HUMAN RESEARCH OPERATIONS MANUAL – BALLAD HEALTH

Policy Manual:	Administration-Operational
Manual Section:	Academics and Research – IRB Research
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This plan applies to:

Ballad Health Corporate

Tennessee: BRMC, FWCH, GCH, HCH, HCMH, HVMC, IPCH, JCCH, JCMC, SSH, UCH, WPH, Niswonger Children's Hospital, New Leaf, Laughlin Healthcare Center, Madison House, Ballad Health Hospice House, Wexford House

Virginia: DCH, JMH, LCCH, LPH, NCH, RCH, SCCH, Clearview Psychiatric Unit, Francis Marion Manor Health & Rehabilitation, Green Oak Behavioral Health (Geriatric Behavioral Health Inpatient Program – DCH), Ridgeview Pavilion, Norton Community Physicians Services (NCPS), Community Home Care (CHC), Abingdon Physician Partners (APP), Norton Community Hospital SNF Unit

Ballad Health Medical Associates

Blue Ridge Medical Management Corporation

Home Health/Hospice

Integrated Solutions Healthcare Network (ISHN)

Mediserve Medical Equipment of Kingsport, Inc.

Mountain States Pharmacy at Norton Community Hospital

Mountain States Physicians Group, Inc. (MSPG)

Strong Futures

Takoma Regional Hospital, Inc.

Wellmont Cardiology Services

Wellmont Medical Associates

Wilson Pharmacy, Inc.

WPS Providers, Inc.

PURPOSE:

The mission of Ballad Health is to honor those we serve by providing the best possible care. As the largest and most comprehensive integrated healthcare organization in the region, Ballad Health focuses on these goals by providing high-quality patient care, decreasing health disparities, removing access barriers, developing new clinical services, and addressing healthcare affordability. Ballad Health team members are dedicated to living the purpose of building a legacy of superior health by listening to, and caring for, those we serve. In support of this mission, Ballad Health, provides a platform for the organization's higher education partners to work together to pave the way for breakthroughs in healthcare delivery, access, and affordability through a unique and dynamic collaboration. This collaboration provides access to professional and workforce development programs, medical schools, a nursing programs, clinical and translational research, and the region's largest healthcare delivery system, just to name a few. Ballad Health is dedicated to helping the health professionals of today and tomorrow to meet the real-world needs of the community. All human research studies operate under the auspices of a system-wide office of Human Research Protection Program (HRPP) with oversight and management from the Vice President of Research and Academics and the Vice President for Research Operations as the responsible organizational officials for its operation. Individual elements of the HRPP operation include the following:

- Education and training of all Ballad personnel as well non-affiliated researchers involved in human subject research to include research staff, IRB committee members, and IRB staff.
- Periodic review of human research protocols submitted to the independent review committee (Institutional Review Board) with relevant expertise and community representation.
- Human subject outreach, communication, and education
- Financial management and review
- Risk management
- Research integrity
- Conflict of interest disclosure and management and
- Quality improvement programs

In addition to the above, the office of Human Research Protection Programs allows research participants and the public at-large to voice complaints, issues, concerns, and suggestions for improvement. Ballad Health is a learning organization and supports continuous improvement and high reliability. All of the integrated elements of the Human Research Protection Program provide a robust and interactive framework for the ongoing management and improvement of the research enterprise.

Table of Contents/Description

FUNCTION:

1. **Acronyms / Definitions**

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

   b. **Administrative Hold** – means a voluntary action by the IRB against an investigator to stop research activities in a currently approved protocol.

   c. **Adult** – means a person who has attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. Who is an Adult may vary depending on the specific treatments or procedures involved in the research and on the jurisdiction in which the research will be conducted.

   d. **Adverse Events (AE)** - Although not defined under either the Department of Health and Human Services (DHHS) or the Food and Drug Administration (FDA) regulations, recent Office for Human Research Protections (OHRP) guidance of January 15, 2007, Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events uses the term to include any event meeting the following definition: Any untoward or unfavorable

medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. An adverse event encompasses both physical and psychological harms; and although they most commonly occur in the context of biomedical research, they can also occur in the context of social and behavioral research.

e. **Advertisement** – means any form of communication aimed directly to potential research subjects and which is under the control of the investigator.

f. **Allegation of Non-Compliance** – means an unproven assertion of non-compliance, suspected non-compliance with human subject protection regulations.

g. **Amendment** is defined as a revision, a change, or an addition (addendum) to an approved research protocol.

   i. Amendment Examples: (This list is not inclusive of all possible protocol addendum, amendment & revisions):

   ii. Revisions to a protocol which include: addition of or changes to a procedure, changes to eligibility or exclusion criteria, administrative or editorial changes or addenda, sponsor amendments, revisions to consents or assents, changes/additions or removal or Principal Investigators or Sub-investigators, changes/additions of study staff;

   iii. Changes in recruitment or advertisements which include: recruitment materials, advertisements, notifications and/or letters to research participants; use of recruitment registries;

   iv. Internet/media advertisements including: referral system, press releases etc.; flyers to be posted, letters to participants, any change in the research population.

h. **Applicant** – means the party who submits a marketing application to FDA for approval of a drug, device or biologic product. The applicant is responsible for submitting the appropriate certification and disclosure statements required by this policy.

i. **Assent** – means a Child's affirmative agreement to participate in research. Failure of a Child to object to participation cannot be construed as Assent. Assent is a process involving communication with the Child. A signature on an Assent document is not, by itself, Assent.

j. **Association for the Accreditation of Human Research Protection Program (AAHRPP)**

k. **Assurance** – means a written agreement that establishes standards for Human Subjects' Research as approved by the Office for Human Research Protections (OHRP) and is executed by the Institutional Review Board.

l. **Case Report** – means a case report is any medical information that is collected and presented to others within Ballad Health to highlight an interesting treatment, presentation, or patient outcome. Case reports will consist of no more

than three patients records that are retrospectively reviewed. Case Reports are different in the state that research protocols collect data with the intent to evaluate a specific hypothesis.

m. **Central Institutional Review Board (CIRB)** – means the CIRB initiative is sponsored by the NCI in consultation with the Department of Health and Human Services (DHHS) Office of Human Research Protections (OHRP). NCI's CIRB initiative is designed to help reduce the administrative burden on local IRBs and investigators when they participate in NCI sponsored multi-center trials. Ballad Health's use of the CIRB review mechanism enables an investigator to enroll subjects into adult, Cooperative Group, Phase II, and Phase III clinical trials in a more expeditious manner.

n. **Child** – means a person, who has not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted.

o. **Clinical Investigator** – means only a listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and dependent children of the investigator.

p. **Clinical Investigation/Trial** – means any experiment that involves a Test Article and one or more Human Subjects, and that is subject to the FDA regulations. FDA regulations consider the terms "Clinical Investigation" and "Research" to be synonymous. The following are considered experiments subject to FDA regulations:

   i. Any use of a drug, other than the use of an approved drug in the course of medical practice.

   ii. Any use of a medical device to evaluate safety or efficacy of that device.

   iii. Any activity where data are being collection to submit to FDA or to be held for inspection by FDA

q. **Closure** – means an action taken by an investigator to permanently discontinue research activities for a study that has current IRB approval.

r. **Cognitively Impaired** – means an Adult with a psychiatric disorder (e.g., schizophrenia, major depression, psychosis, neurosis, personality or behavior disorders), an organic impairment (e.g., dementia), a developmental disorder (e.g., mental retardation), or severe acute illnesses associated with cognitive impairment (e.g., stroke, seizure, metabolic coma, myocardial infarction and severe pain) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Depending on the illness, the impairment may be temporary, cyclical, or permanent. A person who is determined to be Cognitively Impaired is considered to be not able to be of decision-making capacity and requires a guardian or independent witness to complete an Informed Consent.

s. **Co-Investigator** (Co-I) – means a subset of the study team who have special responsibilities on research projects. Co-Is are obligated to ensure that the

project is designed and conducted in compliance with applicable laws and regulations and institutional policy. A Co-I must be qualified by training and experience to conduct the responsibilities on the research project.

t. **Collaborative Institutional Training Initiative (CITI)** - is a web-based educational program in the ethics of human subject research and may be used for both core initial education as well as continuing education requirements. The program is sponsored by the University of Miami (Florida) and may be accessed at: https://about.citiprogram.org .

u. **Collection Protocol** – means the collection of data or specimens that requires separate IRB review and approval and continuing IRB oversight. One or more Collection Protocols may be submitted.

v. **Cold Calling** – means when a person not known to the potential research subject contacts the subject without an introductory letter sent in advance of the call.

w. **Compelling Circumstances** – are those facts that convince Ballad Health COI Committee that a financially interested individual should be permitted to conduct human subject research. When considering a request by a financially interested individual to conduct human subjects research, the circumstances that the COI Committee should evaluate include the nature of the research, the magnitude of the interest and the degree to which it is related to the research, the extent to which the interest could be directly and substantially affected by the research, the degree to which the interest could affect the research, and the degree of risk to the human subjects involved that is inherent in the research protocol. A material conflict of interest requires a written mitigation plan to be monitored by the COI Committee.

x. **Competence** – means a legal term, used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Competence may fluctuate as a function of the natural course of an illness, response to treatment, effects of medication, general physical health, and other factors. Therefore, mental status should be re-evaluated periodically. As a designation of legal status, competence or cognitively impaired pertains to determination in court proceedings that a person's abilities are so diminished that his or her decisions or actions (e.g., writing a will) should have no legal effect. Such decisions are often determined by inability to manage business or monetary affairs and do not necessarily reflect a person's ability to function in other situations.

y. **Compensation** – means refers to payment for treatment of an unexpected adverse outcome that occurs during the research. It should not be used to refer to subject Remuneration.

z. **Compensation Affected by the Outcome of Clinical Studies** – means compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result or compensation to the investigator in the form of an equity interest in the sponsor of a covered study or in the form of compensation tied to sales of the product, such as a royalty interest.

aa. **Conducting Research** – means with respect to a research protocol, designing research, directing research or serving as the principal investigator, enrolling research subjects (including obtaining informed consent) or making decisions related to eligibility to participate in research, analyzing or reporting research data, or submitting manuscripts concerning the research for publication.

bb. **Conflict of Interest / Conflict of Commitment (COI)(COC)** – means the existence of one or more influences that might be strong enough to distract an IRB Member from the IRB Member's primary duty. Conflicting interests are the ordinary factors that can influence judgment, such as personal relationships between an IRB Member and an investigator, competition among departments, authority relationships, financial relationships, etc.

cc. **Continuing Non-Compliance** – means a pattern of non-compliance that, in the judgment of the IRB Chair or convened IRB, indicates a lack of understanding of the regulations or institutional requirements that may affect the rights and welfare of participants, would have been foreseen as compromising the scientific integrity of a study such that important conclusions could no longer be reached, suggests a likelihood that non-compliance will continue without intervention, or frequent instances of minor non-compliance. Continuing Non-Compliance also includes failure to respond to a request to resolve an episode of non-compliance with human subject protection regulations.

dd. **Continuing Research Education Credit (CREC)**

ee. **Continuing Review** – means periodic review of research activities necessary to evaluate the progress of the study and to determine whether the risk/benefit ratio has changed, whether there are unanticipated findings involving risks to participants or others, and whether any new information regarding the risks and benefits should be disclosed to participants.

ff. **Continuing Review Reminder Notices** – means e-mail notices sent at 90, 60 and 30 days by IRBNet to alert the investigator of an upcoming renewal date.

gg. **Covered Clinical Study** – means any study of a drug or device in human subjects submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general not include phase 1 tolerance studies of pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, a parallel track protocols. An applicant may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements.

hh. **Data and Safety Monitoring Board or Committee (DSMB/DSMC)** - A group comprised of expert(s) in the field of medicine and/or science applicable to the research, statistician(s), lay representative(s), and others as necessary to monitor study progress. A data and safety monitoring board reviews study-specific data periodically throughout the research to ensure continued participant safety and scientific validity and to make recommendations whether to continue,

modify, or terminate the study. Note: The following terms are interchangeable – data and safety monitoring board, data and safety monitoring committee, and data monitoring committee.

ii. **Data and Safety Monitoring Plan (DSMP)**

jj. **Data Confidentiality** – means how the participant's identifiable private information (data) will be handled, managed and disseminated.

kk. **Deception Research** – means a prospective agreement by the subject to participate in Research where the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the Research.

ll. **Decision-making Capacity** – means a potential subject's ability to make a meaningful decision about whether or not to participate. It generally includes the following four elements:

i. Understanding is the ability to comprehend the disclosed information about the nature and purpose of the study, the procedures involved, as well as the risks and benefits of participating versus not participating.

ii. Appreciation is the ability to appreciate the significance of the disclosed information and the potential risks and benefits for one's own situation and condition.

iii. Reasoning is the ability to engage in a reasoning process about the risks and benefits of participating versus alternatives.

iv. Choice is the ability to understand the difference between participating and not participating in Research.

decision-making capacity is different from the legal concept of competence. While a court may consider information about a potential subject's decision-making capacity in making a competency determination, the terms are not synonymous. For example, someone who is judged legally incompetent to handle their financial affairs may retain sufficient decision-making capacity to make meaningful choices about participating in a particular Research protocol. Decision-making capacity is situation and protocol specific. Thus, a subject may have capacity to consent to a low-risk Research protocol that is not difficult to understand, but not have the capacity to consent to a complex or high-risk protocol.

mm. **Decisionally Impaired** – means those who have a diminished capacity to understand the risks and benefits for participation and to autonomously provide informed consent. See Cognitively Impaired.

nn. **Delivery** – means the complete separation of the Fetus from the woman by expulsion or extraction or other means.

oo. **Department of Defense (DOD)**

pp. **Department of Education (ED)**

qq. **Department of Energy (DOE)**

rr. **Department of Health and Human Services (DHHS)** – means The United States government's agency for protecting the health of all Americans and

providing essential human services, especially for those who are least able to help themselves.

ss. **Designated Institutional Official (IO)** – means individual responsible for reviewing all Significant Financial Interest disclosures; determining whether a Financial Conflict of Interest (FCOI) potentially exists and sending FCOIs to the COI Committee for review and management. The designated IO will chair the COI Committee and submit the FCOI and other reports to the applicable awarding components and funding sources.

tt. **Discarded Specimen** – means is that portion of a collected specimen that is not needed for assessment of diagnostic, prognostic, and other parameters in the diagnosis and treatment of the patient. Discarded specimens include tissue (both solid and soft), body fluids, urine, blood, nail clippings, hair, and stool.

uu. **Disclosure** – means a release of relevant information about significant financial interests in human subject's research to parties outside Ballad Health System's COI review and management processes (e.g., research subjects or journal editors).

vv. **Emancipated minor** – means a person under the legal age who, because of a special situation, has the legal rights of an Adult. Situations that qualify a person as an Emancipated Minor vary from state to state. In Tennessee, a person under the legal age becomes an Emancipated Minor by order of the court. Grounds for emancipation include marriage or service in the armed forces. Documentation of emancipation by court order is required before this doctrine can apply in the research context.

ww. **Emergency Use** – means the use of an investigational drug, agent, device, or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval.

xx. **Environmental Protection Agency (EPA)**

yy. **Ethics Committee** – means refers to the Ballad Health facility specific Ethics Committee.

zz. **Expedited Review** – means review of research involving human subjects by the Ballad Health IRB Chair, Vice-Chair, or by one or more experienced reviewers designated by the Chair from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110, 45 CFR 46.111, and 21 CFR 56.111.

aaa. **Expired Study** – means when continuing review of the research does not occur prior to the end of the approval period specified by the IRB. IRB approval expires automatically. No activity can occur after the expiration date.

bbb. **Expected Adverse Events** – means any event, the specificity or severity of which is consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is consistent with the risk information described in the general investigative plan or elsewhere in the current application, as amended.

ccc. **Externally funded research** – means all externally funded research including grants, contracts and cooperative agreements. External sponsors include but are not limited to PHS-Awarding Components (e.g., NIH, NCI) or other federal funding agencies (e.g., DoD, NSF) foundations, private companies and individuals.

ddd. **Family Member** – means the spouse or dependent children of an Investigator.

eee. **Federalwide Assurance (FWA)** – means a written agreement that establishes standards for Human Subjects' Research as approved by the Office for Human Research Protections and is executed by the institutional official.

fff. **Financial Conflict of Interest** – means a significant financial interest that could directly and significantly affect the design, conduct or reporting of the results of the research.

ggg. **Financial Interest** – means anything of monetary value whether or not the value is readily ascertainable.

hhh. **Financially Interested Individual** – means a covered individual who holds a significant financial interest that would reasonably appear to be affected by the human subject's research.

iii. **Finders' Fees** – means money paid for recruiting subjects on a per subject basis.

jjj. **Finding of Non-Compliance** – means Non-compliance determined by the IRB to be true.

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

lll. **Food and Drug Administration (FDA)**

mmm. **FDA category A Device** – means Experimental/Investigational. Category A devices are novel first of a kind technology: an innovative device for which the absolute risk of the device has not been resolved.

nnn. **FDA category B Device** – means Non-experimental/Investigational. Category B devices are new generations of proven technology.

ooo. **Full Board Review** – means review of research involving human subjects conducted by the full IRB Board at a convened meeting where quorum is present and is in accordance with the requirements set forth in 45 CFR 46.108.

ppp. **Generalizable knowledge** – means refers to principles, statements, ideas that can be applied to our experiences. Generalizable knowledge refers to clinical practice or teaching, which are used for the well-being or knowledge of an individual.

qqq. **Geocoding** – means the process of transforming a description of a location—such as a pair of coordinates, an address, or a name of a place—to a location on the earth's surface. The resulting locations are output as geographic features with attributes, which can be used for mapping or spatial analysis.

rrr. **Good Clinical Practice (GCP)** – means an international standard for the design, conduct, performance, Monitoring, auditing, recording, analysis, and reporting of clinical trials. It ensures that data reported are credible and accurate and that

subjects' rights and confidentiality are protected. The Good Clinical Practice Program is the focal point within FDA for issues arising in human research trials regulated by FDA.

sss. **Group Practice** – means (defined for this policy) is a group of physicians practicing in the same specialty that uses a combined medical record facility and combined billing for professional services

ttt. **Guardian** – means an individual, who is legally authorized under applicable state or local law, to consent on behalf of a Child or an adult cognitively impaired; to general medical care.

uuu. **Health Insurance Portability and Accountability Act (HIPAA)** – means Health Insurance Portability & Accountability Act (HIPAA) was enacted April 14, 2003. A federal law which is intended to protect all "individually identifiable health information" held or transmitted by a covered entity or its business associate, in any form or media, whether electronic, paper, or oral. Signed authorization must be obtained unless the Institutional Research Privacy Board (IRB) has otherwise designated that this is not necessary.

vvv. **Honest Broker** – means an individual or system who collects and provides de-identified information/samples to a recipient secondary researcher. The Honest Broker collects and collates pertinent information regarding the tissue source, replaces identifiers with a code, and releases only coded information to the researcher. The Honest Broker retains a code which enables him/her to re-identify a donor should the donor choose to later withdraw, or should it be determined that an actionable result or incidental finding should be returned to the participant. For Protected Health Information, the Honest Broker should de-identify data or samples according to HIPAA safe harbor standards before sending it to the researcher. The Honest Broker should not be involved with the recipient's study or co-author on resulting research publications.

www. **Human Biological Specimens and Data** – means these may be deposited in a Research Repository and include, but are not limited to the following:

i. Biological products (organs, tissues, bodily fluids, cells, and other body specimens) obtained through intervention or interaction with a living individual for the purpose of research.

ii. Discarded tissues such as surgical/pathology specimens, organs, tissues, bodily fluids, cells, and other bodily specimens.

iii. Private information (e.g., clinical/treatment notes and related medical information) that can be identified with an individual subject. This includes private information provided for specific purposes by an individual subject, which the individual can reasonably expect will not be made public.

iv. Specimens/data obtained from voice, video, digital or image recordings.

v. Data obtained from surveys, interviews, focus groups, program evaluations, quality assurance/improvements.

xxx. **Human Research Protection Program (HRPP)**

yyy. **Human Research Protection Department (HRPD)**

zzz. **Human Subject** – means as defined by DHHS: a Human Subject is a living individual about whom an investigator (whether professional or student) conducting Research obtains (1) data through Intervention or Interaction with the individual, or (2) Identifiable Private Information (45 CFR 46.102(f)). If the Research involves a medical device, individuals are considered "subjects" when they participate in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control (21 CFR 812.3(p)).

As defined by FDA: An individual who is or becomes a participant in Research, either as a recipient of the Test Article or as a control. A subject may be either a healthy human or a patient 21 CFR 56.102(e). If the Research involves a medical device, individuals are considered "subjects" when they participate in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control (21 CFR 812.3(p)).

aaaa. **Human Subjects Research** – includes all research meeting the definition of "research" performed with "human subjects' as these terms are defined in the federal Common Rule (45 CFR Part 46 and 21 CFR Part 56) regardless of the source of funding or whether the research is otherwise subject to federal regulation. In the event that the Common Rule definitions of "human subjects" or "research" are modified through rulemaking, any such revisions shall apply for the purposes of this guidance.

bbbb. **Identifiable** – means Federal regulations define Identifiable to mean that the identity of the individual subject is or may readily be ascertained by the investigator or may be associated with the information.

cccc. **Immediate Family Member** – Immediate family includes spouse or domestic partner, all dependent children (step, biological, wards) of the IRB Member, siblings, parents, and guardians.

dddd. **Incentive** – means payment for time and discomfort.

eeee. **Individual Conflict of Interest (I-CoI)** – A circumstance such that any action or decision in which an individual is substantially involved may have a direct or predictable effect on a financial interest of the individual, immediate family Member, or organization in which the individual serves as an officer, trustee, partner, or employee.

ffff. **Information Sheet** – means a simplified explanation of the major points of the research. An Information Sheet is not signed by the Child nor used to obtain verbal Assent. An appropriate Information Sheet may be used when Assent has been waived by the IRB and the Child would benefit from being informed about the study.

gggg. **Informed Consent** – means an individual's voluntary agreement, based upon adequate knowledge and understanding of the relevant information, to participate in research either for themselves or for a Child for whom they are the Parent or Guardian (defined as an individual who is authorized under applicable State or local law to consent on behalf of a Child to general medical care).

hhhh. **Institutional Review Board Committee Member** - An individual serving as an IRB Committee Member including Chairs and Vice-Chairs, alternates or expert protocol or scientific consultants regardless of voting privileges.

iiii. **Institutional Review Board (IRB)** - An administrative body established by a local institution to protect the rights and welfare of Human Subjects recruited to participate in Research activities conducted under the auspices of the institution.

jjjj. **Institutional Review Board (IRB) of Record** – means a term utilized when an institution assumes the IRB responsibilities for a Human Subject Research protocol conducted at another institution. An IRB Authorization Agreement signed by institutional officials at both institutions is required.

kkkk. **Intellectual Disability** – Means that the limitation or incapacity was caused by a problem that started any time before a child turns 18 years old. It is not part of the normal growth and development of a child. Is considered a special population and requires a Guardian or Parent for Informed Consent.

llll. **Interaction** – means includes communication or interpersonal contact between an Investigator or his/her Research staff and the Research participant or their private identifiable information**.**

mmmm. **Intervention** – means includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subjects' environment that are performed for Research purposes. As defined by FDA: A process or action that is the focus of a clinical study. Interventions can include drugs, medical devices, procedures, vaccines, and other products that are either investigational or already available. Interventions can also include noninvasive approaches, such as, education or modifying diet and exercise.

nnnn. **Interventional clinical research** – means any prospective study involving human subjects that is designed to answer specific questions about the effects or impact of a particular biomedical or behavioral intervention (i.e., drugs, devices, treatments or procedures, behavioral or nutritional strategies), or designed to answer specific questions about human physiology.

oooo. **Interventional Studies** – means include research designed to evaluate the safety, effectiveness, or usefulness of therapies (e.g., drugs, diet, exercise, surgical interventions, or medical devices), diagnostic procedures (e.g., CAT scans or prenatal diagnosis through amniocentesis, chorionic villi testing, and fetoscopy) or preventive measures (e.g., vaccines, diet, or fluoridated toothpaste). Interventional studies also include studies that include procedures with risk that are done solely for research purposes and are of no benefit to the participant (e.g., bone marrow aspiration or bronchoscopy in normal volunteers).

pppp. **Investigational New Drug (IND)**

qqqq. **Investigational Device** – means the US FDA defines an investigational device as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

i. recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,

ii. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

iii. intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

Please note: Software (e. g. software that controls a pacemaker) is considered a device.

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

ssss. **Investigational Device Exemption(s) (IDE) Number** – means the FDA assigns a special identifier that corresponds to each device granted an IDE.

tttt. **Investigator** – means the Project Director or Principal Investigator and any other person regardless of title or position, who is responsible for the design, conduct, or reporting of research funded by the PHS or proposed for such funding, which may include, for example, collaborators or consultants, and all senior/ key personnel on a project regardless of funding.

uuuu. **Legally Authorized Representative (LAR)** – means an individual, judicial or other entity authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the Research. The term Legally Authorized Representative may include a person properly appointed by an advanced directive (such as a living will or declaration) or a durable power of attorney for health care, certain court appointed Guardians, and next of kin identified below in certain circumstances. Documentation of a person's status as a Legally Authorized Representative for a Research subject is required and must be carefully evaluated to determine the validity of the appointment and scope, if any, of authority granted to make decisions regarding procedures involved in the Research. For example, the existence of a durable power of attorney for health care or advanced directive for health care may not create a Legally Authorized Representative for any or certain kinds of Research decisions. The Legal Department shall be consulted by the IRB and investigator if there are any questions related to a Legally Authorized Representative consent.

vvvv. **Life-threatening Emergency** – means diseases or conditions where the likelihood of death is high unless the course of the disease or condition is interrupted.

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

xxxx. **Member** – means a person who is appointed as a Member of the IRB with the right to participate in all discussions. A Member of the IRB may be voting or non-voting.

yyyy. **Minimal Risk** – means the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(j) and 21 CFR 56.102i).

zzzz. **Minimal Risk for Prisoners** – 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 examinations of healthy persons. Please refer to (45 CFR 46.303, HHS definition).

aaaaa. **Minor Amendment** – means a proposed change in research related activities that does not materially affect an assessment of the risks and benefits of the study and does not substantially change the specific aims or design of the study.

bbbbb. **Minor Non-Compliance** – means non-compliance that is neither serious nor continuing. An example of Minor Non-Compliance includes failure to comply with Ballad Health IRB policies that is administrative in nature (for example, turning in a report of an unanticipated problem a day late, failure to date a consent form or use of a consent form contextually identical to the IRB approved consent form, but without the presence of the IRB approval stamp).

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

ddddd. **Monitoring** – means reviewing a clinical study to ensure proper conduct, records, and reports are performed as stated in the IRB approved protocol. It also involves the review of clinical research standard operating procedures, Good Clinical Practices, and regulatory requirements.

eeeee. **National Institutes of Health (NIH)**

fffff. **Neonate** – means a newborn, birth to twenty-eight (28) days of life.

ggggg. **Non-Compliance** – means any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with federal regulations or the requirements or determinations of the IRB. Non-compliance actions may range from minor to serious, be unintentional or willful, and may occur once or more than once. The degree of non-compliance is evaluated on a case-by-case basis and will take into account such considerations as to what

degree subjects were harmed or placed at an increased risk and willfulness of the non-compliance. Examples include but are not limited to: Failure to obtain IRB approval; inadequate or non-existent procedures for the informed consent process; inadequate supervision; failure to follow recommendations made by the IRB; failure to report adverse events or protocol changes; failure to provide ongoing progress reports; or protocol deviations.

hhhhh. **Non-interventional Studies** – means studies on normal human functioning and development that involve limited invasive or noninvasive procedures, e.g., blood or urine collection, moderate exercise, fasting, feeding, sleep, learning, responses to mild sensory stimulation, surveys or questionnaires, etc. are, for the purposes of this policy, considered non-interventional studies.

iiiii. **Non-Serious Adverse Event** – means any event that causes interference with routine daily activities without major discomfort and these interferences do not persist. Non-serious events also include events that are easily tolerated and do not affect participation in routine daily activities.

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

kkkkk. **Non-Study Related Event** – means an event that would occur regardless of participation in the protocol.

lllll. **Non-Viable Neonate** – A neonate after delivery that, although living, is not able to sustain life.

mmmmm. **Non-Voting Member** – means a person who is appointed to the IRB with the right to participate in all discussions, but who does not vote or count in the quorum.

nnnnn. **Observational Studies** – means includes research that does not involve any intervention, alteration in standard clinical care or use in participants of any invasive or non-invasive procedure. Studies limited to the recording of data on individuals receiving standard medical care, the use of existing specimens or data, or the retrospective review of health information are, for the purposes of this policy, considered observational studies.

ooooo. **Off-Label Use** – means the use of an FDA approved drug for a use that is not included in the approved label. This also includes the use of a drug for an approved illness or condition in an unapproved age group or at an unapproved dose.

ppppp. **Office for Human Research Protections (OHRP)** – means the division of DHHS responsible for providing leadership on human Research participant protections and implementing a program of compliance oversight for DHHS (45 CFR 46).

qqqqq. **Parent** - means generally a Child's biological or adoptive Parent. Foster Parents are not authorized to give research consent.

rrrrr. **Permission** - means the agreement of the Parent(s) or legally authorized Guardian to the participation of a Child in research. This term is often used to emphasize that the Parent is not the subject of the research. In this context Permission has the same meaning as consent.

sssss. **Phase 1 Studies** – means usually conducted in healthy volunteers; however, for more toxic drugs they are often done in patients who do not have any other approved or investigational treatment options. The goal is to determine what the most frequent side effects and, in some studies, how the drug is metabolized and excreted. The number of subjects typically ranges from 20 to 80. Treatment effects are not part of the assessment in Phase 1 Studies.

ttttt. **Phase 2 Studies** – means if Phase 1 Studies don't reveal unacceptable toxicity. While the emphasis in Phase 1 is on safety, the emphasis in Phase 2 is on effectiveness. This phase aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a placebo or a different drug. Safety continues to be evaluated, and short-term side effects are studied. Typically, the number of subjects in Phase 2 Studies ranges from a few dozen to about 300.

uuuuu. **Phase 3 Studies** – means if evidence of effectiveness is shown in Phase 2. These studies gather more information about safety and effectiveness, studying different populations and different dosages and using the drug in combination with other drugs. The number of subjects usually ranges from several hundred to about 3,000 people.

vvvvv. **Phase 4 Studies** – means if after a drug is approved. They may explore such areas as new uses or new populations, long-term effects, and how participants respond to different dosages.

wwwww. **Placebo** – means an inactive substance that may resemble an active agent but has no medical value.

xxxxx. **Placebo-Controlled Trial** – means is a trial in which treatment with a Placebo is compared with treatment with a test drug/treatment. A Placebo-Controlled Trial can be single blind, double blind, or open label.

yyyyy. **Pregnancy** – means the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of Pregnancy, such as missed menses, until the results of a Pregnancy test are negative or until delivery (45 CFR 46.202, Subpart B).

zzzzz. **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. Ankle bracelets or in home restrictions are considered incarceration. Internment in a facility for psychiatric

illness or substance abuse is considered to meet the criteria for incarceration if the commitment has been made as an alternative to a criminal prosecution or incarceration. However, if an individual is in mental health or substance abuse facility is not considered incarcerated if he/she has voluntarily committed his/herself or has been civilly committed. Probation and parole are usually not considered as incarceration unless the parolee is detained in a treatment center as a condition of parole.

aaaaaa. **Private Information** – means includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place. It includes information, which has been provided for specific purposes by an individual, and the individual can reasonably expect will not be made public (e.g., a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order to be considered information to constitute Research involving human participants. An identifiable biospecimen is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen. Private Information also includes all Protected Health Information (PHI).

bbbbbb. **Project Director or Principal Investigator (PD)/(PI)** – of a research project. In funded research, the PD/ PI is included in the definition of senior/key personnel and investigator.

cccccc. **Protocol Deviation** – means any alteration/modification to the IRB-approved protocol that is not approved by the IRB prior to its initiation or implementation.

dddddd. **Protocol Exception** – means a temporary deviation from the protocol that has been approved by the IRB before its initiation. Protocol exceptions are usually for a specific participant (e.g., allowing enrollment of a participant who is close to, but outside of, the age eligibility).

eeeeee. **PHS-Funded Research** – means all research which is sponsored by the Public Health Service of the U.S. Department of health and Human Services and any components of the National Institutes of Health (NIH), the Center for Disease Control (CDC), the Food and Drug Administration (FDA) and the Agency for Health-care Research and Quality (AHRQ).

ffffff. **Propriety Interest in the Tested Product** – means property or other financial interest in the product including, but not limited to, a patent, trademark, copyright or licensing agreement.

gggggg. **Quality Improvement** – means the framework used to systematically improve patient care / outcomes. Quality improvement seeks to standardize processes and structure to reduce variation, achieve predictable results, and improve research workflows within the healthcare system.

hhhhhh. **Rebuttable Presumption Against Financial Interest in Human Subjects Research** – means Ballad Health will presume, in order to assure that all potentially problematic circumstances are reviewed, that a financially interested individual may not conduct the human subjects research in question. This rule in

not intended to be absolute: a financially interested individual may rebut the presumption by demonstrating facts that, in the opinion of the COI Committee, constitute compelling circumstances. The individual would then be allowed to conduct the research under conditions specified by the COI Committee and approved by the Ballad Health System Institutional Review Board (IRB).

iiiiii. **Reimbursement** – means refers to Remuneration for expenses incurred by study subjects such as parking, transportation, or meals while participating in a research study.

jjjjjj. **Remuneration** – means is any payment in dollars or items of value given to subjects participating in a study. It includes both Reimbursement of expenses and payment for time and discomfort (Incentives). It does not include study medications or supplies that are necessary for the conduct of the study. Remuneration may be considered taxable income to the research participant regardless of the dollar amount.

kkkkkk. **Reporting** – means the provision of information about significant financial interest in human subjects' research by a covered individual to responsible institutional official and to the Ballad Health COI Committee, or the transmission of such information within institutional channels (e.g., from the COI Committee to the Ballad Health IRB).

llllll. **Repository PI** – means the principal investigator responsible for oversight of a Research Repository.

mmmmmm. **Repository Protocol** – means the operation of the repository as a storage and data management center.

nnnnnn. **Research** – means as defined by DHHS under 45 CFR 46.102(l) research is any systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. As defined by the FDA under 21 CFR 56.102(c), a clinical investigation (research) involves a test article and one or more human subjects. Research designates activities that are designed to test a hypothesis and conclusions are allowed to be formed to develop or contribute to Generalizable Knowledge.

i. Use of a drug other than the use of an approved drug in the course of medical practice (21 CFR 312.3 (b)).

ii. Use of a medical device other than the use of an approved (means approved by the FDA for marketing) medical device in the course of medical practice (Federal Food, Drug and Cosmetic Act 21 U.S. C. §530 (g)(3)(a)(i)).

oooooo. **Research Activities Involving Human Subjects** – means activities that either (1) meet the DHHS definition of "Research" and involve "Human Subjects" as defined by DHHS OR (2) meet the FDA definition of "Research" and involve "Human Subjects" as defined by FDA. The IRB is in compliance with the Department of Health and Human Services (DHHS) revised Common Rule 2018 Requirements. Any studies given IRB approval for Research prior to January 21, 2019, will fall under the Pre-2018 Requirements of the DHHS Common Rule

pppppp. **Research Misconduct** – means fabrication, falsification, plagiarism in proposing performing or reviewing research or in reporting research results.

qqqqqq. **Research Protocol** – means the use of data or specimens in research. Individual Research Protocols must be submitted to the IRB for each research study that proposes to use data or specimens from the repository.

rrrrrr. **Research Repository** – means a collection of any human biological specimens and/or data that are individually identifiable and intended to be used for research. The terms tissue/specimen bank, data bank, registry, or library are all considered "repositories" for IRB purposes if it involves the accumulation, storage, and later distribution of data and/or biological specimens for future research.

ssssss. **Responsible Institutional Official** – means the Institutional Official who is responsible for the oversight of research programs within Ballad Health System.

tttttt. **Responsible IRB** – is the Ballad Health System Institutional Review Board with jurisdiction over the research as specified in the federalwide assurance (FWA) that Ballad Health System has provided to the U.S. Department of Health and Human Services.

uuuuuu. **Secondary Recruitment** – means refers to asking a study subject for identifying information about friends or family members with the intent to contact them as potential additional research subjects.

vvvvvv. **Secondary Research** – means Secondary research is research with existing specimens/data initially collected for purposes other than the planned research. The specimens/data might have initially been collected for non-research purposes or as part of a different research protocol. Secondary research is encouraged since it maximizes the utility of data and specimens while minimizing risk to subjects since no new procedures will need to be performed.

wwwwww. **Senior/Key Personnel** – means the PD/PI and any other person identified as senior/key personnel by the Institution in the grant application, progress report, or any other report submitted to the funding agency.

xxxxxx. **Serious Adverse Events (SAE)**: (21 CFR 312.32(a)) Adverse events that result in any of the following outcomes: death; a life-threatening experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; or a congenital anomaly/birth defect. In addition, events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Although death is a serious adverse event, the reporting requirements are different.

i. Death is when a person dies while enrolled in a research protocol. Deaths which occur after the subject's research participation has ended do not need to be reported to the IRB unless the death is related to study participation.

yyyyyy. **Serious Non-compliance** – means an action or omission in the conduct or oversight of research involving human subjects that affects the rights and welfare of participants, increases risks to participants, decreases potential benefits or

compromises the integrity or validity of the research. Examples of Serious Non-Compliance include but are not limited to: Conducting non-exempt research without Ballad Health IRB approval; enrollment of subjects that fail to meet the inclusion or exclusion criteria of the protocol, that in the opinion of the Ballad Health IRB Chair, Vice Chair(s), or convened IRB increase the risk to the subject; or enrollment of research subjects while study approval has lapsed; or major protocol deviations that may place subjects at risk from the research.

zzzzzz. **Severely Debilitating** – means diseases or conditions that cause major irreversible morbidity. Examples of Severely Debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis, or stroke.

aaaaaaa. **Significant Equity Interest in the Sponsor of a Covered Study** – means any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a non-publicly traded corporation), or any equity interest in a publicly traded corporation that exceeds $50,000 during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.

bbbbbbb. **Significant Financial Interest** – means a financial interest consisting of one or more of the following interests of the investigator (an/or those of the Investigator's Spouse and dependent children) that reasonably appears to be related to the Investigator's institutional responsibilities:

i. With regard to any publicly traded entity a significant financial interest exists if the value of the remuneration received from the entity in the twelve months preceding the disclosure when aggregated exceeds $5,000. Remuneration includes salary and any payment for services not otherwise identified as salary (e.g., consulting fee, Honoria, paid authorship); equity interest includes any stock, stock option, or other ownership interest as determined through reference to public prices or other reasonable measures at fair market value.

ii. With regard to any non-publicly traded entity a significant financial interest exists if the value of any remuneration received from the entity in the twelve months preceding the disclosure when, when aggregated, exceeds $5,000, or when the Investigator (or Investigator's Spouse or dependent children) holds an equity interest (e.g. stock, stock option, or other ownership interest); or Intellectual Property Rights and Interest (e.g. patents, copyrights) upon receipt of income related to such rights and interest.

iii. Investigators must also disclose the occurrence of any reimbursed or sponsored travel i.e. (that which is paid on behalf of the Investigator and reimbursed to the Investigator so that the exact monetary value may not be readily available), related to the institutional responsibilities except for travel that is reimbursed or sponsored by a federal , state or local government agency, and Institution of higher education (as defined by 20 USC 1001 (a)), an academic teaching hospital, a medical center, or a research institute that is affiliated with an Institute of higher education.

iv. Significant Financial Interest does **not** include:

v. salary, royalties, or other remuneration paid by Ballad Health Systems to the Investigator if the Investigator is currently employed or otherwise appointed by the Institution, including intellectual property rights assigned to Ballad Health and agreements to share in royalties related to such rights;

vi. Income from investments vehicles, such as mutual funds and retirement accounts, as long as the Investigator does not directly control the investment decisions made in these vehicles;

vii. income from seminars, lectures, or teaching engagements sponsored by a federal, state, or local government agency, or an institution of higher education; or

viii. income from service on advisory committees or review panels for a federal, state, or local government agency, an institution of higher education as defined as 20 USC 1001 (a), an academic teaching hospital, a medical center or research institute that is affiliated with an institution of higher education.

ccccccc. **Significant Payments of Other Sorts** – means payments made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or Honoria) during the time the clinical investigator is carrying out the study and/or 1 year following the completion of the study.

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

eeeeeee. **Single Institutional Review Board (sIRB)** – means the selected IRB of record that conducts the ethical review for participating sites of the multi-site study.

fffffff. **Sponsor** - means a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

ggggggg. **Sponsor-Investigator** – means an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a

sponsor- investigator under this part include those of an investigator and those of a sponsor.

hhhhhhh. **Sponsor of the Covered Study** – means the party supporting a particular study at the time it was carried out.

iiiiiii. **Standard Operating Procedure (SOP)**

jjjjjjj. **Study Related Event** – means an event that is related to participation in the protocol. The event can be study-related or possibly study-related and, in the opinion of the investigator, it was more likely than not the result of the research interventions/interactions, or the result of the collection/use of identifiable private information for the research (i.e., there is a reasonable possibility that the event may have been caused by participation in the research).

kkkkkkk. **Sub-investigator (Sub-I)** – means a term used to identify study team members who perform critical clinical trial-related procedures and/or make important trial-related decisions. Generally, these are also study Co-Is, but other study team members with critical and important trial-related roles may serve as Sub-investigators. Roles for the Sub-I can be found in the Key Delegation Log.

lllllll. **Subject Privacy** – means a person's desire to control the access of others to themselves. For example, a person may not wish to be seen entering a place that might stigmatize them, such as a pregnancy counseling center.

mmmmmmm. **Suspension** – means when research on an approved protocol is partially or completely stopped pending future action by the IRB. Examples include: an unanticipated problem in research involving greater than minimal risks to subjects or others; unexpected serious harm to subjects; or when the IRB is investigating a research protocol for possible issues of human subjects' non-compliance or continuing non-compliance with federal regulations, or with the determinations of the IRB. Suspended protocols remain open and require continuing review.

nnnnnnn. **Terminations** – means the IRB permanently stops some or all research procedures associated with an active approved protocol.

ooooooo. **Test Article** – means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to FDA regulation.

ppppppp. **Transitional Device** – means transitional device is a device subject to section 520(l) of the FD&C Act, 21 U.S.C. §360j(l), and which FDA previously regulated as a new drug or an antibiotic drug before May 28, 1976.

qqqqqqq. **Unanticipated Problem (UaP)** – means involving risks to subjects or other includes any incident, experience, or outcome that meets all of the following criteria:

i. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; and

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

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

i. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

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

iii. Is related or possibly related to an individual's participation in the research.

sssssss. **Unexpected Adverse Events (UAE)** – (21 CFR 312.32) Any adverse event, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigative plan (i.e., research plan) or elsewhere in the current application including the consent form, as amended. "Unexpected", as used in this definition, also refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

i. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents.

ttttttt. **Viable Neonate** – means able to survive by independently maintaining their own respiration and heartbeat.

uuuuuuu. **Voting Member** – means a person who is appointed to the IRB with the right to vote and count in determining the quorum at a convened meeting.

vvvvvvv. **Waiver of Authorization** – means the determination and documentation that the Hospital obtains from the IRB that states that the IRB has waived or altered the Privacy Rule's requirement that an individual must authorize the Hospital to use or disclose the individual's PHI for research purposes.

wwwwwww. **Washout Period** – means a period of time without active treatment, usually scheduled prior to initiation of Placebo and active treatment arms. This can refer to a protocol required period of withdrawal from treatment before active treatment starts.

2. **Mission and Purpose of the HRPP**

   a. The mission of the HRPP is to protect the rights and welfare of research participants in research under the oversight of Ballad Health. This includes research conducted at any site that a Ballad staff member agrees to review multi-site research. The HRPP's goals are to promote compliance with relevant legal requirements and ethical standards at all levels, while also addressing the needs and concerns of researchers and enhancing support of their endeavors.

   b. The Vice President for Academics and Research serves alongside the Institutional Official (IO) for human research oversight, HRPP has been established as an integrated system consisting of research leadership, administration, and oversight functions. The oversight component includes education and training; quality assurance and compliance; research review units, including institutional review boards (IRBs); and other organizations charged with responsibility for protecting research participants and promoting excellence in all aspects of human research.

3. **Scope of Human Research at Ballad Health**

   a. Types of Human Research Conducted

      i. Ballad Health supports a broad range of human research including, but not limited to biomedical research, clinical trials, behavioral research, research with vulnerable populations, and genomic research.

   b. Categories of Participants

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

   c. Authority Under which the HRPP Operates

      i. Institutional Authority

         1) The Ballad Health's Chief Physician Executive has assigned the VP of Academics and Research and the VP of Research Operations (Leadership Dyad) the responsibility to maintain a FWA between Ballad Health and United States Department of Health and Human Services, through its Office for Human Research Protections. In that assurance, Ballad Health pledges to comply with Federal regulations for all federally supported research.

         2) The Leadership Dyad, on behalf of Ballad Health have established the IRB and grant the IRB authority to approve, require modifications to secure approval, and disapprove all research activities overseen and conducted by Ballad Health. The IRB functions in coordination with Ballad Health

leadership officials and other committees but always maintains their independence. Individuals who are responsible for Ballad Health business development are prohibited from serving as members of the IRB or carrying out day to day operations of the review process.

ii. Limitations on Institutional Authority

1) All human research conducted by Ballad Health must be approved by Ballad Health IRB or granted an exemption as specified in the IRB's standard operating procedures. Master Reliance Agreements may be established with partnered organizations under certain circumstances. Research that has been reviewed and approved by an external IRB may be subject to further review and approval, by other review bodies or officials (Leadership Dyad); however, no person or organization may override an IRB's disapproval determination.

4. **Ethical Principles**

a. The Leadership Dyad has set forth that for all human research at Ballad Health, regardless of funding source, will be guided by the ethical principles set forth in the National Commission for the Protection of Human Subjects Research (Belmont Report) and will comply with applicable Ballad Health policies and Federal, State, and local laws and regulations.

b. Respect for Persons

i. Research protocols must say how subjects will be recruited.

ii. Subjects must freely agree to participate after receiving complete information about the research and its risks, potential benefits and alternatives.

iii. Subjects must fully understand their rights including the right to discontinue at any time without loss of otherwise available benefits.

iv. Vulnerable populations (fetuses, children, prisoners, those without decisional capacity, and those with economic or educational vulnerability) must receive special consideration and protection.

v. Minimizing Risks and Avoiding Unreasonable Risks

vi. Research may not expose subjects to unreasonable risk of harm (whether physical, psychological, social, legal or economic in nature).

vii. The probability and magnitude of possible harm must be reasonable in relation to the anticipated direct or indirect benefits of participation in any research project.

viii. Identifiable risks that practicably could be avoided without undermining legitimate research objectives must be eliminated.

ix. Sound research designs that minimize risks and maximize benefits of participation must be used.

x. Equitable Recruitment and Selection of Subjects

xi. Research protocols must promote equitable recruitment and selection of subjects, as applicable, with the overall goal of ensuring fair distribution of

the burdens and benefits of research. Subjects should be selected for participation for reasons directly related to the questions under study.

xii. Subjects must not be induced to participate in research projects by means or under circumstances that may overcome the voluntary nature of their participation. Enrollment into a study may never be the product of coercion or undue influence.

c. The Belmont Report principles and their application to human research summarized.

i. Respect for Person

1) Respect for persons requires that protocols (including the informed consent process) be designed to promote personal capacity to consider alternatives, make choices, and act without undue influence or interference from others. The principle is reflected in federal regulations and policy through requirements that legally effective informed consent be sought and obtained unless specific requirements for waiver of informed consent are met and appropriately documented; and that subjects with diminished capacity and others who are vulnerable to coercion or undue influence receive special protection or consideration.

ii. Beneficence

1) Beneficence entails an obligation to protect individuals from harm. The principle can be expressed in two general rules: (1) do no harm; and (2) protect from harm by maximizing possible benefits and minimizing possible risks of harm. It is reflected in federal regulations and policy through a requirement that principal investigators design, and IRBs approve protocols only under circumstances where the benefits to the subjects and the importance of the knowledge to be gained justify the risks to the subjects sufficiently to warrant a decision to allow the subjects to accept those risks.

iii. Justice

1) Justice requires fairness in distribution of burdens and benefits. The principle is often expressed in terms of treating persons of similar circumstances or characteristics similarly. It is reflected in federal regulations and policy through requirements that selection of subjects is equitable and is representative of the group(s) that is intended to benefit from the research.

d. Nuremberg Code

i. The history of human subject protections began in 1949 with the Nuremberg Code. It was published by the Nuremberg Military Tribunal as standards by which to judge the human experimentation conducted by the Nazis. The Code captures ten basic principles governing the ethical conduct of research involving human subject including voluntary consent, the balance of risks and benefits, freedom from coercion, minimizing risks, and sound scientific design.

e. Declaration of Helsinki

i. In 1964, the World Medical Association made recommendations similar to the Nuremberg Code, in a document entitled, the Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects. This document has been revised several times since 1964. Importantly, this document added to the principles of the Nuremberg Code in that it distinguishes therapeutic trials from non-therapeutic trials. It also introduced the idea of an independent ethical committee reviewing research studies.

f. Department of Defense

i. This regulation applies to studies regulated by the Department of Defense. A copy of the directive can be found at: https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/321602p.pdf

g. Additional ethical codes and guidelines, including ethical codes of professional societies, may also provide insight into ethical research.

5. **Human Research Protection Program**

a. HRPP / IRB Staff Protection from Undue Influence

i. Ballad Health will investigate and resolve any reported attempt to inappropriately pressure (i.e. to exercise undue influence upon) an IRB or HRPP team member because of that individual's role. "Undue influence" refers to interference with the normal functioning and decision-making of the IRB / HRPP process or staff member, outside of established processes or through normal and accepted methods, in order to secure a particular determination or outcome. Any attempt to exercise undue influence over IRB / HRPP staff should be reported as follows:

1) Any IRB / HRPP staff member who experiences undue influence should first report the occurrence to the HRPP Director or Leadership Dyad as necessary or appropriate.

2) An IRB chair / member who experiences undue influence should first report the occurrence to the HRPP Director, who will attempt to mediate or resolve the concern, in consultation with the Leadership Dyad.

ii. Any individual who believes that undue influence is being exerted by an official in one of the above reporting chains, or who believes that the undue influence has not been appropriately or timely resolved, should report to the next higher level in the reporting chain and ultimately to the Compliance Department.

b. Operations Manual (OM)

i. Primary location for compiling, organizing, integrating, and pointing to the rules, policies, practices, and guidance encompassing Ballad Health's HRPP. The Leadership Dyad has approved the OM and approves each substantial modification or amendment to it. At least once every 2 years the HRPP Director and Manager initiate a comprehensive review of the OM. Revisions

may be made at any time, however as required by changes in law, ethical standards, institutional policy, quality assurance activities or other considerations. Non-substantive revisions (e.g. to correct typographical errors, update links or incorporate summaries of new or revised laws or regulations governing the HRPP) may be made upon approval of the HRPP Director.

c. IRB and Guiding Principals

i. Ballad Health requires that all human Research projects in which Ballad Health is engaged must be reviewed and approved by Ballad Health IRB. Ballad Health becomes engaged in human Research when its employees, or individuals credentialed to practice within Ballad Health facilities (1) intervene or interact with living individuals for Research purposes; (2) obtain individually Identifiable Private Information for Research purposes; or (3) all projects involving patients, personnel, or resources (property or services) of Ballad Health. A "Human Research" means any activity defined under the DHHS or FDA regulations that meet the definition of "Research" and that involves "Human Subjects" (see definitions below). The definition of Research and Human Subjects must consistently reference the same set of regulations (i.e., DHHS or FDA) and cannot reference the definition of Research from one set of regulations, and the definition of a Human Subject from the other.

ii. Ballad Health IRB has the authority to review, approve, disapprove, waive jurisdiction, or require changes in Research or related activities involving Human Subjects. As stated in 45 CFR 46.109, the IRB has the authority to:

1) Review and approve, require modifications in (to secure approval), or disapprove all Research activities covered by this policy.

