavioral, clinical or other research, except where the information obtained is recorded in such a manner that human participants cannot be identified or the identity of the human participants cannot be readily ascertained, directly or through identifiers linked to the participants.
- The collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual.
- The generation of individual level, human genomic data, regardless of whether the data is recorded in such a manner that human participants can be identified, or the identity of the human participants can readily be ascertained.
- Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identify of an individual.

Castle IRB may require Investigators to request a COC for certain research. Examples may include research that:

- Relates to the use of alcohol, drugs or other addictive products.
- Pertains to illegal conduct.
- Would normally be recorded in a patient's medical record, and the disclosure of which could reasonably lead to social stigmatization or discrimination, including certain genetic information.

When research is covered by a COC, researchers:

- May not disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative ,or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- May not disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.
- May disclose information only when:
    - Required by Federal, State, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding.
    - Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;
    - Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
    - Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human participants in research.
- Must inform participants (e.g., in the consent document) of the protections and limitations of the COC.

- Must ensure that if identifiable, sensitive information is provided to other researchers or organizations, the other researchers or organizations must comply with applicable requirements of the COC.

For research subject to additional federal agency regulations (e.g., DOE and DOJ), additional requirements shall be followed.

21. Recruitment and Compensation:

21.1 Equitable Selection of Participants

In order to approve research, the IRB must find that selection of subjects is equitable (45 CFR 46.111 (a)(3); 21 CFR 56.111 (a)(3). In making this assessment, the IRB will take into account the purposes of the research, the setting in which the research will be conducted, and inclusion/exclusion criteria. In making this assessment, the IRB pays special attention to populations who may be at increased risk of coercion or under influence. See "Vulnerable Subjects, Additional Considerations and Protections" section for more information about considerations for inclusion/exclusion of potentially vulnerable participants.

Recruitment and selection of study participants must be equitable within the confines of the study. Investigators may not exclude participants on the basis of gender, race, national origin, religion, or other such characteristics unless justified by the nature of the research and approved by the IRB.

IRB Submissions must include information about the study purpose(s), setting, and population including inclusion/exclusion criteria and whether any prospective participants are vulnerable to coercion or undue influence.

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

21.2 Recruitment Methods

Recruitment methods, recruitment materials, and plans for participant compensation used in human subjects research are considered part of the consent process and must be submitted for IRB review and approval prior to their use. Investigators are also asked to provide supporting documentation regarding recruitment, including letters of cooperation from entities assisting in the recruitment of participants and recruitment materials, such as scripts and advertisements, with the IRB Submission for IRB review.

Participants may be recruited through a variety of methods, including but not limited to current patients, referrals, through direct solicitation, and/or through advertisements. Investigators and the IRB should be aware of guidelines, such as the FDA "Recruiting Study Subjects" Information Sheet when preparing recruitment materials. For example, the FDA specifies that no claims should be made that the drug, biologic, or device is safe or effective for purposes under investigation that are inconsistent with FDA labeling, or that the test article is known to be equivalent or superior to any other drug, biologic, or device. In addition, terms such as "new treatment," "new medication," or "new drug" should not be used without explaining the test article is investigational. Finally, advertisements should not state that the study offers "free medical treatment" and compensation can be included but should not be over-

emphasized nor include a coupon code for a discount on the purchase price of the product once it has been approved for marketing.

Castle IRBs will review the advertising to assure that it is not unduly coercive and does not promise a certainty of cure beyond what is outlined in the consent and the protocol. This is especially critical when a study may involve subjects who are likely to be vulnerable to undue influence. IRB approval is not required for communications intended to be seen or heard by health professionals (such as 'dear doctor' letters that request referrals), general news story information or, publicity intended for other audiences (such as potential investors).

Offering or accepting a finder's fee for identification and referral of participants is not permitted because of the potential for coercion of participants or conflict of interest on the part of the individual making the referral. Paying or accepting a recruitment bonus or other incentive tied to the timing or rate of enrollment or number of enrolled participants is also not permitted.

21.3 Compensation

Participants may be paid or otherwise rewarded (e.g., small gifts, gift cards) for participating in a research study. Information concerning the remuneration of participants, including its amount or nature and the schedule of its disbursement, is subject to initial and continuing review by the IRB.

Investigators are asked to provide compensation plans in the IRB Submission. When planning compensation, investigators should consider the following:

- The amount of payment should be reasonable, based on the complexities and/or inconveniences of the study and not based on the risks of study participation.
- To minimize the potential for undue influence, payments should be prorated (accrue as the study progresses), and not held to the end of study completion.
- Disbursement of a proportion of the total payment or reward contingent upon study completion is acceptable, provided that the amount of this incentive is not so large as to unduly induce subjects to remain in the study when they might otherwise withdraw voluntarily.
- Payments should be issued in a timely manner.
- For studies involving minors, compensation can be made to minors or guardians as proposed by investigators and approved by the IRB.