2) Require that information given to subjects as part of informed consent is in accordance with 45 CFR 46.116.

3) Require documentation of informed consent or waive documentation in accordance with 45 CFR 46.117.

4) Notify investigators in writing of its decision to approve or disapprove the proposed Research activity, or of modification required to secure IRB approval of the Research activity. If the IRB decides to disapprove a Research activity, it will include in its written notification a statement of the reasons for its decision; however, a detailed critique of the protocol is not provided. The investigator may rewrite and submit the study as a new protocol.

5) Conduct continuing review of Research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year.

6) Have authority to observe or have a third-party observe the consent process or the Research and to review the Research documentation.

7) The IRB also has the authority to suspend or terminate approval of Research that is not being conducted in accordance with the IRB's requirements or that has been associated with serious harm to subjects

(45 CFR 46.113). Any suspension or termination of approval will include a statement of the reasons for the IRB's action and will be reported promptly to the investigator, appropriate institutional officials, and the Department or agency head.

8) The IRB does not have the authority to grant retroactive approval should a Research study be initiated without prior IRB review.

9) No institutional official at Ballad Health can reverse IRB decisions that involve disapproval, deferral, suspension, or termination of a Research study. However, the Ballad Health Institutional Official can disapprove an IRB approved protocol for activation or continuation at Ballad Health.

10) The IRB operates under the rules set forth under DHHS FWA00004221 for Protection of Human Subjects and the Code of Federal Regulations (45 CFR 46) as well as FDA regulations for the performance of all Research activities that involve Human Subjects (21 CFR 50 and 56).

d. The responsibilities of the Institutional Review Board are:

i. To protect Human Subjects from undue risk and deprivation of human rights and dignity.

ii. To disapprove studies of no scientific merit (Belmont Report – Respect of Persons).

iii. To ensure that participation by subjects is voluntary, as indicated by a voluntary and fully informed consent.

iv. To ensure equitable selection of subjects (Belmont Report – Justice).

v. To maintain an equitable balance between potential benefits of the Research to the subjects and/or society and the risks assumed by the subject (Belmont Report – Beneficence).

vi. To determine that the Research design and study methods of a protocol are appropriate to the objectives of the Research and the field of study.

vii. To assist the investigator by providing peer review and institutional approval.

viii. To ensure compliance of protocols with the regulations of the FDA, DHHS, and other funding agencies when appropriate.

ix. Human Subject Research/Non-Human Subject Research Determination

e. Ballad Health IRB has the sole authority to determine whether an activity meets the definition of "Human Subject Research". When activities are conducted that might represent "Human Subject Research", the activities must be submitted to the IRB for a determination. Investigators do not have the authority to make an independent determination and must submit a "Request for Determination of Non-Human Subject Research" to the IRB. An Investigator may request a determination that an activity is "Non-Human Subject Research," but the final determination will be made by the IRB. The IRB will make a determination whether an activity is "Human Subject Research" by considering whether the activity either:

1) Meets the regulatory definitions of "Research" that involves "Human Subjects," or

2) Meets the regulatory definition of "Clinical Investigation."

3) Non-Research

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

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

f. Non-Human Subject (18 HIPAA Identifiers)

i. Activities do not involve humans as participants if they do not involve the process of obtaining specimens or data through Intervention or Interaction with individual participants or Identifiable Private Information. Information is considered "not Identifiable" if it includes none of the following:

1) Name;

2) Any geographic subdivisions smaller than a state, including street address, city, country, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of a ZIP code;

3) All elements of dates (except year) directly related to an individual (e.g., date of birth, admission);

4) Telephone numbers;

5) Fax numbers;
6) Electronic mail addresses;
7) Social security numbers;
8) Medical record numbers;
9) Health plan beneficiary numbers;
10) Account numbers;
11) Certificate/license numbers;
12) Vehicle identifiers and serial numbers, including license plate numbers;
13) Device identifiers and serial numbers;
14) Web Universal Resource Locators (URLs);
15) Internet Protocol (IP) address numbers;
16) Biometric identifiers, including finger and voiceprints;
17) Full-face photographic images and any comparable images; and
18) Any other unique identifying number, characteristic, or code.

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

i. The code is not derived or related to the HIPAA identifiers that must be stripped from the PHI (e.g., patient medical record # + last 4 digits of individuals Social Security Number);

ii. The Private Information or specimens were not collected specifically for the currently proposed Research project through an Interaction or Intervention with living individuals; and

iii. The Investigator cannot readily ascertain the identity of the individuals to whom the coded Private Information or specimens pertain, because:

iv. The key to decipher the code is destroyed before the Research begins;

v. The Investigator and the holder of the key enter into an agreement prohibiting the release of the key to the Investigator under any circumstances, until the individuals are deceased;

vi. The Private Information is received from an IRB-approved repository or data management center that includes written operating procedures that prohibit the release of the key to the Investigator under any circumstances, until the individuals are deceased; or

vii. There are other legal requirements prohibiting the release of the key to the Investigator until the individuals are deceased.

viii. A cadaver is not considered to be a Human Subject. Research involving cadavers must be submitted to the Ballad Health IRB and the IRB will determine which studies qualify as a "Non-Human Subject."

h. Amendments

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

ii. All "Non-Human Subject Research" is subject to all applicable institutional and IRB policies and procedures.

iii. When activities are conducted that might represent "Human Subject Research", the activities must be submitted to the IRB for a determination. Investigators must submit the " Human Subjects Research Determination Form Human Research vs Non-Human Research " in its entirety to the IRB Office for processing. The form and corresponding instructions are located on IRBNet website / IRB Forms and Templates. The Investigator will reply to all requests for revisions and/or clarifications requested by the IRB, when applicable. Investigators must submit any changes that might disqualify an activity from a "Non-Human Subject Research" status. Such changes must not be implemented prior to IRB review. If needed, the Chairperson will be available to assist the IRB staff in determining whether an activity meets the definition of "Human Subject Research." The IRB staff will review the proposed project to determine if the Research qualifies as "Non-Human Subject Research" as defined above. The IRB staff may:

1) Approve the request;

a) Request minor revisions to the submitted documents in order to approve the request, and review and approve the revisions prior to granting final approval; or

2) Disapprove the request.

a) The IRB staff will document the determination and its justification on the Reviewer Comment Form. If the IRB staff disapproves the request, the IRB staff will determine the appropriate level of review, communicate this to the Investigator, and guide the Investigator with the re-submission. If the IRB staff disapproves the request, the IRB staff will sign and send a letter of final approval using the appropriate template. Appropriate database entries will be completed, including notification of approval on the next available agenda.

3) Institutional Oversight of Federalwide Assurance

a) A complete copy of the current Ballad Health Federalwide Assurance (FWA) is maintained in the IRB office and is available for review upon request. The Ballad Health System Vice President of Compliance and Audit Services for Ballad Health System has ultimate responsibility for the institutional commitment made in the institution's Federalwide Assurance (FWA).

iv. In addition, the Ballad Health System Vice President of Compliance and Audit Services of Ballad Health possesses knowledge about the requirements of Federal regulations, applicable state law, the institution's Assurance, and institutional policies and procedures for the protection of Human Subjects.

v. The Ballad Health Assurance is based on the following principles in order to safeguard the rights and welfare of human participants in Research and other Research activities:

1) Ballad Health staff and clinical investigators and their staff operating within Ballad Health facilities are subject to the Assurance and this policy. This includes any Research for which an Assurance or another formal agreement (e.g., IRB Authorization Agreement) identifies Ballad Health IRB as the IRB of Record.

2) Ballad Health agrees to uphold the ethical principles of the Belmont Report to all proposed Research involving human participants. The ethical principles set forth in the Belmont Report are:

3) Ballad Health further agrees to apply additional regulations such as the U.S. Food and Drug Administration Human Subject Regulations (21 CFR 50, 56, 312 and 812), DHHS regulations (45 CFR 46), and the Health Insurance Portability and Accountability Act of 1996 (HIPAA), when applicable, to Research involving human participants.

4) Ballad Health prohibits officials, investigators, employees, and sponsors from attempting to or using undue influence with Ballad Health IRB, any of its members or staff, or any other member of the Research team to obtain a particular result, decision, or action. "Undue influence" means attempting to interfere with the normal functioning and decision-making of Ballad Health IRB or to influence an IRB member or staff, or any other member of the Research team outside of established processes or normal and accepted methods, in order to obtain a particular result, decision, or IRB action.

5) If a Ballad Health IRB Committee member, IRB staff, principal investigator, Research participant, or other individual feels that he/she has been unduly influenced (e.g., coerced to participate, approve a study, or conduct a study), a report should be made to the Ballad Health Chief Medical Officer and/ or designated representative, or to the Ballad Health Ethics Line. The person receiving the report will investigate the allegation and when appropriate, take corrective actions. Appeals related to IRB policies and procedures (including investigator concerns or suggestions regarding the review process) may be reviewed by the CEO and appropriate staff to determine if a change in policy is needed.

vi. Responsibilities of the IRB under the Federalwide Assurance

1) All information provided under the Ballad Health Assurance must be updated at least every 36 months, even if no changes have occurred, in order to maintain an active Assurance approved by OHRP. Amendments to the Assurance must be reported promptly to OHRP. This includes

changes to IRB rosters and the addition or deletion of an IRB Chair or legally recognized entity related to Ballad Health.

2) Changes in IRB membership are reported to OHRP by the IRB Project Manager. An IRB member can only be designated as "non-affiliated" if he/she and or his/her immediate family members do not have any affiliation (including past employment) with institutions within the Ballad Health System.

3) Quality Improvement

a) The HRPP team will systematically and consistently work to improve the workflows and processes within which the researcher(s), study coordinator(s), and directors of research interact with the HRPP / IRB team. They will use multiple different types of assessment tools in order to best understand the workflows to improve the front-line user(s') experience. It is the goal of the HRPP team to ensure that the highest quality of care, respect and time management are given to all persons who interact with the HRPP office. Any results that are collected will be available for the Dyad leadership to review on a quarterly basis.

6. **IRB Membership**

a. Composition

i. Ballad Health IRB may be comprised of Members with multidisciplinary expertise and backgrounds as required by the Federal policy and FDA regulations to provide the expertise needed to review a wide variety of human research studies. The IRB is composed of Members drawn from the following communities:

1) Representatives of the Ballad Health clinical Departments and Centers

2) Representatives of Ballad Health Nursing Department

3) Representatives of Ballad Health Administration

4) Representatives of the Ballad Health Department of Pharmacy

5) Representatives of the community

6) Chair and Vice-Chair(s)

b. Chair and Vice-Chair of the IRB.

i. The Chair of the IRB is appointed by the VP of Research and Academics and the HRPP Director. The IRB Chair does not have a term limit. The Chair can be removed at any time with written notice from the HRPP Director or the VP of Research and Academics. To be considered for IRB Chair the subject must have recent experience as a member of an IRB and have demonstrated regular attendance and participation. Periodic assessment of the Chair will be conducted by the VP of Research and Academics. In addition to the assigned duties as a member of the IRB the Chairperson is empowered to:

1) Ensure that the IRB carries out its responsibilities.

2) Suspend the conduct of a research project or clinical trial that is not being conducted in accordance with the IRB's requirements or that has been associated with serious harm to subjects until such time as the convened IRB has reviewed the project.

3) Assist in investigations of research non-compliance.

4) Facilitate IRB meetings.

5) Review and approve expedited review applications or establish a designee to do so;

6) Work with IRB staff to resolve administrative concerns.

7) Appoint a Vice-Chair with support from the HRPP Director, that were allowed by Federal regulation act in place of the IRB Chair. A delegation of authority letter will be generated by the HRPP office and kept on file.

ii. The Vice Chair of the IRB is appointed by the Chair with support form from the HRPP Director. The Vice-Chair does not have a term limit. The Vice Chair can be removed at any time with written notice from the HRPP Director or the VP of Research and Academics. To be considered for IRB Vice Chair the subject must have recent experience as a member of an IRB and have demonstrated regular attendance and participation. Periodic assessment of the Vice Chair will be conducted by the VP of Research and Academics. The Vice Chair serves as Chair of the IRB in the absence of the Chair, and maintains the same qualifications, authority, and duties as the IRB Chair.

c. Unaffiliated IRB Members

i. An unaffiliated IRB Member is a member who is not affiliated with Ballad Health and who is not part of the immediate family of someone who is affiliated with Ballad Health System. IRB Members with no employment or other relationship to the institutions are questioned about whether their immediate family Members are affiliated with the institution. Unaffiliated Members are selected from the community by nomination. They are interviewed by the IRB staff to inform them about the obligations of being a Board Member and to determine suitability for Board Membership.

d. Alternate Members

i. Alternate Members of the IRB are a vital part of research, community involvement, and overall success of the IRB. Alternate Members must be officially appointed and their role as an Alternate Member must be listed on the Membership roster. Each Alternate Member is permitted to substitute for an IRB Member or a class of IRB Members for whom they have similar background, expertise, and noted on the IRB Roster.

ii. Alternate Members will be subject to the same appointment requirements, terms of service, Conflict of Interest, and responsibilities as regular Members of the IRB. If an IRB Member cannot attend a meeting, his or her alternate will be contacted by IRB Staff as soon as possible so they are aware of the expectation of their voting status.

iii. Alternate Members are required to attend 9 of the 12 IRB meetings that are held, with one being an in-person meeting a year. Alternate Members will be assigned research studies from the IRB Staff to review and present to the board during the meeting. Alternate Members after greater than 12 months serving on the board and are in good standing will be put into rotation to review and approve Expedited Research Studies.

iv. Alternate Members will be given a right of first refusal when a sitting Board Members seat becomes available. If there are multiple Alternate Members that are interested in the available seat, the right of first refusal goes in seniority order.

v. Alternate Members can serve on any IRB that is covered by Ballad Health HRPD. The member may only serve as a sitting Board Member on one active Board at any given time and may serve as an Alternate on any other. Conversely a sitting Board Member may serve as an Alternate Member on another IRB that is served by Ballad Health HRPD.

e. Prisoner Representative

i. When the IRB reviews research that involves prisoners, at least one Voting Member present at the convened IRB meeting must be a prisoner representative with the appropriate background and expertise to serve in that capacity. The prisoner representative must be officially appointed and be listed on the Membership roster, and will be subject to the same appointment, terms of service, Conflict of Interest and responsibilities as regular Voting Members of the IRB.

f. Non-Voting Members

i. The Ballad Health Chief Medical Officer or the Chair of the IRB may appoint Non-Voting Members of the IRB. Non-Voting Members of the IRB will be subject to the same appointment, terms of service, Conflict of Interest, and responsibilities as Voting Members of the IRB. Non-Voting Members do not count toward the meeting quorum.

g. IRB Administrative Staff

i. The Common Rule require that each institution provides its IRB with sufficient meeting space and staff to support the IRB's review and record-keeping responsibilities.

ii. The IRB staff will manage the processing of the application to the IRB; and will establish the operating procedures to promote consistency and efficiency. The IRB staff is required to demonstrate an understanding of the Common Rule as well as the state laws that govern the protection of human subjects in research; comprehend Ballad Health's Institutional commitment under its Federalwide Assurance (FWA); and assist in its administrative duties in maintaining an ethical and compliant program.

iii. The IRB staff will also participate in the same training program in Human Research Protections, which the IRB Members and investigators are required to take.

h. Terms and Conditions of Service

i. Members of the IRB are appointed for a period of three years unless the IRB Chair requests a shorter period of appointment. Members of the IRB may be reappointed to an additional or extended term of service at the discretion of the Chair of the IRB.

ii. Upon appointment to the IRB, a current copy of each Member's Curriculum Vitae (CV) or resume must be provided to the IRB and maintained on file.

iii. Updated copies of Members' CVs/ resumes are requested at the beginning of each calendar year and as re-appointments are made to the IRB.

iv. IRB Members will also complete all required training and continuing education hours.

v. Documentation of this training will be kept on file in the IRB office.

vi. IRB Members will also be asked to sign a Conflict-of-Interest Statement

vii. Members will also receive an IRB Member Handbook which contains the following:

viii. Food and Drug Administration (FDA) Good Clinical Practice Guide

ix. Code of Federal Regulations (CFR) Title 21

x. FDA Information Sheets

xi. International Conference on Harmonization (ICH) Guidelines

xii. Current Policy and Procedure (P&P) for IRB

xiii. Ethics Documents Related to Research

xiv. Members will sign a statement of receipt for this handbook attesting to the fact that they recognize that they are expected to know and understand the information provided and to follow the laws, rules, and guidelines there in contained when making decisions and in the course of fulfilling their duties and responsibilities as IRB Members.

xv. Members of the IRB are preferred to attend all scheduled meetings of the IRB to which they are appointed and participate in the discussion and review of all protocols. Members of the IRB who are not able to attend a scheduled meeting of the IRB should provide sufficient advance notice (at least five working days) to the IRB office of the intended absence(s).

i. Orientation and Education

i. New Members of the IRB will receive a letter of appointment and meet with IRB Project Manager.

ii. The orientation session will review the functions of IRB Members, discuss the confidentiality rules of the IRB, and review the Member Conflict of Interest policy.

iii. Each new Member is provided with an extensive outline of important topics and given various references for information on those topics.

iv. Opportunities for additional education are also provided.

v. IRB Members must have Human Subjects' Protection certification (Documented Training in Human Subjects). Relevant articles are routinely distributed to IRB Members to further their knowledge and educational opportunities are provided by IRB staff to enhance Members' knowledge of regulations and information relating to protection of human subjects.

j. Performance Review

i. The IRB is routinely evaluated for performance, composition, and attendance by the IRB Chair, the IRB Project Manager, and the Vice President.

k. Board Member Performance Review

i. The IRB Chair is evaluated on knowledge of IRB regulations, attendance at Board meetings and other IRB committees, leadership of the IRB, support of the IRB staff, and availability to deal with IRB related issues from investigators.

ii. IRB Vice-Chair(s) are evaluated by the IRB Chair on an ongoing basis. The major criteria for evaluation are knowledge of IRB regulations, attendance at IRB meetings, and availability to substitute for the IRB Chair in his or her absence.

iii. IRB Members are evaluated by the IRB Chair and the Vice Chair on an annual basis. The major criteria are the number of missed Board meetings without advanced notice to the IRB, the number of missed meetings with advanced notice to the IRB, and the overall contribution to the Board discussions.

iv. If any performance review identifies an area that needs correction, this will be discussed with the individual and he or she will be given an opportunity to make corrections. If the individual is not able to improve the deficiency, he or she will be asked to leave the position and a replacement will be appointed.

l. Conflict of Interest for IRB Members, Alternates, Staff and Consultants

i. Federal regulations prohibit a Member of the Institutional Review Board (IRB) from participating in the initial or continuing review of any protocol in which the Member has a "conflicting interest", except to provide information at the IRB's request (45 CFR 46107(e)). This policy applies to IRB Members, alternate Members and IRB staff. Consultants, (ad hoc reviewers who are not IRB Members but sometimes are asked to review a project because of their expertise) who disclose a Conflict of Interest related to the protocol, will be excused from the review of the protocol and the IRB will identify another consultant with the relevant expertise.

ii. IRB Committee Members, alternate Members, consultants, and IRB staff are considered to have a Conflicting Interest if they have any: (a) significant financial interest as defined above; (b) role in the conduct of the research including involvement on the thesis or dissertation committee review; and (c) other individual Conflict of Interest including an immediate family Member or domestic partner of the investigator(s) on the IRB protocol.

iii. Any IRB Member or alternate Member with a Conflicting Interest in a protocol must disclose the conflict to the IRB Chair and leave the room during the discussion of the protocol and the related vote, except if they are providing information at the IRB's request. The absent IRB Member/alternate Member does not count towards the meeting quorum. The meeting minutes will document the recusal (i.e., the temporary absence of the IRB Member/alternate Member during the deliberation and vote on the protocol with respect to which the Member has a conflict).

iv. In the case of expedited IRB review (outside of a convened meeting), the reviewer should disclose any Conflicting Interest in a protocol in advance to the IRB Chair and should not review the protocol. (If the IRB Chair is the reviewer with a conflicting interest, then disclosure should be made to the Vice-Chair).

v. How and when should an IRB Member, alternate or consultant disclose a potential conflicting interest?

vi. When IRB Members or alternate Members receives materials before a meeting, they should review the list of all protocol reviews (initial, continuing review, amendments, and other reviews) with the issue of conflicts in mind and should disclose any potential issue to the Chair in advance of the meeting when possible. At the beginning of each IRB meeting, Members also will be reminded of the conflicts policy and should disclose any potential conflict at that time.

vii. A designated reviewer performing expedited review of projects similarly should review the list of projects and disclose any potential issue in advance to the IRB Chair. (Ad hoc) reviewers/consultants will receive a copy of this policy with materials for the project they are reviewing. The IRB Chair will educate (ad hoc) reviewers/consultants regarding the policy requirements and definitions of Conflict of Interest.

viii. The conflicted Member, alternate, or staff may be present to answer questions during the initial full board discussion but must leave the room for the final discussion and vote.

ix. The IRB Chair will remind the IRB Members of the importance of this conflicts policy at least annually and more often as necessary.

x. It is considered a conflict of interest when a member of the IRB has a direct influence on the business development of Ballad Health or a Ballad Health entity.

m. Consultants

i. The IRB utilizes consultants when it is determined that Members do not have the expertise necessary to review a particular protocol. For example, consultants are asked to provide input to the IRB when Members lack the scientific expertise; or lack the local context cultural competency required to appropriately review a protocol. The Chair, Vice Chair has the authority to consider whether a protocol requires expert consultation and/or a local context reviewer.

ii. In addition, for the review of protocols involving working with vulnerable populations, the IRB administrative office requires one or more individuals who are knowledgeable about or experienced in working with the population. If an IRB Member cannot be identified, then the IRB administrative office would contact an appropriate consultant with special expertise or experience to review the protocol, present the information before the IRB or participate in meeting deliberations.

iii. Determining the need for a consultant will primarily originate during the IRB Office's initial review or pre-review of the protocol but may also result as a request by one or more IRB Members (i.e., during expedited or full board review). When the need for a consultant is established, the IRB Chair, Vice Chair and Project Manager will identify an appropriate consultant, arrange for the review, and require the consultant to provide written documentation of his/her review and comments or concerns in writing to the IRB. The IRB review will be deferred until the consultant has had an opportunity to conduct an in-depth review of the research. A copy of the written communication is provided to each Board Member prior to the meeting for their review. In addition, all written communications between the consultant and the IRB are included in the protocol file.

iv. When a consultant is asked to review a protocol, they are educated by IRB Project Manager, to disclose to the IRB any Conflict of Interest related to the protocol. If they do, they will be excused from the review of the protocol and the IRB will identify another consultant.

v. While it is often sufficient for a consultant to provide his/her comments in writing after reviewing the protocol, the IRB may request a consultant's presence at a full board meeting. In these situations, if a written summary of the review and its findings are not provided to the IRB in advance of the meeting, the key information is provided by the consultant, together with the Board's discussion and deliberation; and their determination, will be recorded in the minutes.

vi. The IRB Office maintains all records of consultant review correspondence in the protocol file. Correspondence may include attachments, correspondence with the IRB office and/or IRB Members, translated documents, amended documents, IRB requests, scientific review, cultural local context review and follow-up documentation from the IRB office to the consultant thanking them for their assistance.

vii. Consultants are usually invited to attend a meeting when the protocol involves greater than minimal risk or highly technical information that is better understood in an in-person format. These individuals participate in the discussion of protocols but do not vote or count toward the quorum.

viii. For expedited and full reviews, a reviewer (IRB Member) can consult with fellow IRB Members with appropriate scientific and/or cultural expertise. The IRB will delay final protocol approval until a suitable expert reviewer is found and the protocol has been adequately reviewed.

7. **IRB Board Meetings & Administration**

a. Board Meetings

i. The IRB is constituted and reviews research involving human subjects according to Federal regulations. Meetings of the IRB will conform to Federal regulations and guidelines for the review of research.

ii. The IRB meets monthly on the second Tuesday of the month. Submissions for review at any monthly meeting are required to be received by the IRB office by noon, three (3) weeks prior to the meeting. Protocols may be submitted to the IRB at any time. An IRBNet package submission does not guarantee discussion and vote at the subsequent IRB monthly meeting.

iii. All Submissions must be complete, for IRB Staff to review package and for placement on the IRB agenda.

iv. If a submission is incomplete the PI and/or Research coordinator and/or designated research staff will be notified of the needed corrections or missing documents.

v. The IRB agenda is locked one (1) week prior to Board meeting.

vi. If the investigator is not known to the IRB, the investigator's credentials will be researched and verified through the Medical Staff office. Any information regarding a FWA (Federalwide Assurance) other than Ballad Health assurance will be verified through the OHRP (Office for Human Research Protections) website. Industry and federally sponsored protocols will be verified using the FDA website.

vii. The protocol and proposed informed consent form will be reviewed by the IRB staff using the protocol checklist. The completed checklist will become a part of the protocol application and available for the IRB members for review.

b. The initial submission will be reviewed by the IRB staff to make sure the following items are present and complete:

i. Investigator and Sub Investigator Current Signed and Dated CV, License and documentation of CITI (Collaborative Institutional Training Initiative) training and other pertinent Research related training;

ii. The Principal Investigator must complete the Investigator responsibilities form;

iii. For any staff other than the PI, that will be conducting the Informed Consent process, documentation of CITI training is also required;

iv. Human Subjects Full Protocol Review Form;

v. Full Protocol and Protocol Synopsis;

vi. Copy of unconditional Food and Drug Administration (FDA) approval letter including FDA issued billing category (if a conditional letter is submitted an unconditional letter is requested once the sponsor has met all of the FDA's (Food and Drug Administration) conditions. Please recognize that submitting a protocol with an FDA conditional approval may result in a longer approval

period from the IRB or could mean repeated submission until all conditions are approved);

vii. Proposed ICF and Separate HIPAA (Health Insurance Portability and Accountability Act) Authorization (if required HIPAA language is not incorporated into the main consent);

viii. Any Surveys, Questionnaires, Patient Diaries or Handouts, Form Letters, Appointment Reminders etc.; and

ix. Patient Recruitment and Advertisement materials.

c. All IRB members will have the ability to review the submission via IRBNet: the protocol application, proposed informed consent documents, patient handouts and recruitment materials. A Scientific and Non-Scientific member of the board will be selected in random to review the packet for presentation to the Board during the meeting. Members are encouraged to review the material in enough depth to be familiar with them and be prepared to discuss them at the convened meeting.

d. IRB Staff will email the random IRB member the submission name, number, and appropriate Reviewer form; for preparation to present at the IRB meeting.

e. In an effort to efficiently and continuously work to better the Ballad Health Community, the IRB Staff will work on processing all submissions to IRBNet expeditiously. This will require good communication between the PI and/ or Research Coordinator. If there has not been any communication received from the Research Coordinator and/or PI after forty-five (45) days of submission an email will be sent noting the inactivity. If after thirty (30) more days (total 75 days) a fifteen (15) day notice will be sent stating that the submission will be remove from the active registry on the 90th day at close of business if there is not significant work made toward getting the project moved forward.

i. If a project is moved to the inactive registry due to PI and/or Research Coordinator lack of engagement it is able to be recalled to the active registry, if a petitioning letter is sent to the HRPP Director / Manager.

ii. The letter will include a timeline of expected outcomes into getting the project launched.

iii. The petitioning letter does not guarantee that the study will be moved to active registry.

iv. If the petition is denied by HRPP, the PI can request an in person meeting with the Leadership Dyad to discuss the project status.

f. Continuing Review: Information Received and Reviewed by IRB Members

i. The IRB members will have access to the Investigator's Progress Report and the informed consent form via IRBNet. If any changes to the consent are requested a highlighted copy of the changes will also be supplied. The Progress Report will include but not be limited to the following information:

ii. Summary of enrollment activity at Ballad Health to include a breakdown of demographic information for enrolled population;

iii. A summary since the last IRB continuing review of all adverse events; unanticipated problems involving risks to participants or others, and protocol deviations (IRB Policy, Event Reporting - Unanticipated Problems, Adverse Events and Protocol Deviations);

iv. A summary of subject complaints, and any withdrawals;

v. Problems associated with the recruitment of participants;

vi. A summary of the study findings, including results and publications; and an assessment as to whether the risks and benefits of the research have changed;

vii. Any relevant publications/data that would affect the risk/benefit ratio;

viii. Data and Safety Monitoring Committee/Board and Data and Safety Monitors' reports, including interim findings and recommendations;

ix. Trial reports from multi-center sites;

x. A change in investigator conflict of interest;

xi. A description of approved amendments since the last review;

xii. A description of the plans for the coming year;

g. All IRB members are encouraged to review the continuing review application, the current informed consent document, any newly proposed consent documents and revised research plan, the complete protocol including any protocol modifications previously approved by the IRB and a status report on the progress of the research via IRBNet, in enough depth to be familiar with them and be prepared to discuss them at the convened meeting. There will be a Scientific and Non-Scientific Reviewer what will be a primary reviewer and be able to lead the discussion to the IRB.

h. If a study has expired because the IRB has not granted continuing approval by the expiration date (regardless of whether the application materials have been received by the expiration date), the IRB staff will send correspondence to the investigator to inform them that all research activities must cease once the study expires. In addition, clarification as to whether any research activities have occurred after the expiration date is requested from the investigator. The correspondence, together with the investigator response is placed in the IRB file. The information is copied and distributed to all IRB members at the IRB meeting when the study is reviewed; or, in case of expedited review, it is provided to the IRB member performing the review.

i. Amendments/Modifications to Previously Approved Research: Information Received and Reviewed by IRB Members

i. The IRB Staff will have access via the IRBNet to the amendment application, all modified documents with the changes highlighted, all relevant current IRB approved documents (approved consent, research plan) the investigator's written explanation for the changes, and a clean copy of the revised documents. All IRB members will review the amendment application, all modified documents with the changes highlighted, all relevant current IRB

approved documents (approved consent, current protocol), the investigator's written explanation for the changes, and a clean copy of the revised documents. Members are encouraged to review the materials in IRBNet in enough depth to be familiar with them and be prepared to discuss them at the convened meeting. There will be a Scientific and Non-Scientific Reviewer what will be a primary reviewer and be able to lead the discussion to the IRB.

j. Additional Information Available to IRB Members:

   i. Before and after the meeting IRB members may come to the IRB office to request hard copies of the documents submitted into IRBNet including the protocol, meeting minutes, or any available material. The IRB Staff will make these items available to them upon request.

   ii. During the meeting, IRB members may ask the IRB staff to review documents via IRBNet such as the protocol, meeting minutes, etc. The IRB staff will make these items available.

k. Quorum and Voting:

   i. A majority of IRB members and at least one member, whose primary concerns are in nonscientific areas, must be present at a convened IRB meeting. Each action to be reviewed and voted upon requires a quorum, which is defined as the presence of at least 51% of the voting members. A protocol must receive approval of a majority of the members present at a meeting for it to be approved. The IRB Chair is responsible for monitoring the members present at convened meetings to determine that the meetings are appropriately assembled and remain appropriately convened. When quorum is lost during a meeting, the IRB must not take further actions or votes until the quorum is restored. If the quorum cannot be restored, the meeting adjourns. Abstentions count toward the quorum but not toward the required majority.

   ii. The IRBs under the Ballad Health HRPD utilize a primary reviewer model for board review submissions. Under this model all submissions that are going to be presented to the full IRB board for an approval vote will have either a board member or an alternate member review the study before the board meeting is convened. The IRB Staff will assign a Scientific and Non-scientific reviewer, primary reviewer designation will be in a rotating basis.

   iii. All assigned reviewers are authorized and encourage to contact investigators or other study personnel to resolve questions or concerns whenever possible prior to the convened IRB meeting. It is recommended that assigned reviewers use the IRB Reviewer Template to assist in organizing and documenting reviews for presentation to committee members.

   iv. If a research study team member is present at the board meeting, after their presentation of the proposed research study, the primary reviewer will lead the discussion regarding any questions, concerns, findings, or recommendations to the board. After all parties have been able to have a clear and concise discussion about the study, the primary reviewer will give their recommendation to the board for risk level, full approval, approval subject to modifications, table or disapproval of the proposed research study.

The Chair will then call for a motion from the board based off the recommendation. If the Chair is the primary reviewer, then the Vice-Chair or designee will call for the motion.

l. Items that require voting:

i. The vote on the actions including the number of voting "for; against; and abstaining." In order to document the continued existence of a quorum, votes should be recorded in the minutes using the following format: Total = xx, For: xx, Opposed: xx, and Abstained: xx. of if a unanimous decision is made the minutes will reflect such action (Board members who abstain are identified by name in the minutes.). Determinations required by the regulations (e.g., waiver or alteration of informed consent; research involving pregnant women, human fetuses, or neonates; research involving prisoners; research involving children); and protocol specific findings justifying those determinations.

1) The IRB's rationale for significant risk/non-significant risk device determinations.

2) Justification of deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample informed consent document.

3) When the suspension of an approved protocol is considered, documentation of the discussion to allow for continued treatment of enrolled subjects must be included.

m. Meeting Location

i. IRB monthly meetings can be held in a variety of locations and methods.

ii. In-person

iii. Telephonic

1) When voting in a telephonic meeting or setting the board member needs to identify themselves before stating their vote, so that the IRB staff recording the votes can accurately document the vote.

iv. Videographic

1) When in a video meeting the voting board member should ensure that their cameras are “on” during discussions and voting.

v. Non-Voting items

1) There are many items that the IRB Board needs to be made aware of in the form of a documented notification. These items are generally designated non-voting items. Non-voting items are to be placed in a separate agenda that is delivered to the board for review in regular intervals. The IRB Manager or designee will plan, review, and publish these non-voting agendas. The IRB program manager will have a legend or roadmap of the details of what items are non-voting and when their assigned agenda is to be published.

n. Criteria for IRB Approval of Research:

i. Initial Review Procedures:

1) Except for research that is exempted or waived under 45 CFR 46.101(b) or 45 CFR 46.101(i), all human subject research conducted under the jurisdiction of Ballad Health IRB will be reviewed, prospectively approved and subjected to continuing oversight and review at least annually by the IRB.

2) For the IRB to approve research it must determine that all of the following requirements are satisfied (45 CFR 46.111 and 21 CFR 56.111):

a) Risks to subjects are minimized (i) by using procedures which are consistent with sound research design, and which do not unnecessarily expose subjects to risk; and (ii) whenever appropriate, by using procedures already being performed on subjects for diagnostic or treatment purposes.

b) Risks are reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may reasonably be expected to result.

c) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which it is conducted.

d) Informed consent will be sought from each prospective subject or the subject's legally authorized representative in accordance with 45 CFR 46.116.

e) Informed consent will be appropriately documented in accordance with 45 CFR 46.117.

f) The research plan appropriately monitors the data collected to ensure safety of subjects.

g) The subject's privacy is appropriately protected, and confidentiality of the subject's data is maintained.

3) Appropriate safeguards are included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, decisionally impaired, mentally disabled persons, or economically or educationally disadvantaged persons.

o. Actions of IRB:

i. The IRB will set conditions as recommended by OHRP, for the approval of research at a convened meeting. In cases where the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111, IRB approval of the proposed research will be deferred, pending subsequent review by the convened IRB of responsive material. Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator, will the IRB Chair, vice-Chairs or another IRB member designated by the Chair,

subsequently approve the revised research protocol on behalf of the IRB under an expedited review process.

ii. The IRB has established the following categories of actions to be taken on protocols (including new protocols, approved protocols at continuing review, and amendments), reviewed at a convened IRB meeting.

1) Approved:

a) The protocol is approved as submitted with no changes. Approval is usually for one year; however, under certain circumstances (e.g., in high-risk studies in which the risks and benefits of the approved research cannot be fully anticipated) the IRB may limit the approval interval to a shorter period of time or require that the research be reviewed after a specific number of subjects are studied.

2) Modifications Needed to Secure Approval, Pending Administrative (Expedited) Review:

a) The protocol is approved pending receipt and administrative review of additional information, which can include minor clarification or modification of the checklist, protocol, consent form, or supporting materials. To qualify for this category, the requested changes must be clearly delineated and not require substantial changes to the protocol or consent form. Written notification of required modifications will be sent to the investigator. The investigator must provide a point-by-point response to all the issues raised by the Board. If a consent form is modified, two copies of the new consent form must be returned with one copy showing all deleted and inserted text. The other copy incorporates all the changes. The responses and requested modified documents will be administratively reviewed by the Chair, Vice-Chair or another IRB member designated by the Chair, on behalf of the IRB; and if appropriate, an approval will be granted. Please refer to Study Closure due to Lack of Response Section in this SOP.

3) Deferred:

a) A protocol is deferred when the changes proposed, or questions raised by the Board are significant enough to warrant re-review of the protocol at a subsequent Board meeting. The investigator will receive notification of the issues the IRB needs addressed or changed. If a protocol is deferred, it will usually be reconsidered by the same Board members that deferred it. In addition to deferring the protocol the IRB may ask for additional review by expert consultants or it may refer the protocol for an ethics consultation. If a protocol is deferred more than once, a recommendation for the Investigator to meet with a Chair or a Vice-Chair.

4) Disapproved:

a) If the protocol is judged to be lacking in scientific merit, if it raises ethical questions that cannot be resolved, or if it is decided that the

risks outweigh the benefits to the subjects, the protocol will be considered unacceptable and disapproved. The investigator will be notified in writing by the IRB including the reason(s) for the disapproval; however, a detailed critique of the protocol is not provided. The investigator may rewrite and submit the study as a new protocol.

5) Special Determinations by the IRB

   a) At Board meetings special determinations will be made, if appropriate, regarding pediatric risk, waiver of assent, waiver of informed consent, and waiver of written consent.

6) Pediatric Risk:

   a) All studies involving children require IRB review in accordance with the provisions of 45 CFR 46 Subpart D. The IRB will determine the pediatric risk level of a protocol and document its determination by the appropriate Federal citation number in the minutes of the IRB meeting. The following determinations may be made according to Federal regulations:

iii. 45 CFR 46.404 – Research not involving greater than minimal risk to the children.

1) To approve this category of research, the IRB must make the following determinations:

   a) The research presents no greater than minimal risk to the children.

   b) Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in DHHS regulations at 45 CFR 46.408

   c) 45 CFR 46.405 – Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.

   d) The risk is justified by the anticipated benefits to the subjects.

   e) The relation of the anticipated benefit to the risk presented by the study is at least as favorable to the subjects as that provided by available alternative approaches.

   f) Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in DHHS regulations at 45 CFR 46.408.

   g) 45 CFR 46.406 – Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition.

   h) The risk of the research represents a minor increase over minimal risk.

i) The intervention or procedure presents experiences to the child subjects that are reasonably commensurate with those inherent in their actual, or expected medical, dental, psychological, social, or educational situations.

j) The intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the disorder or condition.

k) Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in DHHS (Department of Health and Human Services) regulations at 45 CFR 46.408

l) 45 CFR 46.407 – Research that the IRB believes does not meet the conditions of 45 CFR 46.404, 46.405, or 46.406, but finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

2) If the IRB believes that DHHS supported research does not meet the requirements of 45 CFR 46.404, 46.405, or 46.406, but finds that it presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, it may refer the protocol to DHHS for review. Before submitting a protocol to OHRP, the IRB must determine that, in addition to meeting the requirements of 45 CFR 46.407(a) and other applicable sections of subpart D, the proposed research also meets all of the requirements of 45 CFR part 46, subpart A. The research may proceed only if the Secretary, DHHS, or his or her designee, after consulting with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following an opportunity for public review and comment, determines either: (1) that the research in fact satisfies the conditions of 45 CFR 46.404, 46.405, or 46.406, or (2) the following:

a) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

b) The research will be conducted in accordance with sound ethical principles.

c) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in DHHS regulations at 45 CFR 46.408

d) Recent OHRP guidance for review of research classified as 407 by the IRB now states that OHRP will only review DHHS funded research. The DHHS position is:

i) "DHHS will consult with a panel of experts under 46.407 only when the proposed research is conducted or supported by

DHHS. Note that if an institution has elected in its assurance to apply all of the subparts of 45 CFR part 46 to all of its human subjects research regardless of the source of support, and the IRB finds that the proposed research meets the conditions for review under 46.407, the IRB is not required to submit the protocol to OHRP for review if the research under consideration is not supported by DHHS. In such cases, OHRP recommends that the institution consult with appropriate officials at the relevant federal agency or department supporting the research. When such research is supported by a non-federal sponsor, OHRP recommends that the institution consider convening an independent panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and provide an opportunity for review and comment by the local community where the research is to be conducted before deciding whether to proceed with the research."

3) Protocols meeting the conditions of 45 CFR 46.407 also may be subject to Food and Drug Administration regulations under 21 CFR 50.54 if the protocols involve a clinical investigation of an FDA-regulated product. Other protocols may be subject to FDA regulation at 21 CFR 50.54 but not subject to DHHS regulations at 45 CFR 46.407. The reader is advised to consult with The FDA should be consulted in the event that the review process falls within FDA's regulatory purview.

p. Waiver of Assent:

i. The assent plan and documentation of assent for minors must be recorded in the meeting minutes. The IRB will determine if the assent may be waived for all or some of the population, based on the justification provided by the investigator, and according to Federal regulations (45 CFR 46.408). This determination will be documented using the Federal citation number in the minutes of the Board meeting.

q. Alteration or Waiver of Consent:

i. Alteration/Waiver of Consent Approved under 45 CFR 46.116(c)

ii. The research could not practicably be carried out without waiver or alteration. Alteration/Waiver of Consent Approved under 45 CFR 46 116(d)

iii. Involves no more than minimal risk, does not adversely affect rights and welfare of subjects, research could not be carried out without waiver or alteration, and subjects may be provided with information regarding the study.

r. Waiver of Signed Consent:

i. Waiver of Signed Informed Consent Approved under 45 CFR 46.117(c)(1)

ii. The only record linking the subject and the research would be the consent document and the principal risk would be a breach of confidentiality.

iii. Waiver of Signed Informed Consent Approved under 45 CFR 46.117(c)(2)

iv. Research presents no more than minimal risk and involves no procedures for which written consent is normally required outside of the research context.

s. Waiver of Consent in Emergency Settings:

i. The IRB will consider protocols that require waiver of informed consent for emergency research. There is a limited class of research that may be carried out on human subjects who are in a life-threatening situation and in need of emergency therapy for whom, because of the subject's medical condition and the unavailability of legally authorized representatives of the subjects, no legally effective informed consent can be obtained. In these situations, a waiver of consent may be granted. Protocols that request waiver of informed consent for research in emergency settings will always receive convened Board review.

ii. Because of the special regulatory limitations relating to research involving pregnant women, fetuses, and human in-vitro fertilization (45 CFR 46, Subpart B), and research involving prisoners (45 CFR 46, Subpart C), this waiver is inapplicable to these categories of research. The policies are stated in FDA regulation 21 CFR 50.24 and the joint publication by DHHS and the FDA of "Waiver of Informed Consent Requirements in certain Emergency Research, Federal Register, 61:51531-3, 1996." See also FDA Draft Guidance for Institutional Review Boards, Clinical Investigators and Sponsors: Exception from Informed Consent Requirements for Emergency Research Federal Register, 71:51198-9, 2006.

iii. The waiver can only be applied to all subjects in a protocol and never to only some study participants and always requires Ballad Health Office of Legal Affairs Department approval. To qualify for this waiver:

iv. If the research is FDA-regulated, it must meet the requirements of 21 CFR 50.24, Exception from informed consent requirements for emergency research.

v. If the research is not FDA-regulated, it must meet the requirements of the October 31, 1996, 45 CFR 46 Waiver of Informed Consent Requirements in Certain Emergency Research.

vi. In either case, if required by applicable regulations, the research plan will be submitted to the FDA or DHHS following IRB approval but in advance of its implementation.

t. Requirements for Emergency Research Subject to FDA regulation

i. The IRB may review and approve a clinical investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

ii. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled

investigations, is necessary to determine the safety and effectiveness of particular interventions.

iii. Obtaining informed consent is not feasible because: The subjects will not be able to give their informed consent as a result of their medical condition; The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

iv. Participation in the research holds out the prospect of direct benefit to the subjects because: subjects are facing a life-threatening situation that necessitates intervention; appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

u. The clinical investigation could not practicably be carried out without the waiver.

v. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator shall summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

w. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Federal Regulations. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible.

x. Additional protections of the rights and welfare of the subjects will be provided, including, at least: Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn; Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits; public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results; establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and if obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the

investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

y. Procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document, and that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

z. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible.

aa. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

bb. All clinical investigation records, including IRB determinations and regulatory files, shall be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by the regulatory authorities, as applicable.

cc. Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols to the FDA in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments to the existing IND/IDE.

dd. If an IRB determines that it cannot approve a request for exception from informed consent requirements in emergency research because the clinical investigation does not meet the criteria in the applicable Federal regulations or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation, which must disclose the information as required by applicable regulations.

ee. Emergency Research Subject to FDA regulation:

    i. The IRB may review and approve a clinical investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the

IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

ii. The research is not subject to FDA regulations; and

iii. Item A through item H as stated in the Requirements for Emergency Research Subject to FDA regulation is satisfied.

ff. Review of Sponsor-Investigator:

i. As detailed in the IRB Policy, Investigator Responsibility, investigator-sponsors are required to be knowledgeable of the additional regulatory requirements of sponsors and knew how to comply with them. In order to ensure the investigator-sponsor is knowledgeable about the additional regulatory requirements of sponsors and knows how to follow them, the IRB staff will verify that all Investigators and key study personnel have completed the required training upon receipt of a new IRB application. The IRB may request from the Principal Investigator (PI) additional documentation to assure the Investigators and key study personnel have adequate knowledge, processes, personnel, and facilities to conduct human subject research of investigational drugs, agents, biologics and devices. The IRB staff will not process IRB applications until all Investigators and key study personnel have completed the required training. The IRB staff will contact the PI or study contact when required training of all Investigators and key study personnel is incomplete and inform the PI that the study cannot be processed by the IRB until required training is complete. The IRB staff will document the name of the person called, the date called, the discussion and the response in the IRB database.

gg. Determinations on Non-Compliance Issue or Allegation

i. The IRB will review issues or allegations of non-compliance according to IRB policy. The following determination will be made and documented in the minutes according to Federal regulations:

1) Serious Non-Compliance

2) Non-Serious Non-Compliance

3) Suspended or Terminated Protocols

ii. The IRB may suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected or serious harm to subjects (45 CFR 46.113; 21 CFR 56.113). The IRB's actions must be summarized in the minutes and include the reasons for the action and any planned follow up (45 CFR 46.115(a)(2); 21 CFR 56.115(a)(2)). If the decision to suspend or terminate IRB approval takes place outside of a convened meeting (e.g., by the IRB Chair or Institutional Official for subject safety reasons), this should be reported to the convened IRB and the discussion summarized in the minutes.

hh. Post IRB Meeting Document Turnaround

i. The IRB staff has up to ten (10) business days after the meeting to complete the documents.

ii. As documents are completed, they will be published in IRB Net. As soon as items are published in IRB Net, they are available to the PI and delegated staff.

iii. If there is an unforeseen delay in the publishing of documents, the IRB staff will notify the investigative sites affected.

iv. If the submission was for a continuance – if the submission was approved, then during this turnaround time period the board will allow the investigating site to continue to enroll patients using currently approved stamped informed consent documents.

v. If the submission was for a new project – the PI will have to wait for the stamped documents from the IRB office.

ii. IRB Meeting Minutes:

i. It is the policy of IRB that the minutes of a convened Board meeting will contain the relevant information as stipulated by Federal regulations (45 CFR 46.115(a)(2) and 21 CFR 56.115(a)(2)).

ii. The Minutes of the meetings of the IRB are confidential and are available only for inspection by authorized representatives of the DHHS, OHRP, FDA, and Ballad Health Board of Directors. In the event of a protocol sponsor driven audit, redacted minutes with only information pertaining to validation of quorum and protocol specific information will be made available.

iii. The IRB staff or designated substitute will attend each committee meeting and will draft detailed notes to document the discussions and determinations of the Board for each agenda item. The Minutes of each IRB meeting will document the separate deliberations, actions, and votes for each protocol undergoing initial or continuing review by the convened IRB, and the vote on all IRB actions including the number of members voting for, against, and abstaining. The minutes must be sufficient in detail to demonstrate:

1) Attendance at the meeting for each IRB action, to include:

2) If an alternate is present and who they are representing;

3) The initial and continued presence of a majority of members (quorum), including at least one non- scientist;

4) If a consultant is present.

5) For each protocol discussed, the minutes must document:

6) If a Committee Member is excused from the meeting due to a conflict of interest during the discussion and vote on the study. The name of the committee member is also recorded;

7) Actions taken by the IRB (e.g., approved; modifications required to secure approval; deferred; and disapproved);

8) The discussion of any controversial issues and their resolutions, and documentation of a consultant's findings;

9) The basis for required changes in research;

10) The basis for disapproving research;

11) The level of risk involved in the research (e.g., minimal or greater than minimal risk);

12) The approval period for initial and continuing review;

13) Justification for any change in study design or risk level for amendments, including those submitted with the continuing review;

jj. Distribution and Approval of the Minutes

i. Draft minutes will be prepared by the IRB Staff and forwarded to Board members for review. After review by the members, the IRB Staff will make the necessary revisions and present the finalized minutes for approval at the next month's convened meeting. The approval of the finalized minutes will be documented in the minutes of the meeting, along with documentation of the vote (i.e., the number of votes "for," "opposed," and "abstained") if it is not unanimous.

ii. A signed copy of the approved finalized minutes will be retained in the IRB meeting minutes file.

kk. Notification of Action and Review of Responses

i. When the IRB approves a protocol or an Exemption application, written notification in the form of an approval letter is sent to the Principal Investigator/Responsible Investigator from the IRB Administrative Office. When the IRB requires major or minor modifications to secure approval, written notification of the IRB's action, together with the reason(s) for its decision are provided to the Principal Investigator/Responsible Investigator. The results of IRB actions are conveyed in writing usually within one week of the meeting at which the protocol was considered. Furthermore, when a primary reviewer (either through Full Board or expedited review) determines that additional modifications or clarifications are required, these are also forwarded in writing to the Responsible/Principal Investigator. All communications are sent by the IRB Staff.

ii. The investigator must respond to all IRB requests and inquiries in writing or in person. When an investigator responds to the IRB actions, these correspondences are reviewed by the IRB members to determine whether the information provided satisfies the Board's requests and the criteria for IRB approval. The information can be reviewed administratively by expedited review (when the investigator has agreed to the changes requested by the IRB, or the protocol is eligible for review using the expedited procedure). Otherwise, the modifications are reviewed by the convened IRB.

iii. When the IRB disapproves a protocol, the Principal Investigator/Responsible Investigator is provided with written notification for the reason(s) for the disapproval; however, a detailed critique of the protocol is not provided. The investigator is instructed to contact the IRB office with any questions. An investigator may rewrite and submit the study as a new protocol if they wish

but must take in to account the Board's concerns and reason(s) for the disapproval of the protocol.

ll. Investigators at IRB Meetings

i. IRB meetings are not open to investigators. The IRB may invite an investigator to attend during part of the discussion of his or her protocol to respond to questions from members of the IRB or provide additional information. The investigator would not be present during the final discussion about the protocol or the protocol vote.

mm. Visitors at IRB Meetings

i. A visitor is anyone who is not a voting or non-voting member of the IRB. Visitors may attend an IRB meeting with the approval of the Chair of the meeting. Visitors may not be present during discussions and voting on compliance issues. Visitors who attend meetings of the IRB must sign the IRB attendance form. Any visitor who is not a Ballad Health employee or credentialed allied health professional, must register through the Human Relations office prior to the meeting.

nn. Study Closure for Lack of Response

i. If a protocol has been given contingent approval with a request for minor changes; or has been deferred, a written letter outlining the required changes or reasons given for the action will be sent to the investigator. The investigator has 90 days from the time of the IRB meeting at which the protocol was considered to respond in writing to the changes requested by of the IRB. If the investigator does not respond in writing within 60 days from the time of the IRB meeting, a reminder letter will be sent. If the investigator does not respond in writing in 90 days, the protocol will be closed by the IRB. A written notice of study closure for lack of response will be sent to the investigator and placed in the protocol file. If the investigator wishes to seek approval for the study, a new protocol must be submitted and approved. If there are unusual circumstances that prevent a timely response to requested changes, the principal investigator can request an extension of time to respond.

oo. Length of Time of Approvals

i. The DHHS and FDA regulations require reevaluation of approved research at intervals that are appropriate to the degree of risk, but not less than once a year 45 CFR 46.109(e) and 21 CFR 56.109(f). At Ballad Health, the maximum approval period for new protocols and the re-approval of studies at continuing review, is one year. It is important to note, that IRB approval is a temporary authority and may be withdrawn at any time if warranted by the conduct of the research activities.

ii. When determining the approval period of protocols at initial and continuing review, the Board determines whether the estimate of the investigator's assessment of the anticipated results, risks and procedures are reasonable; whether the risk/benefit ratio is appropriate and accurate; and whether there

is an adequate plan for monitoring the data collected to ensure subjects safety.

iii. The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that research be reviewed more often than annually. For example, when a highly vulnerable subject population is being researched, the risks may not be completely known at initial review. The IRB shall monitor the research project closely and require more frequent than annual review. The IRB shall consider the following factors in determining the criteria for which studies require more frequent review and what the time frames generally will be:

1) Probability and magnitude of anticipated risks to subjects;
2) Likely psychological condition of the proposed subjects;
3) Overall qualifications of the Responsible Investigator and other members of the research team;
4) Specific experience of the Responsible Investigator and other members of the research team in conducting similar research;
5) Nature and frequency of adverse events observed in similar research at this and other facilities;
6) Vulnerability of the population being studied;
7) Other factors that the IRB deems relevant.

iv. In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a maximum number of subjects (i.e., after 3 months or after three subjects enrolled). The Office for Human Research Protections recommends that the minutes clearly reflect these determinations regarding risk and approval period.

v. The approval date is determined by the date which the research was reviewed and approved by the full Board. If the full Board requests modifications to secure approval which can be administratively approved, the approval date is calculated from the date that the protocol was reviewed at full Board approval, and not the date the changes were administratively approved. The expiration date is one day less than the period of approval, (e.g., if the approval period is for one year starting April 14, 2006, then the study will expire at midnight on April 13, 2006).

vi. For protocols approved by expedited review, the expiration date is also one day less than the period of approval that is awarded by the IRB Chair or Vice-Chair. When amendments are approved, the expiration date of the protocol does not change. The approved consent form will have the IRB approval stamp stating the approval date of the protocol.

pp. Authorized Signatures

i. The Chair or Vice-Chair of the Ballad Health IRB signs any letters sent on behalf of the Ballad Health IRB. The Chair or Vice-Chair of the IRB is authorized to sign outcome letters for actions taken on behalf of the IRB.

8. **Research and HIPAA Privacy Rule**

a. HRPP and the IRB will ensure that the protection of privacy rights of human research subjects and compliance with the HIPAA Privacy Rule. Failure to comply with the HIPAA do so can result in temporary or permanent suspension of access to protected health information for any researcher.

b. Under the Privacy Rule, health care providers are permitted to use and disclose protected health information (PHI) for research with individual authorization, or without individual authorization under limited circumstances set forth in the Privacy Rule.

c. Concerns for potential or actual HIPAA violations related to research activities should be promptly reported to the Ballad Health HIPAA Privacy Officer in accordance with policy *IM-900-026-BH Reporting Potential or Actual Breaches of Patient Protected Health Information – Ballad Health*

d. Research Use/Disclosure Without Authorization:

i. To use or disclose protected health information without authorization by the research participant, a health care provider must obtain on of the following:

1) Documented IRB Approval: Documentation that an alteration or waiver of research participants' authorization for use/disclosure of information about them for research purposes has been approved by the IRB. See 45 CFR 164.512(i)(1)(i). This provision of the Privacy Rule might be used for example to conduct records research, when researchers are unable to use de-identified information, and the research could not practicably be conducted if research participants authorization were required.

2) A health care provider may use or disclose protected health information for research purposes pursuant to a waiver of authorization by an IRB provided it has obtained documentation of all of the following:

a) Identification of the IRB and the date on which the alteration or waiver of authorization was approved.

b) A statement that the IRB has determined that the alteration or waiver of authorization, in whole or in part satisfies the three criteria in the Rule.

c) A brief description of the protected health information for which use, or access has been determined to be necessary by the IRB.

d) A statement that the alteration or waiver of authorization has been reviewed and approved under either normal or expedited review procedures.

e) The signature of the chair, or other member or designee of the IRB as applicable

3) The following criteria must be satisfied for an IRB to approve a waiver of authorization under the Privacy Rule:

a) The use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals, based on at least, the presence of the following elements:

i) An adequate plan to protect the identifiers from improper use and disclosure in accordance with the Ballad Health De-Identification of Protected Health Information (PHI) policy IM-900-006-BH

ii) An adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and

iii) Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law for authorized oversight of the research project or for other research for which the use or disclosure of protected health information would be permitted by this sub-part

iv) The research could not practicably be conducted without the waiver of authorization

v) The research could not be practicably conducted without access to and use of the protected health information

e. Preparatory to Research:

i. Representations from the researcher, either in writing or orally, that the use or disclosure of the protected health information is solely to prepare a research protocol of/for similar purposes preparatory to research, that the researcher will not remove any protected health information from the health care provider, and representation that protected health information for which access is sought is necessary for the research purpose. See 45 CFR 164.512(i)(1)(ii). This provision might be used, for example, to design a study or assess the feasibility of conducting a study.

f. Research on Protected Health Information of Decedents:

i. Representations from the researcher, either in writing or orally, that the use or disclosure being sought is solely for research on the protected health information of decedents, that the protected health information being sought is necessary for the research, and at the request of the health care provider, documentation of the death of the individuals about whom information is being sought. See 45 CFR 164.512 (i)(1)(iii)

g. Limited Data Sets with a Data Use Agreement:

i. A data use agreement entered into by both the health care provider and the researcher, pursuant to which the health care provider may disclose a limited data set to the researcher for research, public health, or health care operations. The Ballad Health De-Identification of Protected Health Information (PHI policy IM-900-006-BH) should be followed. A limited data

set excludes specified direct identifiers of the individual or of relatives, employers, or household members of the individual. The data use agreement must:

1) Establish the permitted uses and disclosures of the limited data set by the recipient, consistent with the purposes of the research, and may not include any use or disclosure that would violate the Rule if done by the health care provider.
2) Limit who can use or receive the data and
3) Require the recipient to agree to the following:
    a) Not to use or disclose the information other than as permitted by the data use agreement or as otherwise permitted by law
    b) Use appropriate safeguards to prevent the use or disclosure of the information not provided for the data use agreement of which the recipient becomes aware
    c) Ensure that any agents, including a subcontractor, to whom the recipient provides a limited data set agrees to the same restrictions and conditions that apply to the recipient with respect to the limited data set
    d) Not to identify the information or contact the individual
4) Research Use/Disclosure with Individual Authorization:
    a) The Privacy Rule also permits health care providers to use or disclose protected health information for research purposes when a research participant authorizes the use or disclosure of information about him or herself.
    b) To use or disclose protected health information with authorization by the research participant, the health care provider must obtain authorization that satisfies the requirements of 45 CFR 164.508. The Privacy Rule has a general set of authorization requirements that apply to all uses and disclosures, including those for research purposes. However, several special provisions apply to research authorizations:
        i) Unlike other authorizations, an authorization for research purposes may state that the authorization does not expire, that there is no expiration date or event, or that the authorization continues until the "end of the research study;" and
        ii) An authorization for the use or disclosure of protected health information for research may be combined with consent to participate in the research, or with any other legal permission related to the research study.
5) The IRB has an application and process set in place to complete the request. Please refer to IRB forms Waiver Request, HIPAA Authorization

for Research. Additional forms and applications may also be required based on the specific project request. The IRB staff can advise on a project-by-project basis.

6) Research participants can revoke their authorization in accordance with the Ballad Health Release, Use and Disclosure of Patient Information policy IM-900-019-BH.

h. Accounting for Research Disclosures

i. In general, the Privacy Rule gives individuals the right to receive an accounting of certain disclosures of protected health information made by a health care provider. Research disclosures should follow the Ballad Health Accounting of Disclosures of Protected Health Information policy IM-900-002-BH.

ii. In addition, for disclosures of protected health information for research purposes without the individual's authorization pursuant to 45 CFR164.512(i), and that involve at least fifty (50) records, the Privacy Rule allows for a simplified accounting of such disclosures by covered entities. Under this simplified accounting provisions, covered entities may provide individuals with a list of all protocols for which the patient's protected health information may have been disclosed under 45 CFR 164.512(i), as well as the researcher's name and contact information.

iii. Other requirements related to this simplified accounting provision are found in 45 CFR 164.528(b)(4). They are:

1) The name of the protocol or research activity

2) A description, in plain language, of the research protocol or other research activity, including the purpose of the research and the criteria for selection of particular records.

3) A brief description of the type of protected health information that was disclosed.

4) The date or period of time during which such disclosures occurred, or may have occurred, including the date of the last such disclosure during the accounting period.

5) The name, address and telephone number of the entity that sponsored the research and of the researcher to whom the information was disclosed.

6) A statement that the protected health information of the individual may or may not have been disclosed for that particular protocol or research activity.

i. Transition Provisions:

i. Under the Privacy Rule, a health care provider may use and disclose protected health information that was created or received for research, either before or after the compliance date, if the health care provider obtained any one of the following prior to the compliance date:

1) An authorization or other express legal permission from an individual to use or disclose protected health information for the research.

2) The informed consent of the individual to participate in the research.

3) A waiver of informed consent by an IRB in accordance with the Common Rule or an exception under FDA's Human Subject protection regulations at 21 CFR 50.

ii. However, if a waiver of informed consent was obtained prior to compliance date, but informed consent is subsequently sought after the compliance date, the health care provider must obtain the individual's authorization as required by 45 CFR 164.508. For example, if there was a temporary waiver of informed consent for emergency research under the FDA's human subject protection regulations, and informed consent was later sought after the compliance date, individual authorization would be required before the health care provider could use or disclose protected health information for the research after the waiver of informed consent was no longer valid.

iii. The Privacy Rule allows health care providers to rely on such express legal permission, informed consent, or IRB - approved waiver of informed consent, which they create or receive before the applicable compliance date, to use and disclose protected health information for specific research studies as well as for future unspecified research that may be included in such permission.

9. **IRB Record Management**

a. The IRB will maintain protocol files on each study as stipulated by DHHS regulations in 45 CFR 46.115(a)(1), (3), (4), and (7) and 21 CFR 56.115. The minutes of IRB meetings will include all the information stipulated by DHHS regulations 45 CFR 46.115(a)(2) and 21 CFR 56.115.

b. The Federal regulations require all IRB protocol records related to research which is conducted (protocol records), to be retained for at least three years after study completion; and all other IRB records to be retained for three years (45 CFR 46.115(b)). Ballad Health IRB shall maintain records according to the above regulation and will keep them secure in lockable filing cabinets or storage rooms. These records are available to the IRB.

c. IRB Protocol File

i. The following are the basic elements of the IRB protocol file for each study:

1) Complete IRB Application

2) Separate written protocol

3) All approved versions of consent/assent forms (with IRB stamp), including copies of DHHS-approved sample consent documents.

4) Copy of full grant application or full industry protocol, when applicable.

5) Scientific and ethical evaluations (e.g., consultant's reports and Department approvals).

6) Progress reports/continuing review.

7) Amendments to protocol.
8) Correspondence between IRB and investigator.
9) Administrative actions
10) Documentation of IRB determinations required by the regulations and protocol-specific findings supporting determinations (for Expedited review, the completed IRB Reviewer checklist is also included).
11) Statements of significant new findings provided to subjects, as required by 45 CFR 46.116(b)(5).
12) Copies of approved recruiting advertisement/ brochures/materials.
13) File checklists including investigator brochures, data safety monitoring reports, and other items submitted with a file checklist.
14) Reports of internal/external adverse events.
15) Local context review information from investigator and/or consultant (if applicable).
16) Translated consent forms (if applicable)
17) Financial Conflict of Interest for Principal Investigator
18) Final report
19) IRB Protocol File for Exempt Approvals

d. The following are the basic elements of the IRB protocol file for Exempt research protocols:
   i. Request for Exemption application form
   ii. Research Plan
   iii. Approved consent/assent forms and advertising material (when applicable)
   iv. Exemption Determination form citing the specific approved exemption category for the research.
   v. Signed approval letter stating the specific category under which the study was determined to be exempt.

e. IRB Membership Rosters:
   i. IRB Membership Roster
      1) The IRB staff maintain a roster of all IRB membership including:
      2) Name
      3) Earned Degree
      4) Representative Capacities
      5) Scientific (S) / Non-Scientific (NS)
      6) Affiliation status

7) Whether the IRB member or an immediate family member of the IRB is affiliated with the Organization

8) Experience contributions

9) Status as Voting or Alternate or Staff

f. IRB Policies and Procedures:

i. Ballad Health IRB maintains a current Operations Manual reflecting polices to implement Federal regulations for protection of human subjects and the operational implementation of these policies by the IRB.

g. IRB Database:

i. "The IRB participates in the IRBNet National Research Network to process and maintain electronic records. IRBNet is a highly secure electronic system for compliance and research management utilizing industry standard best practice security and data management technologies and tools, including strong password authentication, encryption and both on and off-site data backups. The IRB complies with Federal regulation 21 CFR Part 11 relating to electronic records."

h. Access to IRB Records:

i. All IRB records, in any format, are considered confidential and may be accessed only by authorized individuals or regulatory agencies as required by law. Access to IRB records is limited to the IRB, IRB staff, authorized IRB representatives, and officials of Federal and state regulatory agencies. Investigators or their designated staff shall be provided reasonable access to files related to their research. All other access to IRB records is limited to those who have legitimate need for access, as determined by the Chair of the IRB. All records shall be accessible for inspection and copying by authorized representatives of approved organizations or entities at reasonable times.

i. Investigator Records:

i. Each investigator is required to maintain accurate and complete files for each IRB approved protocols. Investigators must maintain original signed consent forms in their study files. Investigators' files must be available upon request for Ballad Health IRB, Department of Health and Human Services (DHHS), the Office for Human Research Protection (OHRP), and the Food and Drug Administration (FDA), if applicable. Investigators must maintain their study files in a secured and confidential manner to protect subject confidentiality and sponsor confidential information. Investigator records must be kept for a minimum of three years following the end of the study. In addition, research regulated by the FDA may have additional record retention requirements.

10. **Administrative Holds, Suspensions, Terminations of IRB Approval**

a. The IRB has the authority and responsibility to suspend and terminate approval of research that is not being conducted in accordance with the IRB policies and procedures, or that has been associated with unexpected harm to participants or others. The IRB has the ability to temporarily or permanently suspend or terminate approval for some or all research activities. Any letter of Suspension or

Termination of approval to an investigator must include a statement of reason for the action by the IRB (45 CFR 46.113 and 21 CFR 56.113).

b. The IRB Chair and Vice Chair are authorized to suspend or terminate the enrollment of subjects; and the ongoing involvement of subjects in research as deemed necessary to protect the rights and welfare of participants. This also includes compelling and urgent instances when subject safety is a concern. The IRB will review such Suspensions and Terminations at a subsequent convened meeting. A plan will be developed that takes into account the rights and welfare of currently enrolled subjects and those subjects that may need to be withdrawn from the study. If the IRB determines that a Suspension or Termination of the research will place subjects at risk of harm, the investigator will be requested to submit a proposed script or letter to be sent to the participants. This proposed letter will be reviewed and approved by the IRB. The IRB determines the information that is to be provided to subjects and the method of their notification e.g., in writing or by telephone. This includes appropriate follow up and notification of the reasons for the action. All protocol Suspensions and Terminations are reviewed at a subsequent IRB meeting.

c. Depending on the reasons for the Suspension or Termination and the design of the protocol, the IRB may require that the following subjects be notified of the Suspension or Termination:

   i. All Subjects who have been or are enrolled;

   ii. Subjects currently on protocol; or

   iii. Subjects who participated in a certain aspect of the protocol.

d. The IRB will ensure prompt report to the following (as required in 45 CFR 46.110(c)):

   i. All IRB Members

   ii. Signatory Official of the FWA

e. The IRB administrative office will keep all IRB Members advised of activities occurring outside of the full board meetings including protocols that have been suspended or terminated. The IRB members are advised of activities occurring outside of the full board meetings via e-mail as the activities occur. All items occurring outside of the full board meeting are also placed on the next monthly agenda for review and discussion by the full board.

f. During an investigation for human subjects' non-compliance, the IRB Chair or Vice-Chair will notify the Principal Investigator of such Terminations or Suspensions by letter and will include a statement of the reasons for the IRB's actions. The Investigator will be provided with the opportunity to respond in person or in writing. The Suspension letter will include the following:

   i. The nature of the event;

   ii. Name of the institution conducting the research;

   iii. Title of the research project and/or grant;

   iv. Name of the principal investigator over the protocol;

v. A detailed description of the problem including the findings of the organization and the reasons for the IRB's decision;

vi. The activities are to be stopped;

vii. Actions to be taken by the investigator; including those to protect the rights and welfare of currently enrolled subjects;

viii. A request to immediately notify the IRB Chair with a list of the names of participants who might be harmed by stopping the research procedures and a rationale why they might be harmed;

ix. In the case of a Suspension or Termination of IRB approval by an IRB designee the date and time of the IRB meeting at which the Suspension or Termination will be reviewed by the convened IRB; and the actions required to protect the rights and welfare of currently enrolled participants; and

x. An offer for the investigator to respond to the convened IRB in writing.

g. The IRB may find it in the best interest of the enrolled subjects to allow continued participation in the interventions or interactions, but enrollment of new subjects cannot occur during IRB Suspension. The convened IRB will determine the appropriate actions and if a study is to be terminated or may continue with enrollment at the completion of the human subject's non-compliance investigation.

h. The IRB will report events of Suspensions or Terminations of IRB approval to Regulatory Agencies, Department Heads and Institutional Officials.

i. The investigators must plan ahead to meet required continuing review dates specified by the IRB and federal regulations. IRBNet has an established a notification system via email which reminds the IRB and its investigators when an approved IRB research protocol is due to expire. The notices are sent ninety (90) days, sixty (60) days, forty-five (45) days, and thirty (30) days in advance of the IRB expiration. A calendar is published at the beginning of each year with the IRB meeting date and the submission deadline for each agenda. It is the investigator's responsibility to plan ahead and have his submissions completed for a timely review prior to any lapse in approval. Once expired all research activities including enrollment of new subjects must cease.

j. A letter will be issued to the investigator to inform them that the study no longer has IRB approval and that the research cannot be re-opened without a new protocol submission and updated fee processing. The issued letter will be copied to the appropriate study sponsor as well.

k. If the investigator continues to conduct the research after the study has expired, this becomes an issue of non-compliance.

11. **Closure of an IRB Approved Protocol**

a. Investigators have the responsibility to formally close a study with current IRB approval once it is completed or discontinued. Notification must be sent to the IRB office by completing the Investigator's Final Progress Report via IRBNet. Any previously unreported adverse events should be reported at the time the report is submitted. If the project was discontinued by the investigators, include an

explanation of why the project was discontinued and statement of results, if any. Once a protocol is permanently closed all research activities must cease, including data analysis (unless the data is de-identified). If the Principal Investigator wants to continue data analysis with identifiable data, a continuing review should be submitted for review. A protocol that has been closed cannot be reopened. To resume research activities a new protocol must be approved by the IRB.

i. The investigator can also choose to keep a protocol open during data analysis by submitting a continuing review.

ii. After a study has been permanently closed signed consent forms should be available for IRB inspection for three years. In the event of separation of the principal investigator from Ballad Health, copies of signed consent forms should be given to a co-investigator. The IRB should be notified where signed consent forms are kept. It is the Principal Investigator's responsibility to notify the IRB where the consent forms will be stored if he/she has separated from Ballad Health.

iii. After a protocol has been closed the IRB does not accept reports of adverse events unless they impact the rights and welfare of enrolled subjects. The investigator should keep all non-reported adverse events on file for review by regulatory agencies. Findings from the sponsor or publications may be submitted after the Closure of a study.

12. **Reporting to Regulatory Agencies, Department Heads, and Institutional Officials**

a. This policy establishes guidelines to ensure prompt reporting by Ballad Health IRB of those events listed in Federal regulations. These regulatory requirements may be found in 45 CFR 46.103 and 21 CFR 56.108(b)(1).

b. If the IRB determines that an event represents:

i. An Unanticipated Problem involving risks to subjects or others.

ii. A serious or continuing noncompliance with research regulations or determinations of the Research Compliance Office and\or the IRB; or

iii. A Suspension or Termination of IRB approval.

c. In these instances, the Compliance and Audit Services office will prepare a draft report within fifteen (15) working days after the IRB meeting at which the determination occurred or after which time an appropriate administrative action was taken outside of a full Board meeting of the IRB.

d. The contents of the required reporting will include:

i. The nature of the event (Unanticipated Problem, Adverse Events, or Continuing Non-Compliance, Suspension, or Termination of approval of research);

ii. Name of the institution conducting the research and the awardee institution as applicable;

iii. Protocol title;

iv. Name of the Principal Investigator;

v. IRB number and identification numbers of any applicable Federal or non-Federal award(s) (grant, contract, or cooperative agreement, etc.);

vi. A detailed description of the issue including the findings of the institutions involved and the reasons for the Compliance and Audit Services office's investigation and the IRB's decision;

vii. Actions the Compliance and Audit Services office, the institution or the IRB is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.); and

viii. Plans, if any, to send a follow-up or final report by the earlier of a specific date, when an investigation has been completed or a corrective action plan has been implemented.

e. The Ballad Health Compliance and Audit Services office in consultation with the IRB Chair, Vice Chairs, and the IRB Project Manager will review and finalize the report within fifteen (15) working days after the IRB meeting at which the final determination occurred. The reporting will take place within forty-five (45) days of the completion of an investigation and/or determination has been reached.

f. The finalized report will be sent to the following as applicable:

i. The IRB (as an information item with the agenda); or as an administrative action report

ii. Ballad Health Medical Executive Committee of applicable facility

iii. The Office for Human Research Protections (OHRP)

iv. The Food and Drug Administration (FDA) (whenever the research is subject to FDA regulation);

v. Other Federal Agencies* that are a signatory to "The Common Rule" who conduct or oversee the research;

vi. Principal Investigator and other members of the research team, as applicable;

vii. Ballad Health Chief Medical Officer and/or President and CEO of applicable facility.

g. If deemed appropriate, the report will also be forwarded to the following:

i. Department(s) chair(s), program director and supervisor(s) of the investigator, and employee;

ii. Other organizations and departments involved with the research;

iii. The sponsor or funding agency; and\or

iv. The applicable Grants and Contracts offices.

Reporting is not required if the agency has already been made aware of the event through other mechanisms, such as reporting by the investigator, sponsor, or another organization.

13. **Financial Disclosure for Ethical Conduct of Research – Public Health Service (PHS) Funded Research, Oncology, Grants, and Subcontracts**

a. Training: Ballad Health is responsible for informing each investigator of this policy; relevant regulations; and the Investigator's responsibility to disclose significant financial interest. Investigators are required to complete Investigator COI training before engaging in research and at least once every four years. In addition, Investigators will be trained/re-trained immediately when:

i. Ballad Health revises this policy in any manner that affects the requirements of investigators;

ii. An Investigator is new to Ballad Health; and/or

iii. Ballad Health finds that an Investigator is not in compliance with the systems financial conflict of interest policy or management plan(s).

b. Reporting: PHS - Funded Research - Ballad Health is obligated under 42 CFR Part 50 Sub-part F and 45 CFR Part 94 to report to the PHS Awarding Component all related significant financial interest that are deemed financial conflicts of interest (FCOI), as defined by this policy prior to the expenditure of funds and within 60 days of any subsequently identified FCOI. Ballad Health must review, manage, mitigate, report and when appropriate conduct retrospective reviews of potentially conflicted projects as described in this policy.

c. Investigator Disclosure Requirements:

i. Initial Disclosures:

1) Each Investigator as defined by this policy is required to disclose the Investigator's Significant Financial Interest and those of the spouse and dependent children prior to submitting an application for PHS funded research. Disclosing Significant Financial Interest allows Ballad Health to determine whether a "Financial Conflict of Interest" exists, whether it is related to the research and whether management or mitigation strategies must be implemented to ensure objectivity in research.

2) Investigators who are new to Ballad Health must disclose Significant Financial Interest before transferring any research to Ballad Health and before engaging in any research activities at Ballad.

3) Disclosure must be made in writing to the Clinical Trials and Research office in accordance with published Investigator COI disclosure forms.

ii. Subsequent Disclosures:

1) Each Investigator who participates in research must submit an updated disclosure of significant financial interest at least once per year during the period of the award or project to determine whether the interest if any is a " Financial Conflict of Interest" that is potentially related to research.

2) The disclosure must include any information that was not initially disclosed to the Institute and shall also include updated information on any previously disclosed significant financial interests (e.g., updated value of a previously disclosed equity interest).

3) Additionally, Investigators must submit an updated disclosure of significant financial interest within thirty (30) days of discovering or acquiring (through purchase, marriage, inheritance, etc.) a new significant financial interest.

d. Management of Sub-recipients:

i. When Ballad Health carries out research through a sub-recipient (e.g., subcontractors) Ballad Health must take reasonable steps to ensure that the sub-recipient Investigator(s) will comply with either the sub recipient's or Ballad Health Policy.

e. Special Provisions for PHS-funded Sub-recipients:

i. When Ballad Health carries out PHS- funded research through a sub-recipient (e.g., subcontractor), Ballad Health must take reasonable steps to ensure that the sub-recipient Investigator will comply with 42 CFR Part 50 Sub-part F and 45 CFR Part 94 by incorporating one of the following subcontract agreement:

ii. Statement that the sub-recipient will comply with their own financial conflict of interest policy which complies with 42 CFR Part 50 Sub-part F and 45 CFR Part 94. The agreement will specify the time periods for the sub recipient to report all identified financial conflicts of interest to the awardee's institution. Time periods for reporting must be sufficient to allow complete review, management and reporting of sub- recipient Financial Conflict of Interest which are related to the PHS funded research. OR,

iii. Statement that the sub-recipient will comply with this Policy which complies with 42 CFR Part 50 Sub-part F and 45 CFR Part 94. The agreement will specify the time periods for the sub recipient to report all identified financial conflicts of interest to the awardee's institution. Time periods for reporting must be sufficient to allow Ballad Health to complete the review, allow for management and reporting of sub-recipient Financial Conflict of Interest which are related to the PHS funded research.

f. PHS Funding Application Certification

i. In accordance with 42 CFR Part 50 Sub-part F and 45 CFR Part 94 Ballad Health will meet the following PHS expectations when applying for PHS funding:

1) Certification: Ballad Health must certify in each grant application for PHS fund that Ballad Health;

2) Has in effect an up to date, written and enforced administrative process to identify and manage financial conflicts of interest with respect to all research projects for which funding is sought or received from the PHS;

3) Shall promote and enforce Investigator compliance with the requirements under 42 CFR Part 50 Sub-part F and 45 CFR Part 94 (as applicable), including those pertaining to disclosure of significant financial interest;

4) Shall manage financial conflicts of interest and provide initial and ongoing FCOI reports to the PHS Awarding Component;

5) Agrees to make information available, promptly upon request to the HHS relating to any investigator disclosure of financial interest and Ballad Health review of and response to such disclosure whether or not the disclosure resulted in Ballad Health determination of a FCOI and;

6) Shall fully comply with the requirements of 42 CFR Part 50 Sub-part F and 45 CFR Part 94.

g. Review and Management of Potential COI:

i. Institutional Official:

1) In accordance with 42 CFR Part 50 Sub-part F Ballad Health designates an Institutional Official responsible for soliciting and reviewing disclosures of significant financial interest from each Investigator who is planning to participate in or is participating in research. Disclosures must be made, in writing to the Clinical Trials and Research Office prior to the submission of each application for PHS funding, in accordance with Ballad Health published Investigator's COI Disclosure Form. Ballad Health will provide initial and ongoing FCOI reports to the funding agency, if any, in accordance with the funding agency's policies.

2) Ballad Health will provide guidelines consistent with 42 CFR Part 50 Sub-part F and 45 CFR Part 94 for the Institutional Official (IO) to determine whether an Investigator's significant financial interest is related to the research, and if so whether the significant financial interest constitutes a financial conflict of interest. A financial conflict of interest occurs when the designated IO reasonably determines that the significant financial interest could directly and significantly affect the design, conduct or reporting of the research. Ballad Health may not rely solely upon an Investigator's determination to decide whether a significant financial interest or financial conflict of interest is related to research. The IO or COI Committee may however request information and feedback from the Investigator regarding relatedness to research and/or Institutional Responsibilities.

ii. Appeals:

1) Any Investigator who disagrees with a final decision of the COI Committee may appeal in writing to the Institutional Official within 10(10) calendar days of a final decision. The COI Committee must review and consider all appeals and vote to either retain its original findings or to revise its recommended actions. The final decision regarding management of an actual or potential COI in research under this policy rests with the COI Committee, though Investigator feedback is encouraged.

iii. Compliance, Non-Compliance and Institutional Enforcement:

1) All person's subject to this Policy are expected to comply fully and promptly. An Investigator who submits a complete and accurate COI Disclosure and complies with conditions required by the COI Committee shall be deemed to be in compliance with this Policy. Failure to fully and accurately disclose a Conflict of interest or failure to comply with conditions or management plans imposed by the COI Committee shall constitute non- compliance with this policy.

2) Ballad Health Systems encourages Investigators who are aware of an unreported Conflict of Interest to bring the COI to the attention of the Institutional Official who will consult with the COI Committee regarding the possible enforcement actions to be taken. If the COI Committee determines that an Investigator has failed to comply with any aspect of this Policy, the COI Committee shall submit a report in writing to Ballad Health System Vice President of Operations. The report shall include all material facts and recommendations for enforcement actions, if any.

3) The SVP of Operations shall make the final decision regarding enforcement actions, up to and including termination of employment or legal action.

4) Ballad Health will complete and document retrospective reviews within 120 days of the Institutions determination of noncompliance for SFI's not disclosed timely or previously reviewed or whenever a FCOI is not identified or managed in a timely manner. Such reviews will be documented consistent with the regulation.

5) Ballad Health will complete and document retrospective reviews within 120 days of the Institutions determination of noncompliance for SFI's not disclosed timely or previously reviewed or whenever a FCOI is not identified or managed in a timely manner. Such reviews will be documented consistent with the regulation.

6) In instances where the Department of Health and Human Services determines that a PHS-funded research project of clinical research whose purpose is to evaluate the safety or effectiveness of a drug, medical device, or treatment has been designed, conducted, or reported by an investigator with an FCOI that was not managed or reported by Ballad Health as required by regulation, Ballad Health shall require the investigator involved to:

   a) Disclose the FCOI in each public presentation of the results of the research, AND

   b) To request an addendum to previously published presentations.

h. Review and Management of COI:

   i. Mitigation:

      1) For PHS-funded research, Ballad Health must notify the PHS Awarding Component promptly and submit a mitigation report to the PHS Awarding Component. The mitigation report must include at a minimum, the key

element documented in the retrospective review and a description of the impact of the bias on the research project, as well as the Ballad Health plan of action to eliminate or mitigate the effect of the bias. Thereafter Ballad Health shall submit FCOI, Ballad Health may determine that additional interim measures are necessary with regard to the Investigator's participation in the PHS- funded research between the date that the FCOI or noncompliance is determined and the completion of Ballad Health retrospective review. The COI Committee will be responsible for generating all appropriate documentation, including when the retrospective review finds no bias, and the basis for such a finding.

ii. Public Accessibility:

1) Prior to the expenditure of any funds any PHS- funded research projects Ballad Health will ensure public accessibility of information concerning any FCOI disclosed to Ballad Health will ensure such accessibility by responding to any requester within five (5) business days of a request, or posting on Ballad Health external website, when the following criteria are met:

a) A Significant Financial Interest (SFI) was disclosed and is still held by the senior/key personnel as defined in 42 CFR 50, Sub-part F and 45 CFR 94;

b) The designated Institutional Official and/or COI Committee has determined that the SFI is related to the research; and

c) The COI Committee determines that the SFI is a FCOI.

2) The information that Ballad Health must make publicly available includes, at a minimum:

a) Investigator's name

b) Investigator's title and role with respect to the externally funded project

c) The name of the entity with which the SFI is held

d) The nature of the SFI

e) The approximate value of the SFI (dollar ranges are permissible as follows $0-$4,999; $5,000-$9,999;

f) $10,000--$19,999$amounts between $20,000- $100,000 in increments of $20,000; amounts over

g) $100,000 in increments of $50,000)

h) When the value of the SFI cannot be readily determined through reference to public prices or other reasonable measures of fair market value, a statement stating so.

i) A statement that the information is current as of the date of the correspondence and is subject to updates, on at least an annual basis and within 60 days of the institution’s identification of a new financial

conflict of interest, which should be requested subsequently by the requester. Ballad Health is not responsible for continually updating previous requests. The requester must make a new request to obtain updated information.

3) Information concerning conflicts of interest for which the above criteria are met must be available to written requester for a least 3 years from the date that the information was last updated.

i. Reporting to PHS Awarding Components:

i. For PHS-funded research, Ballad Health will prove the PHS Awarding Component with a FCOI report regarding any Investigator's significant financial interest found to constitute FCOI, and to ensure that Ballad Health has implemented a management plan in accordance with 45 CFR94 and 42 CFR 50.

ii. For subsequent FCOI findings during the period of award (e.g., participation of a new Investigator) Ballad Health shall, within 60 days provide the PHS Awarding Component with a FCOI report regarding the financial conflict and ensure that Ballad has implemented a management plan in accordance with federal regulations. Where such a FCOI report involves significant financial conflict that was not disclosed timely by the Investigator, or which was for whatever reason not previously reviewed or managed by Ballad Health, Ballad Health is also required to complete a retrospective review as referenced above. If bias is found Ballad Health is required to notify the PHS Awarding Component promptly and submit a mitigation report to the PHS Awarding Component.

iii. All FCOI reports to PHS Awarding Components must include sufficient information to enable the PHS to understand the nature and extent of the financial conflict, and to assess the appropriateness of Ballad Health management plan. The FCOI report shall include, but is not limited to:

1) Project number and /or title

2) PD/PI or Contact PD/PI if multiple

3) Name of Investigator with the FCOI

4) Name of the entity with which the Investigator has the FCOI

5) Nature of the financial interest (e.g., equity, travel reimbursement, Honoria)

6) Value of the Interest (ranges are allowed as cited in the Public Accessibility section of this Policy)

7) A description of the key elements of Ballad Health management plan, including:

a) Role and principal duties of the conflicted investigator in the research project

b) Conditions of the management plan

c) How the management plan is designed to safeguard objectivity in the research project

d) Confirmation of the investigator's agreement to the management plan

e) How the management plan will be monitored to ensure investigator's compliance

f) How the management plan will be monitored to ensure investigator's compliance

g) Other information as needed.

iv. For any FCOI previously reported by Ballad Health with regard to an ongoing PHS funded project, Ballad Health will provide the PHS Awarding Component an annual FCOI report that addresses the status of the FCI and any changes to the management plan. This reporting shall continue throughout the period of funding in the time and manner specified by the PHS Awarding Component. The annual FCOI report shall specify whether the FCOI is still being managed or explain why the FCOI no longer exists.

j. Maintenance of Records:

i. Ballad Health shall maintain records regarding Investigator COI Disclosures, and Ballad Health review of and responses to , such disclosures (whether or not the disclosure resulted in the IO's determination of a FCOI related to the research) and all actions relating to elimination, management, mitigation, and retrospective reviews (if applicable) for at least three years after final payment of any Externally- funded project to which the potential or actual COI relates; or three years after the resolution of any funding agency action involving those actions; whichever is longer.

14. **Financial Disclosure for Ethical Conduct of Research – FDA Regulated Industry Sponsored Research**

a. Applicability:

i. The purpose of this policy is to promote the identification, disclosure and if required resolution or management of conflicts of interest (COI) when conducting industry sponsored clinical research.

ii. Any person engaging in a research activity has an obligation to avoid conflicts of interest. Individuals engaging in research activities are required to make voluntary and timely disclosures to ensure the necessary steps to avoid the appearance of conflict of interests.

b. Procedure:

i. Individuals engaged in research are to complete a Conflict-of-Interest Statement and link to the appropriate IRBNet package at the following times:

1) At the time of initial submission of contract to appropriate Ballad Health VP for review and protocol review by the Ballad Health IRB;

2) At the time of submitting a continuing review to the Ballad Health IRB office;

3) When any change is made in Investigator circumstance;

4) At the addition of or change in PI to an already approved project.

ii. In place of the Financial Conflict of Interest Form, the Ballad Health IRB Board will accept a Sponsor's Financial Disclosure form that has been completed by the Principal Investigator and all Sub-Investigators. The Sponsor's Financial Disclosure Form will need to be completed and submitted (linked to the appropriate IRBNet package) at the following times:

1) At the time of initial submission of contract to appropriate Ballad Health VP for review and protocol review by the Ballad Health IRB;

2) At the time of submitting a continuing review to the Ballad Health IRB office;

3) When any change is made in investigator circumstance;

4) At the addition of or change in PI to an already approved project.

iii. Upon receipt of the Conflict-of-Interest Statement the Appropriate Ballad Health review the disclosure in conjunction with the study contract and verify that payments to the investigator or research center are considered "reasonable compensation" for services and procedures required by the research. Reasonable Compensation is defined by the IRS as: "the value of services is the amount that would ordinarily be paid for like services by like enterprises (whether taxable or tax-exempt) under like circumstances".

iv. Specific restrictions will not be placed on the compensation received by an individual as long as such compensation meets this definition. Ballad Health relies on the personal integrity, professional discipline and alert common sense of individuals in the conduct of their external activities when conducting clinical research.

v. Disclosing a financial conflict of interest does not automatically mean the financial interest is inappropriate or improper, it only means that disclosure and evaluation and in some cases approval and oversight of the research will be necessary.

vi. The appropriate Ballad Health VP will speak with the individual disclosing the COI to determine if the COI Committee should be consulted for resolution before the research can be reviewed and considered for approval.

vii. The following disclosure will require automatic convening of the COI Committee "Research where an investigator involved in the project holds a license for the patent or invention under study”.

c. Confidentiality:

i. Disclosure of financial interest shall be maintained in careful and discreet manner and made available only to those within Ballad Health who have a need to see them. A regulatory body or government agency may at any time

request submission of, or review on site all records pertinent to the certification by the appropriate hospital or entity within Ballad Health System.

d. Conflicts Identified by the IRB at Continuing Review:

i. The Ballad Health IRB will notify the appropriate Ballad Health VP of any conflicts identified by the IRB at the time of continuing review. The SVP will determine if the COI Committee should be convened.

ii. The IRB will be informed of any recommendations made to manage the conflict by the COI Committee. The recommendations and actions will become a part of the research application and continue for the duration of the research study.

15. **Conflict of Interest Committee (COIC)**

a. membership can consist of:

i. The Institutional Official

ii. A representative from Corporate Compliance Dept.

iii. A Ballad Health Chief Medical Officer

iv. A representative from Corporate Human Resources

v. A representative from Corporate Pharmacy

vi. The Chair of the IRB

vii. HRPP Director

viii. A Medical Professional Peer in the field that there is a COI (Consultant)

ix. An IRB Staff Member (to serve as recorder)

1) Minutes shall be taken at each committee meeting and maintained by the Clinical Trials and Research Office. The Institutional Official shall sign off on the minutes after they are approved by the committee.

b. The COIC will:

i. Determine if there are compelling circumstances which are sufficient to allow the research to continue in the face of the conflict.

ii. Determine the appropriate strategies to properly oversee and manage potential conflict(s), taking into consideration the possible remedies as outlined below.

iii. Inform the Investigator and the IRB of the actions taken, and the decisions made by the committee.

iv. Review any request by a financially interested individual to rebut the presumption that he/she may not conduct human subjects' research.

v. Document the Committee findings and the bases for any recommendations to permit or to recommend against permitting a financially interested individual to conduct human subjects' research. In either case the COI Committee will prepare a summary report describing the nature and amount of the financial interest and the Committee's recommendations. This summary report shall be

made available to the Ballad Health IRB. When the COI Committee has recommended that a financially interested individual be permitted to conduct human subjects research and the Ballad Health IRB has approved the research and the individual's participation the summary report should be provided to the research subjects or the public upon request.

vi. Management and oversight when a financially interested individual is permitted to conduct human subjects research. As a first principal the COI Committee shall encourage the financially interested individual to minimize the potential conflict of interest by reducing or eliminating the individual's direct involvement in the research. The COI Committee should specify the monitoring procedures or other conditions to be imposed when a financially interested individual will be permitted to conduct human subjects research. Such procedures may include: (1) public disclosure of the researcher's conflict, (2) monitoring of a research's clinical or basic science studies, (3) disqualification of a researcher from taking part in research, (4) compelled divestiture of a researchers ownership interest in an outside firm or cooperation, or (5) severance of a researchers business relationship with an outside firm or corporation. Mitigation plans will be monitored by the COI Committee and others as designated by the Chair of the COI Committee.

vii. The COI Committee shall notify each researcher within ten (10) business days of its findings with regard to the existence of a conflict of interest and the action it deems appropriate to manage, eliminate or reduce the conflict.

1) Communications to the Ballad Health IRB, the facility SVP and Ballad Health officials a summary of the information about the nature and amount of any significant financial interest in human subjects research along with the Committees findings and recommendations concerning requests by financially interested individuals to conduct research.

2) For research that is permitted to go forward by the COIC, the IRB will be informed of the nature of the conflict, and of any recommendations made to manage the conflict by the COIC. The recommendations and actions will become a part of the research application and continue for the duration of the research study.

viii. Process

1) The Ballad Health IRB and responsible institutional officials shall be alerted whenever a financially interested individual proposes to conduct humans' subjects' research.

2) At the time of Continuing Review, the IRB staff will report the ongoing status of the continuing review process to the COI Committee prior to the IRB review.

3) Prior to the Ballad Health IRB final approval (whether initial or continuing review) the COIC shall inform the Ballad Health IRB and responsible Institutional Officials of any significant financial interest held by the financially interested individual who will be conducting the research, as well as the COIC's findings and recommendations concerning the same;

4) When financially interested individuals are permitted to conduct human research the financial interest question shall be disclosed in accordance with Ballad Health COI polices.

5) The COIC shall maintain records of all financial disclosures and all actions taken by the institution with respect to any conflict of interest for at least three years from the date of submission of the final expenditures report (for each cited project), or where applicable from other dates specified in 45 CFR 74.53(b) for different situations.

16. **Rebuttable Presumptions that Financially Interested Individuals May Not Conduct Human Subjects Research**

a. This policy establishes the presumption that in the absence of compelling circumstances a financially interested individual may not conduct human subjects research. This presumption should be rebuttable when compelling circumstances exist.

i. This policy allows the COIC after it reviews the relevant facts and circumstances and documents the compelling circumstances to recommend that a financially interested individual be permitted to conduct the research and to make recommendations for appropriate monitoring and oversight.

ii. A summary report indicating the nature and amount of the financial interest and COIC recommendations shall be transmitted to the Ballad Health IRB and to the responsible Institutional Officials.

b. Monitoring

i. Procedures for internal and when deemed necessary external monitoring when a financially interested individual is permitted to conduct human subjects research, include (but are not limited to):

1) The HRPP Director / Manager and the HRPP office will conduct audits of research records and billing records about every 6 months and report summary findings to the COIC and to the IRB at the time of continuing review.

c. Continuing Review of Studies

i. When a sponsored research proposal is submitted to the Ballad Health IRB for continuing review, each covered individual who will conduct the research will submit a COI Questionnaire to the IRB with the Annual Progress report and Request for Continuing Renewal Application. The Ballad Health IRB shall forward any information it receives concerning a significant financial interest in human subject's research to the COIC. The COIC will make a determination regarding the status and will forward that information to the IRB prior to the IRB meeting.

d. Disclosure of Significant Financial Interest:

i. This policy shall require disclosure of the existence of significant financial interest in human subjects research as to state and federal officials as required by statue or regulation; to research funders or sponsors; to the editors of any publications to which a covered individual submits a manuscript

concerning the research; and in any substantive public communication of the research results, whether oral or written.

ii. Research consent forms should as a matter of Ballad Health COI policy disclose the existence of any significant financial interest held by a covered individual who is conducting the human subject's research. The precise wording of disclosure in the consent form will be decided by the Ballad Health IRB.

e. Prohibition on Payments for Results

i. This policy prohibits payments from Ballad Health or the research sponsor to a covered individual if such payments are conditioned upon a particular research result or are tied to a successful research outcome.

f. Process of Review for Non-Compliance

i. The investigator must agree in writing to allow the mitigation process outlined by the COIC. The HRPD will conduct audits every 6 months for compliance with the research plan. Findings will be reported to the IRB and COIC.

17. **Ethics Consultation**

a. The Ballad Health facility specific Ethics Committee develops, reviews, and revises hospital policies related to ethics in the areas of patient care including conduct of medical staff and employees in providing patient care. This may include policies governing patient rights, treatment limitations, and use of advance directives. In addition, the Ballad Health facility specific Ethics Committee provides consultation to physicians, nurses, other health care professionals, and patients and families concerning specific ethical issues or questions.

b. At the request of the IRB Chair or by a vote of the Board, an ethics consultation may be requested as part of the review process of a protocol by the IRB. In consultation with the Ballad Health facility specific Ethics Committee, additional outside ethics consultation may be requested prior to review of a protocol by the IRB.

c. When a protocol is referred to the Ethics Committee, a written report of recommendations will be requested. The Board will utilize this report in the review of the protocol. The IRB remains the final authority for the approval of all research related to human subjects.

d. When ethics consultation is required, the members of the Ethics Committee and its clinical subcommittee are educated to disclose to the IRB if there is a conflict of interest for any of the committee members. Member with a conflict of interest will not contribute to the review of the protocol.

18. **Monitoring Audits**

a. As a means of evaluating responsible conduct of research compliance, the Research Compliance staff will conduct Monitoring visits and compliance reviews, which are designed to identify standards of excellence and potential areas for improvement in order to promote a solid foundation for the conduct of human subjects' research. Compliance Monitoring is conducted in the form of directed

(for cause) and prospective (routine) reviews. Ballad Health Institutional Compliance Monitoring:

i. All human research approved by the IRB and conducted at Ballad Health may undergo Monitoring in order to assure the protection of human research participants and compliance with Federal regulations, state and local law, IRB policies and procedures, and Ballad Health's Federalwide Assurance with Office for Human Research Protections (OHRP). The purpose of a Monitoring visit is to:

1) Assess adherence to Federal regulations as defined by OHRP and FDA.

2) Assess adherence to Ballad Health IRB policies and procedures.

3) Assess adherence to local and state laws and regulations.

4) Determine that the rights and safety of human research participants have been properly protected.

5) Provide education to investigators.

b. External compliance Monitoring audits may also be conducted in the form of prospective and directed audits at affiliated sites or where Ballad Health IRB serves as the IRB of Record.

c. For both directed and prospective compliance Monitoring, the principal investigator will be contacted regarding the upcoming Monitoring visit and informed of any findings subsequent to the Monitoring visit. Prior to the visit, the principal investigator will be asked to schedule an appointed time with the IRB designated monitor during which the Monitoring visit will occur. The principal investigator will provide a list of study participants (initials or ID numbers only) along with the date of informed consent to the monitor for reference.

d. The following information will be reviewed during the Monitoring visit: regulatory binder, informed consent document(s) for each consented participant, participant's research records, source documentation, inclusion/exclusion criteria, study procedures as approved by the IRB, and occurrence and reporting of adverse events, unanticipated problems and protocol deviations.

e. Subsequent to the Monitoring visit, the Principal Investigator will receive a written summary of findings discovered while auditing the protocol. Additionally, results of all Monitoring reviews, both prospective and directed, are reported to the IRB Chair, and when appropriate to the Senior Vice President of Compliance and Audit Services of Ballad Health.

f. Routine proactive Monitoring (proactive Monitoring) is conducted to assess the investigator's compliance with Federal, state, and local law and Ballad Health and IRB policies. Protocols are selected for routine visits by performing a query of the IRB database or may be requested on a voluntary basis by the principal investigator. The prospective compliance audits may include, but are not limited to, the following:

i. Examining the entire research project.

ii. Assigning observers to the sites where the informed consent process is being conducted.

iii. Interviewing investigators, research staff, or research participants.

iv. Auditing advertisements and other recruiting materials.

v. Monitor conflict of interest concerns.

vi. Assure the consent documents include the appropriate information and disclosures.

vii. Requesting progress reports from Investigators.

viii. Other Monitoring or auditing activities deemed appropriate.

g. Directed Monitoring of IRB approved research occurs in response to identified concerns and requires review and action determination at a Board meeting. Upon completion, the results will be reported to the Director of Risk management and the IRB Chair. Initiators of Monitoring activities may include:

i. A response to an externally initiated complaint (OHRP, FDA or sponsor) of potential protocol violations or Non-Compliance.

ii. A response to a complaint or concern from a participant, a participant's family member.

iii. A response to a concern raised by an employee.

iv. A Board directive or concern.

v. An investigator with a history of poor adherence to research policies and procedures.

h. Consent Monitoring

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

ii. Such Monitoring may be particularly warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the IRB has identified concerns associated with a particular investigator or a research project.

iii. If deemed appropriate as a result of routine or for cause audit findings, or if otherwise justified by the nature of the research and/or the subject population, special Monitoring of the consent process will be required for either a set time period or set number of subject enrollments as determined by the convened board or the IRB Chair working in conjunction with the IRB Project Manager. The IRB will include in the written communication to the Principal Investigator the need to have the consent process monitored, the justification for this decision, and any other relevant details. The Principal Investigator will be instructed to inform the IRB designated monitor of all upcoming scheduled visits which might reasonably include efforts to enroll new subjects into the study. The IRB designated monitor will arrange to be

present during the consent process and will be informed of the particular issues which warrant special Monitoring of the consent process. After the Monitoring, a written report of the observation will be provided to the IRB chair.

iv. The report will be shared with the convened board in all cases, which will determine if the process is adequate or if a corrective plan of action is required. The board's decision will be communicated to the Principal Investigator per normal mechanisms.

i. Non-Compliance

i. If any of the above Monitoring activities find that participants in a research study have been exposed to unexpected serious harm or that Non-Compliance with human subjects' research regulations has occurred, such findings will be promptly reported to the SVP of Compliance and Audit Services of Ballad Health for further review (Non-Compliance Involving Human Subjects'). If the Monitoring visit identifies findings or allegations of Non-Compliance, the Compliance and Audit Services team will conduct an investigation or refer to designated individual (Non-Compliance Involving Human Subjects').