22. Additional FDA Regulations:

In addition to the other applicable requirements outlined in this document, for studies involving drugs, biologics or devices, additional requirements apply.

22.1 Research with Investigational Drugs

For research involving investigational drugs or biologics, including use of FDA approved drugs or biologics for non-FDA approved uses, Investigators must submit the following to Castle IRB:

- Evidence that an IND number has been obtained from the FDA (by the Investigator or the Sponsor) or that the FDA has determined an IND is not required;
- Confirmation that an IND application will be/has been submitted; or
- The protocol explicitly and in detail demonstrates to the IRB that the federal requirements for exemption at 21 CFR 312.2(b) are met (see "IND Exemptions" section for details).

The IRB will verify whether the proposed use of a drug or biologic involves the use of a marketed drug, requires an IND, or meets exemption from the FDA IND requirement. If an FDA determination has already been made on the matter, it is final. Castle IRB staff will verify IND numbers to ensure their validity when protocol-specific confirmation (e.g., sponsor's protocol cover sheet, FDA or sponsor correspondence etc.), is provided. An Investigator's Brochure (IB) may not be accurate as a single IB can be used in multiple studies, each requiring its own IND.

The convened IRB will review protocols for proposed research involving investigational drugs or biologics considering the criteria for approval as described by regulations and IRB policies. Research involving a drug for which an IND is required is not eligible for expedited review. While IRB review and approval can take place prior to the IND being issued, if the IND is not yet in place at time of approval, an approval restriction will be included in the approval letter that the study cannot commence until the IND is in place.

It will also specify that any changes required by the FDA in the IND review process must be reviewed and approved by Castle IRB through the submission of an amendment prior to initiating. The convened IRB will also make determinations of whether an exemption from the IND requirement at 21 CFR 312.2(b) is met.

For research involving investigational drugs or biologics, including use of FDA approved drugs or biologics for non-FDA approved uses, the IRB will also require the investigator to provide the following to approve the research:

- Available clinical and non-clinical information on the investigational product that is adequate to support the proposed research.
- An adequate plan for monitoring data to ensure the safety of subjects and for reporting adverse events and unanticipated problems involving risks to subjects or others.

Investigators should also:

- Have a plan for control, accountability, and storage of the investigational drug or biologic that ensures that the product will be used only in the approved research under the direction of the approved investigator(s).
- When following ICH GCP Guidelines, the following must occur:
    - Drug manufacturing, handling, and storage must be in accordance with applicable good manufacturing practice.
    - Where allowed or required, the investigator/site assigns some or all duties for investigational article accountability to an appropriate pharmacist or other appropriate individual who is under the supervision of the investigator/site.
    - The investigator or designated individual maintains records of the product's delivery to the site, inventory at the site, the use by each participant, and the return of product to the sponsor or alternative disposition of unused product. These records include dates, quantities, batch or serial numbers, expiration dates, and the unique code numbers assigned to each participant and the investigational products.
    - The investigator or designated individual also maintains records that participants are provided the doses specified in the protocol and reconciles all investigational products received from study sponsors.
- Be knowledgeable about and comply with the additional FDA requirements associated with conducting research for which an IND has been obtained.

<u>IND Exemptions</u>

To be exempt from the FDA IND requirement, protocols must meet all criteria of one of the IND Exemptions as follows:

- Exemption 21 CFR 312.2(b)(1):
  - The drug product is lawfully marketed in the United States.
  - The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
  - If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product.
  - The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
  - The investigation is conducted in compliance with 21 CFR 50 and 56.
  - The investigation is conducted in compliance with the requirements of 21 CFR 312.7.

- Exemption 21 CFR 312.2(b)(2):
  - A clinical investigation is for an in vitro diagnostic biological product that involves one or more of the following:
    - Blood grouping serum
    - Reagent red blood cells
    - Anti-human globulin
  - The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.
  - The diagnostic test is shipped in compliance with 21 CFR 312.160.

- Exemption 21 CFR 312.2(b)(5):
  - A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

22.2 Research with Investigational Devices

For research involving medical devices, Castle IRB will comply with the requirements set forth in 21 CFR Part 812. FDA regulations describe three types of investigational device studies, "significant risk", "non-significant risk", and “IDE Exempt”. Significant Risk studies must have an IDE application approved by the FDA before they proceed and must follow IDE requirements. Non-Significant Risk device studies must follow the abbreviated IDE requirements at 21 CFR 812.2(b) but, like IDE exempt studies, do not require submission of an IDE application to FDA. IDE Exempt studies must meet criteria for one of the exemption requirements at 21 CFR 812.2(c).

- A "**significant risk device study**" is defined by FDA regulations as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and/or a) is intended as an implant *(An “implant” is defined by the FDA as “a device that is placed into a surgically or naturally formed cavity of the human body and is intended to remain there for a period of 30 days or more”. The FDA may determine that devices placed into human subjects for shorter periods of time are also implants.*); b) is used in supporting or sustaining human life; c) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health or d) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- A "**non-significant risk device study**" is a study of a device that does not meet the FDA’s definition for a "significant risk device study." Investigations in this category are considered to have approved applications for IDEs unless the FDA has notified a sponsor that an application is required but must fulfill all the requirements for an abbreviated IDE at 21 CFR 812.2.(b).
- An **“IDE Exemption”** study meets necessary criteria for one of the categories at 21 CFR 812.2(c).

The determination that a device study presents a "significant risk", "non-significant risk" or is IDE Exempt is initially made by the sponsor/investigator. If the sponsor/investigator considers the device study to be of "non-significant risk" or IDE Exempt, the sponsor/investigator must provide the IRB with an explanation of this determination and copies of the respective research protocol and informed consent document. The sponsor should inform the IRB of the FDA's assessment of the risk status of the proposed device study, if such an assessment has been made. The IRB may question whether other IRBs have reviewed the proposed device study and what determination they made, or the IRB may consult with the FDA for its opinion.

The device study may not commence until the FDA approves the IDE (if significant risk) and the IRB approves the device risk designation, the study protocol, and informed consent document(s). Castle IRB will review and approve a study while FDA IDE review is outstanding; however, it is Castle 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 the FDA. This expectation will be communicated as an Approval Restriction in the IRB approval letter. The approval letter will also specify that any changes required by the FDA in the IDE review process must be reviewed and approved by Castle IRB through the submission of an amendment prior to initiating.

IDE Exempt Studies

Studies may be exempt from FDA's IDE regulations when the research meets the criteria for one of the following categories:

- A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
- A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
- A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c), and;
    - The testing is non-invasive;
    - The testing does not require an invasive sampling procedure that presents significant risk;
    - The testing does not by design or intention introduce energy into a participant; and
    - The testing is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put participants at risk.
- A custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

Device Accountability

Investigators must have a plan for control, accountability, and storage of investigational devices that ensures that the devices will be used only in the approved research under the direction of the approved investigator(s). Investigators must also be knowledgeable about and comply with the additional FDA requirements associated with conducting research for which an IDE or abbreviated IDE (in the case of NSR designations) has been obtained.

In Vitro Diagnostic Devices

In Vitro Diagnostics (IVDs) are reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, to cure, mitigate, treat, or prevent disease. They are test articles subject to FDA investigational device (IDE) and human subject protection regulations. Current FDA guidance

indicates that IRB review is required for any IVD study involving human specimens/samples even when the research involves no identifiers and the biological materials cannot be linked to any identifying information.

IVD studies may be exempt from FDA's IDE regulations when the research meets all of the following criteria:

- The sponsor has labeled the device properly and complies with applicable requirements in 21 CFR 809.10(c);
- The testing is non-invasive;
- The testing does not require an invasive sampling procedure that presents significant risk;
- The testing does not by design or intention introduce energy into a participant; and
- The testing is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

Under FDA regulations, informed consent is required for IVD studies involving samples that are identifiable (i.e., are labeled with identifiers or accompanied by the patient's identifiable clinical information), and in studies where samples are not identifiable but are coded or linked to identifiable information.

Under some circumstances, when samples taken from excess clinical or research specimens cannot be identified (e.g., all linking codes and identifiers have been removed, or the investigator has no access to the code keys or identifying information), FDA will exercise "enforcement discretion" and permit the IRB to approve the study without requiring informed consent of the sample sources.

To be eligible for approval without a requirement for informed consent, FDA indicates that IVD research must meet the following criteria:

- The research must be conducted under an IRB-approved protocol;
- The research must meet criteria for an IDE exemption (see above);
- The research must use specimens left over from clinical care, specimen repositories, or other research (i.e., the specimens may not be collected specifically for the proposed research, and no additional specimen may be collected for the purpose of research);
- Individuals caring for the patients are different from and do not share information about the patient with those conducting the investigation;
- The specimens are provided for research without identifiers (codes are permissible only if neither the investigator nor anyone associated with the study has access to the code key or can identify the person who was the source of the specimen);
- Any clinical information supplied with the specimen must not be individually identifiable;
- No test results from the research may be reported to any subject or that subject's health care provider; and
- The supplier of the specimens must have established policies and procedures to prevent the release of identifying information.