19. **Investigator Responsibilities**

a. The Ballad Health IRB follows the Department of Health and Human Service's (DHHS) revised Common Rule 2018 Requirements. Any studies given IRB approval for Research prior to January 21, 2019, will fall under the Pre-2018 Requirements of the DHHS Common Rule. The primary responsibility of the principal investigator is to acknowledge and accept the responsibility and ethical obligations for protecting the rights and welfare of human Research participants in compliance with current Federal regulations and IRB requirements governing Human Subject research.

i. The Principal Investigator (PI) is ultimately responsible for the conduct and supervision of the study and for assuring compliance with Institutional Review Board (IRB) policies and procedures and with Federal regulations.

ii. Even though a principal investigator may delegate specific tasks to other members of the Research team, he or she cannot delegate the responsibility for ensuring that those tasks are completed according to institutional and Federal regulations. The PI must ensure that each member of the Research team must be qualified by virtue of education, training, and experience (e.g., hospital certification, Human Subjects Research training, state license) to perform each of their delegated tasks.

iii. Investigators play a crucial role in protecting the rights and welfare of Human Subjects and are responsible for carrying out sound ethical Research consistent with Research plans approved by an IRB. Along with meeting the specific requirements of a particular Research study, investigators are responsible for ongoing requirements in the conduct of approved Research that include, in summary:

1) Obtaining and documenting informed consent of subjects or subjects' legally authorized representatives prior to the subjects' participation in the research, unless these requirements have been waived by the IRB (45 CFR 46.116; 45 CFR 46.117);
2) Obtaining and documenting informed consent of subjects or subjects' legally authorized representatives prior to the subjects' participation in the research, unless these requirements have been waived by the IRB (45 CFR 46.116; 45 CFR 46.117);
3) Obtaining prior approval from the IRB for any modifications of the previously approved research, including modifications to the informed consent process and document, except those necessary to eliminate apparent immediate hazards to subjects (45 CFR 46.108(a)(3)(iii)); and
4) Ensuring that progress reports and requests for continuing review and approval are submitted to the IRB in accordance with the policies, procedures, and actions of the IRB as referenced in the institution's OHRP-approved Federalwide Assurance (45 CFR 46.103(b), 45 CFR 46.109(e), 45 CFR 46.115(a)(1)). In certain circumstances, investigators also would be responsible for meeting the following additional regulatory requirements:
    a) Providing to the IRB prompt reports of any unanticipated problems involving risks to subjects or others 45 CFR 46.108(a)(4);
    b) Providing to the IRB prompt reports of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB (45 CFR 46.108(a)(4)(i)); and
    c) Keeping certain records as required by the HHS regulations for at least three years after completion of the study (45 CFR 46.115(b)).

b. To serve as the PI on an IRB-approved protocol, an individual must be at least 18 years of age and have current training in Human Subjects' Research protection with Collaborative Institutional Training Initiative (CITI). Ballad Health IRB's OHRP-approved Federalwide Assurance (FWA) is responsible for ensuring that its investigators conducting HHS-conducted or -supported Human Subjects Research understand and act in accordance with the requirements of the HHS regulations for the protection of Human Subjects. Therefore, as stated in the Terms of the FWA, Ballad Health IRB has established training and oversight mechanisms (appropriate to the nature and volume of their research) to ensure that investigators maintain continuing knowledge of, and comply with, the following:
    1) Relevant ethical principles;
    2) Relevant federal regulations;
    3) Written IRB procedures;
    4) OHRP guidance;
    5) Other applicable guidance;
    6) State and local laws; and

7) Institutional policies for the protection of Human Subjects.

c. The PI must also meet one of the following criteria:

i. A credentialed medical staff member at Ballad Health .

ii. A degree candidate or a medical resident or fellow at Ballad Health. The IRB may require an institutional faculty advisor or Ballad Health medical staff serve as a co-investigator depending on the nature of the study.

iii. The IRB may require a Ballad Health medical staff member to serve as a co-investigator depending on the nature of the study.

iv. A staff person with a Ballad Health appointment such as nurse, respiratory therapist, or dietitian. The IRB may require a Ballad Health medical staff serve as a co-investigator depending on the nature of the study.

v. If the PI is not a credentialed Ballad Health physician and the protocol includes treatment at a Ballad Health facility, a responsible Ballad Health physician investigator is identified in addition to the PI.

d. Since Ballad Health is a teaching system, the IRB encourages studies that serve to train students for future careers in medicine or related fields, provided such studies do not adversely affect any aspect of the care of patients, particularly their right to privacy and confidentiality.

e. The regulations governing the responsibilities of Ballad Health investigators of Human Subject Research include:

1) The Ballad Health Federalwide Assurance agreement with the Office of Human Research Protection (OHRP).

a) With this agreement, Ballad Health commits to following the Terms of Assurance for Protection of Human Subjects for Institutions Within the United States (45 CFR 46). The Terms of Assurance are maintained on file in the IRB office and are available for review upon request. You may also view the Terms of the Assurance by visiting the HHS website (http://www.hhs.gov/ohrp/Assurances/Assurances_index.html).

b) Investigators acknowledge that they understand their responsibilities in protecting human Research participants by signing the Certification of Investigator Responsibilities document. This document can be found on IRBNet under "Forms and Templates," as well as, placing a request to the IRB staff.

2) The Food and Drug Administration (FDA) regulations governing Human Subject protections and good clinical practices for studies involving investigational drugs, devices, and biologics. The specific regulations concerning investigator responsibilities are as follows:

a) Investigational drugs - 21 CFR 312.60

b) Investigational devices - 21 CFR 812.100

c) Biologics - 21 CFR 600.10

3) When conducting Research that involves a product that is regulated by the FDA, investigators must sign an agreement / statement with the FDA indicating that they accept their responsibilities (e.g., Form 1572 for investigational new drugs).

4) Regulations concerning financial disclosure can be found in 21 CFR 54.

f. The principal investigator is the ultimate protector of the Research participant's rights and safety. He or she is obligated to ensure that all Human Subjects' Research Receives IRB Approval before the Research Starts. Investigators may not initiate Research involving Human Subjects without prior IRB review and approval. If data are collected for non-Research purposes and an investigator later finds that the data could contribute to generalizable knowledge, the investigator must submit a proposal to the IRB for review and approval prior to publication or presentation of the data (e.g., journal article, poster session, public speech or presentation, or project report).

20. **Investigator Responsibility in Submission of a Research Project for IRB Review**

a. Before initiating any Research or gathering of any Research data, PI's must have approval from the IRB.

i. The implications of engaging in activities that qualify as Research that is subject to IRB review without obtaining IRB review are significant. Results from such studies may not be published or presented unless IRB approval had been obtained prior to collecting the data. To do so is in violation of this policy. It is also against Ballad Health policy to use inappropriately collected Human Subject Research data to satisfy thesis or dissertation requirements.

ii. If an investigator begins a clinical project and later finds that the data gathered could contribute to generalizable knowledge (i.e., publish or present the results), it is important that the investigator submit a proposal to the IRB for review and approval prior to release of such information. It is in the investigator's best interest to carefully consider the likelihood that he or she will want to use data for Research purposes in the future, and to seek IRB approval prior to commencing the work.

b. Conduct Study in Accordance with the IRB-Approved Protocol and IRB-Approved Informed Consent

i. The principal investigator must not institute any changes to the IRB-approved protocol and/or consent form document without first obtaining IRB approval for such changes. The sponsor must also be notified of an investigator's intent to modify the protocol or consent form. In rare instances, an investigator may deviate from the protocol without first notifying the IRB in order to eliminate immediate hazard to a study participant. Any such protocol deviations must be promptly reported to the IRB. All unanticipated problems, AEs/SAEs, and protocol deviations should be reported promptly to the IRB. Specific timeframes for reporting these events may be located within Unanticipated Problems, Adverse Events, and Protocol Deviations.

Documentation surrounding the event should also be placed in the Research record and the medical record if applicable.

c. Complete Financial and Contractual Requirements before the Research Begins

i. Investigators may not initiate Research without executing all federal and state requirements, as well as all agreements and prerequisites set forth in a grant or contract (including industry, federal grants, and/or foundations) that is to be completed prior to the conduct of research. It is the investigator's responsibility to:

ii. Ensure that appropriate funding is available to support the proposed research,

iii. Obtain budget approval if applicable,

iv. Contract execution procedures are in place to ensure appropriate billing associated with clinical research, including obtaining all appropriate signatures (if applicable), and

v. Ensure that necessary and appropriate contracts, if applicable, are executed prior to the conduct of the study, including individual investigator agreements.

d. Personally Conduct or Supervise the Study

i. The principal investigator may delegate study-related activities, but he or she is ultimately responsible for the conduct of the study. It is the responsibility of each investigator to assure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform them. Every member of the Research team is responsible for protecting participants in research. Co-investigators, study coordinators, nurses, Research assistants, and all other Research staff have a strict obligation to comply with all IRB determinations and procedures, to adhere rigorously to all protocol requirements, to inform investigators of all serious and unexpected adverse reactions or unanticipated problems involving risk to participants or others, to oversee the adequacy of the informed consent process, and to take whatever measures are necessary to protect the safety, rights and welfare of participants. Regardless of involvement in research, each member of the Research community is responsible for notifying the IRB promptly of any serious or continuing noncompliance with applicable regulatory requirements or determinations of the designated IRB of which they become aware, whether or not they are directly involved in the research.

ii. It is the responsibility of the principal investigator to inform all co-investigators about the protocol and consent form. It is also the responsibility of the principal investigator to be aware of any conflicts of interest for any members of the study team. The principal investigator must provide all co-investigators, Research coordinators, and other Research staff with a copy of the current Research protocol and consent form and fully inform them of:

1) Study procedures (including modifications to the protocol);

2) Informed consent requirements and process;

3) Potential risks associated with study participation and the steps to be taken to prevent or minimize these potential risks;

4) Adverse event reporting requirements;

5) Data and record-keeping requirements;

6) Current IRB approval status of the study;

iii. Principal investigators must also ensure that if their protocol lists collaborating investigators at another institution that appropriate IRB approval for the study has been obtained at the other institution.

iv. Any concerns raised by members of their Research team, must also be addressed.

1) Investigators should meet regularly with their Research teams for the purpose of reviewing the progress of the research, and to encourage discussion of any concerns about the Research in general, or about a specific Research subject;

2) Investigators should inform each member of the Research team, individually, of their responsibility to voice any concerns they may have, without fear of repercussions;

3) Investigators should investigate each expressed concern, and report back to the individual who raised it;

4) Investigators may not punish an individual who brings a concern to their attention;

5) Investigators are responsible for reporting to the IRB any concerns that result in findings regarding subject safety or potential breaches to the rights and welfare of a Research subject, compliance with the Research protocol, informed consent violations, or the integrity of the Research data.

e. Recruit Subjects in an Ethical Manner

i. The recruitment of subjects must respect the Research subjects' privacy and confidentiality. An investigator should not contact patients who are not in his or her practice unless the patient's physician or caregiver has previously notified the potential Research subject (or the parent or legal representative of the potential Research subject) and obtained his or her approval for such contact (Recruitment of Subjects).

f. Ensure That the Requirements for Obtaining Informed Consent Are Met

i. It is the principal investigator's responsibility to oversee the informed consent process, making sure that each potential subject fully understands the purpose of the research, the Research procedures, the potential risks of study participation, and his or her rights as a Research study volunteer. Informed consent must be obtained prior to the initiation of any study procedure. It is also the principal investigator's responsibility to be sure that anyone obtaining consent from subjects is certified in Human Subjects' Protection and appropriately knowledgeable about the study. The principal investigator is

also required to include appropriate additional safeguards in the informed consent to protect Research subjects who are likely to be vulnerable to coercion or undue influence (Informed Consent). It is the principal investigator's responsibility to assure that potential subjects have the cognitive ability to give consent. To attest to the appropriateness of the subject for the study and the adequacy of the consent process, all consent forms must be signed by the principal investigator within 30 days of the subject signing the consent form.

g. Maintain a Protocol File of Human Research Project Documents

   i. The principal investigator must maintain a file of Human Subject's Research project documents. Investigators conducting Human Subjects Research will ensure that the following Research activities are properly documented and reported to the IRB as necessary:

      1) A copy of the Human Subject's Research application submitted to the IRB along with all IRB approvals, amendments, continuing reviews, protocol deviations, and adverse events;

      2) A copy of the sponsor's IRB-approved protocol (if applicable);

      3) A copy of the Federal grant application (if applicable);

      4) A copy of the investigator's brochure for an investigational new drug (if applicable);

      5) A copy of the investigational device exemption information (if applicable);

      6) A copy of an investigator-initiated IND or IDE application (if applicable);

      7) A copy of the IRB-approved consent form with the affixed IRB approval stamp;

      8) The original of each IRB-approved consent form signed by each participant enrolled in the research. For studies involving inpatients, the investigator is responsible for ensuring that a copy of the consent form is in the patient's medical record;

      9) A copy of the IRB-approved recruitment materials;

      10) A copy of the IRB-approved study materials (e.g., surveys, questionnaires);

      11) A copy of all correspondence with the IRB, sponsor, funding source, FDA, or others;

      12) A copy of all data derived from the study (case report forms, computer data, adverse event reports, drug/device accountability records, etc.)

h. Comply with Federal and Institutional Time periods for Record Retention

   i. The principal investigator is required to retain records associated with a Human Subject's Research project. The record-keeping requirements vary depending on whether Federal funding was provided for the project or the protocol was conducted under FDA regulations. The data stored must be kept in a secure, protected manner (Records).

ii. Records for projects that involve FDA regulated articles (drugs, devices, biologics, assays, etc.) must be kept for periods required by FDA regulations based on whether the principal investigator is a sponsor or an investigator.

i. FDA Sponsors:

i. Sponsors must maintain adequate records showing the receipt, shipment, or other disposition of the investigational drugs. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, the shipment date, the shipment quantity, and batch or code mark of each such shipment. Sponsors must retain the records and reports required for two years after a marketing application is approved for the drug. If an application is not approved for the drug the sponsors must retain the records and reports required for two years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

j. FDA Investigators:

i. An investigator is. required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor or otherwise provide for disposition of the unused supplies of the drug under 21 CFR 312.59.

k. An investigator is required to prepare and to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual subject administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data, which is typically made of signed and dated consent forms, medical records, progress notes of the physician, the subjects' hospital charts, and the nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.

l. Records are required to be maintained for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, records are required to be maintained for three years after the investigation is discontinued and FDA is notified.

m. Records for non-FDA Projects

i. Projects that are not funded by a Federal agency or that do not involve FDA regulated articles must be kept according to the Ballad Health IRB Policy on Data Retention (Records).

n. Respond To Subjects Who Have an Adverse Event

i. The principal investigator must ensure that subjects who have suffered an adverse event associated with Research participation receive adequate care to correct or to alleviate the consequences of the adverse event (Unanticipated Problems, Adverse Events and Protocol Deviations).

o. Keep Subjects Fully Informed of any New Information

i. The principal investigator must ensure that Research subjects are kept fully informed of any new information that may affect their willingness to continue to participate in the study (Informed Consent).

ii. The principal investigator must provide reports as required by the Sponsor and by the IRB.

iii. The principal investigator must respond promptly to all requests for information or materials solicited by the IRB, including the timely submission of the Research.

p. Make Records Available for Inspection

i. Investigators are required to make Research records available for audit by: the sponsor or its representatives, the FDA, the OHRP, hospital accrediting bodies, and the Ballad Health institutional compliance officer.

q. Ensure Accountability of Investigational Drugs, Devices, or Biologics

i. Accountability of investigational products is the responsibility of the investigator. Maintaining accurate records of drugs, devices, and biologics is vital. Investigators may delegate some of the management responsibilities to an appropriate institutional entity (e.g., Investigational Pharmacy).

ii. Investigators must ensure that investigational products are used only for the specific protocol for which they were provided, that each study participant is given specific instructions for their use, and that each subject is being compliant with study drug/device/biologic. Investigational products must be adequately and appropriately secured, especially in the case of drugs subject to the Controlled Substances Act. The material should be kept in a locked cabinet or enclosure with limited access.

r. Protect the Privacy of Subjects and Maintain the Confidentiality of Data

i. It is the responsibility of the investigator to provide a data privacy and confidentiality plan with justification in the protocol on what steps are taken to maintain confidentiality of subject data. The plan must describe how confidential information will be protected from improper use and disclosure. Discussion of maintenance of subject identifiers or a plan to destroy identifiers at the earliest opportunity consistent with the appropriate conduct of the Research must be included. Assurances must be provided that confidential (private) information is necessary for the conduct of the Research and that this information will not be re-used or disclosed to any other person or entity without written authorization by the subject.

s. Consent Designees

i. The principal investigator does not have to obtain consent personally. The study team may include consent designees who are authorized to obtain consent. Consent designees are added to the study by amendment and may obtain consent only after the approval of the IRB for each designee. Each individual who interacts with potential Research participants as part of the consent process must have completed Human Subjects' Protections Certification (Documented Training in Human Subjects Protection). The

principal investigator must ensure that each of these individuals is knowledgeable about the study and capable of answering study-related questions posed by the potential participant (Informed Consent).

t. Participant Complaints/Concerns

i. The principal investigator is responsible for providing contact information in the consent form to allow participants an opportunity to express complaints or concerns about study procedures or participation. Contact information for the study staff and for the Ballad Health office must be included in the consent form. Complaints received by the IRB office will be investigated, and the result reported to the Institutional Official for Ballad Health and reviewed by a convened Board, if applicable.

ii. Any concern or question raised by a Research subject (or parent, legal guardian, Legally Authorized Representative, as applicable) before, during, or after the conduct of a Research study, must be addressed.

iii. The principal investigator is required to retain documentation in the protocol file of any complaints or concerns and their resolution. Serious complaints should be brought to the attention of the IRB when they occur, and all complaints should be reported at the time of continuing review.

u. Data and Safety Monitoring Plan

i. It is the responsibility of the investigator to provide a Data and Safety and Monitoring Plan (DSMP) for the IRB to review as part of the protocol. Detailed requirements for a DSMP are available in New Protocol Submission Requirements.

v. Sponsor-Investigator Responsibilities

i. The sponsor of a clinical investigation initiates and holds the IND, IDE, or Biologics License for a clinical investigation, but may not actually conduct the investigation. Although the sponsor is usually a pharmaceutical, biotech, or medical device company, an individual, group of individuals, or an institution can also be considered a sponsor for an investigation. An investigator is referred to as the sponsor-investigator when the individual investigator is also the initiator of the clinical investigation. Please see Investigation Devices Used in Research regarding INDs or IDEs for more details regarding Sponsor-Investigator obligations.

21. **New Research Project Protocol Submission Requirements**

a. All protocols must meet the criteria required under Federal regulations. It is the responsibility of IRB members to assure that approved protocols meet these criteria.

b. If an IRB protocol is based on a grant application or an industry-sponsored protocol, a copy of the protocol from the sponsor, and the Investigator's brochure or Instructions For Use (IFU) must be submitted via IRBNet. All identifiable financial information should be deleted.

c. Research Protocol

i. The research protocol describes the study and is used by the IRB to assess the scientific and ethical merits of the proposed study. There is no limit to the number of pages; however, the length of the protocol should be proportionate to the complexity of the study. Information that is not relevant to the IRB review should not be included in the submitted protocol.

ii. Required information in the protocol includes (See the next section for details about the requirements in each section):

1) Introduction/background
2) Justification/rationale/significance of the study
3) Purpose, including specific aims and/or hypotheses
4) Study design including population to be studied, recruitment procedures and available resource
5) Risks and discomforts and how minimized
6) Benefits to subjects
7) Costs to the subject
8) Alternative(s) to participation
9) Payment to the subjects (include both reimbursement and incentives)
10) Plan for obtaining informed consent
11) Provisions for subjects from vulnerable populations
12) Subject privacy and data confidentiality
13) Data analysis plan
14) Data safety monitoring plan
15) Plans for the subjects at the end of the protocol
16) References

iii. The IRB encourages the use of tables and flowcharts when they make the protocol easier to understand. The protocol should include a selective list of references that are related to the protocol. The Protocol should be appropriately page numbered.

d. Detailed Protocol Requirements

i. Human Subjects Full Review Form

1) All new protocols must be submitted with a current Human Subjects Full Review Form. This form provides important information used by the IRB and the administrative staff in evaluating a protocol. All items on the form must be completed.

ii. Purpose, Including Specific Aims and/or Hypotheses

1) This section should state clearly what is hoped to be learned from the research. The purpose should be written at a level to be understood by individuals with a general medical background.

iii. Background and Significance

1) This section should include the relationship of the research to previous studies in the field and include pertinent references. Describe relevant experimental or clinical findings which led to the plan for the project. This must be succinct and comprehensible without reference to other material. For studies designed to compare or evaluate therapies, there should be a statement of the relative advantages or disadvantages of alternative modes of therapy. A few pertinent references should be cited; however, exhaustive literature reviews are not necessary. If earlier studies have produced conflicting evidence, it is necessary to cite these studies and explain the rationale for the study design that was chosen.

2) The significance of the study for both the individuals participating and for the advancement of knowledge should be stated. How significant is the new knowledge being sought in relation to the potential risks in carrying out the research.

iv. Research Plan

1) This section is to inform the IRB of the specific nature of the procedures to be carried out on human subjects in sufficient detail to permit evaluation of the risks. This section should also provide information that will allow the IRB to confirm the claim that methods employed will enable the investigator to evaluate the hypothesis posed and to collect valid data.

e. Study Population

i. Protocols must be precise as well as concise in defining a study population and how the population will be contacted (Recruitment of Subjects). Describe recruitment procedures, including how it will be ensured that subject selection is equitable and that all relevant demographic groups will have access to study participation (45 CFR 46.111(a)(3)). Part of subject selection includes ensuring that no person is unduly denied access to research from which they could potentially benefit, without good reason (Belmont Report, ethical principle of Justice). For example: to exclude non-English speaking individuals purely because it is inconvenient to have the consent form translated into an understandable language; or because the research staff does not speak the language, is not an acceptable reason for their exclusion. The IRB would determine this to be unfair and an injustice to those individuals.

ii. In describing the equitable selection of subjects, please ensure information is provided to justify the defined population(s) with regards to the following:

1) The purposes of the research.

2) The setting in which the research would be conducted.

3) Whether prospective participants would be vulnerable to coercion or undue influence.

4) The inclusion/exclusion criteria.

5) Participant recruitment and enrollment procedures.

6) The amount and timing of payments to participants.

iii. Describe how you will protect the privacy of participants i.e., what you will do to maintain individual's interest in being left alone and being treated in a way that is comfortable to the individual.

iv. The inclusion and exclusion criteria for both subjects and, if appropriate, control subjects should be specifically stated. Assurance is required that there will be equitable selection of subjects. Limited participation or exclusion of minorities or women must be justified.

v. Patients identified from medical records must not be contacted without permission from the responsible physician. The lack of a response from the responsible physician cannot be construed as approval to contact the patient.

vi. If patients are to be involved whose care is the responsibility of departments or special care areas other than that of the responsible investigator, that department or special care area should be identified as having approved the protocol.

vii. If children are included as research subjects the investigator must provide an assessment of the level of pediatric risk (45 CFR 46.404, 405, 406 or 407) involved in the research (Board Meetings and Administrative Policy). The final determination of risk level is made by the IRB.

f. Study Population – Inpatient a Ballad Health Facility

i. For patients receiving care in the hospital, it is mandatory that the responsible physician, or the physician of record, approve the participation of any patients before they are recruited for a protocol. It should be indicated in the consent progress note that the responsible physician has given permission to approach the patient for possible participation in the study.

g. Study Design

i. If a study includes randomization, the procedure for randomization should be discussed. In studies involving the use of a placebo or a "washout" period, the protocol and the consent must discuss what protections are in place if the subject's condition deteriorates (Use of Placebos and Washout Periods in Research).

h. Assessment of resources

i. Investigators must include information in the protocol to ensure: 1) access to a population that would allow recruitment of the required number of participants; 2) sufficient time to conduct and complete the research; 3) adequate numbers of qualified staff; 4) adequate facilities; 5) a process to ensure that persons assisting with the research were adequately informed about the protocol and their research-related duties and functions, and 6) availability of medical or psychological services that participants might require as a consequence of the research.

i. Study Procedures

i. Include a description of the intended procedures as they directly affect the subjects. There need not be a detailed account of techniques that do not directly affect the human subject (e.g., details of laboratory methodology). Include:

1) The number and estimated length of hospitalizations or study visits;

2) The length of time for various procedures and frequency of repetition;

3) Any manipulation that may cause discomfort or inconvenience;

4) Doses and routes of administration of drugs;

5) Amounts of blood to be drawn;

6) Plans for post-study follow-up.

ii. All specific procedures to be performed on human subjects for purposes of research should be detailed. Uncommon medical procedures should be fully explained. It is important to distinguish between usual patient care and any experimental procedures. The protocol should indicate what changes in medical care will occur as a result of the study, how care will be managed, and by whom. If subjects will receive standard care as part of the study, these procedures/tests/interventions must be specifically described and identified as standard care.

iii. A general time schedule for various procedures should be provided, showing what a subject might expect regarding how long each aspect of the study will take; the frequency and timing of ancillary procedures; and the duration of discomfort. It would be helpful to present complicated studies with a simple flow chart to enhance the narrative description. The location of the study, including laboratories for special testing, must be indicated.

j. Electronic Record System Utilization

i. If study procedures require the use of the Ballad Health Physician Portal or other Ballad Health clinical electronic documentation systems, the following information must be included in the research protocol: a) justification for use of the system and why this information cannot be obtained in another manner; b) what information will be collected from the system and the specific process for collection; c) how that information will be protected and secured including how long access to that information will be necessary through the electronic system; and d) who will perform the data collection.

ii. Requests for use of the Physician Portal for research purposes only will be reviewed by Ballad Health Administration, to ensure that the access has been justified and noted in the current IRB approved protocol. Ballad Health personnel who have access to the Physician Portal as part of clinical duties must ensure that the IRB has approved collection of data from the Portal as part of the research protocol prior to using the Portal to obtain information for research purposes.

k. Risks and Discomforts and How Minimized

i. Risks may include side effects of drugs, hazards of procedures, or dangers of withholding a therapy of proven value. Potential research risks include more than physical harm; risks may also include emotional or psychological harm, social risk of stigmatization, and economic or legal risk. There should be a description of all known or potential risks, discomforts, or inconveniences to the subject. This should include the investigator's explanation of how he or she concluded that the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result from the research. The description of risks may be extensive or may be brief, depending on the protocol. When possible, it is appropriate to cite statistical probability of risk occurrence. Risks related to the research need to be distinguished from risks that are part of standard medical treatment.

ii. The subject should be told what will be done to minimize risks and counteract side effects and which, if any, side effects might be irreversible. In addition to the known risks of being in the study, there may be unforeseeable complications; the subject should be made aware of this fact. Describe the procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects.

iii. There are specific risks that may be present when genetic information is part of a protocol. The magnitude of the risks and a description of the risks should be given in both the protocol and the consent form. These risks may include:

1) Future problems with access to, or retention of, benefits or entitlements (e.g., health insurance, life or disability insurance, educational opportunities, employment, etc.,);

2) Stigmatization: negative views of others, within or without the subject's family, about the subject; the possibility of altered family relationships and interactions;

3) Psychological responses to information: altered self-concept; possible feelings of depression, guilt, anger, etc.;

4) Detection of previously unknown biological relationships within a family: paternity, maternity, and adoption.

l. Compensation for Injuries

i. For any research involving more than minimal risk, federal regulations require an explanation as to whether any compensation and/or medical treatment is available if injury occurs and, if so, what it consists of, or where further information may be obtained. The principal investigator may need to distinguish between treatments for injuries related to the investigational intervention versus treatments for routine medical care for complications or conditions associated or expected with the disease or disorder involved. If a study entails minimal risk and if, in the opinion of the investigator, there is

the potential for physical injury, an "in case of injury" section should be incorporated into the protocol and consent form.

ii. "In case of injury" provisions should include:

1) Where and from whom medical therapy may be obtained;

2) What therapy will consist of and its duration;

3) Who will pay for the therapy;

4) Whom to contact in case of injury; and

5) What happens after the study ends or if the subject is dropped from the study because of progression of disease and/or other circumstances.

iii. The source of funds, if any, to cover the costs of medical therapy for injuries should be specified. If none is available, it is important that the subject understand what may be billed to him or her, or to a third-party payer. This includes routine medical care that is normally billed to the subject even when it is performed in conjunction with a research study. Additionally, because there is a responsibility to protect the subject and mitigate risks whenever possible, the principal investigator should attempt to obtain funding sources for treatment of research related injuries whenever possible. When the study is sponsored by a commercial, for- profit entity, the principal investigator is required to attempt to secure from the sponsor a written commitment to pay for the costs of medical therapy. It is preferred that the sponsor's commitment not be that the sponsor's reimbursement begins when the subject's insurance carrier's coverage ends. If a sponsor is willing to pay for research related injuries, this needs to be part of the sponsor's contract with the investigator and Ballad Health.

m. Benefits to Subject

i. Describe the potential benefits to the individual subjects enrolled in the study. If there are no direct benefits, indicate there are none. Reimbursement or compensation is never a benefit. The potential benefits which may result for other individuals, general knowledge, etc., should also be discussed. For studies with greater than minimal risk, discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result.

n. Costs to the Subject

i. The IRB is concerned about the cost accounting of research studies, and investigators must address the problem of extra costs incurred because of the research project. If costs due to research are to be incurred by the subject, such costs must be stated on the consent form. Non-therapeutic studies may not be charged to the subject or third-party payers. Describe and justify any costs that the subject will incur as a result of participation; normally, subjects should not have to pay for research procedures that do not provide some direct benefit. Generally, drugs used under an IND number may not be charged to subjects or third-party payers.

o. Alternative(s) To Participation

i. Discuss the alternatives to participating in the study. Are some or all of the study treatments available without participating in the study? Are similar approved treatments available outside the study? Provide a description of the local standard of care for the condition, if applicable.

p. Payment to the Subjects (Reimbursement and Incentives)

i. Describe any material inducements that will be offered to subjects in return for their participation: e.g., direct payment, free hospitalization, medical care, medication, food, tests, etc. Discuss both reimbursement (compensation for expenses, e.g., parking, meals) and incentives (payment for discomfort).

ii. Describe the schedule of payment to subjects based on their complete or partial participation. Identify whether early withdrawal from the study will result in a reduced payment or whether it makes a difference if it is the subject or the investigator who decides to terminate the subject's participation (Remuneration of Subjects).

q. Description of the Informed Consent Process

i. The protocol must include a description of the "informed consent process. Please consider the following points:

1) The timing/waiting periods for participants to ensure that they are allowed adequate time to make an informed decision and to minimize the possibility of coercion or undue influence. Sufficient time must also be allowed for the participant to review and consider participating with the assistance of family members, research partners or representative if necessary. Other items to consider regarding time/waiting periods are: Is the potential participant given a copy of the consent form to read prior to the discussion of the study? Is the consent form presented in person or mailed to subjects (where they can review it in the privacy of their own home)? How much time elapses between the presentation of the study and informed consent form and the actual signing of the form?

2) The steps taken to minimize the possibility of coercion or undue influence

3) The language used by those obtaining consent

4) The language understood by the prospective participant or the representative

5) Who will be involved in obtaining consent?

6) Who will be approached for consent/assent/permission (parental or guardian)?

r. Comprehension of informed consent

i. In order for the IRB to evaluate issues of comprehension, the protocol needs to describe the steps taken to ensure that participants or their legal representative, and those who are involved in obtaining consent, understand the research. Please consider the following points:

1) Once a potential participant is identified, what process is followed to inform the subject of the study prior to obtaining a signature on the informed consent form?
2) Who introduces the study to the potential subject?
3) Who reviews the informed consent document in depth?
4) Do you require the potential participant to have another person present during the presentation of the study?
5) Who answers the questions presented by the potential participant and/or family?
6) What method is used to determine if the potential participant fully understands the study, what is required from them, risk and benefits, and their rights as a participant?
7) Is the principal investigator usually present during the presentation of the informed consent?

ii. Although written consent forms are generally required, in studies that present no more than minimal risk of harm to subjects and involve no procedures for which written consent is normally required in the context of medical practice, oral consent may be approved. Written consent may also be waived if the consent form is the only record linking the subject to research involving sensitive information and the primary risk of the research would be breach of confidentiality.

iii. If the investigator believes that oral consent is appropriate, the request for waiver of written documentation of consent must be justified in the protocol. If the IRB approves the waiver of written consent, i.e., verbal or oral consent, an information sheet or a document that addresses the required elements of informed consent, will be required for subjects.

iv. No hospitalized patient should be approached to participate in research until his or her responsible physician has approved contact between the investigator and the patient. Investigators who believe that prior approval of the responsible physician is unnecessary for a particular protocol should provide their reasons for this (Informed Consent).

s. Provisions for Subjects from Vulnerable Populations

i. Address whether some or all subjects to be recruited will be vulnerable to coercion or undue influence. If they are, describe the additional protections provided to these subjects to protect their rights and welfare. Under the Belmont report, the ethical principle of Beneficence requires that risks to subjects are outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society (i.e., knowledge to be gained). In reviewing research involving vulnerable subjects, the IRB are required to determine whether the presented risks are fully justified; and the appropriateness of their inclusion has been demonstrated. For example, if subjects who may not be competent to give consent are to be included, a description of how competency will be assessed needs to be included.

Additional information for vulnerable populations is provided in this policy, Assent from Children in Research Studies; Pregnant Women and Human Fetuses; Neonates; and Prisoners as Research Subjects.

t. Subject Privacy and Data Confidentiality

   i. Describe the provisions to protect a subject's privacy and the confidentiality of their data in connection with their participation in the research study. (NOTE: While confidentiality concerns data, privacy concerns people). Ensure that you include a description of (i) how any identifiable information will be accessed and how the information obtained will remain confidential; and (ii) that it will be disclosed only with the subject's permission or as required by U.S. or Tennessee law. Examples of information that are legally required to be disclosed include abuse of a child or elderly person, and certain reportable diseases.

u. Privacy of participants

   i. Privacy refers to a person's desire to control access of themselves to others. Describe how you will protect the privacy of participants i.e., what you will do to maintain individual's interest in being left alone and being treated in a way that is comfortable to the individual. Describe specifically, the procedures for identifying participants; how you will gather information from or about them; and how any invasion of privacy will be minimized. Please also consider the location where the information is to be gathered and whether the participants will be comfortable in the research setting being proposed. EXAMPLES: People may be uncomfortable answering questions about their employer in an open cubicle, so investigators may arrange for a more private interview location; or people may not want to be seen in a place that might be stigmatizing to them, such as a pregnancy counseling center, so investigators may arrange for questionnaires to be mailed to subjects.

v. Confidentiality of data

   i. Describe how research data will be stored and secured to ensure confidentiality. If data will be shared with other investigators, explain why this is necessary and, if relevant, justify releasing data with identifiers that would permit the recipient investigator to know or infer the identity of the subject (45 CFR 46.111(a)(7) and 21 CFR 56.111(a)(7)). If highly sensitive information is to be gathered, such as information that would put the subject at risk of criminal or civil liability, either provide a Certificate of Confidentiality or explain why one was not requested. If audio or video tapes are made for research purposes describe how they will be kept secure and when they will be destroyed.

   ii. Further describe the disposition of information obtained during a study. When a study is of a diagnostic or therapeutic modality, information is very often entered in the subject's medical record, discussed with the subject, and transmitted to anyone else whom the subject designates. If the intent of a study is not directly related to diagnosis or therapy of a particular subject, he or she has the right to decide whether or not such information shall be

entered into the medical record or transmitted directly to the private physician.

iii. When subjects will be tested for reportable diseases, such as HIV or hepatitis the protocol must clearly reflect these exceptions to confidentiality.

iv. Limits on confidentiality, such as inspection of medical records by the IRB or agents of the FDA and the industrial sponsor in studies involving investigational drugs and devices, should also be explained.

w. Data Analysis Plan

i. Summarize the statistical/analytical methods to be used. This should include a statement about the statistical power of the study to test the major hypothesis.

x. Data and Safety Monitoring Plan

i. The IRB requires a Data and Safety Monitoring Plan (DSMP) for all research to be conducted at Ballad Health. The level of required data and safety monitoring must be sufficient so that it is congruent to the level of risk associated with the research.

ii. The IRB requires investigators proposing interventional clinical research with human subjects to address plans for monitoring the data to ensure the safety of subjects. The plan may be described by the sponsor, or by the investigator (for investigator-initiated research) in the protocol. The DSMP must be described in sufficient detail for the IRB to determine whether the plan is appropriate for the research proposed. This responsibility stems from DHHS and FDA regulations stating a criterion for study approval be 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) and 21 CFR 56.111(a)(6)).

iii. Data and safety monitoring is the process for accumulated outcome data for groups of subjects to determine if the research should be altered or stopped. Ongoing review of the aggregate data ensures that the study can continue without undue risk to participants. Safety monitoring also includes the continual assessment of risks and benefits through the review of individual adverse events and other safety parameters (i.e., unanticipated problems) as they occur during the study to determine whether individual participants can safely continue to participate. Data monitoring is the process for ensuring the scientific integrity of the research data including its accuracy, validity, reliability, completeness and its collection in compliance with the protocol.

iv. A DSMP is unique to the trial and should be tailored to the nature, size, and complexity of the research protocol, the expected risks of the research, and the type of subject population being studied. It should also include an appropriate statistical analysis plan. Appropriate DSMPs may fall anywhere along a continuum from monitoring by the principal investigator or group of investigators to the establishment of an independent Data and Safety Monitoring Board (DSMB)/Data and Safety Monitoring Committee (DSMC).

Regardless of the type of DSMP, the individuals participating in the monitoring plan must be objective.

y. Information required in the DSMP for IRB Review

i. For greater than minimal risk studies the plan needs to include the following:

1) A statement to clarify whether there is a DSMB or DSMC associated with the research. If there is a DSMB/DSMC, the contact information of the committee member(s) or a contact person (as applicable) is required. This is particularly important for investigator-initiated studies where specific information and detail regarding who the member(s) are, is required for review;

2) Whether the DSMB/DSMC is independent from the study sponsor and participating investigators; and

3) How often the DSMB/DSMC meet; the type of data that will be used; and the timing of written reports etc.

z. Minimal risk studies or studies with no DSMB or DSMC

i. For minimal risk studies or for studies that do not have a DSMB/DSMC, the plan needs to include the following:

1) Details of the person(s) who will be performing the data and safety monitoring;

2) The frequency of the data review; and

3) Information related to the scientific integrity of the research data to be collected i.e., to ensure its accuracy, completeness and collection is in compliance with the protocol.

ii. Note: For multi-site studies the information in the DSMP must be provided in sufficient detail for the Board to determine that external adverse events and unanticipated problems will be appropriately monitored to assure participant safety.

iii. The IRB considers the following points when assessing the plan for monitoring the data:

1) How will the trial be monitored? Who will monitor the trial? Will there be an independent data and safety monitoring board? Independent data and safety monitoring should be considered for studies involving greater than minimal risk and in studies with any perceived conflicts of interest.

2) How will decisions about stopping the trial be made? By whom? On what basis?

aa. Plans for the Subjects at the End of the Protocol

i. For treatment studies describe how the subjects will be transitioned to their usual medical care. Is the study medication available to subjects after the end of the study? Are there any post follow-up contacts.

bb. Multi-Site Research Studies

i. When a Ballad Health investigator is the PI or responsible site investigator or the institution is the lead site (e.g., prime recipient of award; or IND or IDE holder) in a multi-site study, the investigator must describe in the protocol, the management of information obtained in the multi-site research that might be relevant to the protection of human research participants, such as:

1) Unanticipated problems involving risks to participants or others;

2) Interim results; and

3) Protocol modifications

ii. In their review, the IRB will consider whether the plan adequately protects the research participants.

iii. In addition, if an investigator plans to conduct research at sites external to the organization, for each site, the investigator needs to include the following information in the application (research plan):

1) Whether the site has an IRB;

2) Whether the site has granted permission for the research to be conducted;

3) Contact information for the site;

4) If the site has an IRB, whether the IRB has approved the research or plans to defer review to the organization's IRB.

cc. Optional Modified Protocol Format for Industry-sponsored Studies

i. A modified format may be used for industry-sponsored or commercial protocols. Instead of preparing a protocol specifically for the IRB, selected pages from the sponsor supplied official protocol may be copied and submitted to the IRB. For this format to be acceptable to the IRB, the industry protocol must be well written and appropriately organized. The protocol must include all the elements listed for an investigator-written protocol.

ii. Additional topics that are necessary for the IRB submission which may need to be added to industry- sponsored protocols:

1) Payment to subjects;

2) Comparing the treatment in the protocol to the local standard of care;

3) Alternative treatments;

4) Costs to participants;

5) How the study will be carried out at Ballad Health;

6) The Data and Safety and Monitoring Plan; and

7) Plans for the subjects at the end of the protocol.

dd. Protocols with Approval of IRBs from Other Institutions

i. On occasion, members of the faculty who are working primarily at institutions other than Ballad Health may have protocols approved by their respective

institutional review boards and these investigators may want to conduct these studies at Ballad Health. It is the policy of Ballad Health that all studies involving human subjects carried out on the premises of the Ballad Health requires the approval of this IRB. If the investigator is not a physician and/or does not have admitting privileges at Ballad Health, a member of the medical staff must be identified as the responsible physician, listed as a co-investigator, and co-sign the review form.

ii. The protocol is submitted to the IRB as a new protocol. A copy of the approval from the other IRB should be included with the submission. If only part of the protocol will be done at Ballad Health this should be clearly indicated. All consent documents must be in the Ballad Health required format.

ee. Training

i. Training will be reviewed with each new protocol being submitted into IRBNet, and with Continuing Reviews and Amendments if applicable. (CITI, CVs, Licenses, Financial Disclosure Forms (Ballad Health), and Certification of Investigator Responsibilities Forms). A list of the Principal Investigator, Sub-Investigators and staff that are consenting subjects will also be submitted with the Initial submission, Continuing Review and the applicable Amendments.

ff. Electronic Signatures

i. Electronic Signatures are required by the Principal Investigator for each submitted package into the IRBNet system. The Electronic Signature will represent that the Principal Investigator has entered the IRBNet system and reviewed the contents of the package and agrees with the submission.

22. **Research Project Protocol Amendment**

a. Changes in approved research that are initiated without IRB approval to eliminate apparent immediate hazards to the participant must be to be promptly reported to the IRB. They are reported as unanticipated problems involving risks to participants or others, using the Report Unanticipated Problem or Protocol Deviation Checklist (U/D), accessible via IRBNet. The IRB will review all changes to approved research, initiated without IRB approval to eliminate apparent immediate hazards to the participants, to determine whether the change are consistent with ensuring the participants' continued welfare.

b. Major changes in study design or the application of a study to a very different population usually require a new protocol.

c. Investigator Amendment Submission Requirements

i. Investigators who wish to make alterations to an active IRB protocol must submit a written addendum/revision to the IRB in a timely manner, prior to initiation of the alteration.

ii. A written description of the proposed changes and the reason for the change should be included in a memo which should be submitted with the amendment/ revision.

iii. All new or revised materials/updates should be uploaded to IRBNet with the memo.

iv. The IRB policy states that any revisions, changes or additions in procedures, alterations of risk compared to the original protocol, or changes in subject population, must be reviewed by the IRB prior to continuation of the research.

v. Prior approval by the IRB is required except when necessary to eliminate apparent immediate hazards to the subject [21 CFR 56.108(a)(4) and 45 CFR 46.108 (a)(3)(iii)]. These changes must be promptly reported to the IRB. These should be reported as Unanticipated Problems involving risks to participants or others. These are reported by using the Significant Protocol Deviation Reporting Form. The IRB will review all changes to approved research, initiated without IRB approval to eliminate apparent immediate hazards to participants, to determine whether the changes are consistent with ensuring the participants' continued welfare.

vi. Major changes in study design or the application of a study to a very different population usually require a new protocol submission.

vii. The IRB will reassess the balance of risks to benefits in light of the proposed change and may require the research to be modified or terminated. Only those individuals noted as Responsible Investigator or Co- Investigator have the authority to submit addenda requests on his or her protocol.

viii. The investigator must determine if the amendment significantly alters the basic design of the study or changes the risk/benefit ratio for participants. Amendments that alter the research method design, in particular the inclusion and exclusion criteria or the risk/benefit ratio, will receive full Board review. If the risk/benefit ratio has changed the investigator must also determine whether participants currently and/or previously enrolled on the study will be re-consented. The investigator will need to amend the currently approved informed consent document/s to reflect the change. In addition, when reviewing information relating to protocol changes, the IRB is required to assess whether the information should be provided to the participants, when such information might affect their willingness to continue to take part in the research.

ix. The investigator must submit one copy of the revised document with the changes highlighted, and one copy of the revised document without the changes highlighted. For amendments such as advertisements, flyers, etc., one original document and one copy must be submitted to the IRB office for review and approval.

d. IRB Review

i. The IRB Chair, Vice-Chair, or experienced designated IRB member may utilize expedited procedures to review a proposed change to previously approved research if it represents a minor change to be implemented during the previously authorized approval period. The IRB defines a minor change to be one that makes no substantial alteration in any of the following:

1) The probability or magnitude of risks to subjects

2) The research design or methodology
3) The number of subjects enrolled in the research
4) The qualifications of the research team
5) The facilities available to support safe conduct of the research
6) The likelihood of subjects' willingness to participate
7) Any factor that might warrant convened review

ii. If the IRB administrative office or expedited reviewer determines that the proposed change to previously approved research represents more than a minor change to be implemented during the previously authorized approval period, the request will be reviewed by the full board.

iii. All amendments that significantly alter the basic design of a study or increase the risk/benefit ratio must be reviewed and approved by a convened IRB. All IRB members have access to the amendment application, all modified documents, and all relevant currently IRB approved documents (approved consent, current protocol) via IRBNet. Each member should be familiar with the changes and be prepared to discuss them at the convened meeting. Before and after the meeting IRB members may come to the IRB office to request hard copies of the: meeting minutes and information uploaded to IRBNet if the board member would like a hard copy printed. Electronic copies are also located on IRBNet for board members to review at any time. During the meeting, IRB members may ask the IRB staff to view a copy of the original protocol, meeting minutes, and information submitted.

iv. When reviewing amendments using the expedited procedure, the reviewer will receive and review the same information, outlined above.

v. The IRB will determine whether re-consenting of currently enrolled participants is necessary. This determination should be based on new information regarding a change in the risk/benefit ratio that would possibly affect the participant's decision to continue with the research activities. The IRB will also decide whether participants who have completed the study should be contacted and provided with additional information.

vi. The minutes should reflect the IRBs determinations regarding whether the amendment has changed the risk/ benefit ratio of the study and whether the approval period is appropriate to the level of risk.

vii. Approval of an amendment to a protocol does not change the date of the protocol Continuing Review unless the IRB assigns an earlier review date based on the amended information.

viii. Amendments that receive administrative approval are included in the monthly report to the IRB of administrative activities and are reviewed and acknowledged by the Board.

23. **Expedited Review**

a. The Federal regulations 45 CFR 46.110 and 21 CFR 56.110 allow for certain kinds of research involving no more than Minimal Risk to human subjects and for minor changes in approved research to be reviewed using the Expedited Review procedure. The Department of Health and Human Services (DHHS) has established a list of categories of research that may be reviewed by the IRB through Expedited Review (45 CFR 46.110(a)). Under 21 CFR 56.110(b) and 45 CFR 46.110(b), an IRB may use the Expedited Review procedure to review the following:(1) some or all of the research appearing on the list and found by the reviewer(s) to involve no more than Minimal Risk, (2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized, and (3) review of non-FDA regulated research for which limited IRB review is a condition of exemption.

b. The initial and continuing review of protocols; and minor addendum requests are initially reviewed by the IRB Staff, in consultation with the Chair as needed, to determine if the proposed research meets the regulatory criteria for Expedited Review. If the research meets the criteria stipulated under 45 CFR 46.110(b), it is forwarded for Expedited Review.

c. Ballad Health IRB is in compliance with the Department of Health and Human Service's (DHHS) revised Common Rule 2018 Requirements. Any studies given IRB approval for research prior to January 21, 2019, will fall under the Pre-2018 Requirements of the DHHS Common Rule.

d. Continuing Review of non-FDA regulated research is no longer required under the DHHS revised Common Rule 2018 Requirements (45 CFR 46.109(f)(1)) for: (1) Research initially approved under Expedited Review; (2) Ongoing research approved by a convened IRB (when only certain specified activities are all that remain for the study); and (3) Research reviewed in accordance with limited IRB review.

e. Expedited Review Procedure and IRB Responsibilities

i. The Expedited Review is conducted by the Ballad Health IRB Chair, the Vice-Chair or by one or more experienced voting IRB members designated by the Chair. The criteria for determining whether a Board member is experienced to perform an Expedited Review is based on the following: They must have a minimum of one year's experience as an IRB member and have attended more than 50% of their scheduled convened meetings; show a high level of understanding of the human research protection regulations and an ability to appropriately apply them to human subjects' research; and routinely contribute to the discussions and resolution of controversial issues related to IRB reviews. They must also be currently certified in Human Subjects' Protections under the Ballad Health / CITI education program.

ii. Once a submission has been forwarded for Expedited Review, the Ballad Health Chair or Vice-Chair will conduct the review. However, if the Chair deems that an experienced voting IRB member(s) has the appropriate expertise in the area of the research, the voting IRB member(s) will be requested to conduct the review. The selection of the IRB member(s) will be

made by the Ballad Health Chair (or Vice-Chairs in the Chair's absence). The IRB member(s) will be contacted by the Chair or a member of the IRB administrative staff, at the request of the Chair, and be supplied with the relevant documents needed to perform the review.

iii. Reviewers determine if a submission meets the regulatory criteria for Expedited Review and whether the submission satisfies the criteria for IRB approval as outlined in Federal regulation (45 CFR 46.111 and 21 CFR 56.111).

f. Expedited Review of new protocols, continuing review, and amendments to approved protocols.

g. The reviewer is responsible for first confirming whether the submission, assuming it is a new protocol; continuing review; or proposed modifications to an approved protocol, meet the criteria for Expedited Review. If the criteria are met, the reviewer will complete an in-depth review of the research, and the following actions may be taken: approved as submitted; request for minor modifications/additional information to secure approval; or refer for discussion at a convened meeting. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review by a fully convened IRB as described in 45 CFR 46.108(b).

h. If the proposed new; continuing review; or amendment of approved protocol is not eligible for review through the Expedited Review procedure, the Ballad Health IRB Chair will request that the protocol is scheduled for discussion at a convened IRB meeting.

i. Continuing Review Previously Approved at Convened IRB meeting:

i. If an IRB chooses to conduct continuing review on research that is non-FDA regulated even when it is not required by the regulation (45 CFR 46.109(f)(1)), the rationale for doing so must be documented (45 CFR 46.115(a)(3)). Expedited review procedures may still be used for optional continuing review of non-FDA regulated research. Optional administrative review does not need to occur within any specified period of time for non-FDA regulated research, and the IRB has the option to decide that re-review after initial approval of non-FDA regulated research is not required at all.

ii. The Federal regulations have provisions to allow Ballad Health IRB to approve research previously approved at Full Board, using the Expedited Review procedure. In order for the reviewer to approve the continuing review of research by Expedited Review, they must ensure that the research has met the applicability criteria stipulated under 45 CFR 46.110 and 21 CFR 56.110. These Federal regulations authorize Expedited Review procedure if the non-FDA regulated research (1) presents no more than Minimal Risk to human subjects, and (2) involves only procedures listed in one or more of the categories eligible for Expedited Review for continuing review as found in the Federal Register located at the following URL:

http://www.hhs.gov/ohrp/policy/expedited98.html

iii. When conducting continuing review of studies using Expedited Review, the reviewer ensures the following per the Guidance on IRB Continuing Review of Research located at the following URL:

http://www.hhs.gov/ohrp/policy/continuingreview2010.html

1) The determination that no additional risks have been identified.