The FDA's allowance for IRBs to waive informed consent under the following conditions may also apply to research with IVDs:

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

22.3 Emergency Use, Planned Emergency Research, and Expanded Access

Castle IRB currently only reviews Emergency Uses for the clinical use of a HUD. Castle IRB does not review Planned Emergency Research or Expanded Access submissions, but can provide information and guidance about the regulatory criteria.

Emergency use of a HUD must be reported to the FDA of its use within five (5) days through submission of an IDE Report as outlined in 21 CFR 812.35(a)(2) when an IDE exists for the device. When no IDE exists, the physician must submit to the FDA a follow-up report within five (5) days to the appropriate FDA address in 21 CFR 812.19.

Within five (5) working days of the emergency use, the physician must provide written notification to Castle IRB of such use outlining the circumstances of patient involved, the date on which the device was used, the reason for use, and monitoring plan to be followed. Reporting of this information should be done through the Emergency Use Form.

Criteria for Emergency Use of a HUD

IRB approval is not required prior to emergency use and prior to receiving FDA approval, all of the following must be met:

- The patient has a life-threatening condition that need immediate treatment.
- No generally acceptable alternative treatment for the condition exists; and
- There is no time to use existing procedures to obtain FDA approval for the use.

When a HUD is used for emergency use as outlined in the above criteria, the physician will follow as many of the following patient protections as possible:

- Concurrence of an IRB chair prior to use.
- Obtain informed consent from the patient or a legally authorized representative if one is available.
- Obtain clearance from the institution, if any, as required by their policies.
- Independent assessment from an uninvolved person that the patient's condition warrants the use of the device.
- Authorization from the device manufacturer.

23. Community Engagement

Gene therapies have the potential for great impact in certain patient populations, such as rare diseases. Thus, when feasible, sponsors and investigators designing studies should consider engaging representatives from these communities, both at the front (design) and back (dissemination of results) end of clinical trials.

Though not specific to gene therapy (as patient engagement has the potential to benefit any clinical trial), TransCelerate Biopharma Inc. has issued guidance, such as the Patient Protocol Engagement Toolkit (P-PET) as a comprehensive set of materials that sponsors can use to engage patients during protocol development.

24. Filing Complaints and Concerns

Participant Concerns to Investigators

As part of informed consent, Investigators must include information to participants on who to contact for study questions and concerns. This will include contact information for the Investigator and research team as well as for Castle IRB, should a participant wish to take the concern to someone not on the research team. Castle IRB maintains a participant page on its website to assist study participants with some frequently asked questions about research, and contact information for Castle IRB is readily available on the Castle IRB website, in addition to being in consent documents.

Investigators are encouraged to swiftly assist study participants with questions, requests for information, and concerns; however, Castle IRB is available to support if the research team cannot fully address concerns or need

additional support. Investigators can contact the Castle IRB team via phone or email for immediate support with a participant concern, though may be asked to follow-up with submission of a Reportable Event Form.

Concerns Filed with Castle IRB

Any person with concerns regarding the conduct of Castle IRB, or of human subjects research under the oversight of Castle IRB, is encouraged to contact officials through any of the following means:

- Calling Castle IRB or Sabai Global at 888-442-2472.
- Emailing irbteam@castleirb.com.
- Contacting the Compliance Hotline (for anonymous reporting):
    - Website: **www.lighthouse-services.com/clinicalbiosafety**
    - Toll-Free Telephone (English speaking): 833-370-0002
    - Toll-Free Telephone (Spanish speaking): 800-216-1288

Complaints or concerns may be submitted by anyone, including research participants or their family members, Sponsors, CROs, Institutions, Investigators and research team members, Castle IRB staff, IRB Members, or others. Reports can include concerns of noncompliance or general comments or suggestions about performance of research investigators or of Castle IRB. Castle IRB Staff will attempt to resolve concerns if appropriate. This may include referring the reporter to the study team. Complaints regarding the IRB Chair or Director of IRB Operations will be handled by the President, Sabai Global or designee.

Client feedback is importance to us! Though you can expect to receive a customer satisfaction survey at least annually, upon which you can provide feedback, you are welcome to submit questions, concerns or suggestions at any time using methods provided above.

25. Noncompliance:

Noncompliance may be identified in a number of ways, such as:

- Routine quality assurance reviews;
- Sponsor or CRO monitoring;
- Reports by a research participant, research team member or other.