2) Any significant new findings that may be related to the subjects' willingness to continue participation are provided to the subject in accordance with 45 CFR 46.116(c)(5). If the reviewer identifies new findings that may impact subjects' willingness to continue participation, the reviewer will consider whether the continuing review still qualifies for Expedited Review or requires review by the convened IRB.

j. Amendments Reviewed at Convened IRB meeting:

i. The Expedited Review procedure may also be used to review minor changes in previously approved research during the period for which approval is authorized. Examples of modifications/additions that are deemed to be minor can be found in Protocol Amendments. In order to approve amendments using the Expedited Review process, the reviewer must determine that the proposed changes/additions to the approved protocol are minor. Minor changes are those that neither increase risk nor materially change the risk/benefit ratio.

ii. Ballad Health IRB submissions eligible for Expedited Review may include, but are not limited to the following: study amendments; consent form/parental permission form modifications; study Chair response to stipulations as outlined in the approved pending modification notification; recruitment materials; and medical procedures that are added as a change in research and are on the current list of categories that may be reviewed using Expedited Review located at:

http://www.hhs.gov/ohrp/policy/expedited98.html

iii. In addition to the above, when a protocol is reviewed and voted upon at a convened IRB meeting, the Board may determine that any minor clarifications/modifications that are needed to secure approval; can be reviewed by a voting member of the IRB using the Expedited Review process. The IRB will give clear and specific recommendations on what clarifications/modifications are needed to satisfy the IRB's concerns before final approval will be granted.

k. Amendments / Modifications to Research Initially Approved by a Convened IRB

i. Modifications to applications previously approved by a convened IRB may be reviewed by the Expedited Review process if they meet the following criteria:

1) Minor modifications that do not alter the level of risks to subjects;

OR

ii. Any additional procedures that fall within categories 1-7 of research that may be reviewed using the expedited procedure.

l. The following table provides examples of minor changes (generally can be reviewed via Expedited Review) and major changes (generally reviewed by Full Committee pending upon the overall risk level) to previously approved protocols:

Minor Changes	Major Changes
• Administrative changes • Minor consent form changes • Minor changes to recruitment procedures, recruitment materials, or submission of new recruitment materials to be used in accordance with approved recruitment methods • Minor changes to study documents such as surveys, questionnaires, or brochures • New study documents to be distributed to or seen by subjects that are similar in substance to those previously approved • Changes in payment to subjects or the amount subjects are paid or compensated that are not significant enough to affect the risk/benefit ratio of the study • Decrease in the number and volume of sample collections as long as they do not negatively alter the risk/benefit ratio of the study • Editorial changes that clarify but do not alter the existing meaning of a document • Addition of or changes in study personnel • Addition of a new study site (in many but not all cases) • Translations of materials already	• Changes that adversely affect the risk/benefit ratio of the study or specifically increase the risk to subjects • Changes in inclusion/exclusion criteria that impact the risk/benefit ratio of the study • Significant changes in study design, such as the addition of a new subject population or the elimination of a study arm • New risk information that is substantial or adversely affects the risk/benefit ratio of the study • Significant changes to the study documents to be distributed to or seen by subjects • New study documents to be distributed to or seen by subjects that include information or questions that are substantively different from the materials already approved by Ballad Health IRB • New or revised financial conflict of interest management plans (e.g., change in PI or change to study design)

reviewed and approved by Ballad Health IRB	

m. Amendments / Modifications to Research Initially Approved by Expedited Review

i. Modifications to applications previously approved by Expedited Review process may be reviewed by the Expedited Review if they meet the following criteria:

1) With the modification implemented, the research would continue to pose no more than Minimal Risk to subjects,

AND

2) The modifications do not involve any procedures that do not meet Expedited categories 1-7, or procedures that do not meet exemption categories 1-6.

n. Limited IRB Review

i. Limited IRB review is relevant to certain exemptions (Categories 2, 3, 7, and 8) of non-FDA regulated research. The Expedited Review procedure may be used to conduct limited IRB review.

ii. In a limited IRB review of non-FDA regulated research, an IRB must conduct a review and make certain determinations as a condition of exemption. For example, that "there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data" (45 CFR 46.111(a)(7)).

iii. Limited IRB review for Categories 2, 3, and 8 invokes criteria found at 45 CFR 46.111(a)(7), however, limited IRB review for Category 7 invokes criteria found at 45 CFR 46.111(a)(8).

o. Review of Protected Populations (45 CFR 46, Subparts B, C, and D)

i. Subpart B: Additional Protections for Pregnant Women, Human Fetuses, and Neonates Involved in Research

1) Clinical studies of drugs or devices (Expedited Category 1) that involve participant contact with pregnant women, human fetuses, or neonates will be forwarded to the convened IRB for review and determination.

2) The convened IRB will determine whether Expedited procedures may be used for continuing review of these studies in accordance with 45 CFR 46.110.

3) Proposed research projects involving the collection of data through noninvasive procedures (Expedited Category 4), may be reviewed by the IRB Chair or Vice Chair for assessment of the level of risk.

4) In all cases, the Expedited Reviewer reserves the authority to refer any study involving Subpart B to the convened IRB for review.

ii. Subpart C: Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

1) Research involving prisoners as subjects would need to be reviewed by a fully convened IRB or follow the Expedited Review process with one of the reviewers being a prisoner representative of the IRB. The IRB Chair is responsible for reviewing and determining whether the research is eligible for review through the Expedited Review process.

2) Exception: Research aimed at involving a broader subject population that only incidentally includes prisoners may be reviewed by the expedited procedure for purposes of determining exemption from 45 CFR 46.

iii. Subpart D: Additional Protections for Children Involved as Subjects in Research

1) Research involving Children as subjects will be reviewed using Expedited procedures providing the research is no greater than Minimal Risk in accordance with 45 CFR 46.404.

2) In all cases the Expedited Reviewer reserves the authority to refer any study involving Subpart D to the convened IRB for review.

p. Investigator Responsibilities

i. The Expedited Review of a new protocol is requested by the principal investigator. The investigator must also complete and include with the submission the Request for Expedited Review Form, and clearly indicate under which of the categories the research qualifies. In addition, the submission must include a copy of the protocol, consent forms and any questionnaires, data collection forms, and recruitment materials that are to be used in the research.

ii. A request for Expedited Review of a continuing review requires completing the appropriate IRB Progress Report and the Expedited Review Form. A list of the required documents that must be included for review can be found on IRBNet entitled Checklist: Continuing Renewal Tips and Guidelines.

q. IRB Material Required for Review

1) For research reviews using the expedited procedure, the voting IRB reviewer will review the materials and conduct an in-depth review of the materials as outlined below:

a) Initial Review of new protocols: Information Received and Reviewed by Reviewer:

i) Initial review may occur through Expedited Review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110 if the research (1) presents no more than Minimal Risk to human subjects, and (2) involves only procedures listed in one or more of the expedited categories and the reviewer determines that the study is Minimal Risk. For research approved after January 21, 2019, the following additional category may be used for Expedited Review of initial reviews (3) research of

non-FDA regulated research for which limited IRB review is a condition of exemption. The categories eligible for Expedited Review for continuing review as found in the Federal Register are located at http://www.hhs.gov/ohrp/policy/expedited98.html.

ii) The reviewer will receive and conduct an in-depth review of the protocol application (investigator checklist and research plan), proposed informed consent documents, recruitment materials, the full protocol, any relevant grant applications, the investigator's brochure (when one exists), the Department of Health and Human Services (DHHS)-approved sample informed consent document (when one exists) and the complete DHHS-approved protocol (when one exists).

iii) When conducting initial review of non-FDA regulated studies using Expedited Review, the reviewer ensures the regulatory criteria for approval of research are met (45 CFR 46.109).

iv) The reviewer may elect to forward to the convened IRB even if the submission meets the criteria for Expedited Review, but may not disapprove the submission.

r. Continuing Review: Information Received and Reviewed by Reviewer

i. If an IRB chooses to conduct continuing review of non-FDA regulated research even when it is not required by the regulation 45 CFR 46.109(f)(1), the rationale for doing so must be documented (45 CFR 46.115(a)(3)). Expedited review procedures of non-FDA regulated research may still be used for optional continuing review. Optional administrative review does not need to occur within any specified period of time for non-FDA regulated research, and the IRB has the option to decide that re-review after initial approval is not required at all.

ii. If the reviewer conducts an in-depth review of the continuing review protocol application (investigator checklist and current research plan), the current informed consent document, any newly proposed consent documents and revised research plan, the complete protocol including any protocol modifications previously approved by the IRB and a status report on the progress of the research. The information required for review in the status report is outlined below (also see Continuing Review):

1) Summary of enrollment activity at Ballad Health and other sites, including withdrawals, patient demographic information.

2) A summary since the last IRB continuing review of all adverse events; unanticipated problems involving risks to participants or others; and protocol deviations (Unanticipated Problems, Adverse Events and Protocol Deviations)

3) A summary of subject complaints.

4) Problems associated with the recruitment of participants.

5) A summary of the study findings, including results and publications; and an assessment as to whether the risks and benefits of the research have changed.

6) Any relevant publications/data that would affect the risk/benefit ratio.

7) Data and Safety Monitoring Committee/Board and Data and Safety Monitors' reports, including interim findings and recommendations.

8) Trial reports from multi-center sites.

9) A change in investigator conflict of interest.

10) A description of approved amendments since the last review.

11) A description of the plans for the coming year.

iii. Amendments/Modifications to Previously Approved Research: Information Received and Reviewed by Reviewer

1) The reviewer will receive and conduct an in-depth review of the amendment application, all modified documents with the changes highlighted, all relevant currently IRB approved documents (approved consent, research plan) the investigator's written explanation for the changes, and a clean copy of the revised documents. The reviewer documents that the modifications to previously approved research undergoing review represent "minor" modifications and that the criteria for approval are met.

2) When an Expedited Reviewer finds additional areas which need modifications or clarifications, these are forwarded to the Primary Investigator/ Responsible Investigator for his/her comments.

3) Documentation of the actions and determinations of the reviewer including protocol-specific findings supporting those determinations will be part of the protocol's file and will include (1) the category and circumstances that justify using expedited procedures; (2) any decision or actions by the reviewer; (3) any findings required under the regulations (including protocol-specific findings supporting this determination); and (4) frequency for the next continuing review for each initial or continuing review application. Protocols which have received Expedited Review as new studies, continuing reviews, or addendums are listed in the monthly report of IRB out of board activities that is presented to the Board for review and approval (45 CFR 46.110(c)).

4) The Secretary, DHHS, has established, and published as a Notice in the Federal Register, a list of categories of research that may be reviewed by the IRB through an Expedited Review procedure. Only research that presents no more than Minimal Risk and falls under one of these categories can receive expedited approval. The IRB also requires prior Department Review Committee approval.

5) Documentation of the rationale for an Expedited Reviewer's determination that non-FDA regulated research appearing on the Expedited Review list is more than Minimal Risk (applicable for the 2018 Requirements only). If

the Expedited Reviewer determines that the study involves more than Minimal Risk, the reviewer can override that presumption, but they have to document their rationale (45 CFR 46.115(a)(8)).

6) The activities listed should not be deemed to be of Minimal Risk simply because they are included on this list. Inclusion on this list only 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.

iv. Other qualifications that apply

1) The categories in this list apply regardless of the age of subjects, except as noted.

2) 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.

3) The Expedited Review procedure may not be used for classified research involving human subjects.

4) IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

5) Categories 1 through 7 pertain to both initial and continuing IRB review.

6) Some research under categories 5 and 7 may qualify for exempt status (Exempt Human Research), in which case the expedited rules do not apply.

s. Category 1 - Drugs and Devices

i. Clinical studies of drugs and medical devices can qualify for Expedited Reviews only when one of the following conditions is met:

ii. Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. 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.

iii. 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 or approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

t. Category 2 - Blood Samples

i. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

ii. From healthy, non-pregnant 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 two times per week.

iii. 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 two times per week.

u. Category 3 - Biological Specimens

i. Prospective collection of biological specimens for research purposes by noninvasive means:

ii. Hair and nail clippings in a non-disfiguring manner.

iii. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.

iv. Permanent teeth if routine patient care indicates a need for extraction.

v. Excreta and external secretions (including sweat).

vi. Un-cannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue.

vii. Placenta removed at delivery.

viii. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.

ix. 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.

x. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.

xi. Sputum collected after saline mist nebulization.

xii. OHRP agrees with the Food and Drug Administration's position that for purposes of Expedited Review Category 3, the following procedures are considered non-invasive (OHRP Correspondence on Non-Engaged Scenarios (Sept. 22, 2011)):

xiii. Vaginal swabs that do not go beyond the cervical os;

xiv. Rectal swabs that do not go beyond the rectum; and

xv. Nasal swabs that do not go beyond the nares.

v. Category 4 - Non-invasive Data Collection

i. 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.)

ii. 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.

iii. Weighing or testing sensory acuity.

iv. Magnetic resonance imaging.

v. Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography.

vi. Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

w. Category 5 - Data Collected for Non-research Purposes

i. Non-exempt research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

ii. Some research in this category may be exempt from the DHHS regulations for the protection of human subjects (45 CFR 46.104). Please refer to the Exempt Human Research, in which case, the expedited rules to not apply.

x. Category 6 - Data from Recordings

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

y. Category 7 - Behavioral Research

i. Non-exempt 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.

ii. Some research in this category may be exempt from the DHHS regulations for the protection of human subjects (45 CFR 46.104). Please refer to Exempt Human Research, in which case, the expedited rules to not apply.

z. Category 8 - Continuing Reviews previously approved by the IRB

i. Continuing review of research previously approved by the convened IRB as follows:

ii. the research is permanently closed to the enrollment of new subjects, all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects; or

iii. no subjects have been enrolled and no additional risks have been identified; or

iv. the remaining research activities are limited to data analysis.

aa. Category 9 - Continuing Reviews not conducted under an IND or IDE and approved by the Board

i. Continuing review of research, not conducted under an investigational new drug application (IND) or investigational device exemption (IDE) where categories 2 through 8 do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than Minimal Risk and no additional risks have been identified.

bb. Category 10 – The modification is no more than a minor change

i. A change that will neither (1) meaningfully increased risk nor meaningfully decrease benefit, when considered in light of any changes proposed to mitigate risk and improve benefit; nor (2) meaningfully decrease scientific merit; nor (3) adversely affect the assessment of the research with respect to the criteria for approval.

ii. Project modifications may be reviewed and approved by expedited procedures if the modification represents a minor change in previously approved research during the period for which approval is authorized (45 CFR 46.110(b)(ii)).

24. **Exempt Human Research**

a. Exempt Eligibility:

i. The Federal regulations allow certain Research Activities Involving Human Subjects to be exempt from IRB full or expedited review [see 45 CFR 46.104; 45 CFR 46.401(b); and 21 CFR 56.104(d)]. There are however restrictions for Research involving children (see 45 CFR 46, Subpart D); and Research involving prisoners does not qualify for exempt Research except for Research aimed at involving a broader subject population that only incidentally includes prisoners (see 45 CFR 46, Subpart C). In addition, any HHS funded Research using newborn dried blood spots collected on or after March 18, 2015, does not qualify as exempt Research: (see National Institutes of Health Guide Notice NOT-OD-12-127: Preliminary Guidance Related to Informed Consent for Research on Dried Blood Spots Obtained Through Newborn Screening). FDA regulated Research does not qualify for IRB exemption unless it falls under the FDA's emergency use provision for the use of a Test Article3 [21 CFR 56.104(c)] or Taste and Food Quality Evaluations and Consumer Acceptance studies [21 CFR 56.104(d)]. [Exempt Category 6]. The following are a list of categories as noted in the Federal Regulations 45 CFR 46.104 that are permitted to be classified as Research that is "exempt" from IRB full or expedited review:

1) Research, conducted in established or commonly accepted educational settings, involving normal educational practices, that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction, such as Research on regular and special education instructional strategies, or Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior (including visual or auditory recording), unless:

   a) Information obtained is recorded in such a manner that Human Subjects can be identified, directly or through identifiers linked to the subjects; and

   b) Any disclosure of the Human Subjects' responses outside the Research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

   c) Information obtained is recorded in such a manner that the identity of the Human Subjects can readily be identified, directly or through identifiers linked to the subjects, and the IRB conducts a limited IRB review to make the required determination (45 CFR 46.111(a)(7)).

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

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

5) Research involving benign behavioral Interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the Intervention and information collection and at least one of the following criteria is met:

   a) The information obtained is recorded in such a manner that the identity of Human Subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

b) Any disclosure of the subjects' responses outside the Research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

c) The information obtained is recorded by the investigator in such a manner that the identity of the Human Subjects can readily be ascertained, directly or through identifiers linked to the subjects, and the IRB conducts a limited IRB review to make the determination required by 45 CFR 46.111(a)(7).

6) Secondary Research for which consent is not required: Secondary Research uses of identifiable Private Information or identifiable biospecimens, if at least one of the following criteria is met:

a) The identifiable Private Information or identifiable biospecimens are publicly available;

b) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the Human Subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

c) The Research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "Research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or

d) The Research conducted by, or on behalf of, a Federal department or agency using government generated or government-collected information obtained for non-research activities, if the Research generates identifiable Private Information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) for the E-Government Act of 2002, 44 U.S.C. 3501, *et seq*., if all of the identifiable Private Information collected, used, or generated as part of the activity will be maintained in systems or records subject to the Privacy Act of 1974, 5 U.S.C. 552a, *et seq*. and, if applicable, the information used in the Research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501, *et seq*.

7) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

a) 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.

b) Each department or agency must establish a list of the Research and demonstration projects they support on a publicly accessible Federal Web site. This list must be published prior to commencing the Research involving Human Subjects

8) Taste and food quality evaluation and consumer acceptance studies:

a) If wholesome foods without additives are consumed or

b) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

9) Storage or maintenance for secondary Research for which broad consent is required:

a) Storage or maintenance of identifiable Private Information; or

b) Identifiable biospecimens for potential secondary Research use if an IRB conducts a limited IRB review and makes the determinations required by 45 CFR 46.111(a)(8).

10) Secondary Research for which broad consent is required:

a) Research involving the use of identifiable Private Information; or

b) Identifiable biospecimens for secondary Research use, if the following criteria are met:

i) Broad consent for the storage, maintenance, and secondary research use of the identifiable Private Information or identifiable biospecimens was obtained in accordance with 45 CFR 46.116(a)(1) through (4), (a)(6), and (d);

ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with 45 CFR 46.117;

iii) The IRB conducts a limited IRB review and makes the determination required by 45 CFR 111(a)(7) and 45 CFR 104(d)(8) that the Research to be conducted is within the scope of the broad consent;

iv) The investigator does not include returning individual Research results to subjects a part of the study plan; however, this does not prevent an investigator from abiding by any legal requirements to return individual Research results.

b. Exempt Determination:

i. The Human Research Protection Department determines what Human Subject Research activities qualify as "exempt" under the Federal regulations; one category applies to each project. Investigators do not have the authority to make an independent determination that Research involving Human Subjects

is exempt. Human Research Protection Department approval of exempt status is required prior to initiation of the Research. A request for determination as to whether or not a human Research protocol is considered "exempt" is submitted electronically through the IRBNet Electronic System. The Human Research Protection Department (or investigators) may not create new categories of exempt Research.

1) Review of requests. The IRB Staff or HRPP Staff determines the applicability of exempt status.

2) An investigator may request a particular category of exemption by selecting their choice on the IRB Exemption Determination Form. However, the final determination of applicability will be made by the Human Research Protection Department namely the IRB Staff or HRPP Staff.

ii. Approval. If the request is approved, the investigator receives an approval notification in the IRBNet Electronic System. The approval letter lists the applicable exempt category under the Federal regulations and a statement to indicate that the Human Research Protection Department is required to review any changes prior to implementation to determine if the study still qualifies.

iii. Disapproval. If the request is disapproved, the Human Research Protection Department indicates that the study does not meet the Federal requirements to be classified as "exempt" and is given instruction about how to proceed. Depending on the type of Research, minor revisions are to be made in order to qualify for exempt status or a new application for full or expedited IRB review is to be submitted for reconsideration.

iv. Institutional Authority. Ballad Health IRB has authority to approve, require modifications of (to secure approval), or disapprove Research Activities Involving Human Subjects. For studies approved after January 21, 2019, this includes exempt Research activities under 45 CFR 46.104 for which limited IRB review is a condition of exemption (under 45 CFR 104(d)(2)(iii), (d)(3)(i)(c), and (d)(7), and (8)). Ballad Health IRB also has the authority to suspend or terminate approval of Research not being conducted in accordance with WHS IRB or regulatory requirements, or that has been associated with unexpected serious harm to study participants. The regulatory basis for this authority is as follows:

1) For Research that is not FDA regulated, Department of Health and Human Services (DHHS) regulations pertaining to rights and welfare of subjects (45 CFR 46)

https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html (Assessed 12-19-2023)

2) For Research that is regulated by the U.S. Food and Drug Administration (FDA), FDA regulations pertaining to rights and welfare of subjects participating in Research involving investigational drugs, devices, or

biologics (21 CFR 50 and 21 CFR 56) in addition to the regulations in 45 CFR 46.

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50 (Assessed 12-19-2023)

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56 (Assessed 12-19-2023

c. Duration of approval:

i. The study has an approval expiration date set 3 years from date approved by the IRB. While there is not an annual Continuing Review required for Research that has been determined to be exempt, there is an annual exemption update that is required to be submitted on the approval anniversary month every year. If on the third year, there is a need for more time to complete the study, the standard continuing review process shall be used as guidance. The annual exemption review form shall be used for all updates.

d. Amendments:

i. Changes to an exempt study are required to be submitted in the IRBNet Electronic System as an "amendment" prior to implementation. A narrative is required on the amendment which discusses:

1) Changes that are being made

2) Revisions to electronic components that were affected by the change (e.g., study application, information sheets, surveys, etc.).

ii. Approval of an amendment. After the Human Research Protection Department reviews the proposed changes, the investigator receives an approval for the amendment through the IRBNet Electronic System. Approved amendments do not change the current Exemption IRBNet number. Please note, changes in Research staff or persons accessing or using the data during the conduct of the Research, must also be formally submitted to the Human Research Protection Department office.

iii. Disqualification of exempt status. Certain changes can disqualify the Research from exempt status (i.e., recruiting prisoners). If the project no longer qualifies for Exemption, the investigator is notified accordingly. The investigator can then choose to:

1) Forego the proposed changes and continue with the study as currently approved or

2) Close out the current exemption and resubmit for full or expedited IRB review and approval.

iv. HIPAA Authorization: Use and Disclosure of PHI (applicability of the HIPAA Privacy Rule):

1) Health Insurance Portability and Accountability Act (HIPAA) regulations apply to exempt Research. Investigators are required to indicate applicability of HIPAA Privacy Rule as part of the IRB application process.

Investigators are required to also submit the appropriate supporting documentation for review.

2) If the proposed Research involves Protected Health Information (PHI), Health Insurance Portability and Accountability Act (HIPAA) regulations still apply, even if the Human Research Protection Department has determined that the Research qualifies for IRB Exemption, or if the Human Research Protection Department has determined the activity is not Human Subject Research. Investigators must submit an Authorization Form or a request for a waiver of HIPAA Authorization for review and approval in addition to their Exemption application.

e. Certification in Human Subjects Protections:

i. Investigators requesting a determination of exemption are required to be educated in Human Subjects Protections through the CITI training program.

f. Guidance for submitting IRB Exemption requests and describes the responsibilities of Investigator's for the conduct of approved exempt Research. It also outlines the procedures and responsibilities of the IRB staff in the review and approval process of exempt Research.

i. Investigator

1) Investigator submits an exemption request by completing the IRB Request for Exemption Form (accessible via IRBNet) a Research plan fully describes the proposed Research activities (see New Protocol Submission Requirements); and HIPAA Authorization Template (or Request for HIPAA Waiver, if applicable).

2) Investigator must reply to all requests for revisions and/or clarifications requested by the reviewers.

3) Once the exemption has been approved, any changes to the study must be reported to the Human Research Protection Department to determine whether a new submission is required. Changes may not be implemented prior to Human Research Protection Department review and approval.

4) Investigator is responsible for assuring that the exempt Research is carried out in an ethical manner that includes appropriate participant protections i.e., confidentiality.

5) Responsibilities of the Human Research Protection Department staff in the review and approval process of exempt Research

ii. Staff Responsibilities

1) The IRB staff will screen the initial submission to determine whether the application is complete.

2) Documentation of their determination will be accomplished by reviewing the site's completed Ballad Health IRB Exemption Review Application.

3) The IRB Staff or when a conflict of interest presents HRPP may (1) approve the request; (2) request minor revisions to the submitted

documents in order to approve the request; or (3) disapprove the request.

4) If the request is approved, the IRB staff will submit an approval letter to the Investigator which can be reviewed and printed in IRBNet. The letter will include the approved IRB exemption category; the expiration date; and request for new application if Research is to continue after the expiration date or is amended in the future.

5) If the request is disapproved, the IRB staff will submit a disapproval letter to the Investigator which can be reviewed and printed in IRBNet. The letter will state the reason for the denial and provide guidance to indicate that the investigator may resubmit for review as full board or expedited.

25. **Continuing Review**

a. Criteria for IRB Review Process

i. Ballad Health IRB conducts Continuing Review of all approved research activities in accordance with the requirements of 45 CFR 46.109(e) and, when applicable, 21 CFR 56.109(f).

ii. For research meeting the following criteria, DHHS and FDA regulations require the IRB to continually review ongoing research at intervals appropriate to the potential risk to participants, but at least annually.

1) Research that involves greater than Minimal Risk to subjects

2) Research that is FDA regulated:

a) Involves a drug

b) Clinical investigation of a medical device

3) Research that involves no greater than Minimal Risk to subjects, funded/supported by federal entities, and initially approved by the IRB prior to January 21, 2019.

iii. It is the policy of the IRB that all ongoing research protocols are periodically reviewed and that the review is conducted within 1 year of the previous approval (IRB Policy, Board Meetings and Administrative Policies), unless the research has been determined to be Exempt from Full Board or Expedited Review (IRB Policy, Exempt Human Research).

iv. While initial IRB review is based on the researcher's best assessment of the anticipated benefits, risk, and procedures, the Continuing Review process is important because it is based on the conduct of the study; actual risk can be evaluated, and preliminary results used to assess the risk/benefit ratio. In addition, the risk/benefit ratio may change not only because of unexpected results and effects of the research intervention itself, but because new knowledge resulting from related research may affect the balance.

v. All ongoing research (including for clinical investigations that are subject to both HHS and FDA jurisdiction) must receive Continuing Review (i) as long as the research remains active for long-term follow-up of participants (even when the research is permanently closed to the enrollment of new

participants and all enrolled participants have completed the research-related interventions); and (ii) when the remaining research activities are limited to data collection.

vi. Ballad Health IRB is in compliance with the Department of Health and Human Services (DHHS) revised Common Rule 2018 Requirements. Any studies given IRB approval for research prior to January 21, 2019, will fall under the Pre-2018 Requirements of the DHHS Common Rule.

b. Full Board Review

i. Research protocols that were initially or previously reviewed by a convened IRB, will receive Full Board Review at Continuing Review, unless the study is eligible for Expedited Review (45 CFR 46.109(f)(i)).

ii. All IRB members will have access and review the Continuing Review application, the current informed consent document, any newly proposed consent documents and revised research plan, the complete protocol including any protocol modifications previously approved by the IRB and a status report on the progress of the research, in enough depth to be familiar with them and be prepared to discuss them at the convened meeting. All IRB Members will have access to the documents via IRBNet.

iii. During the meeting, IRB members may ask the IRB staff to view the protocol file, meeting minutes, and any information associated with the study via IRBNet and viewing screen. In addition, all IRB members may come to the IRB office at any time before and after the meeting, to review the protocol file, meeting minutes, and any information provided to the IRB Members via IRBNet. The IRB staff will make these items available to them upon their request.

iv. Access to all study information is available in the electronic IRB submission system, IRBNet. The IRB Members may access IRBNet at any time to view the study documents. The IRB Minutes are also available for viewing via IRBNet. However, a copy of the IRB meeting minutes will be emailed to board members.

v. The IRB may request additional review from expert consultants for any protocol where the Board believes it needs additional expertise to appropriately evaluate information presented in the Continuing Review submission.

vi. Although Continuing Reviews are usually assigned an expiration date of 1 year, the Board may require certain projects, as determined by an evaluation of the risk-benefit ratio, to be reviewed more frequently than yearly. This can be either after a fixed period of time such as at six months or after a certain number of subjects have been studied. The expiration date of each study can be located in the continuation letter header.

vii. The minutes of the IRB meetings will document separate deliberations, actions, and votes for each protocol undergoing Continuing Review. The rationale for any requested revisions must be documented. The minutes of IRB meetings will reflect the IRB's determination regarding which protocols

require Continuing Review more often than annually. The minutes will reflect any change in the level of risk (e.g., minimal, or greater than minimal). All requested changes and/or requests for additional information will be communicated to the principal investigator.

c. Expedited Review

i. Research protocols that were initially reviewed using the Expedited Review process may receive Continuing Review on an expedited basis, unless the previously met criteria in 45 CFR 46.110 have changed. The Expedited Review procedure is conducted by the IRB Chair; Vice-Chair, with the assistance of the IRB administrative staff (Expedited Review). When reviewing research using the expedited procedure, the reviewer will receive and review the same information provided at Full Board review, as outlined above.

ii. Research protocols initially reviewed by a convened IRB but meeting one of the following criteria may also qualify for Expedited Review at Continuing Review:

1) Subject Follow-up Only:

a) The research is permanently closed to enrollment of new participants, all participants have completed all research-related interventions, and the research remains active only for long-term follow-up of participants; OR, no subjects have been enrolled and no additional risks have been identified.

2) Data Analysis Only:

a) The remaining research activities are limited to data analysis.

3) Prior Board Approval for Expedited Continuing Review:

a) New protocols that met the criteria for Expedited Review but, by the option of the IRB Chair, were initially reviewed at a Board meeting can receive expedited Continuing Review if expedited Continuing Review was approved by the Board at the time of the initial review.

d. Criteria for IRB Approval

i. IRB Responsibilities

1) Continuing review must be substantive and meaningful and must follow the same approval criteria as that for initial review. The IRB must determine that all of the following requirements are satisfied (45 CFR 46.111 and 21 CFR 56.111):

a) Risks to subjects are minimized (i) by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk; and (ii) whenever appropriate, by using procedures already being performed on subjects for diagnostic or treatment purposes.

b) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risk and benefits, the

IRB should consider only those risks and benefits that may result from the research (as distinguished for the risks and benefits of therapies that subjects would receive even if not participating in research).

c) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which it is conducted.

d) Informed consent will be sought from each prospective subject or the subject's legally authorized representative in accordance with 45 CFR 46.116.

e) Informed consent will be appropriately documented in accordance with 45 CFR 46.117.

f) The research plan appropriately monitors the data collected to ensure safety of subjects.

g) The subject's privacy is appropriately protected, and confidentiality of the subject's data is maintained.

h) Appropriate safeguards are included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, decisionally impaired, or economically or educationally disadvantaged persons.

2) IRB recognizes that protecting the rights and welfare of subjects sometimes requires independent verification that no material changes or other problematic events have occurred during the IRB-designated approval period. In these situations, the IRB will utilize sources other than the investigator, such as compliance and sponsor monitoring reports; data and safety monitoring board/committee reports; and Conflict of Interest committee reports.

3) The IRB will consider the following factors in determining which studies require such independent verification:

a) The probability and magnitude of anticipated risks to subject;

b) The likely psychological condition of the proposed subjects;

c) The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed;

d) Prior experience with the Responsible Investigator and research team;

e) Any other factors that the IRB deems relevant.

4) In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period or may retrospectively require such verification at the time of Continuing Review.

5) When reviewing the Continuing Review application, the IRB ensures the following:

a) That all informed consent document(s) are still accurate and complete.

b) All significant new findings that arose from the Continuing Review process and relates to a participant's willingness to continue participation, are provided to participants by the Responsible/Principal Investigator.

e. Additional review

i. Additional or more frequent Continuing Reviews may be required for protocols conducted by principal investigators who previously have failed to fully comply with Federal regulations or the requirements or determinations of the IRB. This also applies if information provided in Continuing Review reports or from other sources suggests that noncompliance with IRB policies and procedures may have occurred.

f. Audits of protocols

i. If the IRB finds that the amount of risk to be incurred by participants in a research protocol requires independent verification, from sources other than the investigator, the IRB will perform an audit under the direction of the HRPP Director. Reports of the audit will be forwarded to the IRB for review (Non-compliance Involving Human Subjects Research).

g. Investigator Responsibilities

i. Research approved by the IRB may only continue for the approved duration set by the IRB. i.e., stipulated time period or a specified number of subjects. The Continuing Review submission must include detailed information about the progress of the study, the number and type of participants consented since the last approval, a summary of protocol events and deviations (if any), a report of subject complaints (if any), and a review of any significant, relevant literature published since the last approval. If any changes are proposed since the last IRB review, the amendment should be described, and the revised documents submitted.

ii. All significant new findings that arise from the Continuing Review process and relate to a participant's willingness to continue participation must be provided to participant by the Responsible/Principal Investigator.

iii. A copy of the current consent form(s), if any, should be submitted, with the Continuing Review application. Continuing Review must occur until data collection and data analysis is complete. However, data analysis (not data collection) can continue after study termination if the data is de-identified.

iv. The required information that must be submitted for a Continuing Review listed on the IRB Annual renewal Checklist and outlined below.

h. Investigator's Annual Progress Report

1) Per OHRP and FDA the progress report must be as informative and as succinct as possible, and must address the following – summary of enrollment activity:

a) The total number of participants enrolled at the Ballad Health site. Including a demographic breakdown of gender, age, race, and ethnicity.

b) The number of participants enrolled at the Ballad Health site since the last review.

c) The number of participants active in the study at the Ballad Health site.

d) The number of participants that have withdrawn from the study and the reason for their withdrawal.

e) A summary since the last IRB Continuing Review of all adverse events; unanticipated problems involving risks to participants or others; and protocol deviations (Unanticipated Problems, Adverse Events and Protocol Deviations)

2) A summary of subject complaints.

3) Problems associated with the recruitment of participants.

4) A summary of the study findings, including results and publications; and an assessment as to whether the risks and benefits of the research have changed.

5) Any relevant publications/data that would affect the risk/benefit ratio.

6) Data and Safety Monitoring Committee/Board and Data and Safety Monitors' reports, including interim findings and recommendations.

7) Trial reports from multi-center sites.

8) A change in investigator conflict of interest.

9) A description of approved amendments since the last review.

10) A description of the plans for the coming year.

11) All training must be linked and if applicable updated.

12) A list of site staff to include Sub-Is, Consenting Staff and PI.

i. Chart review or discarded tissue studies

i. The status report must include: the number of charts reviewed, or the tissue samples obtained; unanticipated problems and protocol deviations; a summary of study findings; description of approved amendments since the last review; and a description of the plans for the coming year. Continuing reviews for chart review studies and discarded tissue studies usually qualify for expedited review (Expedited Review).

j. Informed Consent Documents

i. The current approved informed consent documents, along with any revisions submitted at the time of Continuing Review, will be reviewed by the IRB to ensure that the information is still accurate and complete, and that subjects are fully informed of the risk and benefits associated with the research. Any

significant new findings that may affect the participants' willingness to continue to participate must be disclosed in an updated informed consent document. In addition to copies of the currently approved consent forms, clean copies of the consent forms for the IRB to stamp must be submitted (Informed Consent). All active protocols with informed consent documents must have approved stamped consent forms at all times even if the protocol is closed to subsequent subject enrollment; however, this is not required if all study participants have completed their study requirements and responsibilities.

k. New Amendments to Protocol Submitted at the Time of Continuing Review

   i. Amendments or revisions to a research protocol, including informed consent documents, may be submitted at the time of Continuing Review. All the appropriate documentation addressing the amendment must accompany the submission. The investigator must submit two copies of the revised document with the changes highlighted or tracked and clean copies. The IRB must review and approve an amendment prior to its implementation (Protocol Amendments).

l. Expiration of IRB Approval

   i. The Federal Regulations (45 CFR 46.109(e)) and Ballad Health IRB do not allow for the conduct of research beyond the expiration date of IRB approval. The Principal Investigator is responsible for ensuring that the research is submitted to the IRB for Continuing review in an appropriate time frame, in order to avoid a lapse of IRB approval. In order to avoid a lapse in Continuing Review, the investigators must plan ahead to meet the required Continuing Review dates specified by the IRB.

   ii. If a study has expired because the IRB has not granted continuing approval by the expiration date (regardless of whether the application materials have been received by the expiration date), a member of the IRB staff will send a correspondence to the investigator to inform them that all research activities must cease once the approval expires. In addition, clarification as to whether any research activities have occurred after the expiration date is requested from the investigator. The correspondence, together with the investigator response is placed in the IRB file. The information is copied and distributed to all IRB members at the IRB meeting when the study is reviewed; or in case of expedited review it is provided to the IRB member performing the review.

   iii. In addition, if the IRB has not reviewed and approved a research study by the Continuing Review date specified by the IRB, all research activities must stop. Research activities include but are not limited to the following:

      1) recruitment;

      2) enrollment;

      3) study interventions and subject interactions (i.e., any involvement of current participants including the scheduling of study visits); and

      4) data analysis, this also includes looking at new subject information.

iv. The IRB has the authority to allow the continued participation of subjects in research for which IRB approval has lapsed while the Continuing Review process occurs, if there are overriding clinical or safety concerns or ethical issues that indicate it is in the best interest of the participants to continue. In such cases, the study will be closed to new enrollment and all data analysis must stop until the IRB completes the review process.

v. If an investigator makes a clinical determination that immediately stopping all or some of the research activities would not be in a subject's best interest, the investigator must inform the IRB in writing on a subject-by-subject basis. This formal request must be made in advance of the protocol expiration date and must include the rationale and justification as to why the research activities should be allowed to continue. It should also include a confidential list of the research participants (identified by study number or initials only) for whom suspension of the research would potentially increase risk.

vi. In addition, any such exception for clinical necessity must be well documented and justified by the investigator in the information provided to the IRB as part of the Continuing Review application. The investigator must also include the list of research participants (identified by study number or initials only) for whom suspension of the research would potentially increase risk.

m. If a response is not received in the IRB Office before the study expires, the IRB Chair will issue a letter to the investigator to inform them that the study no longer has IRB approval and that the research cannot be re-opened without a new protocol submission. Multiple expirations of studies from investigators will be brought before the board.

n. If the investigator continues to conduct the research after the study has expired, this becomes an issue of noncompliance and will be processed as described in the Non-Compliance section. Subjects studied after a lapse in approval for the research must be formally reported must be reported and explained to the IRB, Ballad Health Compliance Officer, and to applicable regulatory or funding agencies. The incidences must be submitted to the IRB on the following event reporting checklist: Report Unanticipated Problem or Protocol Deviation (U/D). The IRB is required to report federally funded studies where subjects have been studied after approval has expired, to the Office for Human Research Protections. If the study uses investigational drugs or devices a report to the Food and Drug Administration is required (see, Non-Compliance with Human Subjects Regulations and Reporting to Regulatory Agencies, Department Heads, and Institutional Officials).

26. **Documented Training in Human Subjects Protection**

a. The Ballad Health System Human Research Protection Program (HRPP) requires education of the Principal Investigator and all individuals obtaining consent (co-investigators, coordinators, RNs, research assistants etc.) on any research protocol regardless of funding. In addition, the Ballad Health System HRPP education requirements are applicable to research determined by the IRB to be exempt from IRB review and approval.

b. Once initial education modules are documented, investigators must maintain valid educational training by participating in ongoing continuing research education programs. Clinical investigators and research staff members (key personnel and especially individuals obtaining informed consent) must earn twelve (12) CRECs or must complete the CITI refresher course.

c. Professional certification as clinical research investigator through an organization such as ACRP (Association for Clinical Research Professionals) or SOCRA (Society of Clinical Research Associates) is not required but is highly encouraged. Likewise, research coordinators are not required for IRB purpose to obtain certification- however they must obtain certification as per the conditions of the hospital privileging requirements.

d. Failure to meet the requirements for human subjects' protections certification is considered a major protocol deviation and must be reported to the IRB within fourteen (14) calendar days of discovery (Unanticipated Problems, Adverse Events and Protocol Deviation). When research consent is obtained by an individual who is not certificated in human subjects' protections, it will become an issue of non-compliance and be processed as described in the Non-Compliance with Human Subject Regulations section.

e. Previously Certified at Other Institutions:

   i. Investigators who come from other institutions are encouraged to achieve certification as soon as possible. The IRB will accept written evidence of certification in human subject protection from another institution.

f. Initial Certification Options:

   i. Initial certification lasts for three years. The only option for initial certification is the CITI Online Training course. All training is done via the Internet and can be completed in multiple sessions.

   ii. All education requirements must be completed and maintained for IRB members prior to sitting and voting on a monthly meeting. All education requirements for HRPP and IRB staff must be completed and maintained in order to engage with research study submission and / or active studies. If at any time a staff member or board member lapses their education, they are not allowed to engage in any research work until they have re-certified in Human Subject Research education. It is expected that all staff work to complete the initial education requirements within the first 30 days of hire.

g. Continuing Education Options

   i. Once initial certification has been received, an investigator must accumulate twelve (12) Continuing Research Education Credits (CRECs) every three years to be re-certified or must complete the CITI refresher course. For continuing education, investigators may combine CRECs from the Options below to meet the required twelve (12) CRECs for re-certification. There are multiple options for earning CRECs for re-certification:

      1) Option 1: CITI Core Course (only if it has not been taken before) the CITI Core Course may be taken for twelve (12) CRECs.

2) Option 2: CITI Refresher Course

a) If an investigator has previously taken the CITI Core Course for initial certification, the CITI Refresher Course may be taken for four (4) to twelve (12) CRECs.

3) Option 3: Attend Continuing Education Seminars at other Institutions

a) Investigators may earn CRECs towards re-certification by attending relevant conferences and programs on clinical research issues offered elsewhere. To obtain CRECs, investigators must submit a completed CREC Credit Application and supporting information to allow awarding of CRECs. The number of CRECs for the course is determined by the materials provided by the attendee.

4) Option 4: Approved Online Courses

a) There are many websites that provide approved online courses that can be used to earn CRECs.

27. **Informed Consent**

a. The patient is the primary and preferred person to sign an Informed Consent and Authorization to Use and Disclose Protected Health Information. In cases where the patient cannot physically sign the document due to physical incapacity, position, distress, or any other significant medical interference, the patient may designate a Legally Authorized Representative (LAR) to sign in compliance with the laws of Tennessee and Virginia and in accordance with existing and applicable institutional guidelines. Such designation will cease to exist when the specified condition is corrected.

b. Informed Consent is a process, not just signing a form. The written consent form is the preferred means of consent for treatment. Consent may also be verbal or obtained by telephone or fax in certain circumstances. Witnesses must state they heard the verbal or telephone consent.

c. Health Insurance Portability and Accountability Act (HIPAA) elements should be contained in any consent.

d. Federal regulations that govern Research involving human subjects define a Legally Authorized Representative as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the Research. 45CFR 46.102 (i) and 21 CFR 50.3(l).

e. Tenn. Code Ann. § 68-11-1806 and Va. Code § 54.1-2986 allows an Adult or emancipated minor to designate a surrogate by informing the supervising health care provider of his/her decision. Further, the Acts provides guidance for those situations in which a patient who lacks capacity has not appointed an agent, surrogate, or Guardian. The TN Act states:

i. The patient's surrogate shall be an Adult who has exhibited special care and concern for the patient, who is familiar with the patient's personal values, who is reasonably available, and who is willing to serve…

1) Consideration may be given in order of descending preference for service as a surrogate to:
    a) the patient's spouse, unless legally separated;
    b) the patient's Adult Child;
    c) the patient's parent;
    d) the patient's Adult sibling;
    e) any other Adult relative of the patient; or
    f) any other Adult who satisfies the requirements of subdivision (C) (2).
2) In the event of a challenge, there shall be a rebuttable presumption that the selection of the surrogate was valid. Any person who challenges the selection shall have the burden of proving the invalidity of that selection.

ii. Documentation of the signature of the patient or LAR shall describe the patient's state of mind and physical capacity, circumstances, and all required elements, including any questions the patient or LAR may have. In the case of an LAR signature, the supervising physician, designee, or supporting family member shall also sign the form as a witness to the circumstances and agreement with the consent process.

iii. This Informed Consent Policy is based upon the essential principles established in the Belmont Report (http://ohsr.od.nih.gov/guidelines/belmont.html): respect of persons, beneficence, and justice, and is in accordance with both the Department of Health and Human Services (45 CFR 46.116) (http://www.hhs.gov/ohrp/humansubjects/guidance45cfr46.htm) and the Food and Drug Administration (21 CFR 50.20) (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50). It is the policy of the IRB to assure that for Research involving human subjects' provisions are made to obtain legally authorized Informed Consent from each prospective subject or Legally Authorized Representative. However, the IRB may grant a waiver of Informed Consent if conditions presented are in accordance with the requirements for a waiver or alteration of Informed Consent. Any such waiver or alteration must be consistent with applicable Federal and Tennessee state laws and regulations, such as 45 CFR 46.116(e).

f. The IRB also requires that documentation of Informed Consent be obtained from all participants unless alternate procedures are approved by the IRB, as discussed within 45 CFR 46.117(a). The IRB will review all Informed Consent documents to assure the adequacy of the information contained in the consent document and adherence to Federal regulations regarding the required elements of Informed Consent.

g. All approved Informed Consent forms must have the Ballad Health IRB stamp and contain the consent approval date; there will be no expiration date. Unless the Informed Consent forms are changed or modified in any way, the Informed Consent forms will not require re-stamping by Ballad Health IRB; however, the

consent forms will be reviewed at each annual review. The IRB requires that the most recently approved consent documents be used when obtaining consent from participants.

h. General Requirements

i. The IRB requires that all Informed Consent documents include the nine basic elements of Informed Consent listed below (45 CFR 46.116(b) and 21 CFR 50.25(a) for FDA-regulated studies). The IRB may also require any or all of the nine additional elements of Informed Consent (45 CFR 46.116(c), and 21 CFR 50.25(b), and 21 CFR 50.27(b)(1) for FDA-regulated studies), depending on the nature of the Research. The IRB is in compliance with the Department of Health and Human Services (DHHS) revised Common Rule 2018 Requirements. Any studies given IRB approval for Research prior to January 21, 2019, will fall under the Pre-2018 Requirements of the DHHS Common Rule.

ii. There may not be discrepancies within the Informed Consent documents, the IRB application, the sponsor's or investigator's protocol, the investigator's brochure, the grant and/or the contract regarding the purpose, risks, and benefits of the Research. The Informed Consent document must be in a language understandable to the subject or the subject's Legally Authorized Representative (45 CFR 46.116 and 21 CFR 50.25). Verbal consent is not acceptable unless the IRB has specifically waived the requirement for a written consent (45 CFR 46.116(e) and 45 CFR 46.116(f)). Electronic consent is acceptable as long as it falls within the strict confines described within 45 CFR 46.117(a). Consent must be obtained before initiation of any study procedures unless delayed consent is approved by the Board.

1) Investigators must provide potential Legally Authorized Representatives the same information that would be given to potential Research subjects. If there are ongoing decisions during the study regarding the subject's participation or changes to the study, the Legally Authorized Representative must be willing to remain involved in the decision process. Investigators must clearly describe the consent process in the protocol/Research plan; including how the consent process will be documented.

2) When reviewing Research involving individuals who are determined to be decisionally impaired and/or lack decision making capacity and for which there is no authorized Guardian or advance directive, the Board must find and document in the minutes that the use of a next of kin is appropriate and that the next of kin consent process was reviewed and approved for such use. The Board must also determine that the Research objective is important and that there is no way to accomplish the Research objective in a population that is not decisionally impaired (Board Meetings and Administrative Policies).

iii. When seeking Informed Consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement shall be provided to each clinical trial subject in consent forms and processes. The statement is: "A description

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

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

i. Nine Basic Elements of Informed Consent

i. Under 2018 Requirements (45 CFR 46.116(a)(5)), the following is required:

1) Informed Consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or Legally Authorized Representative 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.

ii. Informed Consent as a whole must present information in a 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 subject's or Legally Authorized Representative's understanding of the reasons why one might or might not want to participate.

1) Research Statement - The Research statement must include the following:

a) A statement that the study involves Research

b) An explanation of the purposes of the Research

c) An explanation of the expected duration of subjects' participation

d) A description of what procedures are involved

e) Identification of procedures that are experimental

i) It is important to explicitly state that the individual is being asked to participate in a Research study so as to clearly differentiate

ii) The relationship between patient-physician from the relationship between the participant-investigator; and

iii) Informed Consent for participation in Research from the Informed Consent for invasive clinical treatment procedures

2) Risks and Discomforts

a) A description of the foreseeable risks and discomforts.

3) Benefits

a) A description of any benefits to the participant or others that may reasonably be expected from the Research. A Presumed positive outcome of a trial is not a benefit.

4) Alternatives

a) A disclosure of appropriate alternative procedures or courses of treatment, if any, including those that might be advantageous to the subject.

5) Confidentiality

a) A statement describing the extent, if any, to which confidentiality of the records identifying the subjects will be maintained. For Research involving test articles regulated by the U.S. Food and Drug Administration (FDA), a statement must be included to indicate that the FDA may inspect the records, to verify information submitted or if there is reason to believe that the records do not represent the actual cases studied or results obtained.

6) Compensation

a) Research involving more than minimal risk must include an explanation as to whether any compensation and medical treatments are available if injury occur and, if so, what they consist of, or where further information may be obtained.

7) Contact Person

a) An explanation of whom to contact for answers to pertinent questions about the Research and Research subjects' rights (IRB Hot Line Phone Number) and whom to contact in the event of a Research-related injury to subjects (the study investigator). Compliance will be notified if a subject notifies the IRB concerning an issue.

8) Voluntary Participation and Right to Withdraw

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

9) One of the following statements about any Research that involves the collection of identifiable private information or identifiable biospecimens (45 CFR 46.116(b)(9)):

a) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future Research studies or distributed to another investigator for future Research studies without additional Informed Consent from the subject or Legally Authorized Representative, if this might be a possibility; or

b) A statement that the subject's information or biospecimens collected as part of the Research, even if identifiers are removed, will not be used, or distributed for future Research studies.

iii. Nine Additional Elements of Informed Consent

1) When applicable, the additional elements of Informed Consent must be included in the consent document per 45 CFR 46.116(c) and 21 CFR 50.25(b) for FDA-regulated studies. Below is a description of each of the elements, as well as guidance to when they are required. The main determination is whether the additional information will have an impact on a subject's willingness to voluntarily participate in the Research; and whether the information meaningful protects their rights and welfare.

2) Pregnancy Risks

a) A statement that if the subject is or may become pregnant the particular treatment or procedure may involve risks which are currently unforeseeable to the embryo or fetus (This is required if the study involves pregnant women or women of Childbearing potential; OR if it involves procedures whose risk profile in pregnancy are not well known).

3) Termination of Participation

a) Investigators must describe any anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent. This is usually only done when the safety and welfare of the subject is in question. (This is required if there are any anticipated circumstances under which a subject's participation may be terminated without the subject's specific concurrence).

4) Costs

a) Any additional costs to the subjects that may result from participation in the Research (This is only required if there are any anticipated additional costs above and beyond what would be reasonable and customary).

5) Consequences of Withdrawal

a) The consequences of a subject's decision to withdraw from the Research must be described by the investigator (need to include information relative to if there are any potential adverse consequences for a subject); and the specific procedures for orderly termination of participation by the subject (only include if there are procedures described in the protocol).

6) New findings will be given to Subjects

a) A statement that significant new findings developed during the course of the Research which may relate to the subject's willingness to continue participation will be provided to the subject. This is not required if the Research is long term, new information may be

obtained during the course of the Research; there are no procedures described in the protocol).

7) Number of Participants

a) The approximate number of participants involved in the study (This is required if stating the number of participants could potentially impact a subject's decision to participate).

8) Biospecimens

a) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit (45 CFR 46.116(c)(7)).

9) Results

a) A statement regarding whether clinically relevant Research results, including individual Research results, will be disclosed to subjects, and if so, under what conditions (45 CFR 46.116(c)(8)).

iv. Genome Sequencing

1) For Research involving biospecimens, whether the Research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen) (45 CFR 46.116(c)(9)).

j. Unknown Risks to the Participants

i. A statement that the particular treatment or procedure may involve risks which are currently unforeseeable to the subject (this is required if the Research involves unapproved drugs, devices, or biologics; or if the risk profile of any of the procedures are not well known).

k. Review of Consent Form Additional Requirements

i. No Exculpatory Language

1) No Informed Consent, whether written or oral, may contain any exculpatory language through which the participant or their legal authorized representative is made to waive or appear to waive any of the participant's legal rights, or releases or appear to release the investigator, the sponsor, the institution, or its agents from liability for negligence as stated in 45 CFR 46.116 and 21 CFR 50.20.

l. Examples of Acceptable Language:

i. Tissue obtained from you in this Research may be used to establish a cell line that could be patented and licensed. There are no plans to provide financial compensation to you should this occur.

ii. By consenting to participate, you authorize the use of your bodily fluids and tissue samples for the Research described above.

m. Examples of Unacceptable Exculpatory Language:

i. By agreeing to this use, you should understand that you would give up all claims to personal benefit from commercial or other use of these substances.

ii. I voluntarily and freely donate any and all blood, urine, and tissue samples to the U.S. Government and hereby relinquish all right, title, and interest to said items.

iii. By consent to participate in this Research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the Research.

iv. I waive any possibility of compensation for injuries that I may receive as a result of participation in this Research.

n. FDA Regulated Test Articles

i. For all Research involving test articles regulated by the U.S. Food and Drug Administration (FDA) under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, Informed Consent documents should include a statement that a purpose of the study includes an evaluation of the safety of the test article. Statements that test articles are safe or statements that the safety has been established in other studies are not appropriate when the purpose of the study includes determination of safety. In studies that also evaluate the effectiveness of the test article, Informed Consent documents should include that purpose, but should not contain claims of effectiveness. In addition, subjects need to be informed that their records may be inspected by the FDA.

1) No Unproven Claims of Effectiveness

a) No unproven claims of effectiveness or certainty of benefit, either implicit or explicit, may be included in the Informed Consent documents.

2) Phase I Studies

a) Potential participants should be told, and a statement included in the purpose of the Informed Consent document, that Phase I studies are designed to determine safety, but not effectiveness. They are also designed to determine toxicity, and severe toxicity is a planned event for a subset of participants, and direct benefit is both not intended and extremely unlikely. In addition, the Informed Consent document should include an explicit statement that the dose administered is not chosen to maximize the chance of effect.

3) Phase II and Phase III Studies

a) Potential participants should be told, and a statement included in the purpose of the Informed Consent document, that Phase II and III studies are designed to determine both safety and effectiveness.

28. **Ballad IRB and Consent Requirements**

a. Ballad Standard Research Consent Language

i. It is the requirement of the IRB that the Standard Research Consent Language be included in all written consent forms unless specifically waived

by the IRB. However, Research that is not being regulated by the FDA, the following sentence may be deleted, "If this study is regulated by the Food and Drug Administration (FDA), there is a possibility that the FDA might inspect your records."

b. Remuneration

   i. If there is remuneration for participation, the details must be included in the consent form. Remuneration includes both reimbursement for expenses and incentives for time and discomfort (Remuneration of Subjects).

   ii. Legally Authorized Representatives are prohibited from receiving any remuneration for providing consent. This does not prohibit the Legally Authorized Representative from being compensated for their time and reasonable expenses the Legally Authorized Representative incurs, related to the Legally Authorized Representative's own participation in the Research.

c. Compensation for Injury

   i. Included in the standard paragraph is the obligation of the investigator to direct a Research subject experiencing physical injury or illness as a result of participating in a study to appropriate medical care. If compensation for injury is available from the study sponsor this should be explained in the body of the consent form.

d. Signature Section

   i. The Research participant or Legally Authorized Representative must sign his or her own name unless waived by the IRB per 45 CFR 46.117 and, if applicable, 21 CFR 56.109. The participant must also date the consent in his or her own handwriting. If the document requests time of consent, this must also be documented in the participant's own handwriting. Should a subject prove unable to provide their signature or date (i.e., hand tremors), a member of the IRB-approved Research staff may assist the subject with signing and dating their name. Helping a subject in this manner must be documented in a note-to-file explaining the deviation from the normal consenting procedure and placed within the subject’s Research records. Documentation of the Informed Consent process may utilize a pre-printed sticker with the subject’s name in lieu of printing the subject’s name. The pre-printed sticker does not replace the subject’s or Legally Authorized Representative’s signature or date.

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

e. Use of First- or Second-Person Language

i. The language of the consent document should be consistent throughout with the use of either the first-person pronoun (i.e., "I, me, my"); or second person pronoun (i.e., "you, your"). The Ballad IRB strongly encourages the use of second person; however, first person consent forms are allowed.

1) Language Level

a) Informed Consent documents must be written in language that is at the appropriate reading and comprehension level for the targeted population. The target language level for consent forms is 8th grade reading ability.

2) No Complex Technical Language

a) The Informed Consent documents must be in lay language and should not include complex language that would not be understandable to all participants. Technical and scientific terms should be adequately explained using common or lay terminology. The IRB discourages the use of lists of medical terms followed by the lay term (e.g., syncope (fainting), rhinorrhea (runny nose)) and prefers the use of only the lay term. Generic names are preferable when describing pharmaceuticals unless the brand name is more commonly known and understood. Regardless of which name is preferred, it should be used consistently throughout the Informed Consent documents. Devices and procedures should also be described consistently throughout the documents and explained in simple language. The IRB allows the use of selected medical terminology when the study population has a chronic illness that would create familiarity with the terms (e.g., "pulmonary function tests" in a consent form for individuals with cystic fibrosis; "EEG" in a consent form for individuals with a chronic seizure disorder).

f. Telephone Informed Consent

i. This option is used when the study is a minimal risk study. Two copies of the Informed Consent form must be mailed so that the participant has a copy to keep and another to mail back to the site. Appropriate notes to the file must document the phone call. The following information must be placed in the note-to-file:

1) All questions asked by the participant and all answers given by the consenting physician or Research coordinator;

2) The consent was obtained via telephone with the actual date of the telephone conversation;

3) The date the signed consent was received at the Research site;

4) The reason for performing the Informed Consent discussion over the telephone;

a) The participation of the witness of the Informed Consent discussion;

b) No Research-related activities will occur or did occur prior to the receipt of the signed Informed Consent form.

5) When the discussion or consent process takes place by a means via telephone, but still requires written documentation of consent, follow the procedures below to ensure adequate documentation of prospective Informed Consent for Research. This procedure establishes the Informed Consent process in certain situations that may require telephone consenting of a subject, such as data review for pre-screening approval prior to a procedure and enrollment into a registry. The following consent process must be adhered to and documented:

i. The study site personnel will follow all federal regulations as they pertain to 45 CFR 46.116 and, when applicable, 21 CFR 50.20;

1) The study site personnel will send currently approved Informed Consent documents to the patient in time to review prior to the telephone call. Take special precautions to protect confidentiality (e.g., verify with the subject that the mailing address, fax, or e-mail is correct and it is acceptable to send the consent this way);

2) Identified subjects will be called, using a speaker telephone. They will be informed that there is a witness on the telephone call – name identified – who testifies to their agreement. The use of a speakerphone ensures that the witness will be able to hear both sides of the conversation;

3) Include a method to ensure the person being consented is the correct (e.g., verification of state identification or other identifying documents or use of personal questions, biometric methods, or visual methods). For FDA regulated studies, FDA Guidance on Use of Electronic Informed Consent requires verification of identity if any or all of the consent process takes place remotely;

4) The person consenting the subject will have the same consent discussion via telephone that they would have had in-person (including asking questions to gauge comprehension and answering the subject's questions);

5) A Research coordinator or physician, in the presence of a witness, will explain the protocol, purpose, risks, benefits, expected duration of subject's participation, describe the procedures to be followed, appropriate alternative treatments, compensation, and whom to contact and how to contact in cases of possible study-related injury, whom to contact and how to contact for questions regarding the Research and/or patient rights of study/registry participation;

6) The subject will be informed of who will receive their Protected Health Information (PHI) and how medical record confidentiality will be maintained; that participation is voluntary, and they can withdraw by contacting the physician on the consent form; the subject can refuse to participate or withdraw from participation at any time without penalty or loss of benefits to which the subject is entitled;

7) The subject will, additionally, be informed of any additional costs that could be incurred, that the treating physician could withdraw the subject

and what procedures to take for discontinuation, any potential risks to fetus or breastfeeding women, the possibility that new findings could develop and how the information will be shared with the subject, and the approximate number of anticipated subjects to be involved with the study;

8) The subject will be notified that return of one of the signed and dated Informed Consents is mandatory. The other copy will be for the subject to keep. The consenting coordinator or physician and witness will, also, sign and date the consent;

9) Once the subject-signed consent form is received at the Research site, it should be signed with the date it is received (not the date the subject was consented) by the consenting physician or Research coordinator and the attending witness.

g. Telephone Re-Consent/Notification

i. When circumstances arise which necessitate that new information be provided to a Research participant, the Research team should take into consideration the subject population, the status of the participants, the information to be conveyed, and the length of the consent document. Two copies of the consent form must be mailed, faxed, or emailed so that the participant has a copy to keep and another to mail, fax, or email back to the site. It is required that a follow-up telephone call be placed to ensure that the participant understands the changes in the Informed Consent. Once the signed consent form is received at the Research site, it should be signed with the date it is received by the re-consenting/notifying Research team member authorized to obtain Informed Consent that spoke with the subject via the follow-up telephone call. Appropriate notes to the file must document the changes and the telephone call that was made to answer any questions by the participant about the changes.

ii. The following must be placed in the re-consent note-to-file:

1) All questions asked by the participant and all answers given by the consenting physician or Research coordinator;

2) The re-consent was obtained via telephone with the actual date of the telephone conversation;

3) The date the signed consent was received at the Research site;

4) The reason for performing the Informed Consent discussion over the telephone;

5) The participation of the witness of the Informed Consent discussion;

6) No updated Research-related activities will occur or did occur prior to the receipt of the signed Informed Consent form.

iii. The following re-consent process must be adhered to and documented:

1) The study site personnel will follow all federal regulations as they pertain to 45 CFR 46.116 and, when applicable, 21 CFR 50.20;

2) The study site personnel will send currently approved Informed Consent documents to the patient in time to review prior to the telephone call. Take special precautions to protect confidentiality (e.g., verify with the subject that the mailing address, fax, or e-mail is correct and it is acceptable to send the consent this way);

3) Identified subjects will be called, using a speaker telephone. They will be informed that there is a witness on the telephone call – name identified – who testifies to their agreement. The use of a speakerphone ensures that the witness will be able to hear both sides of the conversation;

4) Include a method to ensure the person being consented is the correct subject (e.g., verification of state identification or other identifying documents or use of personal questions, biometric methods, or visual methods). For FDA regulated studies, FDA Guidance on Use of Electronic Informed Consent requires verification of identity if any or all of the consent process takes place remotely;

5) The person consenting the subject will have the same re-consent discussion via telephone that they would have had in-person (including asking questions to gauge comprehension and answering the subject's questions);

6) A Research coordinator or physician, in the presence of a witness, will explain the changes to the protocol, purpose, risks, benefits, expected duration of subject's participation, describe any changes to the procedures to be followed, appropriate alternative treatments, compensation and whom to contact and how to contact in cases of possible study-related injury, whom to contact and how to contact for questions regarding the Research and/or patient rights of study/registry participation;

7) The subject will be informed of who will receive their Protected Health Information (PHI) and how medical record confidentiality will continue to be maintained; that participation is voluntary, and they can withdraw by contacting the physician on the consent form; the subject can refuse to participate or withdraw from participation at any time without penalty or loss of benefits to which the subject is entitled;

8) The subject will, additionally, be informed of any updated additional costs that could be incurred, that the treating physician could withdraw the subject and what procedures to take for discontinuation, updated potential risks to fetus or breastfeeding women, possibility that new findings could develop and how the information will be shared with the subject, and the approximate number of anticipated subjects to be involved with the study;

9) The subject will be notified that return of one of the signed and dated Informed Consents is mandatory. The other copy will be for the subject to keep. The consenting coordinator or physician and witness will, also, sign and date the consent;

10) Once the subject-signed consent form is received at the Research site, it should be signed with the date it is received (not the date the subject was consented) by the consenting physician or Research coordinator and the attending witness.

h. Non-English-Speaking Participants

i. Participants who do not speak English must be given an Informed Consent document written in a language understandable to them. Translated consent documents for populations that are non-English speaking must be submitted for review and approved by the IRB. The principal investigator must provide the qualifications of the individual or the service that was used to translate the Informed Consent documents. The principal investigator may wish to delay translating the consent documents until IRB has granted approval for the English version to avoid extra translation costs.

ii. When Informed Consent is obtained from non-English speaking participants using a translated consent form all the following must be done:

1) The oral presentation must be approved by the IRB and be provided to participants in language understandable to them.

2) A translator who is fluent in both English and the language of the participant must be present if the person obtaining consent does not speak the language of the participant.

3) The consent document must be signed and dated by the participant or the participant's Legally Authorized Representative (unless the IRB has waived written consent) (45 CFR 46.116(f)).

4) Documentation of Informed Consent in Participants Records

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

1) How consent was obtained.

2) The participant's level of comprehension (did they appear to understand, did they ask questions, were they able to reiterate the main purpose of the study, procedures, risks, etc.).

3) The participant's decision-making capacity at the time of consent (Were they alert and oriented?).

4) The time given for the participant to consider the Research and whether others were involved in the decision-making.

5) Identify who was present during the consenting process.

6) If a legal authorized representative signs the Informed Consent the reasons and situation leading to the use if the LAR must also be documented in the consent note.

29. **Obtaining Permission for Children to Participate in Research**

a. For Children who are potential Research subjects it is the responsibility of the principal investigator and the study team to obtain permission from the appropriate persons under applicable law. A Guardian is a person who can consent on behalf of the Child to general medical care. In cases where permission is to be obtained from the Guardian, it is important that legal authorization to consent on behalf of the Child to general medical care was established by a court and is not just based on informal agreements by the parents or current living arrangements (e.g., a Child living with an aunt does not make the aunt legally authorized to consent on behalf of that Child to general medical care unless the authorization has been made by a court). Documentation of status of Guardian is required.

b. Children who have had custody taken by a social agency, or are in foster care, are wards of the State. Although foster parents have the authority to sign consent for urgent medical treatment for their wards, they do not have the authority to consent to general medical care and therefore cannot sign consent for Research protocols. In addition, the state may or may not have the authority to consent for general medical care, so the state may or may not be the Guardian as defined by The Department of Health and Human Services (DHHS) and FDA regulations. Investigators who are studying conditions that have an increased frequency in foster Children (e.g., aids, Child abuse) are encouraged to develop a plan for including Children in foster care in the protocol. This is especially true for treatment protocols where non-Research treatment alternatives are inferior or not available. This is consistent with the Belmont Report expectation for equipoise in selecting Research subjects.

c. In approving Research involving Children, the IRB must determine that adequate provisions are made for soliciting the permission of each Child's parents or Guardian (45 CFR 46.408(b)). When parental permission is to be obtained, the IRB may find (but is not required to find) that the permission of one parent is sufficient for Research determined to be not involving greater than minimal risk (45 CFR 46.404); or Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects under 45 CFR 46.405. Research determined by the IRB to be greater than minimal risk and with no prospect of direct benefit under 45 CFR 46.406; or Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of Children (45 CFR 46.407) and Research where the IRB determines that the permission of one parent is not sufficient, the permission of both parents must be obtained, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the Child.

d. Children who reach legal age to consent to the treatment or procedure involved in the Research during the Study If the Research involves Children who will continue to undergo Research interventions (including the collection of identifiable private information) after they reach the legal age to consent to the treatment or procedure involved in the Research, the IRB Research protocol should address

how consent for continued participation in the Research study will be obtained from these individuals at the time they reach such status.

e. IRB Responsibilities

i. For protocols presented to the Board for review, the planned Research activities are reviewed to assure that the Informed Consent document is congruent with the IRB application, investigator's brochure, sponsor's or investigator's protocol, grant and/or contract, and contains the necessary elements of Informed Consent as required by the Federal regulations. When reviewing the Informed Consent document, the board may request revisions to the content, language, punctuation, and/or grammar to allow the intended target population to clearly understand the proposed Research activities and make an informed decision on whether to participate in the Research.

f. Elements of Broad Consent

i. Broad consent for the storage, maintenance, and secondary Research use of identifiable private information or identifiable biospecimens (collected for either Research studies other than the proposed Research or Non-Research purposes) is permitted as an alternative to the Informed Consent requirements in paragraphs (b) and (c) of this section. If the subject or the Legally Authorized Representative is asked to provide broad consent, the following shall be provided to each subject or the subject's Legally Authorized Representative (45 CFR 46.116(d), (d)(1), (d)(2), (d)(3), (d)(4), (d)(5), (d)(6), and (d)(7)):

1) The information required in paragraphs 45 CFR 46.116(b)(2), (b)(3), (b)(5), and (b)(8) and, when appropriate, (c)(7) and (9);

2) A general description of the types of Research that may be conducted with the identifiable private information of identifiable biospecimens. This description must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of Research conducted:

3) A description of the identifiable private information or identifiable biospecimens that might be used in Research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or Researchers that might conduct Research with the identifiable private information or identifiable biospecimens;

4) A description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which period of time could be indefinite), and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for Research purposes (which period of time could be indefinite);

5) Unless the subject or Legally Authorized Representative will be provided details about specific Research studies, a statement that they will not be informed of the details of any specific Research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, including the purposes of the Research, and

that they might have chosen not to consent to some of those specific Research studies;

6) Unless it is known that clinically relevant Research results, including individual Research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject; and

7) An explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and whom to contact in the event of a Research-related harm.

g. Waiver or Alteration of Informed Consent Requirements

i. The IRB may approve a consent procedure that eliminates or alters the required elements of Informed Consent, or to waive the requirement to obtain Informed Consent altogether. Alteration or Waiver of Informed Consent is defined as a variation from the traditional Informed Consent process. However, this process still includes a considerate and thorough discussion of the study with the subject and verification that the subject understands the study and will participate voluntarily. The IRBs may alter or waive the requirement for Informed Consent of subjects. In order to approve such a waiver or alteration, the IRB must find and document the following:

1) The Research involves no more than minimal risk to the subjects and involves no procedure for which written consent is normally required outside the Research context. The IRB may still require the investigator to provide subjects with a written statement regarding the Research (45 CFR 46.117(c)(2), 21 CFR 56.109(c)(1) and (d));

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

3) The Research could not practicably be carried out without the waiver or alteration;

4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation;

5) The Research is not subject to FDA regulation;

6) The only record linking the subject and the Research would be the consent document and the principal risk would be potential harm resulting from breach of confidentiality. In these cases, each subject will be asked whether the subject wants documentation linking the subject with the Research and the subject's wishes will govern (45 CFR 46.117(c)(1)(i)). This option does not apply to Research activity that is regulated by the FDA;

7) If the subjects or their Legally Authorized Representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the Research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for

documenting that Informed Consent was obtained (45 CFR 46.117(c)(1)(iii)); and

8) If the Research involves identifiable private information or identifiable biospecimens, the Research could not practicably be carried out without using such information or biospecimens in an identifiable format (45 CFR 46.116(f)(3)(iii)).

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

i. 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

ii. Public benefit or service programs;

iii. Procedures for obtaining benefits or services under those programs;

iv. Possible changes in or alternatives to those programs or procedures; or

v. Possible changes in methods or levels of payment for benefits or services under those programs

vi. The Research could not practicably be carried out without the waiver or alteration; and

vii. The Research is not subject to FDA regulation.

i. These findings and their justifications must be clearly documented in the meeting minutes when the IRB approves the waiver provision.

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

k. Waiver of Subject Consent for Emergency Research

i. There is a limited class of Research that may be carried out in human subjects who are in a life-threatening situation and in need of emergency therapy for whom; and because of the subject's medical condition and the unavailability of Legally Authorized Representatives of the subjects, no legally effective Informed Consent can be obtained. In these situations, a waiver of consent may be granted. However, because of the special regulatory limitations relating to Research involving pregnant women, fetuses, and

human in-vitro fertilization (45 CFR 46, Subpart B), and Research involving prisoners (45 CFR 46, Subpart C), this waiver is inapplicable to these categories of Research. The waiver can only be applied to all subjects in a protocol and never to only some study participants and always requires Legal Department approval. To qualify for this waiver:

1) If the Research is FDA-regulated, it must meet the requirements of 21 CFR 50.24, Exception from Informed Consent requirements for emergency Research.

2) If the Research is not FDA-regulated, it must meet the requirements of the October 31, 1996, 45 CFR 46 Waiver of Informed Consent Requirements in Certain Emergency Research (see Board Meetings and Administrative Policy,).

l. Waiver of Signed Written Consent

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

1) That the only record linking the participant and the Research would be the consent document, the principal risk would be potential harm resulting from a breach of confidentiality, each participant must be asked whether the participant wants documentation linking the participant with the Research, the participant's wishes will govern (45 CFR 46.117(c)(1)(i)), and the Research is not subject to FDA regulation; or

2) That the Research presents no more than minimal risk or harm to the participants and involves no procedures for which written consent is normally required outside of the Research context (45 CFR 46.117(c)(1)(ii) and 21 CFR 56.109(c)(1)). (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm)

ii. Waiver of Written Documentation

1) When the IRB waives the requirement to obtain written documentation of the consent process, (45 CFR 46.109(c), 46.117, and when applicable 21 CFR 56.109(c)), the IRB will review a written script of the information to be provided to participants and the script must include all the required and appropriate elements of consent disclosure. The investigator will provide the participants with a copy of the script unless the IRB determines that this is not possible, or that a copy of the script will not add to the protections of the participants. The consent waiver must be in accordance with 45 CFR 46.116(d).

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

iii. Re-Consenting Subjects

1) This document describes the process of re-consenting, required by the Institutional Review Board (IRB) in specific situations.

a) The IRB requires investigators to re-consent subjects when specific conditions are met. Study sponsors may also require re-consent of subjects. If the re-consent process includes a revised consent form, it must be submitted to the IRB as a protocol Addendum and must be approved by the IRB before implementation. If the changes increase subject risk, the addendum usually requires approval at a convened IRB meeting.

i) Re-consenting Children Who Become Adults While Participating in a Research Study: When a Child who has been enrolled in a Research study reaches 18 years of age, the subject must be reconsented as an Adult.

ii) Addition of Risks or Significant Revision to Consent Form: Enrolled subjects must sign a revised consent form if the consent has been significantly revised and/or includes the addition of risks to the subject. The changes from the original consent form should be explained to the subject.

iii) As Part of Compliance Review: As a consequence of a compliance determination by the IRB, a corrective action may require re-consenting subjects before previously collected data can be used for Research.

m. Special Categories of Research

i. This document describes some categories of Research that present specific issues related to obtaining Informed Consent.

1) Questionnaire Studies

a) The need for written Informed Consent for questionnaire studies will vary depending on the involvement of the subject and the nature of the information being collected. An information sheet may be substituted for the written consent, indicating the nature of the study, the time requirement for the subject, and other information required for consent. The information sheet must indicate that completion of the questionnaire implies consent. A protocol must contain specific justification of the use of an alternative (i.e., information sheet) to written Informed Consent. The use of in information sheet requires an IRB waiver of the need for written consent.

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

2) Blood Drawing Studies

a) All blood drawn for Research purposes must be done with an IRB approved Research protocol. Some protocols that only involve blood samples are appropriate for oral consent and waiver of written consent. Studies involving multiple blood drawings (unless the Research samples are drawn as an additional sample done at the time of a clinically indicated blood draws) require written consent. Written consent for venous blood drawing should include the amount of blood in lay terms (teaspoons, tablespoons, ounces, or cups), the number of samples, the number of needle sticks, whether an indwelling catheter will be used, and risks of infection, discoloration, and some pain. Consent forms should indicate what will be done with the blood including what will be measured, how long the blood will be stored, and whether results will be available to the subjects. If personal identifying information will be removed from the sample this should be stated.

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

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

ii. Adults

1) Adult Healthy Volunteers

a) Protocols involving a single collection of blood up to one unit (475 ml) from Adult healthy volunteers who come to an investigator for this purpose require an approved protocol and verbal consent, but do not require written consent. This amount should not be taken at intervals of less than two months. Subjects may repeat participation in a single blood draw study as long as more than 475 ml is not taken within 2 months; however, verbal consent must be obtained for each blood draw.

2) Adult Patients

a) Protocols involving a single collection of 50 cc or less of blood from an Adult subject usually are appropriate for oral consent. The usual limit for blood drawing is a maximum of 475 ml over 2 months; however, this limit includes both clinical and Research samples.

iii. Children

1) It is usually inappropriate to draw blood from Children as control subjects unless it is an extra sample of blood obtained at the time a blood sample is scheduled to be drawn as part of clinical care.

iv. Samples Obtained at the Time of a Clinically Indicated Blood Draw

1) Oral consent and Assent is sufficient for protocols involving the one-time collection of blood in Children weighing less than 40 kg when volume to be drawn is less than 1 cc/kg. Oral consent and Assent is sufficient for protocols involving Children weighing more than 40 kg when less than 50 cc of blood will be drawn once. The script for obtaining oral consent and Assent must be reviewed by the IRB. Multiple blood drawings, regardless of amount of blood to be drawn, require written consent/Assent.

v. Research Samples Requiring Additional Venipunctures

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

vi. Multiple Samples

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

vii. DNA and Genetic Studies

1) All studies using blood or tissues for DNA or genetic studies (excluding discarded tissue studies) must describe the study in the protocol and consent form. Unless the samples are anonymous, how the data will be kept confidential must be discussed. The protocol and consent form must discuss what results, if any, will be told to the participant. Regarding paternity issues, it may be appropriate to include the disclaimer statement "It is the policy of this institution not to report information regarding paternity." If the genetic studies are only a part of the protocol, subjects should have the option to "check off" participation or refusal in the genetic part of the study. Subjects cannot be asked to sign away any rights to such materials.

viii. Studies Involving Investigational Drugs

1) According to Food and Drug Administration regulations, administration of substances with an IND number, but not approved by the FDA, requires approval by the IRB or notification to the IRB that an emergency situation exists. In the absence of an emergency situation IRB approval is required. The FDA policy allows for the emergency use of an investigational drug for medical care of patients, without IRB review and approval. However, the resulting data cannot be used for Research (Emergency Use of Investigational Drug, Biologic, or Device).

2) The use of a FDA approved drug in a non-approved manner (Off-Label Use) in patient care does not require approval by the IRB unless it is being used for Research purposes. An IND number is usually not required for off-label Research use of a previously approved drug unless the

studies are for the purpose of changing the recommended use of the drug in the package insert. See the FDA regulations (21 CFR 312.2 (b)), for complete criteria.

3) The Investigational Pharmacy will maintain records of all investigational drug receipt, dispensing, and disposal. For outpatient studies it is the responsibility of the principal investigator to maintain secure drug storage and meet all applicable laws regarding dispensing and accounting for Research medications. The IRB encourages the use of the Investigational Pharmacy for outpatient studies. For off-site studies it is the investigator's responsibility to maintain drug storage and drug administration records in a secure location.

4) The FDA has the authority to audit all records concerning the use of investigational drugs (drugs with an IND number). FDA regulations require IRB approval for administration of substances with an IND number.

n. Studies Involving Investigational Devices

i. Certain investigational devices are billable to the subject. This is determined by the Cost Management System and linked to the FDA Investigational Device Exemption (IDE) number. The consent form must acknowledge whether the subject is to be charged. All studies involving investigational devices require IRB approval regardless of category of risk. The FDA has defined three categories:

1) Significant Risk

2) Non-Significant Risk

3) Investigational Device Exemption

o. Decisionally Impaired Research Participants

i. Illnesses causing impaired decision-making capacity in adults are a considerable health problem in the United States. These include Alzheimer's disease, Huntington's chorea, cerebrovascular disease, psychiatric disorders, chronic alcoholism, and AIDS dementia complex. There are also acute illnesses that are associated with impaired decision-making capacity such as seizures, stroke, myocardial infarction, and metabolic encephalopathy. Conducting clinical Research to advance our understanding of these conditions is extremely important; however, these and other disorders may compromise or eliminate a potential Research subject's ability to give legally effective Informed Consent to participate in Research. Institutions and investigators conducting research on decisionally impaired subjects must balance the societal commitment to advance important scientific knowledge with the ethical obligation to protect the rights and welfare of human Research subjects. For these reasons special protections must be considered by the Institutional Review Board (IRB) when reviewing Research involving subjects with impaired decision-making capacity. Therefore, the principal investigator, in concert with the IRB, is responsible for providing specific additional safeguards appropriate to the Research study. However, few regulations or

guidance documents specifically address Research-involving Adults who have impaired decision-making capacity. The IRB has developed these guidelines to assist investigators in addressing this issue.

p. Important Issues for Research in the Decisionally Impaired

i. Fundamental Principles

1) For studies proposing to include Adult subjects with impaired decision-making capacity the following principles always apply:

a) Decisionally impaired subjects must comprise the only appropriate population and the Research question must focus on an issue unique to this subject population. If the Research question can be answered using non impaired subjects, then subjects with impaired Decision-making Capacity cannot be studied. There can be exceptions to this rule, but they are rare and require individual review by the Ballad Health Ethics Committee. An example may be a patient with schizophrenia who has a rare cancer where the only treatment is an unapproved medication available only by participation in a Research protocol.

b) If the Research involves greater than minimal risk, the risk must be commensurate with the degree of potential benefit to the individual subject.

q. Problems of Consent and Competence

i. Because decision-making capacity is task specific, some decisionally impaired individuals remain capable of making informed decisions for themselves regarding Research participation. The capacity to obtain Informed Consent should be assessed in each individual, for each Research protocol being considered. The determination of cognitive impairment does not automatically confer decisional incapacity on affected individuals. Especially in the earliest stages of cognitive impairment, many people with cognitive impairment remain capable of making a wide variety of decisions, including deciding whether or not to participate in Research. Identification of these individuals is important both because they should be the highest priority subjects for enrolling in studies (if they meet other inclusion criteria), and because they may be able to provide guidance for Research decision making for future projects when they may no longer retain decision-making capacity.

ii. Procedures should be developed to enhance the possibility that subjects can consent for themselves. The setting in which consent is sought and the person seeking consent should be conducive to promoting a potential subject's ability to comprehend and appreciate what is being asked. Because there are no generally accepted criteria for determining competence to consent to Research, the investigator must propose criteria for assessing potential subjects, and the criteria must be reviewed by the IRB. Criteria for determining competence vary according to the degree of risk or discomfort presented by the Research procedures and the extent to which therapeutic gains can be anticipated.

iii. There have been several approaches proposed to assess a subject's ability to give Informed Consent. Whatever approach is taken it is essential to document the plan in detail in the Research protocol. Examples may include:

1) A screening standard mental status examination, such as the MINI-Mental Status Exam (MMSE). A MMSE score less than 24 suggests impaired cognitive ability and would require further assessment of the potential Research subject's decision-making capacity, or exclusion of that subject from the Research.

2) The development of a decision-making capacity assessment tool that is specific for the Research project.

3) A post-consent quiz documenting the subjects' knowledge of critical elements in the Informed Consent form (i.e., nature of the illness being studied, voluntary nature of participation, ability to withdraw at any time, consequences of withdrawing, possible risks and benefits of participation, procedures involved, time required, confidentiality, and whom to call with any questions).

4) The study investigators may ask a physician/psychologist outside the Research team to evaluate the potential subject's decision-making capacity.

r. Risk with No Direct Benefit

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

s. Limiting Risks

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

t. Assent

i. Despite the fact that consent may be obtained from a Legally Authorized Representative, the feelings and expressed wishes of an incompetent subject should still be respected. Participation in Research is essentially an optional activity and even an uninformed or uncomprehending refusal should usually be respected. In the case of Research involving more than minimal risk, the objection of an Adult subject with limited decision-making capacity to provide Assent should be binding, except in rare cases when the IRB makes and specifically documents that the intervention is expected to provide a direct

health benefit to the subject and the intervention is available only in the context of the Research.

u. Temporary Cognitively Impaired

i. This policy applies to individuals who have acute cognitive impairment with the expectation of recovery, as well as to individuals with chronic cognitive impairment. In addition to individuals with seizures, strokes, myocardial infarction, encephalitis, etc., acute cognitive impairment also includes individuals who have normal brain functioning but are unable to make Research decisions due to severe pain; severe duress; or effects of medication/anesthesia. This situation may occur in protocols doing Research in emergency care locations. Individuals with temporary cognitive impairment rarely have advanced directives or Guardians, so next of kin consent may be appropriate in some instances. The IRB criteria for protocols done in emergency care settings are detailed in Board Meetings and Administrative Policies. As soon as Research subjects regain the ability to consent, their consent must be obtained. If the subject refuses consent, then any data collected must not be used for Research.

ii. For Research studies in which the nature of the subject population is such that an individual may not be capable of initially providing direct consent for study participation but may recover adequate decision-making capability for direct consent at a later time, the IRB Research protocol/Informed Consent document must address a mechanism whereby direct consent for continued participation in the Research study will be obtained from the individual at the time he/she regains adequate decision-making capability.

iii. Decisionally Impaired Research Subjects: If consent has been obtained from a Legally Authorized Representative, and if the subject regains the capacity to consent, the subject must be re-consented using standard consenting procedures. If the subject refuses consent, any data previously collected cannot be used for Research purposes. In protocols where a return to normal cognitive functioning is likely, investigators must include their plan to re-consent the subjects, including the time frame. Consent must be obtained as soon as possible, once a subject has regained the capacity to provide consent.

v. Institutionalized Subjects

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

w. Waiver of Subject Consent for Emergency Research

i. There is a limited class of Research that may be carried out in human subjects who are in a life-threatening situation and in need of emergency therapy for whom, because of the subject's medical condition and the unavailability of Legally Authorized Representatives of the subjects, no legally effective Informed Consent can be obtained. In these situations, a waiver of consent may be granted. However, because of the special regulatory limitations relating to Research involving pregnant women, fetuses, and human in-vitro fertilization (Subpart B of 45 CFR 46), and Research involving prisoners (Subpart C of 45 CFR 46), this waiver is inapplicable to these categories of Research. The waiver can only be applied to all subjects in a protocol and never to only some study participants and always requires Law Department approval. To qualify for this waiver:

1) If the Research is FDA-regulated, it must meet the requirements of 21 CFR 50.24 Exception from Informed Consent requirements for emergency Research.

2) If the Research is not FDA-regulated, it must meet the requirements of the October 31, 1996, 45 CFR 46 Waiver Of Informed Consent Requirements In Certain Emergency Research (see IRB Policy, Board Meetings and Administrative Policies, Waiver of Consent for Research in Emergency Settings (section F8), for more details).

x. Other Vulnerable Populations

i. The IRB recognizes that additional safeguards need to be included for other categories of subjects who are likely to be vulnerable to coercion or undue influence such as house staff/students, persons who do not speak English, illiterate persons, and other classes of potential subjects. The following information will assist investigators in addressing this issue within the context of the Research.

1) Obtaining Consent from Subjects Who Are At Risk of Coercion:

a) Students and Employees

i) Justification of the intention to enroll Ballad Health employees or students must be provided in the protocol. The actions to prevent coercion or undue influence must also be detailed in the protocol. Anyone with an employment or academic relationship to Ballad Health must be informed that their participation in a study or refusal to do so, will in no way influence their grades, employment, or subsequent recommendations. Employees must never be made to feel that their job, promotion, salary, or status in any way depends on participation in Research studies.

ii) The Principal Investigator or any other co-investigator may not be responsible for directly recruiting and/or obtaining Informed Consent from any person under his or her direct supervision/employee. Direct recruitment of students and employees may be undertaken using IRB approved recruitment text via standard recruitment methods.

iii) A Principal Investigator may not enroll his or herself into his or her own Research protocol unless provisions are made in the Research protocol to allow for the enrollment. In these cases, the IRB may allow the inclusion if the study outcomes are objectively measured and provisions are there with respect to recruitment and affirmation of eligibility (e.g., by a study co-investigator).

iv) Research protocols that do not directly recruit Ballad Health employees or students (e.g., a clinical trial enrolling general population patients with arthritis) and whereby the investigators would not have any knowledge of the persons affiliation with Ballad Health (e.g., the subject is not requested to disclose this information during the course of the Research) do not need to include provisions in the protocol or consent form to address enrollment of this population.

ii. Principal Investigator's Clinical Patient Population

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

iii. Family members of the study team

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

iv. Illiterate/Seeing Impaired Participants

1) The IRB allows for illiterate persons who understand English and individuals who are seeing-impaired to participate in Research studies. In these situations, the consent document must be read to the participant and the process documented in the Research file. For illiterate subject, the consent should be subsequently signed by the participant "making their mark" on the signature section of the consent document, in order to document their understanding. The IRB also requires a witness to be present to confirm the consent process has taken place. Both the witness and the person conducting the consent or interview to obtain permission must sign and date the consent document. If someone other than the Principal Investigator conducts the interview and obtains consent, the Principal Investigator should formally delegate this responsibility, and the

person delegated, should receive appropriate training to perform this activity.

v. Subjects Who Are Mentally Capable Of Consenting But Physically Unable To Sign the Consent Document

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

vi. Other Vulnerable Adult Populations:

1) The IRB recognizes that the ability of Adult populations to give voluntary Informed Consent may be compromised by circumstances. Such circumstances can include economic or educational disadvantages, and physical handicap. The IRB will review the potential risks and benefits of each proposed study on a case-by-case basis to assure rights and welfare are protected, coercion is minimized, and the study is conducted with the utmost regards for ethical standards.

30. **Pregnant Women and Fetuses**

a. Pregnant Women and Fetuses

i. The IRB allows Women and Fetuses to be involved in research and the research protocol must address how the conditions are met and provide sufficient justification for the inclusion of pregnant women. The IRB allows women and Fetuses to be involved in research if all of the following conditions are met in accordance with 45 CFR 46.204:

1) Where scientifically appropriate, preclinical studies, including studies on pregnant animals and clinical studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and Fetuses.

2) The risk to the Fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the Fetus; or, if there is no prospect of benefit, the risk to the Fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

3) Any risk is the least possible for achieving the objectives of the research.

4) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of direct benefit for the woman or the Fetus; or no

prospect of benefit for the woman nor Fetus when risk to the Fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of 45 CFR 46(a).

5) If the research holds out the prospect of direct benefit solely to the Fetus, then the consent of the pregnant woman and the father must be obtained in accord with the informed provisions of 45 CFR 46(a), except that the father's consent need not be obtained if he is unable to consent because of unavailability, cognitively impaired, or temporary incapacity or the Pregnancy resulted from rape or incest.

6) Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the Fetus or Neonate.

7) For children who are pregnant, assent must be obtained from the pregnant child and consent from her parent or legal guardian.

8) No inducement, monetary or otherwise, will be offered to terminate a Pregnancy.

9) Individuals engaged in the research will have no part in determining the viability of a Neonate.

31. **Neonates**

a. The IRB allows Neonates of uncertain viability and nonviable Neonates to be involved in research if all of the following are met (45 CFR 46.205(b)):

i. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risk to Neonates.

ii. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the Neonate.

iii. Individuals engaged in the research will have no part in determining the viability of a Neonate.

b. Neonates of Uncertain Viability

i. Until it has been ascertained whether or not a Neonate is viable, a Neonate may not be involved in research unless the following are met:

ii. The research holds out the prospect of enhancing the probability of survival of the Neonate to the point of viability, and any risk is the least possible for achieving that objective, or

iii. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the Neonate resulting from the research; and

iv. The legally effective informed consent of either parent of the Neonate or, if neither parent is able to consent because of the unavailability, cognitively impaired, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained, except that the

consent of the father or his legally authorized representative need not be obtained if the Pregnancy resulted from rape or incest.

c. Nonviable Neonate

i. After delivery nonviable Neonate may not be involved in research unless all of the following additional conditions are met:

ii. Vital functions of the Neonate will not be artificially maintained.

iii. The research will not terminate the heartbeat or respiration of the Neonate.

iv. There will be no added risk to the Neonate resulting from the research.

v. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

vi. The legally effective informed consent of both parents of the Neonate is obtained unless either parent is unable to consent because of unavailability, cognitively impaired, or temporary incapacity, the informed consent of one parent of a nonviable Neonate will suffice to meet the requirements. The consent of a legally authorized representative of either or both of the parents of a nonviable Neonate will not suffice to meet the requirements.

d. Viable Neonates

i. Viable Neonates may be included in research to the extent permitted by and in accordance with OHRP. (Subpart D) and FDA requirements.

e. Newborn Dried Blood Spots

i. Use of Newborn Dried Blood spots collected clinically for Federally Funded Research is considered Human Subject Research (De-identified or Identifiable). The Ballad Health IRB must review and approve these studies prior to initiation of the research. Parental permission to use the dried blood sample for research must be obtained for Federally Funded research. Federal law no longer permits the waiver of informed consent (Waiver of parental consent) in these research studies.

ii. Research that is involving the use of newborn dried blood spots that are not Federally Funded are not subject to this requirement, but will need to be submitted to the IRB for review and may require expedited, full board, may qualify as "non-human research" or exempt review. The IRB has the ability to waive or alter the requirements for Parental consent to the non-federally funded research for the dried newborn blood spots for research. The Chair or Vice Chair will make the determination as to how the submission will be processed.

32. **Assent From Children**

a. It is a requirement that the investigator propose an Assent plan as part of a research protocol that includes children as subjects. If the investigator believes that Assent is not appropriate for the Child population being studied, appropriate justification must be provided in the protocol. Requests for waivers of Assent need to be specifically requested and subsequently approved by the IRB.

b. The investigator must also describe the additional safeguards in place to protect the rights and welfare of the children.

c. The IRB must determine that the proposed research meets all the requirements of 45 CFR 46, subpart A including the provisions for obtaining and documenting Assent are adequate (45 CFR 46.408(a)(e)). The Child should be given an explanation of the proposed research procedures in a vocabulary and language that is appropriate to the Child's age, experience, maturity, and medical condition. This explanation should include a discussion of any discomforts and inconveniences the Child may experience if he or she agrees to participate in the study.

d. If Assent is solicited, the investigator must respect the Child's decision. If the Child is asked for Assent and refuses, the Child's Parent(s) or Guardian may not override the Child's decision.

e. To obtain valid written Assent, the investigator must use the current IRB approved and stamped Assent form. Assent expires when a Child becomes an Adult. At that time the subject must sign the IRB approved Adult consent form for the study (Informed Consent).

f. In general, Tennessee law does not permit persons under the legal age to consent to research. An exception may apply, however, in the following instances when Tennessee law permits minors to consent to: diagnosis or treatment of venereal disease; diagnosis or treatment of any condition caused by drug or alcohol abuse; HIV testing; examination if reported as a victim of sexual abuse; performance or inducement of abortion by court order; or for certain outpatient mental health services (excluding the use of medication) when the minor is fourteen years of age or older. The IRB shall consult with the Office of Legal Affairs for guidance in each case prior to approving a protocol invoking these exceptions.

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

h. The IRB must also determine that adequate provisions are made for soliciting the Permission of each Child's Parent or Guardian. When parental Permission is to be obtained the regulations require *in all cases* that both Parents provide Permission, unless one Parent is deceased, unknown, incompetent, or not reasonably available, or when only one Parent has legal responsibility for the care and custody of the Child. However, for certain categories of research (research involving minimal risk or greater than minimal risk with the prospect of direct benefit (45 CFR 46.404 or 45 CFR 46.405), the IRB may, when appropriate, determine that the Permission of one Parent is sufficient, even when the other Parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the Child.

i. When approving research involving children, the meeting minutes must document the determinations required by the regulations to approve the research along with protocol specific findings to justify each of the regulatory determinations (IRB

Policy, Board Meetings and Administrative Policies) in accordance with 45 CFR 46.404, 405 or 406 and 407 and 21 CFR 50, 51, 52, and 54 as applicable. The minutes must also document the Assent process, including whether Assent is required, or a waiver of Assent has been approved, in accordance with, as applicable, 45 CFR 46.408 and 21 CFR 50.55 and 45 CFR 46.116(a).

j. When the IRB approves research involving children in accordance with 45 CFR 46.407, the following requirements must be met and are irrespective of the funding of the research. The IRB follows the Office for Human Research Protections (OHRP) guidance for situations when research meets the fourth category of pediatric research.

   i. Assent of Child and Permission of both Parents

   ii. IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children

   iii. The DHHS (Department of Health and Human Services) Secretary or the Federal Drug Administration (FDA) Commissioner approves, after consultation with a panel of experts in pertinent disciplines (i.e., science, medicine, education, ethics, law) and following public comment.

k. The IRB will submit the protocol and supporting documents to OHRP (Office for Human Research Protections) for DHHS consideration under the provisions of 45 CFR 46.407(b). When the proposed research is being conducted or supported by DHHS, the DHHS will consult with a panel of experts.

l. If a study lasts for multiple years, Assent may need to be re-assessed as the Child's cognitive ability matures. Also, if a Child enters a study at an age where Assent is not required, but during the study the Child attains the Assent age where Assent is required, Assent must be obtained for the Child to continue in the study.

m. Age Guidelines for Assent

   i. The following guidelines, based on the Child's age, are often followed by the IRB in determining Assent requirements. Because of the many variables involved in research with children (age, maturity, cognitive ability, degree of study benefit to the Child, health of the Child, etc.), the guidelines listed below may not be applicable to a specific study and the investigator may propose and justify a different plan. This may include more than one of the applicable categories listed below based on the investigator's determination in specific cases (e.g., studies involving children of differing ages; and maturity of all children). The plan must be fully described in the protocol/research plan and be approved by the IRB prior to implementation. Also, the IRB has the option to require a different approach.

   ii. Six (6)Years of Age or Younger, Verbal or Written Assent Is Usually Not Required

      1) Consent is based on the Permission of the Parent or Guardian, and no Assent is required. A brief verbal explanation of the research procedure

should be provided to the Child. In addition, if the investigator or IRB determines that the Child is capable of understanding the research, an Information Sheet must be provided to the Child. The Information Sheet must describe the research in language understandable to the Child and must be approved by the IRB prior to its use.

iii. Between The Ages of seven (7) to thirteen (13), a Separate Assent Form Is Required

1) In addition to the Parents' consent form, a separate Assent form is required for the Child. It should be in language appropriate for children seven to thirteen (7-13 years of age). The Assent form should outline what is involved for the Child and emphasize the voluntary nature of the study. Depending on the research study, it will usually be one to two pages in length. All Assents must at a minimum involve communication of the information in the Assent form to the Child and obtaining the Child's verbal agreement to participate in the study. The plan to obtain and document the Assent process must be fully described and justified in the protocol/research plan. The IRB will make the final determination of the Assent process.

iv. Fourteen to seventeen (14 to 17) Years of Age, a Consent or Assent Form May Be Used

1) Children fourteen to seventeen (14 to 17 years old) may give Assent after the information in the Assent form has been communicated to them; and the Child's verbal agreement to participate in the study has been provided. The IRB may determine that the Child sign the Informed Consent document that has been signed by the Parent(s) or Guardian. A separate Assent form may also be provided to the Child if the investigator believed it would better describe the information provided to the Child about the nature of the study. This would most likely apply to fourteen (14) or fifteen (15)-year-old subjects in very complex studies, or children with mild cognitive impairment. The plan to obtain and document the Assent process must be fully described and justified in the protocol/research plan. The IRB will make the final determination of the Assent process.

n. Verbal Assent

i. To obtain verbal Assent the investigator must communicate the information in the approved Assent form to the Child. If the IRB determines that the communication of the Assent process must be documented in writing, this can be achieved either by the Child (preferred) or investigator signing the paragraph below. Sample wording that can be used is as follows: I have discussed this clinical research study with the Child, using language which is understandable and appropriate. I believe I have fully informed this subject of the nature of the study and its possible risks and benefits. I believe the subject understood this explanation and assented to participate in this study.

o. Request for Waiver of Assent (45 CFR 46.408 & 46.116(a))

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

ii. Below are the circumstances under which an IRB may determine that Assent is not a requirement:

1) If the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or Guardian Permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in 45 CFR 46.116(a), and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

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

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

4) A determination that Assent is not a requirement for protocols involving greater than minimal risk must be approved at a convened IRB meeting. The IRB's determinations and protocol-specific findings are documented in the IRB minutes. Waiver approvals are listed on the IRB approval letter.

p. Alteration of Parental Permission:

i. When parental Permission is to be obtained the regulations require *in all cases* that both Parents provide Permission, unless one Parent is deceased, unknown, incompetent, or not reasonably available, or when only one Parent has legal responsibility for the care and custody of the Child. However, for certain categories of research (research involving minimal risk or greater than minimal risk with the prospect of direct benefit (45 CFR 46.404 or 405), the

IRB may, when appropriate, determine that the Permission of one Parent is sufficient, even when the other Parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the Child.

q. Waiver of Parental Permission:

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

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

r. Special Circumstances That Alter Standard Consent or Assent Criteria:

i. Emancipated Minors:

1) Tennessee law provides that persons under the legal age of consent achieve emancipation only by court order. Documentation of emancipation by court order is required before a minor may be recognized as an Emancipated Minor in the research context.

ii. Pregnant Minors:

1) In Tennessee, parenthood does not emancipate a minor (although it does in some other states). Consent for treatment procedures on a Child of an unwed minor must be obtained from the Parent or Guardian of the unwed Parent.

iii. Parent Conflict of Interest:

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

iv. Waiver of Assent for Experimental Therapies for Life-threatening Diseases:

1) When research involves the provision of experimental therapies for life-threatening diseases such as cancer, investigators should be sensitive to the fact that Parents may wish to try anything, even when the likelihood of success is marginal, and the probability of extreme discomfort is high. Should the Child not wish to undertake such experimental therapy, difficult decisions may have to be made by the Parents in conjunction with

the investigator, Child's physician, and the Child. If the Child is a mature adolescent, waiver of Assent is usually not appropriate.

2) Child Abuse or Neglect:

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

3) Children who are Wards of the State:

   a) Research involving children who are wards of the state or any other agency, institution, or entity (including children in foster placement) must have consent for research given by the agency that has custody of the Child. This usually requires the agency to appoint a Child advocate with the appropriate background and experience to act in the Child's best interests. The inclusion of children who are wards of the state usually requires that the research is:

      i) Related to their status as wards.

      ii) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

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

4) The Board meeting minutes must document that the research is in accordance with 45 CFR 46.409 and 21 CFR 50.56 and is appropriate for the inclusion of participants who are wards.