Events that meet the definition of a Protocol Deviation or Noncompliance as defined in this Investigator Guide must be reported to Castle IRB by investigators/conduct sites within 7 calendar days of the issue becoming known, even if only preliminary information is known at that time.

Investigators and study team members are expected to report known or suspected Noncompliance to Castle IRB through submission of a Reportable Events Form or through one of the reporting mechanisms described in Section "Filing Complaints and Concerns," including the Compliance Hotline, if wanting to remain anonymous.

Noncompliance is defined as conducting research in a manner that violates federal regulations, applicable state or local laws, or IRB policies. Noncompliance includes failure to adhere to the approved research protocol, except for minor or technical violations resulting from inadvertent errors, inattention to detail, or failure to follow operational procedures that do not pose risk to subjects and/or violate subject's rights and welfare.

Examples of Noncompliance include:

- Conducting human subjects research without IRB Approval.

- Protocol Deviations.
- Lapses in IRB Approval (failure to submit for timely Continuing Review).
- Failing to halt research activities during a lapse in IRB approval or as otherwise instructed by the IRB.

Serious Noncompliance is defined as Noncompliance that may reasonably be regarded as having increased the risk of harm to participants, adversely affected the safety, rights, or welfare of research participants, or adversely affected the integrity of the data and research. **Apparent serious noncompliance** describes an event that appears to constitute serious noncompliance, and so requires reporting to an appropriate IRB for consideration, but the IRB has not yet made a formal assessment of the event.

Continuing Noncompliance is defined as a pattern of repeated noncompliance which continues after initial discovery, including inadequate efforts to take corrective actions within a reasonable timeframe. **Apparent continuing noncompliance** describes an event that appears to constitute continuing noncompliance, and so requires reporting to an appropriate IRB for consideration, but the IRB has not yet made a formal assessment of the event.

Review considerations and possible IRB actions resulting from IRB reviews of noncompliance include:

- Verify that any changes implemented to remove apparent, immediate hazards to participants were made appropriately, and in accordance with federal regulations and IRB policies.
- Require changes to the protocol or study materials as needed to protect human participants and others, and or to keep the study in alignment with ethical principles, federal regulations, state or local laws, ICH-GCP as applicable, or other sponsor or agency requirements, as applicable.
- Verify that plans for additional consent from participants are adequate and appropriate, and request modifications as needed.
    - Notifications to participants is typically expected when information might relate to the participants' willingness to continue to take part in the research or could impact the safety or wellbeing of current or past participants.
- Consider whether the IRB should seek information from sources other than the Principal Investigator (e.g., from the Institution or research participants) to ensure full understanding of events, including performing or requiring an investigation.
    - Incidents appearing to involve serious or continuing non-compliance with a basis in fact, or if it cannot be determined if there is basis in fact, may be subject to further inquiry or investigation.
    - The inquiry/investigation may be conducted by Castle IRB staff, IRB Chair or designated IRB Members (or any combination thereof), the conduct site Institution or another party if approved by Castle IRB.
    - Investigators are expected to respond promptly to any requests for information or documentation during an inquiry/investigation.
    - Inquiries/investigations should aim to complete within 30 days, including the reporting of findings to Castle IRB.
- Determine whether the incident is Continuing or Serious Noncompliance.
- Determine whether the incident is an Unanticipated Problem.
- Accept or request changes to the investigator's corrective action plans, and determine whether corrective action plans require verification, audit or monitoring.
- Suspend enrollment of new participants, if needed for safety.
- Suspend continuation of current participants, if needed for safety.
- Suspend or terminate IRB approval of the study.

- In such cases, the IRB must consider impact on the rights and welfare of enrolled participants and whether participants in active intervention or inactive (those who withdrew or completed participation) should be informed of the suspension/termination of IRB approval.
- Ensure that any related reporting requirements are understood by all responsible parties.
- Issue correspondence to the Investigator that summarizes the incident of noncompliance, relevant regulations/policy expectations, and potential outcomes should there be recurrence in the future.
- Require additional education in human subjects research protections, Good Clinical Practice, the protocol, federal regulations, IRB policies or other.
- Require audit or monitoring of the research or consent process; require more frequent continuing reviews.

IRB Determinations and actions will be promptly communicated to Investigators, copied to Institutional Officials, and other parties (including Sponsors or Regulatory Agencies) in accordance with the terms of the Reliance Agreement in place between Castle IRB and the Conduct Site/Relying Institution.

26. Suspension or Termination of IRB Approval:

Suspension of IRB Approval is defined as an action taken by the IRB Chair or convened IRB to temporarily withdraw IRB approval for all activities in an IRB-approved research study, or to temporarily or permanently withdraw IRB approval for only certain activities in an IRB-approved research study. Similar actions taken by a Sponsor, Site, or Investigator do not fall under this definition.