33. **Prisoners as Research Subjects**

a. Prisoners constitute a research population who are at risk for coercion due to their confinement. Very specific Federal rules apply to research involving Prisoners. The special vulnerability of Prisoners makes consideration of involving them as research subjects particularly important. Prisoners may be under constraints because of their incarceration, which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research. To safeguard their interests and to protect them from harm, special ethical and regulatory considerations apply for reviewing research involving Prisoners. For research involving Prisoners, the definition of minimal risk differs from the definition of minimal risk in the Common Rule (45 CFR 46.303(d)). The definition for Prisoners requires reference to physical or psychological harm, as opposed to harm or discomfort, due to risks normally encountered in the daily

lives, or routine medical, dental, or psychological examination of healthy persons. A research protocol is considered to include Prisoners when:

i. Prisoners are the target population that will be recruited; or

ii. The subject is a Prisoner at the time of enrollment; or

iii. A currently enrolled subject becomes incarcerated during the course of the trial.

b. When a protocol involves the use of Prisoners as subjects, both the general IRB policies and procedures apply as well as the additional rules as determined by Federal, state, county, and local regulations. The IRB may approve research involving Prisoners only if these special provisions are met. 45 CFR 46 Subpart C (additional protections pertaining to Biomedical and Behavior research involving Prisoners).

c. The IRB must review all research in which Prisoners are the target population when:

i. The subject is a Prisoner at the time of enrollment.

ii. When a currently enrolled subject becomes incarcerated and research interventions and interactions would occur during the incarceration period or if identifiable private information will be obtained during the incarceration period.

iii. Prisoners are the target population for recruitment.

d. Although Federal regulations allow for certain categories of research involving Prisoners to be reviewed via expedited review, protocols involving Prisoners will be reviewed at a convened IRB meeting. The IRB will review the research in accordance with Ballad Health Institutional Policies, OHRP, and FDA regulations related to 45 CFR 46 Subpart C - additional protections pertaining to research involving Prisoners. There also may be additional rules determined by State, Federal, local, or county regulations which may be applicable. If a study the study participants are pregnant or a minor, there is an IRB policy regarding these additional vulnerable populations as well may be applicable - 45 CFR 46 Subparts B & D. If a protocol involving Prisoners is designated for expedited review, the IRB Prisoner representative member will be involved in the review as appropriate. None of the exemption categories in the HHS regulations for research involving human subjects at 45 CFR 46.101(b) apply to research involving Prisoners. Permitted research involving Prisoners includes studies that examine conditions, practices and antecedents specifically related to Prisoners, Prisons, and incarceration (45 CFR 46.306 When a protocol involves the use of Prisoners as subjects, both the general IRB policies and procedures apply as well as the additional rules as determined by Federal, state, county, and local regulations. The IRB may approve research involving Prisoners only if these special provisions are met. 45 CFR 46 Subpart C (additional protections pertaining to research involving Prisoners).

e. When a Prisoner is a minor (e.g., an adolescent detained in a juvenile detention facility is a Prisoner), the IRB policy regarding children in research will also apply.

f. All persons who obtain consent from Prisoners for research participation must be certified in human subjects' protections.

g. Additional Protocol Requirements for recruiting Prisoners as subjects:

i. All protocols involving Prisoners are reviewed at a convened IRB meeting; expedited review is not allowed. It must clearly articulate that it meets all applicable criteria under 45 CFR 46 Subpart C. In addition to the usual requirements a protocol involving Prisoners must meet all the following seven criteria:

1) The research under review represents one of the following categories of research permissible under 45 CFR 46.306(a)(2):

a) A study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the participants.

b) A study of Prisons as institutional structures or of Prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants.

c) Research on conditions particularly affecting Prisoners as a class (e.g., vaccine trials and other research on hepatitis which is much more prevalent in Prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary of the Department of Health and Human Services (DHHS) (through the Office for Human Research Protections (OHRP) 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.

d) Research on 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 DHHS (through OHRP) 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.

2) Discussion which makes it clear that the protocol satisfies all additional criteria for research with Prisoners as subjects (see 45 CFR 46.305), including:

a) "The Risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers."

b) "That any possible advantages accruing to the Prisoner through his or her participation in the research, when compared to the general

living conditions, medical care, quality of food, amenities, and opportunity for earnings in the prison, are not of such a magnitude that [the Prisoner's] ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired."

c) "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 board justification in writing for following some other procedures, control subjects must be selected randomly from the population of available Prisoners who meet the characteristics needed for that particular research project."

d) Discussion of the process for obtaining informed consent and study procedures to ensure that the information is presented in language that is understandable to the subject population.

e) "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," and

f) [If]"…there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual Prisoners' sentences, and for informing Prisoners of this fact."

h. Any possible advantages accruing to the Prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities, and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the Prisoner is impaired.

i. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.

j. Procedures for the selection of participants 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 participants must be selected randomly from the group of available Prisoners who meet the characteristics needed for that research project.

i. The information is presented in language that is understandable to the subject population.

ii. 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.

iii. Where the IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual Prisoners' sentences, and for informing participants of this fact.

iv. The informed Consent Form and any study materials must be in a language that is understandable to the study population. Risks of participation, a voluntary nature of participation, participation will not have any effect on a Prisoner's parole, must be clearly addressed in the informed consent form. In very limited circumstances, the Informed Consent may be altered or waived by the IRB, however if consent is waived or altered, it is required that the study participants be clearly informed in advance that their participation or refusal to participate will have no effect on their parole. (45 CFR 46.116 and 117) Prisoners, however, cannot be involved in emergency research where the requirement for informed consent has been waived by the Secretary under the authority of, 45 CFR 46.101(i).

v. Additional IRB Requirements

1) The IRB must also meet additional requirements to allow review of protocols with Prisoners as subjects (45 CFR 46.304 (a) and (b)).

2) A majority of the IRB (exclusive of Prisoner members) shall have no association with the prison(s) involved, apart from their membership on the IRB.

3) At least one member of the IRB must be a Prisoner, or a Prisoner representative with appropriate background and experience to serve in that capacity, except that, where a particular research project is reviewed by more than one IRB, then only one IRB needs to satisfy this requirement. If a Prisoner representative is selected to serve on the IRB, the person must have a close working knowledge, understanding and appreciation of prison conditions from the perspective of a Prisoner. Suitable individuals could include present or former Prisoners; prison chaplains; prison psychologists, prison social workers, or other prison service providers; persons who have conducted advocacy for the rights of Prisoners; or any individuals who are qualified to represent the rights and welfare of Prisoners by virtue of appropriate background and experience.

4) The IRB must meet the special composition requirements for all types of review for the protocol: initial review, continuing review, review of protocol amendments, review of reports of adverse events or unanticipated problems involving risk to participants or others, or in the event an individual becomes a Prisoner while participating in a research protocol.

5) For Ballad Health IRB to approve research involving Prisoners, the IRB must find that the proposed research falls into one of the permissible categories of research (45 CFR 46.306) and make seven other findings

under 45 CFR 46.305. The meeting minutes must document the IRB's discussion of these elements and affirm that the research meets the regulatory criteria. Additionally, the minutes must reference that a majority of the IRB (exclusive of Prisoner member/representative) has no association with the prison(s) involved and a qualified Prisoner representative was present and voted on the protocol.

6) The IRB must also find that the proposed research meets the requirements of 45 CFR 46.305, including that the research represents one of the categories of permissible research under 45 CFR 46.306. OHRP notes that in order to make some of these seven findings and meet the requirements of subpart A of 45 CFR part 46, the IRB must be familiar with the specific conditions in the local prison(s) or jail site(s) that are pertinent to subject protections, before approving the proposal for the local site (45 CFR 46.107(a)).

vi. Prisoner Certification Letter to OHRP:

1) An institution that intends to conduct DHHS-supported research involving Prisoners as subjects must certify to the Secretary (through OHRP) that the IRB has made the seven findings required under 45 CFR 46.305(a), including the finding that the proposed research represents one of the permissible categories of research under 45 CFR 46.306(a)(2). The institution must send OHRP a certification letter, to that effect, which should include the name and address of the institution and specific identification of the research protocol, including the relevant grant number.

2) The OHRP requires the responsible institution to submit a copy of the research proposal so OHRP can determine whether the proposed research involves one of the categories of research permissible under 45 CFR 46.306(a)(2), and if so, which one. The term "research proposal" includes:

a) The IRB-approved protocol.

b) Any relevant DHHS grant application or proposal.

c) Any IRB application forms required by the IRB.

d) Any other information requested or required by the IRB to be considered during initial IRB review.

3) OHRP also encourages the institution to include the following information in its Prisoner research certification letter, to facilitate processing:

a) OHRP Assurance number.

b) IRB registration number.

c) Date(s) of IRB Meeting(s) in which protocol was considered, including a brief chronology that encompasses the date of initial IRB review and date of Subpart C review.

4) While OHRP certification is not mandatory for non-DHHS supported research, it is the policy of the IRB to require investigators to abide by the OHRP certification requirements as stated above.

5) Other Approvals that may be required:

6) There may be other approvals required depending on the rules of the prison system (e.g., Federal Bureau of Prisons, Tennessee Department of Corrections and the County Jail). It is the investigator's responsibility to determine and meet these requirements prior to beginning any research.

vii. Special Rules also apply if a Research Subject Becomes a Prisoner:

1) If a subject becomes a Prisoner after enrolling in a research study, the investigator is responsible for immediately reporting the event in writing to the IRB. This is not required if the study was previously approved by the IRB for Prisoner participation. If research interactions and interventions or obtaining identifiable private information will not occur during the incarceration, IRB review and approval under the Prisoner rules is not required. The Principal Investigator should provide the incarceration, the extent of the subject's participation in the research trial up to becoming a Prisoner, what are the outstanding study activities that are remaining for the subject and the plan to include or exclude the Prisoner for the research activities.

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

3) If the study was not previously reviewed and approved by the IRB in accordance with the requirements of Subpart C, all research interactions, and interventions with, and obtaining identifiable private information must cease until the requirements of Subpart C are satisfied. This is necessary because it is unlikely that review of the research and the informed consent documents contemplated the constraints imposed by the possible future incarceration of the subject.

4) The convened IRB is to review the current research protocol in which the subject is enrolled, taking into special consideration the additional ethical and regulatory concerns for a Prisoner involved in research.

34. **Recruitment of Subjects**

a. Recruitment of subjects is one of the most challenging aspects of research involving human subjects. It is an essential part of the research protocol and

must be presented in sufficient detail to allow the Institutional Review Board (IRB) to fully assess the investigator's plan. Recruitment of subjects must be equitable and include racial, ethnic, educational, socioeconomic, and gender diversity appropriate to the condition that is studied. Exclusion of any specific group (e.g., women of child-bearing potential) must be justified in the protocol. Both the benefits and risks of research participation must be equitably distributed. All recruitment efforts must respect personal rights to privacy and confidentiality and be compliant with the Health Insurance Portability and Accountability Act (HIPAA) regulations. The recruitment plan must avoid coercion of subjects. Financial compensation, reimbursement for expenses, or other inducement for participation must not be coercive and should be reasonable for the expenses, discomfort, or inconvenience of participating. In addition to IRB requirements, the HIPAA regulations put further restrictions on research recruitment activities. Details are available via the U.S. Department of Health and Human Services Website.

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

c. Contacting Potential Subjects:

   i. Prospective participants often have their first contact with a research coordinator or third-party that follows a script to determine basic eligibility for the specific study. The IRB must review these procedures to assure that they adequately protect the rights and welfare of the prospective participants. The IRB must have written assurance that any information collected about prospective participants will be appropriately handled. Submission of scripts are needed for the following: When phone screeners will be contacting potential patients, when the screeners will be contacting another physician's patients, any phone conversations that communicates standard information, any scripts that are made throughout the research study, when surveys, questionnaires, or other instruments are administered as part of the research.

   ii. A physician who has a treatment relationship with a prospective research subject may approach that patient about participation in any IRB approved protocol. The physician may approach the potential subject about participation in his or her own protocol or on behalf of another investigator. If the protocol is by another investigator, the permission of potential subject is required before identifying information is given to the study investigator.

   iii. For potential subjects who are inpatients the permission of the attending physician must be obtained before the patient is approached about a study. An attending physician may give permission for all of his or her patients to be approached without asking individually about each patient.

   iv. Contacting outpatients for recruitment to research studies is usually allowed but the method of obtaining names and contact information, who will contact the potential subjects, how permission will be obtained from the attending

physician, and how data confidentiality will be protected, must be presented in detail in the protocol.

v. The IRB strongly discourages Cold Calling of potential research subjects unless the potential subject knows the person making the telephone call. A letter giving brief information about the study and informing the potential subject that he or she will be receiving a call from the study staff is usually required.

vi. The IRB strongly discourages the use of per patient payment to recruiters ("Finders' Fees") for recruitment or identification of potential study subjects. If Finders' Fees are proposed, they must be justified in detail in the protocol including defining the work that is done by the recruiters. The protocol must also explain what measures are taken to be sure that Finders' Fees will not lead to coercion of subjects. The use of Finders' Fees will always be reviewed by the full Board and is not eligible for expedited review.

vii. Payments to physicians, research staff and the institution as an incentive to accelerate the enrollment of subjects (i.e., bonus payments) are prohibited. The IRB requires full disclosure of any financial arrangements that may encourage physician to recruit subjects for research participation that may not be in the subject's best interests. In some special circumstances, physicians who are not formally listed on the protocol may be performing specific research related activities (such as conducting screening examinations or tests, or participating in the consent process), but solely in the role of service provider. These physicians and investigators may be reasonably compensated for their time and effort.

d. Advertisements

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

ii. Advertisements should be submitted as part of the initial IRB application. If advertising materials become available after the initial approval or the approved material is changed the advertising must be submitted as an amendment to the study. The material may not be used until IRB approval is received. Advertisements submitted as part of a new protocol receive full Board review. Advertisements submitted as amendments to approved protocols normally receive expedited approval but can be referred to the full Board for review.

iii. The IRB pays particular attention to risk and potential benefit information to ensure it is presented in a balanced and fair manner. The information presented should not mislead, for example, by promising benefits or implying a benefit beyond that potentially provided by the research.

iv. The investigator must obtain IRB approval for all television, radio, videotape or print Advertisements, posters, flyers, handouts, e-mail solicitations, Internet websites, and other recruitment methods and materials intended for the recruitment of prospective subjects to a research protocol. Final copies of printed materials must be submitted because, in addition to the content, the IRB also reviews the type size and other visual effects. When Advertisements are to be taped for broadcast, the IRB must review the final audio/video tape. The IRB may review and approve the wording of the Advertisement prior to taping to preclude re-taping because of changes requested by the IRB.

v. In addition, print Advertisements may only be posted in designated approved on-campus and off-campus areas (such locations DO NOT include restrooms or elevators); and must possess the IRB Advertisement Approval Stamp. Please contact the IRB Office for questions regarding designated approved posting locations.

vi. When information about a study is presented on a website, IRB approval of the information is not required if the information is limited to the following:

1) Study title
2) Purpose of the study
3) Protocol summary
4) Basic eligibility criteria
5) Study site location(s)
6) How to contact the study site for further information

vii. Inclusion of information exceeding the above basic listing information (including description of risks and potential benefits, mention of incentives, or solicitation of identifiable information) requires IRB review and approval (OHRP Guidance on Clinical Trial Websites).

viii. Clinical trial websites may ask viewers to answer questions regarding eligibility for a specific clinical trial. If identifiable private information is collected via the clinical trial website, the IRB will review plans for protecting the confidentiality of that information and ensure that the website clearly explains how identifiable private information might be used.

ix. The first contact prospective study participants make is often with a receptionist who follows a script to determine basic eligibility for the specific study. The IRB must review the procedures to ensure that they adequately protect the rights and welfare of the prospective participants. The IRB must have assurance that any information collected about prospective participants will be appropriately handled including the destruction of identifying information if the potential subject is not interested or eligible for participation.

x. The following do not qualify as an Advertisement and do not require IRB review:

1) Communications intended only to be seen or heard by health professionals, such as letters to physicians.

2) News stories where reporters or other non-study personnel are responsible for the final content.

xi. Any Advertisement to recruit participants should be limited to the information the prospective subject needs to determine eligibility and interest. When appropriately worded, the following items may be included in Advertisements:

1) The name, address, e-mail, and facility/institution of the investigator or study coordinator if applicable.

2) The condition under study and/or the purpose of the research in summary form.

3) Statement that the study is research.

4) If the study includes non-FDA approved medications include the word "investigational."

5) The criteria that will be used to determine eligibility for the study in summary form.

6) A brief list of participation benefits, if any (e.g., a no-cost health examination).

7) The time or other commitment required of the participants.

8) The location of the research and the person or office to contact for further information.

9) Compensation may be mentioned, but not as a specified amount or as a benefit.

xii. Advertising materials should not include the following:

1) Claims, either explicitly or implicitly, that the drug, biologic, device or other type of intervention is safe or effective for the purposes under investigation.

2) Claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic, device or intervention.

3) Terms such as "new treatment," "new medication," or "new drug" without explaining that the test article is investigational.

4) Promises of "free medical treatment," when the intent is only to say that participants will not be charged for taking part in the investigation.

5) Mention of a specific amount of financial remuneration or overemphasize in the materials that remuneration is available.

6) Include any exculpatory language.

xiii. All Internet recruitment materials directed at potential subjects are considered Advertisements and the same rules apply. Two specific Internet clinical trial listing services (National Cancer Institute's cancer clinical trial listing and the government-sponsored AIDS Clinical Trials Information Service) have been given an exemption to this requirement and do not require prospective IRB approval.

e. Secondary Recruitment:

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

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

f. Preferred Method for Contact:

i. An investigator wishing to obtain the names of potential subjects (e.g., family members for a genetic study) should give a stamped envelope containing the solicitation materials (letter, study brochures, return postcard, etc.) to the subject. The subject is then asked to address the envelope to his or her relative and mail it. If the investigator does not receive a response from the secondary recruit, it is reasonable to ask the study subject to contact the individual to be sure that he or she received the materials.

ii. The investigator may contact potential subjects by mail and enclose a card to be returned indicating the desire to be contacted to participate in a study. Potential subjects may be sent two to three letters, but if the person does not respond the investigator must remove that person from the contact list. Failure to respond cannot imply consent to contact. Potential subjects may not be contacted for a different research study. Initial telephone contact of potential subjects is not acceptable unless specifically approved by the Board.

iii. The IRB must approve letters to be sent to potential subjects prior to sending the letter. This approval is requested by submitting a letter template in the original protocol submission, or as an addendum to an already approved study.

g. Exception to the Standard Method for Contact:

i. The IRB allows investigators to obtain information about potential subjects from enrolled study subjects if ALL the following criteria are met:

1) No health information about the relative is shared with the investigator either directly or by implication. For example, this cannot be used if only relatives with a specific condition are to be contacted.

2) Only name, address, email, and telephone number are requested.

3) The person is not called without sending an IRB approved letter in advance.

4) The rationale for this approach, including how the contact information will be kept confidential, is justified in the protocol.

ii. It is the IRB policy that investigators may ask enrolled subjects in an approved IRB study only for the names and addresses of relatives or other persons who may be contacted by the investigator to participate in the study or an aspect of the study (e.g., genetic screening). Telephone numbers and other health related information maybe NOT be solicited by the investigator or provided by the study subject to the investigator. This includes health information by implication (e.g., requesting identifying information to contact the subject's relatives who have diabetes). The enrolled subject should be asked to inform the person that their name, address, and/or e-mail have been provided to an investigator.

35. **Remuneration of Subjects**

a. Payment amounts, timing, and method of payment must be described and justified in the Human Subjects Protocol Full Review Form. Payment amount, including the timing and method of payment must be specified in the consent form. The Board encourages describing Reimbursement of expenses separately from payment for time and discomfort. The IRB does not view the Remuneration as a benefit to offset research risks in deciding whether a protocol should be approved. Risks that are otherwise acceptable cannot be made acceptable offering increasing amounts of money to participants. The IRB will consider the cultural and educational status of potential research subjects when determining whether the Compensation plans are appropriate.

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

c. Remuneration is not considered a benefit of research but is for the time and effort devoted to participation in research by subjects. Any change in the payment to subjects must be submitted to the IRB as an addendum to the protocol with appropriately modified consent/assent forms. The IRB encourages describing Reimbursement of expenses separately from payment of time and effort.

d. Tax laws and HIPAA regulations regarding the privacy of personal health information must be followed when the decision is made to provide Remuneration to research participants. Participants receiving more than $600 in one calendar year need to be told that they must supply their social security number and that a 1099-Misc form will be sent to the Internal Revenue Service by the research site.

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

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

36. **Investigational Devices Used in Research**

a. Under FDA regulations 21 CFR 812.2(a) all clinical investigations that involve determining the safety or efficacy of a medical device must have an Investigational Device Exemption unless the device meets one of the exemptions from the requirement for an IDE in 21 CFR 812.2(c).

b. There are two ways that a medical device can have an Investigational Device Exemption:

i. FDA issues an Investigational Device Exemption.

ii. The device meets the requirements for an abbreviated Investigational Device Exemption.

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

d. Abbreviated Investigational Device Exemption:

i. The device is not a significant risk device:

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

2) Is not purported or represented to be for a use in supporting or sustaining human life and does not present a potential for serious risk to the health, safety, or welfare of a subject;

3) Is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject;

4) Does not present a potential for serious risk to the health, safety, or welfare of a subject; or

5) The device is not a banned device.

ii. The sponsor labels the device in accordance with 21 CFR 812.5;

iii. The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;

iv. The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under §56.109(c);

v. The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations;

vi. The sponsor maintains the records required under 21 CFR 812.140(b)(4) and (5) and makes the reports required under 21 CFR 812.150(b)(1)-(3) and (5)-(10);

vii. The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 21 CFR 812.150(a)(1)(2)(5) and (7); and

viii. The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

ix. There are seven categories where research involving a medical device is exempt from the requirement for an Investigational Device Exemption: [21 CFR 812.2(b)]

1) Exemption #1: A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

2) Exemption #2: 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 21 CFR 807 in determining substantial equivalence (i.e., "FDA-approved device").

3) Exemption #3:

a) A device is a diagnostic device.

b) The sponsor complies with applicable requirements in 21 CFR 809.10(c).

c) The testing is noninvasive.

d) The testing does not require an invasive sampling procedure that presents significant risk.

e) The testing does not by design or intention introduce energy into a subject.

f) The testing is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

4) Exemption #4: A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

5) Exemption #5: A device intended solely for veterinary use.

6) Exemption #6: A device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c).

7) Exemption #7: A custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

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

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

i. A description of the device;

ii. Reports of prior investigations conducted with the device;

iii. The proposed investigational plan;

iv. A description of subject selection criteria;

v. Monitoring procedures;

vi. The sponsor risk assessment and the rationale used to make the sponsor's risk determination; and

vii. The IRB may also request additional information, if necessary, from the sponsor or investigator or ask the FDA to provide a risk assessment.

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

h. In accordance with FDA regulations 21 CFR 812.3, and Good Clinical Practice (GCP) guidelines; the requirements applicable to a sponsor-investigator under part 812 include both those of an investigator and a sponsor. The responsibilities include the following:
    i. Maintaining the Investigational Device Exemption
    ii. Obtaining Qualified Investigators and Monitors
    iii. Providing Necessary Information and Training for Investigators
    iv. Monitoring the Investigation
    v. Controlling the Investigational Agent
    vi. Reporting Significant Adverse Events to FDA/Investigators
    vii. Maintaining and Retaining Accurate Records
    viii. Implementing and maintaining quality assurance with written Standard Operating Procedures (SOP's)
i. When an Investigator is the sponsor of the Investigational Device Exemption (sponsor- investigator), the IRB requires the investigator to meet with the Chief Medical Officer or designee of the respective medical facility and the Ballad Health legal Department to review his/her FDA responsibilities as a sponsor-investigator. The Chief Medical Officer is responsible for providing the IRB with documentation in writing that the review has taken place, and that the investigator understands his/her FDA Investigational Device Exemption responsibilities. Approval to initiate the research is contingent upon receipt of written documentation from the Chief Medical Officer or designee.
j. In accordance with FDA regulations 21 CFR 812 and Ballad Health policies, the Sponsors and/or Investigators are responsible for the proper ordering, handling, storage and disposition of investigational devices in clinical trials at Ballad Health.
k. Ordering:
    i. Ordering of an investigational device must be done by the Principal Investigator or designated study personnel according to the terms of the executed agreement and only after the protocol has been approved by the IRB.
l. Receipt:
    i. Investigational devices may only be received by the Principal Investigator or designated study personnel at a Ballad Health business address.
m. Storage/Labeling:
    i. Investigational devices used in conjunction with a research protocol must be kept in a locked and secured area and must be labeled "Caution: Investigational Device-Limited by Federal (or United States) Law to Investigational Use."
    ii. Access to investigational devices must be limited to the Principal Investigator or designated study personnel.

iii. Study device supplies must be labeled as investigational by the manufacturer and maintained and stored separately by research personnel.

n. Dispensing:

i. The investigational device may not be given to anyone not enrolled in the study.

ii. The Principal Investigator must not supply the investigational device to any person not authorized.

iii. For accountability purposes an investigational device accountability log(s) must be kept for all investigational device studies. Documentation of the following elements should be recorded for each device used:

1) The type of device

2) Model Number

3) Serial Number

4) Lot Number (if applicable)

5) Date received

6) Research subject name and medical record ID number (for internal tracking purposes)

7) Research subject study ID number

8) Date implanted or used

iv. Personnel may not remove any device(s) from the standard device inventory and substitute them for an investigational device, even if the device, under study, is approved and used in practice.

v. If the sponsor provides an investigational device accountability log, research personnel must review the log to determine if the required elements are included on the log. If the log provided by the sponsor does not include all of the required elements, a separate log including those elements must be maintained.

o. Maintaining an Investigational Device Log(s):

i. Investigational device logs must be maintained in the study's regulatory binder for the period of time required by the federal regulations or terms of the agreement, whichever is longer.

ii. The full names, titles/positions, signatures and/or initials of all Ballad Health personnel or non-Ballad Health personnel with Allied health privileges responsible for maintaining or documenting in the log(s) must be indicated on either a cover sheet or in the log itself.

iii. The Principal Investigator or designated study personnel must regularly review the device logs to ensure that there is an adequate amount of devices or the appropriate type of devices available (sizes, etc.) to conduct the scheduled procedures.

p. Disposition

i. Upon conclusion or termination of the clinical investigation, or by the sponsor's request, the principal investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device(s) as the sponsor directs. Investigational device(s) should not be destroyed by the principal investigator or study personnel without obtaining advanced written permission from the sponsor.

ii. Documentation of why, when, and the personnel involved is required.

iii. In the event of research software, disposition must include the date the software was deprogrammed or removed from the device(s).

q. Radioactive Materials:

i. Radioactive Material in a Radiation Delivery Device: Obtain approval from the site-specific Radiation Safety Committee (RSC) for all research protocols involving a radioactive device. The Radiation Safety approval process involves designation of an individual with the appropriate training to be the Authorized User Physician.

ii. Radiation Generating Equipment: Contact Radiation Safety regarding new and transferred radiation generating equipment (e.g. x-ray unit). Radiation Safety must be notified at least 3 weeks prior to delivery. New and transferred radiation safety equipment must be tested and accepted by a Radiation Expert in Radiology or Radiation Oncology, as appropriate, prior to use on a human research subject.

r. Maintenance and Cleaning:

i. All investigational devices must be properly maintained and cleaned.

37. **Emergency Use of Investigational Drugs, Biologics, or Devices**

a. The Food and Drug Administration (FDA) and other Federal agencies have strict regulations about the use of investigational agents in emergency situations. The regulations state "Nothing in this policy is intended to limit the authority of a physician to provide emergency medical treatment for patients who need such care" (45 CFR 46.116(f)). These regulations mean that emergency medical care for patients may be provided without regard to Institutional Review Board (IRB) review and approval.

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

included in any report of a DHHS-regulated research activity but may be used in a report of an FDA regulated research activity that is not DHHS-regulated.

c. The FDA regulations do NOT allow expedited (administrative) IRB approval of research in emergency situations. Therefore, terms such as "interim approval," "compassionate approval," "temporary approval," will not be utilized for requests for Emergency Use of FDA regulated products. The IRB must either grant approval at a convened full Committee meeting (may use the data for research), or if the conditions of 21 CFR 56.104(c) are met and it is not possible to convene a quorum within the time available, the Emergency Use may proceed without IRB approval (may not use the data for research).

d. It is the policy of Ballad Health IRB to recognize the provisions found in the Food and Drug Administration (FDA) regulations for the Emergency Use of investigational drugs, biologics, agents, or devices. The Emergency Use of investigational drugs, agents, biologics, or investigational (unapproved) medical devices, will be handled in accordance with FDA regulations and institutional policies and procedures. Ballad Health IRB requires prior notification of Emergency Use of investigational drugs, biologics, or Investigational Devices (21 CFR 56.104 (c)).

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

      1) The patient is in a life-threatening or Severely Debilitating situation.

      2) There is no standard acceptable treatment available.

      3) There is insufficient time to obtain approval from the IRB at a convened meeting.

      4) Any subsequent use will be reviewed by a convened IRB.

   ii. The Emergency Use provision in the FDA regulations is an exemption from prior review and approval by the IRB. It allows for one Emergency Use of a test article without prospective IRB review. Any subsequent use of the investigational product at the institution must have prospective IRB review and approval.

   iii. When the investigator notifies the IRB in advance of an Emergency Use, the IRB Chair (or in the Chair's absence, the Vice-Chair) will review the circumstances of the use and ensure that FDA regulations 21 CFR 56.104(c) and 21 CFR 50 will be followed. When an Emergency Use report is discussed at an IRB meeting, the minutes of the meeting must document that the IRB considers the use of the investigational agent to meet the requirements of 21 CFR 56.104(c) and 21 CFR 50. If not, the matter will be handled as non-compliance.

   iv. It is the Principal Investigator's responsibility to notify Ballad Health IRB prior to the Emergency Use of an investigational drug, biologics, or device. The Investigator must contact Ballad Health IRB by telephone and complete and submit the Emergency Use Checklist and Request to Ballad Health IRB. If the

patient's condition allows waiting for review at an IRB meeting, then the FDA Emergency Use restrictions do not apply. The IRB will review and possibly approve the protocol and the study documents to include protocol, informed consents, etc.

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

e. Informed Consent and Waiver of Informed Consent

i. Even in an emergency situation, the investigator is required to obtain written informed consent from the patient or Legally Authorized Representative. Relevant items required in a research consent form should be present. The consent form is not approved or stamped by the IRB. The IRB is willing however to review the consent and offer suggestions. For those studies possessing the criteria for granting exceptions to the requirement of obtaining informed consent, and in turn wishes to utilize this waiver, the investigator is required to submit documentation supporting the waiver to the IRB within five days. For all protocols utilizing the exceptions to the requirement to obtain informed consent for Emergency Use of a test article, the IRB will review all submissions to determine whether the exception complied with regulatory requirements.

f. IRB Responsibilities

i. The initial review is performed by the Ballad Health Chair or Vice-Chair; and if they determine that the criteria have been met, the Chair/Vice-Chair they will communicate this in writing to the investigator.

ii. The Emergency Use of FDA regulated products requires the involvement of an IRB Chair or his/her designee. The IRB Chair or his/her designee will be promptly notified of the Investigator's intent for Emergency Use of an investigational drug, agent, biologic, or device. The IRB Chair or his/her designee will evaluate the Investigator's notification and guide the Investigator in adherence to the FDA regulations and institutional policies and procedures. The IRB Chair or his/her designee may request:

1) An authorization from the sponsor or manufacturer to allow the use by the Investigator for the test article;

2) An approved IND/IDE or a letter explaining exemption from the FDA;

3) An adequate description of the situation regarding the use of the test article with an independent physician's certification, if applicable;

4) The informed consent document or the certification for the exception from obtaining informed consent; and

5) Any other materials that may aid in the evaluation of the request.

iii. The full Board will be notified of the Emergency Use of an FDA regulated product and the IRB Chair or his/her designee will review the five (5) day follow-up report submitted by the Investigator with the full Board.

iv. Some manufacturers or sponsors will agree to allow the use of the investigational agent, but their policy requires "an IRB approval letter" before the agent will be shipped. The manufacturer will be provided a written statement that the IRB is aware of the proposed use and based on the information it has been provided by the Investigator that the proposed use meets the requirements of 21 CFR 56.102(d). Although this is NOT an "IRB approval," the acknowledgement letter is usually acceptable to the manufacturer and allows shipping the experimental agent to the investigator.

v. The investigator is required to submit a written follow-up report to the IRB within five working days of the Emergency Use of an investigational drug, agent, biologic, or device. This report should include the name of the investigational drug, agent, biologic, or device; a copy of the informed consent document (or justification for a waiver of informed consent); a description of the conditions, including date and time, under which the investigational drug, agent, biologic, or device was administered/utilized; measures taken to protect participants; adverse events or unanticipated problems to the recipient or others; and outcomes if known. The written follow-up report, protocol; and consent form (or justification for a waiver) is reviewed by the Board at the next convened meeting. The IRB will review the documents provided, together with the criteria to waive the requirements to obtain informed consent (if applicable) and determine whether the regulatory criteria for planned emergency research have been met and that the circumstances of the Emergency Use met the requirements of the FDA regulations. The criteria for allowing Emergency Use of a test article in a life-threatening situation are listed on the "Emergency Use Involving Human Subjects Checklist" determination form. The Board's determinations are communicated in writing to the investigator (Board Meeting and Administrative Policies).

g. Subsequent Use

i. Investigators must understand that under NO circumstances, can an Emergency Use procedure be done more than once for a single investigational drug, agent, biologic, or device. The Investigator is to evaluate the likelihood of a similar need for the drug, agent, biologic, or device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IND or IDE for subsequent use. If investigators think they may need to use the investigational drug, agent, biologic, or device again, a complete IRB protocol must be submitted in time for full Board review. Since it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the protocol, it is permissible to treat a second patient prior to full IRB approval if the protocol has been submitted to the IRB and IRB review is in process.

h. FDA Requirement to Obtain an Emergency IND/IDE (Investigational New Drug / Investigational Drug Exemption) for Drug, Device, or Biologics

i. The Emergency Use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study

protocol the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the Emergency Use under the company's IND. The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, the FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means (21 CFR 312.310(d)).

ii. If an IDE for the use of an investigational device does exist, the Investigator is to notify the sponsor of the Emergency Use, or if an IDE does not exist, the Investigator is to notify the FDA of the Emergency Use and provide the FDA with a written summary of conditions constituting the emergency, subject protection measures, and results.

38. **Use of Placebos and Washout Periods in Research**

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

i. The study is ethically justified.

ii. There is a clear and detailed rationale for the use of a Placebo in the protocol.

iii. Potential risks are identified and minimized.

iv. The subject is adequately informed of the potential use and risks of the Placebo in the study.

b. At the discretion of the Chair of the IRB, or at the request of the IRB, a protocol may be referred to the Ballad Health facility specific Ethics Committee for consultative review prior to approval by the IRB.

c. Protocol Requirements When a Placebo Is Used:

i. When submitting a protocol in which a Placebo will be used, the investigator must justify the use of the Placebo, compare the use of Placebo to standard therapy, and outline the methodology that will be used to minimize risks to subjects. If vulnerable populations (children, cognitively impaired subject, etc.) are included in the study, the investigator must discuss and justify their participation and detail how subjects will be adequately protected.

ii. The following are methods that can be used to minimize risks associated with the use of Placebo:

1) Exclude subjects with an increased risk of harm from non-response.

2) Include in the protocol increased monitoring for subject deterioration and the use of rescue medications.

3) "Early escape" mechanisms and explicit withdrawal criteria may be built in so subjects will not undergo prolonged Placebo treatment if they are not doing well.

4) The size of the population placed on Placebo may be smaller than the number in active treatment arms.

5) Placebo and active treatment may be compared in an "add-on" method, keeping the subjects on identical maintenance treatments, and then adding the active treatment to one arm and Placebo to the other. This design is especially applicable when the available treatment is known to decrease mortality or morbidity.

6) Shortened treatment periods reduce the risks associated with delayed treatment. In situations in which long-term Placebo treatment would not be acceptable, the use of a Placebo group for a short period at the beginning of a trial could establish short-term effects. The trial would then continue without the Placebo group.

7) Unblinded data review by a Data and Safety Monitoring Board with interim analysis of study results and safety issues. This is especially important for multi-center site studies.

d. Informed Consent and Use of Placebo:

i. If a Placebo is used in a study, the informed consent form must include all of the following information:

1) Subjects must be informed that they may be given a Placebo.

2) A clear lay definition of the term "Placebo."

3) The rationale for using a Placebo must be explained to the subjects.

4) If applicable, subjects must be informed of any viable medical alternatives to being placed on Placebo.

5) The duration of time that a subject will be on a Placebo, degree of discomfort, and potential effects of not receiving medication must all be explained.

6) Any consequences of delayed active treatment must be explained to the subjects.

7) A statement in the Risk section of the consent that the subject's condition may worsen while on Placebo.

8) A discussion in the Benefits section that subjects who receive Placebo will not receive the same benefit as those who receive active treatment if that treatment is effective.

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

e. Protocol and Consent Form Requirements When a Washout Period is used

i. Protocols that involve Washout Periods (with or without the use of a Placebo) present similar concerns about risk to subjects as protocols using Placebos because both involve withholding available, proven therapy from subjects. Therefore, similar attention should be paid to the justification of the use of a Washout Period including methods to minimize risks to subjects.

ii. The protocol must describe the reason why active therapy is being withheld, the duration of the Washout Period, the risks specific to this phase of the

study, increased subject monitoring during the Washout Period, and instructions to the subjects about what to do if they experience problems while off active treatment. Use of a Washout Period, possible risks to the subject, and methodology to address problems that may occur during the Washout Period must be included in the consent form.

39. **Unanticipated Problems, Adverse Events, and Protocol Deviations**

a. Reporting Requirements of Unanticipated Problems Involving Risks to Subjects or Others

i. If the problem poses an immediate risk of serious harm to a participant or others, it must be reported immediately to Ballad Health IRB via email or phone.

ii. Unanticipated problems involving risk to subjects or others, in other words events that meet the three criteria in the definition presented above, always need to be reported to the IRB. Adverse events that do not meet those three FDA criteria nor the OHRP definition of SAE necessarily need to be reported. Adverse events are only reported if:

1) They meet the FDA definition of an unanticipated problem involving risk to subjects or others; that is, if the event is unexpected, related to or possibly related to participation in the research, and increases risk beyond what was previously known or recognized.

2) They meet the OHRP definition of an adverse event that is unexpected, related or possibly related to participation in research and serious: SAE that results in death; is life-threatening (places the subject at immediate risk of death from the event as it occurred); results in in-patient hospitalization or prolongation of existing hospitalization; results in a persistent or significant disability/incapacity; results in a congenital anomaly/birth defect; or based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

iii. All unanticipated problems involving risks to subjects or others must be reported to Ballad Health IRB within seven (7) calendar days of discovery of the problem or event. The only exception to the above time frame is for the reporting of deaths. All study related deaths must be reported to the IRB within five (5) calendar days of their discovery with the exception of Oncology related deaths. Oncology related Deaths are not viewed as Serious unless the death is within 30 days of the last dose of study drug. Most oncology studies follow subjects until death. If a death occurs in an Oncology study, but after 30 days of the last dose of study drug, the death will be reported on and Adverse Event Log with the Annual Continual Review.

iv. The following are examples of unanticipated problems that need to be reported by the Principal Investigator (PI) to Ballad Health IRB as soon as possible, but in all cases within seven (7) calendar days:

1) Adverse events, which in the opinion of the PI, are both unexpected and related.

a) An adverse event is "unexpected" when its specificity and severity are not accurately reflected in the informed consent document.

b) An adverse event is "related to the research procedures" if in the opinion of the PI, it was more likely than not to be caused by the research procedures, or if it is more likely than not that the event affects the rights and welfare of current participants.

c) Internal adverse events that are unexpected and related or possibly related to the research and that indicate there are new or increased risks to subjects.

d) External adverse events that are serious, unexpected, and related or possibly related to the research and that indicate there are new or increased risks to subjects that require some action (e.g., modification of the protocol, consent process, or informing subjects).

b. Information that indicates a change to the risks or potential benefits of the research. For example:

   i. An interim analysis indicating that participants have a lower rate of response to treatment than initially expected.

   ii. Safety monitoring indicating that a particular side effect is more severe, or more frequent than initially expected.

   iii. A paper is published from another study that shows that an arm of your research is of no therapeutic value.

c. A breach of confidentiality including inappropriate disclosure, lost, or stolen confidential information.

   [NOTE: The PI and members of the Ballad Health workforce (including Ballad Health employees and other members of the workforce as described in Ballad Health's HIPAA policies and procedures), are also required to report breach of patient information/protected health information/PHI in accordance with Ballad Health HIPAA policies and procedures and other policies and procedures of Ballad Health. These reporting obligations may include notification to the Ballad Health Privacy Officer.]

d. Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.

e. Changes to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.

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

g. Event that requires prompt reporting to the sponsor such as disqualification or suspension of investigator.

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

i. Protocol Deviation (including accidental or intentional protocol deviation) that caused harm to participants or others or indicates participants or others are at increased risk of harm.

j. Unanticipated adverse device effect (UADE) is (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if the effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application); or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

i. A report of a UADE must be submitted to the sponsor and Ballad Health IRB as soon as possible but not later than ten (10) working days after the investigator first learns of the event (21 CFR 812.150(a)(1)).

ii. Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to the FDA, all reviewing IRBs, and participating investigators within ten (10) working days after the sponsor first receives notice of the effect (21 CFR 812.46(b), 21 CFR 812.150 (b)(1)).

iii. Unanticipated adverse device effects that are serious and caused by, or associated with, the device.

40. **Adverse Events**

a. An unanticipated problem is unexpected, whereas an adverse event may be either expected or unexpected. Unanticipated problems may or may not be adverse events. Adverse events relate to harm to participants; unanticipated problems may involve an increased risk of harm even if no actual harm occurred.

b. In practice, only a small subset of adverse events occurring in human subjects participating in research, meet the three criteria for an unanticipated problem involving risks to subjects or others.

c. The primary responsibility for the evaluation of internal and external adverse events lies with the principal investigator of the protocol. This includes the documentation, investigation, and follow-up of these events. For those events that require reports to the IRB it is the principal investigator's responsibility to submit the reports in a timely manner. How the event is reported depends on the risk level of the research and the severity of the event. These requirements are detailed below. If new risks to the participants are identified, they must be included in a revised consent form.

d. If an adverse event meets the definition of an unanticipated problem (i.e., unexpected, related to the research, suggests increased risk of harm to subjects or others), it must be reported to the IRB. In general, the following types of adverse events are considered to be unanticipated problems that must be reported to the IRB:

i. Single occurrence of a serious, unexpected event that is strongly associated with the research;

ii. Multiple occurrences of an adverse event that, based on aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of adverse events represents a signal that the adverse events were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups in the drug treatment arm versus a control);

iii. An expected adverse event (that is described in the investigator's brochure, protocol, or informed consent documents) that occurs at a severity or rate/frequency that is inconsistent with prior observations.

e. Reporting an event to the IRB does not relieve the investigator of the obligation to report the event to other agencies such as the FDA and/or study sponsors. The mechanism and timing of the reports vary depending on the type of protocol, severity of the event and whether it occurred on-site (internal) or is reported to the investigator by the sponsor (off-site/external).

f. Multiple factors determine when and how an adverse event is reported. One of the most important distinctions is whether the event is expected or unexpected. To make this determination it is necessary to know the underlying condition of the subject including co-morbidities, and the severity and frequency of events in patients who qualify for the study.

i. An expected adverse event meets one or more of the following criteria:

1) Attributed to the underlying condition of the patient being studied.

2) Attributed to the patient population being studied.

3) Anticipated on the basis of prior experience with the drug under investigation or with related drugs.

4) Identified in the investigator brochure, informed consent, or study drug labeling.

ii. An unexpected adverse event meets one or more of the following criteria:

1) Not listed in the informed consent, protocol, or investigator brochure.

2) Not attributed to the underlying condition of the subject taking into account co-morbid conditions.

3) Not attributed to the patient population

iii. Severity and/or frequency of the event is beyond the range previously known.

iv. For all reporting periods "days" refers to calendar days after the investigator learned of the event. All reportable events need to be reported to the IRB within the timeline even if the information about the event is incomplete. Further information can be added with a follow-up report.

g. How to Report an Adverse Event or Unanticipated Problem

1) The reporting form is available in IRBNet as the document titled, "SAE Report Form".

h. External Adverse Events

i. External (Off-site) event refers to an event reported to a Ballad Health investigator that occurred involving a participant who gave consent using consent documents that were approved by another IRB and not by the Ballad IRB. External events occur at another site (a non-Ballad Health location/location unrelated to Ballad Health) participating in a protocol that is active at Ballad Health. Unanticipated problems should be reported to the Ballad IRB even if occurring at external sites. However, external events that do not constitute unanticipated problems , where the event involves a participant not enrolled at a Ballad Health site and where the Ballad Health investigator is not responsible for the reporting of the event to a regulatory agency are expected to submitted to and reviewed and analyzed by the monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a Data Safety Monitoring Boards (DSMB)) in accordance with a monitoring plan described in the IRB-approved Data and Safety Monitoring Plan (DSMP) for the protocol (IRB Policy, Protocol Submission Requirements).

NOTE: Ballad Health IRB does not accept sponsor IND/IDE safety reports describing adverse events that have occurred at sites other than those subject to this policy unless the report is of an incident that is: (1) serious; (2) unexpected or unanticipated; (3) related to the investigational drug/device; and (4) suggests that subjects are at an increased risk of harm and as such warrants changes in the research, consent process, or informing subjects. IND/IDE safety reports that warrant changes are to be submitted through IRBNet.

i. Other events are reported as follows:

i. All serious adverse events that do not affect the risk/benefit ratio for study participants and/or require a change in the protocol are reported based on the study sponsors' requirements.

ii. All non-serious events are kept in the investigator's files and are reported based on the study sponsors' requirements.

j. Reporting Adverse Events after a Participant Has Completed a Study

i. If a participant has an adverse event after completing all of his or her study activities, and the study remains open at Ballad Health for other participants, the adverse event is only reported if it was study related.

k. Reports of Events to Governmental Agencies

i. The study principal investigator must be familiar with DHHS, FDA regulations, and Ballad Health policies governing adverse event reporting requirements. There may also be other different or additional agency specific reporting requirements that the principal investigator must meet. There are additional reporting requirements for a principal investigator who is also the sponsor/investigator of a clinical trial on an investigational drug. He or she must submit written IND safety reports to the FDA on a timely basis. The reports must include any adverse event associated with the use of the drug that is both Serious and Unexpected; or any finding from tests in lab animals that suggests a significant risk for human participants.

ii. The principal investigator who conducts sponsored research projects funded by a federal agency is obligated to report adverse events that are serious and unanticipated simultaneously to both the Federal agency and to the IRB. The IRB has a separate and distinct obligation to report the adverse events to government authorities. Ballad Health institutional officials will determine when an adverse event reported to an IRB should be reported to the Office of Human Research Protections (as part of the Institutional Assurance on file with OHRP), to the FDA, and to the Office of Research Integrity. Federally required reports from a principal investigator regarding termination for cause or suspension of a research project must be co-signed by the Ballad Health Signatory Official before they are sent to the funding agency.

iii. Trials for which the National Cancer Institute is also the IND Sponsor have somewhat different reporting requirements.

iv. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm (assessed 11/16/2023)

v. Trials involving recombinant Deoxyribonucleic Acid (DNA) molecules have reporting requirements in addition to those listed above. See OHRP guidelines.

vi. https://www.hhs.gov/ohrp/sachrp-ommittee/recommendations/attachment-d-november-2-2016-letter/index.html , as well as, the NIH Guidelines, https://osp.od.nih.gov/biotechnology/nih-guidelines/ (assessed 11/16/2023)

41. **Independent Safety Monitoring Reports**

a. It is the responsibility of the investigator to submit any independent safety monitoring report to the IRB. Safety monitoring reports that do not result in a change in the protocol or consent form are submitted as per the sponsor requirements.

b. Failure to Report an Adverse Event

i. Failure to report an adverse event in a timely manner may be considered a compliance matter and referred to the IRB for review and a compliance determination (Non-Compliance with Human Subjects' Regulations).

c. Unanticipated Problems

i. There are other types of incidents, experiences, and outcomes that occur that represent unanticipated problems, but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems that are not adverse events may also place subjects or others at increased risk of harm, but no harm occurs to the participant.

ii. The primary responsibility for the evaluation of unanticipated problems lies with the principal investigator of the protocol. This includes the documentation, investigation, and follow-up of these events. For those events that require reports to the IRB it is the principal investigator's responsibility to submit the reports in a timely manner. How the event is reported depends on

whether: the event involved a study participant that signed a Ballad Health IRB approved informed consent form; and whether the event involved a risk, potential risk, or harm to the rights, safety, or welfare of a study participant. If the Unanticipated Problem does not meet these criteria, then the event does not meet reporting criteria and should be retained in the investigator's file for reference. If, however, both criteria are met, the Unanticipated Problem must be reported to the IRB within 7-14 calendar days depending on whether it qualifies as a serious event or not. Failure to report an unanticipated problem in a timely manner may be considered a compliance matter and referred to the IRB for review and a compliance determination (Non-Compliance with Human Subjects' Regulations).

d. Report the following information items to the IRB within seven (7) calendar days:
    i. New or increased risk
        1) For example, publications indicating a new risk, new risk in an investigator brochure, FDA black box warning, new risk identified in a data safety monitoring report, information or change that adversely affects subject safety, or information or change that adversely affects the conduct of the research.
    ii. Protocol Deviation that harmed a subject or placed subject at risk of harm
    iii. Protocol Deviation made without prior IRB approval to eliminate an immediate hazard to a subject
    iv. Audit, inspection, or inquiry by a federal agency
    v. Written report or action of a government agency, regarding the research, the PI, or the research staff, or if research staff are added, a past history of such report or action, including:
        1) Conviction of a crime
        2) FDA Warning Letter
        3) Suspension or termination by an IRB
        4) Suspension by a federal or governmental agency (such as, FDA or HHS)
        5) OHRP Determination Letter, FDA Inspection Letter with observations, or similar
        6) Form FDA 483 in the past 5 years
    vi. Allegation of Noncompliance or Finding of Noncompliance
    vii. Unauthorized disclosure of confidential information
    viii. Unresolved subject complaint
    ix. Suspension or premature termination by the sponsor, investigator, or institution
    x. Incarceration of a subject in a research study not approved to involve prisoners

xi. Adverse event or IND safety report that requires a protocol or consent change

xii. State medical board or hospital medical staff actions, (denial, revocation, suspension, reduction, limitation, probation, non-renewal, relinquishment, sanction, fine, or discipline) regarding any of the following for the PI or research staff, or if research staff are added, a past history of such action:

1) Clinical privileges at any site
2) DEA licensure
3) Fellowship/board certification
4) Medical licensure in any state or nation
5) Membership on any hospital staff
6) Prescribing privileges
7) Professional sanctions including fines and public reprimands
8) Professional society membership
9) Research privileges at any site

xiii. Unanticipated adverse device effect

xiv. Change in financial interest disclosure (submit as a modification)

xv. Change in any other information previously submitted to the IRB (submit as a modification)

xvi. Events Not Requiring Prompt Reporting

1) Potential risks and adverse events that may be reasonably anticipated (i.e., "expected") should be described in the informed consent process/form and do not require prompt reporting to the IRB by PIs. The following are examples of events that do not require prompt reporting:

a) Adverse device effects that are non-serious, anticipated, or unrelated;

b) Adverse events or injuries that are non-serious, expected, or unrelated;

c) Deaths not attributed to the research (e.g., from "natural causes," accidents, or underlying disease when the Principal Investigator has ruled out any connection between the study procedures and the subject's death);

d) DSMB reports; interim analyses; or other reports, findings, or new information not altering the risk/benefit profile;

e) Protocol Deviations or violations unlikely to recur or not involving risks to subjects;

f) Subject complaints that were resolved or complaints not involving risks;

g) Problems or findings not involving risk (unless the PI believes the information could affect subjects' willingness to continue in the research).

xvii. All related internal and external events involving risk but not meeting the prompt reporting requirements should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented. In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

xviii. External events that do not meet the reporting requirements (e.g., not related or not involving risk) and that are not relevant to the protection of Ballad Health research subjects or others should NOT be reported to the IRB.

e. IRB Review

i. When unanticipated problems are reviewed at an IRB meeting, the Ballad IRB will consider whether any corrective actions or substantive changes to the research are required. The Ballad IRB may consider any of the following and determine that corrective actions or substantive changes are required.