Termination of IRB Approval is defined as an action taken by the convened IRB to permanently withdraw IRB approval for all activities in an IRB-approved research study, except for activities deemed allowable to protect participant safety, rights, and welfare. Similar actions taken by the Sponsor, Site or Investigator do not fall under this definition.

<u>Suspension of IRB Approval</u>

The convened IRB and IRB Chair have the authority to suspend IRB approval of research that is not being conducted in accordance with applicable regulations and IRB requirements or has been associated with unexpected, serious harm to participants or others.

Review considerations and possible IRB actions for Suspensions of IRB Approval can include:

- Consideration of the impact on the safety, rights, and welfare of enrolled participants (e.g., availability of medical care outside of the research, availability of transfer to another research site).
- Notification of the Suspension to participants in active intervention and/or those who are inactive (those who have withdrawn or completed participation).
- Halting all or only some research activities. For example, some activities may be allowed if their continuation is determined to be in the best interest of participants, when considering their rights, safety, and welfare (e.g., continued monitoring).
- Requiring transfer of PI or other research team member responsibilities.
- Requiring arrangements for care of participants outside of the research study or conduct site (transfer to another conduct site).
- Requiring or permitting follow-up care of participants for safety reasons.
- Arranging for compensation of active and/or inactive participants.
- Requiring all reportable events to be submitted to the IRB, if any have not yet been reported.

When study approval is suspended at the study-wide level, the reason(s) and related required actions will be communicated to the Sponsor/CRO, with copy to all Investigators. When study approval is suspended at the site level, the reason(s) and related required actions will be communicated to the Principal Investigator, copied to the Site's Institutional Officials and the Senior Official of Castle IRB, who will determine whether additional reporting (e.g., to study sponsor, CRO, or other parties) is appropriate based on the Agreements in place for the research or other reasons.

Suspensions of approval may be lifted by the convened IRB or IRB designee if there are no longer concerns regarding:

- Actual or genuine substantive risk of harm to participants, research staff or others.
- Potentially Serious Noncompliance.
- Other concerns or issues that contributed to the Suspension of IRB Approval.

Only suspensions made by the IRB Chair outside of the Convened IRB may be lifted by the IRB Chair.

Termination of IRB Approval

The Convened IRB may terminate IRB approval of previously approved research in cases of Serious or Continuing Noncompliance, when significant concerns arise about patient safety, or when new knowledge results in the study no longer meeting the regulatory criteria for approval.

When IRB approval of research is terminated, the convened IRB will consider actions such as the following to protect the rights and welfare of participants, as appropriate:

- Notification to participants in active intervention and/or those who are inactive (those who have withdrawn or completed participation).
- Requiring arrangements for care of participants outside of the research.
- Requiring or permitting follow-up care of participants for safety reasons.
- Arranging for compensation of active and/or inactive participants.

When study approval is terminated at the study-wide level, the reason(s) and related required actions will be communicated to the Sponsor/CRO, with copy to all Investigators. When study approval is terminated at the site level, the reason(s) and related required actions will be communicated to the Principal Investigator, copied to the Site's Institutional Officials and the Senior Official of Castle IRB, who will determine whether additional reporting (e.g., to study sponsor, CRO, or other parties) is appropriate based on the Agreements in place for the research or other reasons.

Upon notification that IRB approval of research has been suspended or terminated by the IRB, the investigator(s) is responsible for the following:

- Confirming receipt of the notification.
- Stopping enrollment and other/all research activities as required by the IRB.
- Cooperating with any inquiries, requests for information or other actions taken by the IRB, including those taken to protect the rights and welfare of research participants.
- Reporting any adverse events or outcomes encountered due to the suspension or termination of IRB Approval and research activities.

Investigator- or Sponsor-Initiated Suspensions or Terminations

If a determination to suspend or terminate research is made by the Sponsor or Investigator of research, it shall be reported to the IRB, and activities shall not resume until approved by the IRB and other authorities, such as the FDA if applicable.

Submissions should include the primary reason for suspension/termination, status of participants and whether suspension/termination will impact them, whether participants will be notified, procedures that will be undertaken to ensure safe discontinuation, and for suspensions, what steps are being taken to consider resuming research.

In deciding whether the study can be suspended or terminated, Investigators and the IRB should consider potential impact to participants' rights, safety and welfare. Additional review considerations and actions match those used for IRB-initiated Suspensions and Terminations of IRB Approval.

27. Reporting IRB Determinations

Federal Regulations at 45 CFR 46 and 21 CFR 56 require the reporting of the following IRB determinations to Investigators, Institutional Officials, and Regulatory Agencies:

- Unanticipated Problems involving risks to subjects or others (UP)
- Serious or Continuing Noncompliance
- Suspensions or Terminations of IRB Approval

Any such IRB determinations made by Castle IRB will be reported in compliance with Federal Regulations and in accordance with the terms of the Reliance Agreement in place between Castle IRB and the Conduct Site/Relying Institution.

28. Appeal of IRB Determinations:

Principal Investigators may appeal IRB Determinations. A written request for reconsideration must be submitted to the IRB Chair and include the reason for requesting the reconsideration. At the discretion of the IRB Chair, the Committee may be convened to reconsider IRB Determinations (e.g., based on the presentation of new or refuting information).

29. Concluding IRB Oversight:

A Castle IRB Closure Form shall be submitted to conclude Castle IRB oversight of studies.

Investigators must seek approval of continuation unless all of the following are true:

- The research is permanently closed to the enrollment of new subjects.
- All subjects have completed all research–related interventions.
- For research subject to federal oversight other than FDA, collection and analysis of private identifiable information has been completed.

For multi-site studies where a Sponsor/CRO has contracted Central IRB services from Castle IRB (i.e., the sponsor/CRO has Submitted the protocol to Castle IRB with the intention of multiple Conduct Sites relying on Castle IRB as the Reviewing IRB), the Sponsor/CRO must seek approval of continuation unless all of the following are true for all Conduct Sites relying on Castle IRB:

- The research is permanently closed to the enrollment of new subjects.
- All subjects have completed all research–related interventions.
- For research subject to federal oversight other than FDA, collection and analysis of private identifiable

information has been completed.

In the case of premature termination of research, a Reportable Event Form shall be submitted to enable prompt IRB review of human subjects safety considerations until the Closure Form can be submitted to finalize IRB oversight.

After IRB approval has concluded, Investigators must continue to abide by obligations to protect the rights, safety and welfare of research participants, including the reporting of new information that may impact participant safety and welfare, and maintaining participant privacy and confidentiality in accordance with the terms of the consent form, agreements in place related to the research, and all applicable laws.

APPENDIX A
Protocol Template

This Template can be used to fulfill New Protocol Submissions [Multisite Initial Protocol Application if submitting the master protocol and related materials without a conduct site; Single Site Application if submitting the protocol and a conduct site].Information in *italics* provides instructions or guidance, including links to relevant sections of this Investigator Guide.

Sections that are not applicable may be deleted or skipped.

1. **BACKGROUND INFORMATION:**
   - Provide an introduction and rationale for the study.
   - Describe the importance of the research question and gaps in current knowledge.
   - Include any past experimental and/or clinical findings leading to the formulation of the study.
   - Provide an overview of the literature and relevant data.
   - Include a description of the study intervention or investigational product, if applicable.

2. **STUDY PURPOSE/OBJECTIVES:**
   - Describe the overall purpose of the study.
   - List research objectives (specific aims and hypotheses of the study).

3. **STUDY DESIGN:**
   - Provide an overview of the study type/design to be conducted (e.g., single/double blind, parallel group, crossover, case-control, cohort, randomized, placebo-controlled, open-label, experimental, observational, descriptive, pharmacokinetic-pharmacodynamic study, natural history, etc.).
   - Outline the various study groups and arms.
   - Describe the randomization process, if applicable.
   - Indicate if this is a single site or multi-center study.
   - Provide a timeline of the anticipated duration for participants and the study as a whole.
   - Including a study diagram is often helpful, but not required.
   - *Refer to "Study Design Considerations" section of this Guidance.*

4. **STUDY POPULATION:**
   - Provide the total number of participants and the number of research sites.
   - Describe the characteristics of the subject population(s), such as age range, gender, ethnic background and health status. If there is more than one subject population being studied, each should be separately described.
   - Explain the rationale for selected population, including rationale for inclusion of special populations such as minors, pregnant women, fetuses, neonates, prisoners, or others who are likely to be vulnerable, such as those with diminished capacity to consent, educationally disadvantaged, or illiterate participants. Indicate if employees or students will be specifically targeted as a research population. Indicate whether the study population will include participants whose primary language is not English.
   - If women of child-bearing age, minorities, or minors are excluded, provide justification.
   - *Refer to "Vulnerable Subjects, Additional Considerations and Protections" section of this Guidance*

5. **INCLUSION AND EXCLUSION CRITERIA:**
   - List the inclusion criteria and exclusion criteria.
   - If there are multiple study groups, please list separately for each group.

- *Refer to "Equitable Selection of Participants" section of this Guidance*

6. STUDY PROCEDURES:

- Describe research procedures, observations, and measures that will be followed at each study visit.
- Identify the procedures be carried out with each group of participants.
- For clinical studies, differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project.
- Describe circumstances under which a participant's involvement may be discontinued, and the process to be followed.
- Including a table of events for studies with numerous subject interactions or procedures is helpful, but not required.

7. STUDY OUTCOME MEASURES:

- Describe the methods for assessing how the objectives are met, including how and when these measurements will be made.
- Including a table of measurements is helpful, but not required.

8. STATISTICAL CONSIDERATIONS:

- Describe how data analysis will be performed (statistical tests, methods for evaluating data).
- Include the sample size justification and power analysis, if appropriate.
- State the primary and secondary endpoints.
- Describe any planned interim analyses for efficacy or safety, and a description of any stopping rules.
- Describe the measures to be taken to avoid bias.

9. RISKS ASSESSMENT:

- List the reasonably foreseeable physical, psychological, economic, social, legal or other risks for each research intervention/procedure.
- Assess the probability, magnitude, and reversibility of all study-related risks.
- For clinical studies, distinguish between risks associated with routine clinical care from those that will occur as a result of research.
- Address how the study design and execution will minimize the risks of harm.
- Describe why the risks to participants are reasonable in relation to the anticipated benefits to participants and in relation to the importance of the knowledge that may reasonably be expected to result (i.e., risk/benefit analysis).
- *Refer to "Risks" section of this Guidance*

10. SAFETY MANAGEMENT:

- Describe plans to monitor for and report adverse events.
- Describe plans for ensuring necessary medical or professional intervention for emergencies that might develop during the course of the study.
- Describe the provisions for monitoring the data collected to ensure the safety of participants (e.g., a Data Safety Monitoring Board or monitoring plan), tailored to the risks of the study intervention. Include the time points/frequency of safety assessments.
- Include who is responsible for data quality management and ongoing assessment of safety (e.g. the PI, independent medical monitor, internal safety committee, or the Data Safety Monitoring Board).
- *Refer to Data and Safety Monitoring section of this Guidance*

11. POTENTIAL BENEFITS:

- Describe potential benefits to participants. If no direct benefit is anticipated, this should be stated.

- Describe the potential benefits to society that might result from the research findings.

12. ALTERNATIVES:

- Describe any alternative treatments and procedures that might be advantageous to the participants, including risks/benefits of those alternatives, should they choose not to participate in the study.
- If no such alternatives exist, please state that the alternative is nonparticipation. For some studies, such as record reviews, a description of alternatives would not be applicable.
- For clinical studies, include the alternative of standard therapy and provide a brief description.

13. RESEARCH-RELATED COSTS:

- Describe how study-related costs will be covered.
- Describe any costs that participants may be responsible for due to participation in the research.

14. PRIVACY, CONFIDENTIALITY, AND DATA MANAGEMENT:

- Describe safeguards employed to protect the privacy of the participants.
- Describe safeguards employed to protect the confidentiality of the participants.
- Describe who will have access to the study data.
- Describe the systems used for maintaining primary records and case report forms.
- Identify the sources of research material (e.g., specimens, records, data). Provide enough detail to clarify that the material or data will be obtained specifically through an interaction with participants and/or indicate that the specimens, records, or data are already in existence.
- *Refer to "Privacy and Confidentiality" section of this Guidance*

15. INFORMED CONSENT, ASSENT, and HIPAA AUTHORIZATION:

- Describe the process that will be used to obtain and document informed consent. *[See "Informed Consent" section].*
- Describe the process that will be used to obtain and document parental/legal guardian consent and assent from minors, if applicable. *[See"Assent in Research Involving Minors" section]*
- Discuss the additional safeguards that will be taken during the informed consent process if other potentially vulnerable subjects (including adults with diminished capacity to consent with use of a Legally Authorized Representative) will be enrolled in the study. *[See "Vulnerable Subjects" section]*
- Describe the process that will be used to obtain and document HIPAA Authorization, if applicable. *[See "Authorization to Use or Disclose Protected Health Information" section]*
- If requesting a waiver of alteration of consent, assent, or HIPAA authorization, please state. *[See "Waiver or Alteration of Consent" section]*
- If consent documents are being created for the study, refer to *"Informed Consent, Elements of Informed Consent" section* for required and additional elements. *Note: if the consent will be translated to additional languages, Castle IRB recommends obtaining approval of English versions.*
- *Investigators should be aware of the specific consent requirements of the regulations the research is subject to, including ICH-GCP Guidelines, if applicable, which are specified in this Investigator Guide.*

16. REFERENCES

- List all references cited within the protocol.