1) Review changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;

2) Request modification of inclusion or exclusion criteria to mitigate the newly identified risks;

3) Implementation of additional procedures for monitoring subjects such as additional monitoring by an independent monitor;

4) Suspension of enrollment of new subjects;

5) Suspension of research procedures in currently enrolled subjects;

6) Modification of informed consent documents to include a description of newly recognized risks;

7) Require notification of additional information about newly recognized risks to current and previously enrolled subjects;

8) To accept the report with no changes to the risk/benefit ratio or the informed consent documents;

9) Request further information from the investigator or Data and Safety Monitoring Board;

10) Increase the frequency of continuing review;

11) Halt new enrollment in the study pending a revised approved consent form and require currently active participants to be re-consented using the revised consent form;

12) Terminate all study activities; and

13) Referral to other organizational entities. The minutes must document the discussion of the Ballad IRB; their determinations and actions. This includes but is not limited to:

a) Whether the study is to continue as written and approved.

b) Whether the protocol and/or consent form needs to be revised to address any additional risks.

c) Whether participants need to be re-consented.

d) Whether additional information about the event needs to be provided.

e) Whether the protocol is to be suspended.

ii. The IRB will communicate its determination and finding to the principal investigator by sending a letter outlining the findings of the IRB and any required actions of the principal investigator.

iii. At its discretion, the IRB may request outside consultation to assist in its review of an adverse event (Ethics Consultations).

iv. All unanticipated problems involving risks to subjects or others will be reported to Regulatory Agencies, Department Heads and Institutional Officials as established in Reporting to Regulatory Agencies, Department Heads, and Institutional Officials.

f. Protocol Deviations

i. A principal investigator with an IRB approved protocol must conduct the protocol under the terms and specifications of the study as approved by the IRB. An investigator may not deviate from the requirements for procedures or testing of participants as outlined in the protocol except where consistent with regulatory standards (e.g. to eliminate apparent immediate hazards to the subject in compliance 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(4)). Protocol Deviations must be reported by the principal investigator to the IRB in a timely manner. Major Deviations are reported to the IRB within five calendar days of discovery. Minor Deviations are kept in the investigator's file and reported using a cumulative spreadsheet at the annual renewal submission.

g. Examples of Major Deviations

i. Failure to obtain informed consent, i.e., there is no documentation of informed consent or informed consent was obtained after initiation of study procedures.

ii. Informed consent obtained by someone not approved to obtain consent for the protocol.

iii. Use of invalid consent form, i.e., consent form without IRB approval; or outdated/expired consent form.

iv. Enrollment of a participant who was ineligible for the study.

v. Performing a research procedure not in the approved protocol.

vi. Failure to report serious adverse event to IRB; sponsor; and/or regulatory agencies.

vii. Study medication dispensing or dosing error.

viii. Failure to follow the approved study protocol that affects participant safety or data integrity (e.g., study visit missed or conducted outside of required time frame, or failure to perform a laboratory test).

ix. Failure to follow safety monitoring plan.

x. Continuing research activities after IRB approval has expired.

xi. Use of recruitment procedures that have not been approved by the IRB.

xii. Participant giving study medication to a third-party.

xiii. Enrolling significantly more subjects than proposed in the IRB protocol.

h. Examples of Minor Deviations

i. Missing original signed and dated consent form (only a photocopy available).

ii. Missing pages of executed consent form.

iii. Failure to follow the approved study protocol that does not affect participant safety. (e.g., study procedure conducted out of sequence, failure to perform a required test, missing laboratory results, study visit conducted outside of required time frame.)

iv. Failure of a participant to return study medication.

1) Study sponsors may have different reporting requirements than the IRB and it is the principal investigator's responsibility to be knowledgeable about, and meet, the study reporting requirements.

i. IRB Actions

i. Unanticipated Event reports and accompanying information will be screened for completeness by the Ballad Health IRB staff members, who will make an initial determination confirming that the event represents a possible Unanticipated Event before referring them on to an IRB Chair or other qualified designee for confirmation. Reports of events determined during screening to represent possible Unanticipated Events will be forwarded to the IRB for convened review, as necessary, after review by the IRB Chair or other qualified designee. Reports of events that do not meet the requirements for prompt reporting may be returned.

ii. When the IRB receives SAEs or safety reports that do not meet the Unanticipated Event criteria (as defined by the FDA and OHRP), the submitting party will receive acknowledgement of receipt only. The item will not receive IRB review. When these items are submitted by a sponsor or contract research organization (CRO), Ballad Health IRB’s default process is to generate an acknowledgement of receipt to submitting party.

iii. If the IRB determines that a report does represent an Unanticipated Event or Serious or Continuing Non-Compliance, the determination is reported to appropriate institutional officials, regulatory agencies (e.g., OHRP, FDA).

iv. If the IRB determines that the report does not represent an Unanticipated Event or Serious or Continuing Non-Compliance, no further reporting is required.

v. A summary of the problem with be presented to the Ballad IRB. The Ballad IRB will have the opportunity to determine if the event represents an Unanticipated Event:

1) Unexpected,

2) Related or possibly related to participation in the research, and

3) The research places subjects or others at a greater risk of harm than was previously known or recognized.

a) If the Ballad IRB determines all three criteria are met, the IRB will deliberate and vote to determine the appropriate action. Actions the IRB may consider include, but are not limited to:

i) Requiring no action

ii) Requiring changes in informed consent documents,

iii) Requiring changes in the protocol or other study documents,

iv) Requiring re-consenting or informing current or previously enrolled research subjects (to occur whenever the information may relate to subjects' willingness to continue participation in the research,

v) Requiring steps to reduce any immediate risks to subjects or others,

vi) Modifying the continuing review schedule,

vii) Suspending or terminating the research study (according to the IRB policy regarding suspensions and terminations),

viii) Requesting more information pending a final decision,

ix) Referring to other organizational entities (e.g., legal counsel, risk management, institutional official), or

x) Taking other actions appropriate for the local context.

xi) The principal investigator will receive a written response from the IRB upon review of the reported event.

42. **Non-Compliance Involving Human Subjects' Research**

a. The IRB, as part of their oversight responsibilities must establish procedures for the evaluation of all non-compliance with human subject protection regulations and the prompt reporting of any serious or Continuing Non-Compliance with the Federal regulations or institutional policies. Ballad Health IRB requires

investigators to report all non-compliance to the IRB. If an Allegation of Non-Compliance is reported from any source (including monitoring/auditing reports, subject complaints, internal allegation, or investigator self-reporting), the Ballad Health VP of Research and Academics, in consultation with the IRB Chair or Vice-Chair, and System Chair of Clinical Research, will make an initial assessment to determine:

i. whether there is sufficient information present to verify and determine if the allegation is true;

ii. whether additional information is needed to make a determination; and

iii. whether a determination of non-compliance, is serious or Continuing Non-Compliance.

b. All reports of alleged non-compliance or inappropriate involvement of humans in research are investigated by Ballad Health VP of Research and Academics, in consultation with the IRB Chair or Vice-Chair, and System Chair of Clinical Research. If it is determined that the non-compliance might be serious or continuing, the suspected non-compliance is forwarded to a convened meeting for full Board review and determination.

c. Goals of the Ballad Health VP of Research and Academics, System Chair of Clinical Research, and the IRB in investigating and managing issues of potential non-compliance include:

i. Assuring the safety, rights, and welfare of human subject research participants;

ii. Developing action plans to prevent re-occurrence and promote a culture for future compliance;

iii. Educating research staff to assure the understanding of the Department of Health and Human Services (DHHS), the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) regulations and guidelines, and Ballad Health IRB Policies; and

iv. Reporting serious or Continuing Non-Compliance to the appropriate regulatory agencies and institutional officials.

d. Instances meeting the definition of research misconduct will be reported to the respective facility CEO and Medical Executive Committee as deemed necessary by the IRB, the VP of Research and Academics, and the System Chair of Clinical Research.

i. Identification and Investigation of Non-Compliance:

1) An Allegation of Non-Compliance will result in the IRB Chair, IRB Vice-Chair, IRB staff, VP of Research and Academics, and the System Chair of Clinical Research conducting an investigation of the suspected non-compliance. Allegations and/or findings of non-compliance are identified in a variety of ways including notification by investigators, research team members, regulatory bodies, sponsors, research participants, institutional personnel, or committees, and/or public or anonymous sources. The initial

allegation may be presented orally; however, a follow-up written statement of the allegations is required.

2) When findings and allegations of non-compliance are reported it is initially reviewed by the IRB Chair and/or Vice-Chair and the IRB staff. The IRB Chair and/or Vice-Chair and the IRB staff will review the documentation and request additional information, as needed. The investigation will begin within 5 working days of learning of the recognized concern. The purpose of the investigation is fact-finding and may involve examination of study records and discussion with investigators, the research team, other personnel, research participants, and others as appropriate. A communication will be sent to the principal investigator describing the issue or allegations, any interim immediate action, and a request for additional information and response from the investigator.

3) If requested by the individual reporting the allegation, the IRB Chair, Vice-Chair, IRB staff, and ultimately the IRB will attempt to keep his or her identity confidential; however, confidentiality cannot be assured. If an anonymous allegation is made, the IRB Chair, Vice-Chair, IRB staff, and ultimately the IRB will decide if sufficient detail is available to determine if non-compliance has in fact occurred and whether the allegation can be investigated in the absence of an identified complainant.

ii. Expired Studies:

1) If a study has expired, the Ballad Health IRB Chair will be notified by the IRB Project Manager or the IRB Assistant. The IRB Chair will send a Certified Letter to the Principal Investigator and the responsible physician for supervising the study if applicable. The expired study will be brought forth to Ballad Health IRB as a Full Board review, and the Principal Investigator will be asked to address the non-compliance. If the Principal Investigator would like to open the study back up, a new study submission will need to be presented to Ballad Health IRB as a Full Board review. The Federalwide Assurance (FWA) Signatory Official will be notified of all Expired Studies and steps taken to bring the study into compliance.

iii. Minor Non-Compliance:

1) Ballad Health IRB Chair, Vice-Chair, and staff will try to resolve reports of minor non-compliance with the principal investigator and research team. If the Ballad Health IRB Chair, Vice-Chair, and staff cannot work out a corrective action plan with the principal investigator, then the report will be referred to the reviewing IRB for recommendations.

2) Allegations of minor non-compliance will be investigated by the Ballad Health IRB Chair, Vice-Chair, and staff by contacting the principal investigator and research team for verification. The Ballad Health IRB Chair, Vice-Chair, and staff that receives allegations or reports of non-compliance will conduct the initial fact-finding and compile information regarding the non-compliance. If non-compliance is clearly minor and the proposed action plan seems adequate, the Ballad Health IRB Chair, Vice-

Chair, and staff may handle the allegation or report by documenting the event and the proposed corrective action and reporting the incident to the IRB voting members. No further action is required. If, in the course of handling the allegation or report of non-compliance, the IRB Chair, Vice-Chair, and staff are concerned that the non-compliance may be serious or continuing, the matter will be referred to the VP of Research and Academics and the System Chair of Clinical Research for further action as established in this policy withing the section IRB Review of Allegations of Serious or Continuing Non-Compliance.

43. **IRB Review of Allegations of Serious or Continuing Non-Compliance**

a. When the IRB Chair, Vice-Chair, or staff determines the information regarding an alleged report of non-compliance is serious, the information is forwarded to the full IRB for review, consideration of suspension criteria, or consideration of termination. An investigation by the Ballad Health VP of Research and Academics and the System Chair of Clinical Research can occur simultaneously with IRB review for consideration of suspension. If the IRB Chair or Vice Chair has suspended the research because of findings or alleged findings of serious or continuous non-compliance, the IRB will vote to confirm or reverse that decision.

b. All materials will be compiled and sent to the IRB members for review prior to the convened IRB meeting. The IRB will then:

i. Review the information;

ii. Vote on the information provided as indicated in 3 and 4 as follows, or defer the vote and gather additional information if needed from the investigator or others involved;

iii. Vote on whether the non-compliance is serious; and

iv. Vote on whether the non-compliance is continuing.

c. The discussion, determination, and vote will be recorded in the IRB meeting minutes. The minutes must also include a description of the non-compliance issue and allegations and also document the vote as to whether the study is to continue with or without change, is suspended, or is terminated and whether corrective action is required.

d. Unless otherwise approved by the IRB Chair or Vice Chair, no visitors may be present during the portion of the IRB meeting when a non-compliance matter is discussed. If a member of the IRB has or declares a conflict of interest regarding a specific investigator or protocol scheduled for a compliance discussion, he or she will leave the meeting while the non-compliance issue is discussed and will not vote on the issue.

e. Format of Non-Compliance Report Reviewed by the IRB

i. To assist in making a determination, a report outlining the facts surrounding the allegation, appropriate supporting documentation, and corrective action plan will be forwarded to all members of the IRB for review prior to the meeting. The following documents will be forwarded to all IRB members:

1) A statement of the non-compliance allegation;

2) Supporting documents including a copy of the current IRB approval letter, protocol, and consent form (as applicable to the investigation);
3) A statement of previous IRB administrative actions related to the non-compliance;
4) Any relevant additional information or special circumstances;
5) Assessment of increased risk (if any) to subjects resulting from the non-compliance;
6) Recommendations for possible actions or resolution;
7) Review of the status of the investigator's other IRB approved protocols;
8) The current IRB approved Investigator's Brochure, if applicable;
9) Any pertinent information (e.g., questionnaires, DSMB reports, etc.)

ii. After voting, the IRB may require:

1) No action, protocol continues as previously approved;
2) Modification of the study protocol;
3) Modification of the informed consent process;
4) Require current participants to re-consent to participation;
5) Provide information about the non-compliance to current study participants;
6) Additional information provided to past participants;
7) Obtain more information pending a final decision;
8) Modify the continuing review schedule;
9) Require additional training of the investigator or research team;
10) Monitor the research;
11) Monitor the consent process;
12) Suspend the research;
13) Terminate the research;
14) Destruction of data collected at the time the non-compliance event occurred;
15) Withdraw or limit the privileges of the investigator to conduct human research;
16) Referral to other Organizational entities (Compliance, Ethics, General Counsels); and\or
17) Other actions deemed appropriate.

iii. The principal investigator will receive written notification from the IRB regarding the non-compliance issue, including recommendations for corrective actions.

iv. An IRB determination of serious or Continuing Non-Compliance will be reported to the appropriate regulatory agencies and institutional officials, (Reporting to Regulatory Agencies, Department Heads).

v. The IRB Chair or Vice Chair using the expedited review process will review and approve all minor modifications to previously approved research taken in response to non-compliance. All modifications that are determined by the Board to be more than minor will be reviewed at a convened IRB meeting.

f. Suspension or Termination

i. If, in the opinion of the IRB Chair, the allegation concerns non-compliance that might be serious or continuing, the IRB Chair and/or Vice Chair may suspend research activities immediately until such time that the full IRB can convene if they believe that research participants may be exposed to immediate harm. If the Chair or Vice Chair is unavailable, and in the opinion of the Ballad Health VP of Research and Academics and/or the System Chair of Clinical Research, the allegation concerns non-compliance that might be serious or continuing, the Ballad Health VP of Research and Academics and/or the System Chair of Clinical Research may suspend research activities immediately (Administrative Hold, Suspension, or Termination of IRB Approval) until such time that the full IRB can convene if it is believed that research participants may be exposed to immediate harm.

ii. Suspension or termination of IRB approval of research will be reported to the appropriate regulatory agencies and institutional officials (Reporting to Regulatory Agencies, Department Heads).

g. Additional Considerations for Non-Compliance Issues:

i. Continuing Non-Compliance or Serious Non-Compliance

1) If the investigator is a member of the medical staff of a specific Ballad Health facility, a Continuing Non-Compliance issue may also be referred to the Chief Medical Officer or designated representative for assistance in seeking an appropriate resolution.

ii. Non-Compliance with HIPAA (Privacy Language) Requirements

1) Failure to comply with HIPAA (Privacy Rule) requirements for research studies will not be treated as a non-compliance issue by the IRB. Instances of non-compliance with HIPAA requirements will be referred to the Ballad Health HIPAA Privacy Officer for investigation and resolution.

44. **Case Reports**

a. Any activity that has the potential to involve humans, living or deceased, data or specimens obtained from humans has the potential to be considered research. Ballad Health IRB will make the determination if the nature of the project is considered research and type of review the project will require.

b. If a provider develops a case report that he/she would like to present, publish or use to fulfill a scholarly activity outside Ballad Health and associated holdings, the case report must be submitted to the Ballad Health IRB for review prior to dissemination, publication or presentation.

c. The following instances meet the definition of research and will require IRB review and approval prior to engaging in activity:
    i. More than 3 cases will be written up as part of the report or presentation;
    ii. The investigator intends to use an intervention to prove/disprove a hypothesis, or requires treatment, or record keeping modification for research rather than clinical purposes.
d. If the Investigator thinks that the case report meets the criteria for human subject research the protocol should be submitted according to the Ballad Health IRB New Protocol Submission.
e. If an investigator develops a case report (regardless of how many case/s are reviewed, that he/she wants to present, publish, or use to fulfill the requirement for scholarly activity outside of Ballad Health Systems, the Case Report must be reviewed by Ballad Health IRB.
f. A case report that includes information from 3 or fewer patients generally does not meet the definition of a "systematic investigation leading to generalizable knowledge" and therefore does not meet the definition of "research" (45 CFR 46.102(l). If the case report does not qualify as human research, the Ballad Health IRB will issue a determination as such.
g. In some instances, when one of the following occurs, the case report may in fact be considered "research" and will require IRB review and approval prior to engaging in the activity:
    i. The investigator intends to use an intervention to prove/disprove a hypothesis, or requires treatment or record keeping modification for research rather than clinical purposes or;
    ii. More than three (3) cases will be written up as part of the report.
h. If an investigator believes that the case report meets the criteria for "human subject research" (as noted above), the protocol should be submitted according to the Protocol Submission Requirements.
i. If an investigator believes that the case report does not qualify as “human subject research” (as noted above), the investigator/author of a case report must submit a summary of the case, including information about what information will be used, how it will be obtained, and whether or not the patient will be notified of its use (especially relevant if the patient is an active patient within the Ballad Health System). A copy of the actual case report presented/submitted should also be provided once it is available.
j. An investigator must ensure that the case report does not include any of the following patient identifiers:
    i. Personally identifiable private information about a living human person;
    ii. Any of the 18 protected health information identifiers (PHI) noted in the HIPAA regulations unless authorization from the individual(s) has been obtained.

k. If the report will contain either of these identifiers, additional HIPAA requirements will have to be considered, per the HIPAA and the Privacy Rule.

l. If the Ballad Health IRB Chair/Vice Chair reviews the request regarding the case report activity and agrees that the activity does not constitute "human subject research" per DHHS and FDA regulations, the investigator will receive notification via IRBNet.

m. If the Chair/Vice Chair concludes that the submitted proposal qualifies as "human subject research", the investigator will be notified of the decision and the rationale. The investigator must then submit the project to the Ballad Health IRB for review and approval. Please note that the IRB will not provide "after the fact" approval of the research as this is prohibited by Federal regulation. Authors are encouraged to seek advice from the Ballad Health IRB Office prior to developing a case report when difficult questions arise about whether IRB review may be required.

n. Failure to follow this policy could result in an allegation of non-compliance or disciplinary action. Violations of this policy will be reported following the procedures in the Ballad Health IRB Policies.

45. **NCI – Waiver of Jurisdiction**

a. The following division of responsibilities is based on the "Authorization Agreement/Division of Responsibilities between the NCI Central Institutional Review Board and the Signatory Institution" which outlines the CIRB's primary responsibilities as well as those of the Signatory Institution, Ballad Health.

b. The responsibilities of the CIRB are:

i. Maintain an NCI CIRB membership that satisfies the requirements of 45 CFR 46 and 21 CFR 56 and provides special expertise as needed to adequately assess all aspects of each study;

1) Post the roster of NCI CIRB membership on the public side of the NCI CIRB website;

2) Conduct initial, amendment, and continuing review of studies, as well as review of any other study-specific documents submitted to the Study Chair and to the NCI CIRB;

3) Conduct review of local context considerations as outlined in the following Worksheets:

a) The Annual Signatory Institution Worksheet About Local Context for NCI CIRB Review;

b) The Annual Principal Investigator Worksheet About Local Context; and

c) The Study-Specific Worksheet About Local Context;

ii. Conduct review of potential unanticipated problems and/or serious or continuing non-compliance when the Signatory Institution or other entity reports an incident, experience, or outcome to the CIRB. This review includes the following steps:

1) Report any unanticipated problem and/or serious or continuing non-compliance determination to the Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA), and the NCI Signatory Official;

iii. Conduct review of individual Adverse Event Reports for studies without a Data Safety Monitoring Board (DSMB) or equivalent monitoring body;

iv. Post all study-specific documents related to CIRB reviews to the restricted access side of the CIRB website;

1) Notify research staff and institutional designees of all CIRB actions, per written procedures, via institution-specific correspondence, broadcast emails, and access to the restricted area of the CIRB website.

v. Notify the Signatory Institution immediately if there is ever a suspension or restriction of the CIRB's authorization to review a study; and

vi. Post the NCI CIRB Standard Operating Procedures on the public side of the CIRB website.

c. The responsibilities of the Signatory Institution (Ballad Health System) are to:

i. Comply with the NCI CIRB's requirements and directives;

ii. Report to the NCI CIRB the names of any Component or Affiliate Institutions that rely on the Signatory Institution's IRB;

1) Component Institutions are defined by the NCI CIRB as meeting all of the following criteria:

a) The Component Institution operates under a different name than the Signatory Institution, but the Signatory Institution has legal authority for the Component Institution;

b) The Federalwide Assurance (FWA) number for the Component Institution is the same as the Signatory Institution;

c) The local context considerations of the Component Institution are the same as the Signatory Institution. Local context considerations are reported by the Signatory Institution in the Annual Institution Worksheet About Local Context;

d) The boilerplate language and institutional requirements of the Component Institution are the same as the Signatory Institution. The boilerplate language and institutional requirements are reported by the Signatory Institution in the Annual Institution Worksheet About Local Context; and

e) The conduct of research at the Component Institution is monitored by the same office as the Signatory Institution.

iii. Affiliate Institutions are defined by the NCI CIRB as meeting all of the following criteria:

1) The local context considerations of the Affiliate Institution are the same as the Signatory Institution. Local context considerations are reported by the

Signatory Institution in the Annual Institution Worksheet About Local Context;

2) The boilerplate language and institutional requirements of the Affiliate Institution are the same as the Signatory Institution. The boilerplate language and institutional requirements are reported by the Signatory Institution in the Annual Institution Worksheet About Local Context;

3) The conduct of research at the Affiliate Institution is monitored by the same office as the Signatory Institution; and

4) Ensure the safe and appropriate performance of the research at the Signatory Institution and at all Components and Affiliates.

iv. This includes, but is not limited to:

1) Ensuring the initial and ongoing qualifications of investigators and research staff;

2) Overseeing the conduct of the research;

3) Monitoring protocol compliance;

4) Maintaining compliance with state, local, or institutional requirements related to the protection of human subjects;

5) Providing a mechanism to receive and address concerns from local study participants and others about the conduct of the research; and

6) Investigating, managing, and providing notification to the NCI CIRB of any study-specific incidence, experience, or outcome that seems to rise to the level of an unanticipated problem and/or serious or continuing non-compliance. When notifying the NCI CIRB of a potential unanticipated problem and/or serious or continuing non-compliance, the institution must provide a plan to manage the incident, experience, or outcome, including measures to prevent similar occurrences; NOTE: As part of ensuring safe and appropriate performance of research the Signatory Institution has the authority to observe any aspect of the research process including observing the consent process. The CIRB retains the authority to direct this to be done when necessary.

v. Provide updates in a timely manner to the NCI CIRB whenever a Signatory Institution Principal Investigator is no longer the responsible party for a study under the purview of the NCI CIRB;

vi. Notify the NCI CIRB when a regulatory deficiency has been cited on an audit that occurred during the time that the NCI CIRB was responsible for study review;

vii. Complete and submit the Annual Institution Worksheet About Local Context, the Annual Investigator Worksheet About Local Context, and any other worksheets/forms required by the NCI CIRB for participation; and

viii. Decide on a study-by-study basis whether to open the study through the NCI CIRB or to conduct its own local IRB full Board review. Indicate the decision to

open a study through the NCI CIRB by submitting a Study-Specific Worksheet About Local Context.

ix. In the local informed consent:

1) Incorporate NCI CIRB-approved boilerplate language into the NCI CIRB approved model consent form;

2) NOTE: The CIRB does not approve the HIPAA Authorization language as it does not function as a Privacy Board;

3) Make no language changes to the consent form with the exception of NCI CIRB approved boilerplate language;

4) Obtain NCI CIRB approval of changes to the boilerplate language prior to implementation;

5) Obtain NCI CIRB approval of translations of the consent form prior to implementation;

x. Maintain a regulatory file for each study under NCI CIRB preview as local institution and sponsor policy; and

xi. Conduct full board review of any study enrolling prisoners, since the NCI CIRB is not constituted to review studies enrolling prisoners.

d. Steps for Study Review:

i. Ballad Health IRB, through the Ballad Health IRB Chair and Vice Chair, will decide on a protocol-by-protocol basis whether the study should be opened locally, and consequently, the status of the CIRB as the IRB of Record. Ballad Health IRB will also directly oversee the review of HIPAA-related concerns.

ii. The Office of Human Research Protection (OHRP) Policy and Guidance standards states that when an institution holding a Federalwide Assurance (FWA) wishes to avoid duplication of effort, in accordance with the Department of Health and Human Services (DHHS) regulations at 45 CFR 46.114, by relying upon the IRB review of another Assurance-holding institution:

1) The review arrangement must be approved in writing by the appropriate officials of the institutions involved; and

2) The institution relying upon another institution's IRB has a responsibility to ensure that the particular characteristics of its local research context are considered through subsequent review by appropriate designated institutional officials, such as the Chairperson or other members of its local IRB.

iii. In accordance with this OHRP guidance, Ballad Health IRB will conduct a review of CIRB studies to determine if each study is acceptable for the institution. (Facilitated Review Form)

iv. The principal investigator submitting the protocol will be notified by Ballad Health IRB as to the outcome of this review.

e. Steps for Protocol Submission:

i. The studies will be submitted in accordance with the standard application procedures of Ballad Health IRB. The new study application will include a copy of the entire IRB review packet from the CIRB website. Ballad Health IRB requires additional submission forms and attachments to accompany protocol submissions. Current submission forms can be downloaded from the electronic submission software (www.IRBNet.org), which will include the Human Subjects Protocol Full Review form and a request form for NCI Waiver of Jurisdiction (via the Facilitated Review Form) must also be completed and submitted.

f. Continuing Reviews and Amendment Requests:

i. Continuing Reviews and Amendment Request reviews of CIRB studies will be conducted locally after approval and release of the NCI CIRB Activity Update notification. The local Investigator must submit each of these requests to Ballad Health IRB via the electronic submission site (www.IRBNet.org). The submission package should contain a copy of the entire packet from the CIRB, as well as, any additional Ballad Health IRB submission forms requested, which is available for download from the electronic submission site. These forms may include: The Continuing Review Form and the Facilitated Review Form. Ballad Health IRB Chair and the Ballad Health IRB Vice Chair will conduct the continuing and amendment reviews ensuring the previously approved consent contains the required local context.

ii. This is applicable to all research studies that are requesting Waivers of Jurisdictions for NCI studies at Ballad Health.

46. **Chart Review and Discarded Tissues Study**

a. Research activities involving the use of discarded tissue or chart reviews must be reviewed and approved by the Ballad Health IRB prior to commencement. However, certain discarded tissue/chart review studies may qualify for an IRB exemption. Although an investigator can request an exemption, this determination can only be made by the IRB after a formal application has been submitted (Exempt Human Research and the IRB Exemption Request Checklist Tips and Guidelines Form (accessible via IRBNet) for guidance regarding IRB exemption submissions).

b. Research requiring IRB approval:

i. Discarded tissue and/or chart review study applications must include a complete protocol/research plan. In addition, informed consent must be sought unless the regulatory criteria for waiving the consent process are met (Informed Consent). If children are involved, parental permission and assent must also be obtained unless the criteria for waiving parental permission and waiving assent are met (Assent from Children)Written justification for all waiver(s) is required in the research plan and must be approved by the IRB. Greater than minimal risk discarded tissue and/or chart review study applications must include a complete protocol/research plan (Protocol Submission Requirements). In addition, informed consent must be sought unless the regulatory criteria for waiving the consent process are met (Informed Consent). If children are involved, parental permission and assent

must also be obtained unless the criteria for waiving parental permission and waiving assent are met (Assent from Children)Approval for Informed Consent and HIPAA Waivers are required and must be approved by the Ballad Health IRB.

c. Discarded Tissue

i. Discarded Specimen Studies:

1) The protocol/research plan for discarded tissue must contain sufficient detail to fully describe the proposed research activities. Unless waived by the IRB, informed consent and HIPPA must be obtained from potential participants using a current approved research consent form. In addition, the Ballad Health patient consent forms for diagnostic studies and operative procedures have a section that allows a subject to consent for the use of their discarded tissue for research purposes. This clinical consent cannot be used as a substitute for the research consent process.

2) When informed consent is not obtained, in order to use Discarded Specimens removed for diagnostic or therapeutic purposes for research, the following criteria must be met:

a) No extra specimen will be taken;

b) Any data collected about the subject are de-identified making the specimen anonymous to the research investigator (Exemption Human Research); and

c) There is no commercial development from the specimen.

ii. Discarded Specimens with Subjects Identified:

1) If patient identifiers are kept with the research specimen, then consent from the patient will usually be required. If it would be extremely difficult, impractical, or impossible to obtain individual consent, or if the patient identifying data are very tightly controlled (as in a research tissue bank that releases specimens but does not release identifying data), the IRB will consider waiving consent if they determine the waiver meets the regulatory criteria.

iii. Surgical Pathology Specimens:

1) Obtaining extra tissue from surgical specimens requires release from the patient and protocol review and approval from the IRB. The tissue from each patient does not qualify as "discarded" until it has been released by the surgical pathologist.

iv. Autopsy Tissue:

1) Since autopsy tissue is not from a living human being, IRB regulations do not apply. Unless the tissue is anonymous to the investigator, HIPAA regulations may apply and the investigator may need to request a HIPAA (Health Insurance Portability and Accountability Act) waiver (see Request for HIPAA waiver for additional guidance). The HIPAA waiver request needs to be included with the IRB application.

d. Medical Records Studies (Chart Reviews):

i. The Ballad Health IRB requires a protocol to be submitted for review for all Chart Review Studies (Protocol Submission Requirements). The IRB's main concern with chart reviews for research is the possible invasion of privacy and the use of confidential and privileged data or information. For any study to qualify as a chart review all the data accessed must have been collected (or will be collected) as part of routine clinical care. As with discarded tissue studies, informed consent must be obtained unless a waiver can be fully justified and meets the regulatory requirements. If an investigator has the opportunity to obtain consent from a subject, they must do so as usual under the human subject protection regulations. The consent process and all requests for waivers must be addressed in the protocol/research plan.

ii. Access to a Physician's own Records for Research:

1) With an IRB approved protocol, physicians may access their patients' existing medical records (or those of their group practice) for research, without obtaining patient consent. As part of the protocol the investigator must assure that all collected data will be kept confidential and any study results will be presented in a way that preserves patient anonymity. If prospectively collected patient data are to be entered into a database with both clinical and research uses, then other rules apply.

iii. Access to Other Physician's Records for Research:

1) If access to medical records of patients outside of a physician's practice is desired for research, then the protocol submitted to the IRB must describe how patient privacy will be protected and how the confidentiality of the information will be maintained. The best way is for the patients' physician (or his or her staff) to extract the data from the charts and de-identify it before giving it to the researcher. If this is not possible and a member of the research team must review the charts, then only de-identified data may be taken from the physician's office and the person reviewing the charts must agree to keep all identifying data confidential. If identified data leaves the physician's office, then consent from the patient is usually required before they are included in the study. Due to HIPAA requirements, a telephone call or letter to the patients must come from their physician (or staff) and not be processed by the research staff.

iv. Access to Ballad Health Medical Records:

1) Before permitting inspection and/or copying medical records the Department of Health Information Services at Ballad Health requires each responsible investigator to sign the Ballad Health System Confidentiality Agreement, which shall be kept on file by the Health Information Services Department together with a record of identity of those patients' charts furnished to the investigator. The investigator(s)'s responsibility for the use of the record is to be designated by the principal investigator. Further are available in the Ballad Health Policies and Procedures regarding Privacy. A list of all records that the researcher reviews can be requested via Compliance Department if requested.

v. Contact with Potential Subjects from Chart Reviews:

1) Any investigational or research project involving use or review of medical records where contact will be made with patients or patients' families as a result of chart review requires approval by the IRB. The investigator is required to submit a protocol to the IRB indicating:

a) Justification for contact of the patient\subject;

b) Method of contact the patient\subject; and

c) Indication that prior approval will be obtained from the responsible physician of record to contact his/her patients

2) No patient can be contacted to participate in research without the consent of the treating physician. If seeking approval from the physician via correspondence the lack of reply from a physician can never be construed as approval to contact the patient.

47. **Research Registries / Repositories**

a. The establishment and operation of all research repositories will require review and approval by Ballad Health IRB.

b. The IRB does not consider prospective collection and storage of data/specimens for very specific or well-defined research purposes as part of a single IRB-approved protocol as a Research Repository.

c. Research repositories must comply with applicable federal, state, and Ballad Health regulations and policies.

d. Adequate provisions must be in place to protect the privacy and confidentiality of the subjects and their specimens and/or data.

e. Specified uses of the repository will be respectful of the subjects, meaning that informed consent must be obtained from subjects to whom the data/specimens pertain for the storage in the repository and for the intended future use of the data/specimens.

i. Minors Who Reach Legal Age of Consent:

ii. In some repositories, the subjects may be minors at the time the specimens/data are initially collected. Unless the IRB determines that the requirements for obtaining informed consent can be waived (Informed Consent), the investigators will seek and obtain the legally effective informed consent for the now-adult subject for the continued inclusion of identifiable specimens/data for the repository.

1) When determining if consent can be waived in these circumstances, the IRB may also consider:

a) The ability of the researchers to locate and contact the subjects.

b) Whether the collection of specimens/data is ongoing or a one-time donation.

c) Whether the specimens/data continue to meet the regulatory definition of human subjects research.

d) The nature and sensitivity of the research being done with the specimens/data in the repository.

e) If assent was obtained from the minors at the time specimens/data were collected for the repository.

f. Research Repository study team members must comply with the Ballad Health IRB's human subject research training requirements.

g. If the repository will include protected health information (i.e., individually-identifiable physical and mental health information created or maintained by a covered entity which may only be used/disclosed to researchers in certain circumstances and under certain conditions), the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule applies.

i. Although research involving specimens/data from deceased individuals no longer meets the regulatory definition of human subjects, decedents' protected health information is subject to the Privacy Rule.

h. Researchers:

i. The researcher must complete the submission form through the IRB's electronic application system. The description of the research design must indicate that the submission contains a repository component or is for the sole purpose of creating a repository.

ii. There is extensive variation in how registries operate. The IRB submission should include sufficient information regarding the scientific goals, functions, and operational procedures. The description of the operations of the repository must include the following:

1) Mission/purpose of the repository

2) Entity funding the registry

3) General description of specimens/data that will be included in the repository including:

a) Scope of the data set, patient outcomes, and target population

b) If/how the specimens/data are identified

i) Data procurement - whether data will be extracted from a specific source (e.g., electronic medical record) or if data will be obtained through interaction with a participant

c) If existing, whether the specimens/data were obtained with the IRB-approved informed consent of the subjects or under an IRB-approved waiver of informed consent

d) The plan for prospective collection of specimens/data to be included in the repository (with informed consent of subjects or under a waiver)

e) Management and physical storage of data, (medical record information; etc.)

f) The informed consent and authorization document describes the intended use and procedures for using and sharing material with others for future research. The purpose may be described as broad and unspecified to allow for a wide range of potential future uses in research. However, even when future use is unspecified, the consent document and process should clearly describe key registry concepts such as, unlimited medical record access, incidental findings and obligations to return research results, procedure to withdraw material, large-scale data sharing, etc. so that participants understand the implications of participating.

g) Whom research data will be collected from (e.g., minors, adults, healthy subjects, patients)

h) Diagnosis or conditions of study (e.g., specific disease area or broad unspecified use)

i. Types of research to be conducted (be as specific as possible) using the data/specimens in the repository

j. If specimens/data were/will be included with the informed consent of the subjects, the consent process must contain all the basic elements of informed consent. Specifically, the following issues need to be addressed in the consent form:

i. Purpose of the repository.

ii. All type(s) of research that will, or may be conducted, including whether genetic analysis will be performed. This should be as specific as possible.

iii. Specific specimens/data that will be deposited in the repository and how these will be collected. Brief description of the operation of the repository. If data/specimens will be released to outside investigators, the conditions under which these will be released (e.g., with direct or indirect identifiers, or stripped of any identifiers), and with whom the data/specimens may be shared, if known.

1) The personal identifying information to be collected and stored

2) A list of any data extracted from the medical record

iv. Potential risks of disclosure of the information, such as negative effects on insurance coverage, employment status, emotional discomfort, familial strife, or even harm to a cultural group.

v. Procedures to protect confidentiality and privacy.

vi. Information regarding ownership of data/specimens and whether use of data/specimens may lead to new discoveries or commercially valuable products, and whether subjects will receive any financial benefits from these discoveries/products.

vii. Describe if the subjects can have their sample(s) destroyed or all personal identifiers removed if he or she decides to withdraw from the research.

viii. The consent process (who obtains, documentation, place, time allotted)

ix. Tracking participant choices where options are provided

x. The ability and procedure for locating/contacting participants (re-consent, incidental findings)

xi. The process of re-consent of research participants who are minors at the time of collection of data but turn 18 while the registry is active

xii. Participant withdraw procedures

k. Duration of storage of sample(s); if indefinite, provide a justification.

i. Length of time personal identifying information will be kept (indefinitely, end of Research Protocol)

l. Procedures for storage (i.e., where repository will be housed) and for protecting the privacy of subjects and maintaining the confidentiality of specimens/data. Since breach of confidentiality is the major risk for stored repository specimens/data, there must be adequate plan for protecting the security and confidentiality of the repository specimens/data and prevent accidental or inappropriate release of information. At a minimum, the following measures need to be in place:

i. A method of coding the specimens/data, including a process to protect/maintain the key to the code and limit access to the key. The coding system must be adequate to reduce the possibility of re-identification. If the repository must have individual identifiers, the IRB will require extensive electronic protections, such as multiple firewalls or passwords, for accessing the repository.

ii. Access to the code and individually identifiable specimens/data must be restricted to authorized individuals who are trained about the repository and human research protections, including the preservation of confidentiality.

iii. Access to the code and individually identifiable specimens/data must be restricted to authorized individuals who are trained about the repository and human research protections, including the preservation of confidentiality.

iv. A Certificate of Confidentiality is recommended as an additional protective measure, especially if the repository includes collection of genetic specimens/information or sensitive data. If a Certificate of Confidentiality will be obtained, a copy of the certificate should be provided to the IRB once this becomes available.

v. Risk associated with a breach of confidentiality including impact on privacy, insurability, stigmatization etc.

m. If outside researchers (i.e., those who are not members of the repository team) will be allowed to receive/access repository data/specimens, the submission should include documentation that the researcher receiving the specimens and/or

data has IRB review and approval for each specific research study that requests specimens/data from the repository.

i. How personal identifying information will be shared and procedures for coding, de-identification, encryption data-use agreements, etc.

ii. Role of an honest-broker in sharing with recipient researchers and who will serve in that role

iii. With whom personal identifying information will be shared, (e.g., anyone, internal researchers, external collaborators, academic only, commercial industry)

n. If the specimens and data collected for the Research Repository will be made available to non-Ballad Health researchers, the repository Principal Investigator (PI) is responsible for ensuring that non-Ballad Health investigators meet the requirements for Ballad Health IRB review of the research project. Investigators at other sites should also check their institutional policies regarding the transfer of specimens and data for research. A Specimens/Data Use Agreement may also be required.

i. Data collection – both paper and electronic program/software – and levels of security to protect participant privacy and data confidentiality.

o. Unless appropriately waived by the IRB, a key responsibility of data/specimen collection is the obtaining of informed consent from each donor-subject in accordance with regulations at 45 CFR 46.116 and 21 CFR 50 Subpart B. Informed consent is required since standard treatment and surgical consents rarely meet the regulatory standards for research informed consent.

p. If the scope of a registry expands, update the IRB protocol and informed consent accordingly. Do not expand the scope of the registry by adding and removing researchers as study personnel. Study personnel/researchers may have access to identifiers. Research with identifiable material requires additional protocol-specific IRB review.

q. Secondary Research

i. Additional IRB review is required. The secondary researcher may obtain an official Not Human Subject Research (NHR) determination from the IRB. In making the NHR determination, the IRB considers whether the information was properly de-identified according to HIPAA standards prior to receipt by secondary researcher; the recipient researcher has no knowledge of or way to readily identify participants providing the information, and the registry personnel will not be involved in the conduct or reporting of the secondary research.

ii. In addition, the proposed secondary use must be consistent with the use described in the original consent used to obtain the participant's information. Ballad IRB provides informed consent templates that include language to inform participants that it is possible that their information will be de-identified and shared with other researchers for future research, without the participant's additional informed consent.

iii. Informed consent may not be required if the IRB determines the recipient researcher's proposed use is consistent with the use described in the informed consent. If use is not consistent, additional consent may be required, or the researcher may submit a request to their IRB to alter or waive the requirement for additional consent. Specific criteria must be met for the IRB to consider approving a waiver. The IRB would likely not approve a waiver in cases where the recipient researcher has an opportunity to obtain informed consent from registry participants who have agreed to future contact.

iv. Other regulatory statutes prohibit the IRB from waiving informed consent, even if data is de-identified, (e.g., Department of Defense Classified Research, NIH Funded Genomic Data Sharing).

r. Institutional Review Board

i. The requirement for IRB approval of collection, repository, and Research Protocols applies regardless of whether the repository was initially created for research or clinical purposes.

ii. The collection, storage, and distribution of personal identifying information (18 HIPAA Identifiers) for research purposes is subject to IRB review and human subjects research regulations. The IRB is charged with reviewing protocols for obtaining, storing and sharing information, verifying informed consent, and protecting privacy and confidentiality. To establish a registry, the Principal Investigator (PI) submits a Full or Expedited (as applicable) IRB application outlining the collection, storage, and sharing of personal identifying information.

iii. The IRB will review the submission to determine if it involves creating a Research Repository.

iv. If this involves a Research Repository, the IRB will make an initial determination at a fully convened meeting.

v. The IRB staff will offer the investigator the opportunity to provide additional information/specimens and/or to revise the submission in appropriate review correspondence prior to the fully convened meeting that describes missing information or required modifications.

vi. The IRB Staff will document information pertaining to determinations that the requirements of this policy have been met in the meeting minutes.

vii. IRB approval and oversight is not required for repositories created, maintained and operated for purposes that are totally unrelated to research. Such purposes may include diagnosis, treatment, billing marketing, quality control, and public health surveillance.

viii. Prospective IRB approval and continuing IRB oversight is required for repositories established, maintained, and operated for present or future research purposes.

ix. Prospective IRB approval and continuing IRB oversight is required for each non-exempt study using collected items from the repository.

x. Prospective IRB approval of a Research Protocol and continuing IRB oversight is required for studies using data or specimens from repository even if this repository was created for purposes unrelated to research.

48. **Geocoding**

a. Geocoding has become an innovative way and soon to be crucial way for population health researchers to analyze and project health care trends in a community. Geocoding allows the researcher to have a better understanding of a populations health in a region. There are concerns that come with Geocoding:

i. A narrow research subject,

ii. Reverse identifying a patient,

iii. Few results that do not produce a productive product for understanding the subject.

b. With the capabilities that are in place within the ability to find results and understanding with Geocoding, Ballad Health is encouraging researches to engage in population research.

c. To receive a Geocoding product the research package submission must meet the approval of the BHS IRB.

d. The actual PHI locational data will be managed by a Ballad Health team member at all times.

e. The Team Member will work the Geocoding machine that has been verified through the HRPP team for PHI safety and security to get the geocoding spatial analysis created for the researcher.

f. The Team Member with the PHI locational data will destroy the data in accordance with Ballad policy

49. **Fee Schedule**

a. Ballad Health IRB will only invoice for the review of those protocols that are industry and/or pharmaceutical sponsored. The fee is requested at the time of submission. A paid in full invoice will be provided so that the Principal Investigator (PI) may submit for reimbursement from the sponsor. The IRB may invoice the sponsor directly if the investigator request, however payment is still expected before the IRB will review the protocol. Submission fees will not be waived for industry sponsored research because the fee is a negotiable part of the research study budget. The fee will not be refunded regardless of the IRB's decision.

b. Ballad Health IRB may not charge for the following submissions from Ballad Health entities:

i. NIH (National Institutes of Health) and NCI (National Cancer Institute) sponsored studies.

ii. Human Subjects research conducted without corporate/industry financial support by a physician credentialed as a medical staff member of Ballad Health acute care facility.

iii. Retrospective Chart Review Studies

iv. Studies written and conducted as a thesis or dissertation required for the completion of a graduate degree without financial support from corporate sponsors.

v. Emergency use of investigational drugs or devices because this approval is granted for one patient only.

vi. IRB review of a Food and Drug Administration (FDA) approved Humanitarian Use Device (HUD)

c. If the Principal Investigator is not a Ballad Credentialed Physician, or Personnel from a Ballad entity, a service fees will be charged as described below.

TYPE OF REVIEW	**DESCRIPTION**	**FEE**
Initial Review	Review Includes: A. Initial Review of Protocol B. Review and/or modification of proposed Informed Consent (includes 1 consent form) C. Verification of Principal Investigator's Credentials D. Review of Site Information	$ 3000.00
	E. Investigator's Brochure F. Review of amendments, revisions or modifications to protocol or the Informed Consent prior to the initial review G. Review of proposed advertisement(s) H. Review of questionnaires, dairies and patient QOL's	
Principal Investigator (PI)	Change of Principal Investigator (each)	$ 1000.00

Continuing Review	A. Review of Protocol and Continuing Review/Re-Approval B. Review of Interim Reports C. Reinstatement of Investigator whose IRB approval has lapsed (in addition to Continuing Review Fee) D. Study Close-Out	A. $ 1500.00 B. $ no charge (N/C) C. $ 500.00 D. $ 250.00
Amendments/Revisions/ Modifications/ notification memos/ Consent forms, patient documents that are already approved by the IRB or have not been reviewed by the IRB, etc. after Initial Review,	Full Board Review:	A. $ 1000.00
Expedited Review	A. Initial Review B. Continuing Review C. Study Close-Out D. Modification	A. $ 1750.00 B. $ 1500.00 C. $ 250.00 D. $ 500.00
Translation/Back Translation	Conversion of documents from English to a foreign language Conversion of documents from a foreign language into English	Cost + 20%
Safety Reports	Investigational New Drug Reports (IND Reports) Serious Adverse Events/Adverse Events (SAE/AE)	$ no charge (N/C) $ no charge (N/C)
IRB Exemptions	Review of Application for	$ 500.00

	IRB Exemption	
Reliance Agreement	External IRB review	$ 1500.00
OTHER SERVICES		
Overnight Delivery Service	FedEx or UPS	Billed at Cost
	Informed Consent /Assent Preparation	$ 50.00 per hour

50. **Research Endorsement Non-Student, Employee, or Allied Health**

a. The following items must be completed and submitted to Ballad Health IRB office and the Medical Staff Office of the appropriate facility to initiate endorsement:

i. Endorsement in Research Application

ii. Ballad Health Confidentiality and User Agreement

iii. Patient Identifier Agreement

iv. Signed and Dated Current CV or Resume

v. Current Professional License (if applicable)

vi. Completed CITI Training Certificate as per Documented Training in Human Subjects Protection

vii. Collaborative Agreement with Supervising PI

viii. IRB Approval Letter for Appropriate Study

ix. Proof of Current TB test with in past 12 months or Chest X-Ray within three (3) years

b. All applications for endorsement will be assessed on an individual basis by Ballad Health Institutional Review board and the appropriate medical Staff Office. Additional proof of vaccinations and other medical drug testing and a background check may be requested. If this is felt to be needed the applicant will be assessed a non-refundable fee to cover the cost of this process.

c. Identification badges will be issued to researchers obtaining endorsement and must be worn and visible at all times while participating in research within Ballad Health facilities.

d. Obtaining endorsement alone is not enough to begin a research study. There must be a paired principal investigator with an IRB approval letter and a signed Collaborative Agreement before an individual can begin work.

e. Research Scope of Practice for Endorsed Personnel:

i. An endorsed researcher's activities are limited to non-patient contact in nature.

ii. The endorsed researcher may not document procedures or services in the medical record or issue orders.

iii. The endorsed researcher may not act as a representative or on behalf of Ballad Health.

f. Endorsement may be revoked at any time by the IRB, the facilities Medical Staff Office or the Health System. The following are example of reasons for revocation; this list is not intended to be all inclusive:

i. The researcher is found to be a danger to patients or staff;

ii. The researcher does not comply with restrictions regarding patients or patient areas;

iii. Failure to follow Ballad Health policies or procedures;

iv. Behavior inconsistent with Ballad Health mission or values;

v. Failure to follow the IRB approved protocol;

vi. Failure to comply with the law, rules or regulations governing human subject research.

51. Ballad Health Serving as the IRB of Record for a Non-Ballad Health Human Research

a. When the Ballad Health IRB serves as the IRB of Record for a Relying Organization, it accepts the responsibility for the oversight of the protection of the rights, privacy and welfare of the human subjects.

b. The method by which the Ballad Health IRB will serve as the IRB of Record for a Relying Organization not otherwise affiliated with Ballad Health or not covered by Ballad Health's Federalwide Assurance is an IRB Authorization Agreement.

c. An IRB Authorization Agreement may be made for a single research study or multiple different studies with a Relying Organization.

d. Employees and agents of a Relying Organization will not be added to the Ballad Health IRB application as Ballad Health study team members, without a Ballad Health appointment (as applicable). These individuals are not considered agents of Ballad Health and are not covered under Ballad Health’s Federalwide Assurance.

e. If a Relying Organization receives a grant and then contracts out all human research to investigators at Ballad Health, the Ballad Health IRB may agree to serve as the IRB of Record for the research project(s).

f. Students fulfilling degree requirements from an academic institution are considered agents of the academic institution and, thus, the academic institution is engaged in the research regardless of where the research takes place. An exception of this is outlined within the Master Reliance Agreement with ETSU.

g. Students engaged in research at Ballad Health are required to have an appointment at Ballad Health.

h. The Ballad Health IRB may not serve as the IRB of record for international research sites.

i. Effective January 20, 2020, Single IRB Mandate for Cooperative Research:

i. Per 45 CFR Part 46.114 (b)(1) Any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States.

j. Procedure Statements

i. The Relying Organization which is engaged in the research must have a Federalwide Assurance (FWA) with the Federal Office for Human Research Protections (OHRP). The Federalwide Assurance (FWA) is the only type of assurance currently accepted and approved by OHRP. Through the FWA, an institution commits to HHS that it will comply with the requirements in the HHS Protection of Human Subjects regulations at 45 CFR Part 46.

ii. Ballad Health and the Relying Organization must each maintain a separate, active FWA with the Federal Office for Human Research Protections (OHRP).

iii. The Relying Organization is responsible for meeting the terms and conditions of their FWA.

iv. An IRB Authorization Agreement must be executed between the Ballad Health IRB and the Relying Organization:

1) An IRB Authorization Agreement documents the agreement and signatures of the Signatory Officials from the Relying Organization and the Ballad Health Institutional Official.

2) The roles and responsibilities of the reviewing IRB and the Relying Organization are outlined in the IRB Authorization Agreement.

3) Copies of the signed IRB Authorization Agreement must be kept on file at both organizations and made available upon request to the Federal Office for Human Research Protections (OHRP) or any agency supporting research to which the FWA applies.

k. Principal Investigator Responsibilities

i. Prior to approval of the reliance:

1) To request Ballad Health IRB to serve as the IRB of Record for a Relying Organization, the Principal Investigator or their designee will complete the Request to Rely on Ballad Health IRB Form, located on the IRBNet under IRB Forms.

2) The Principal Investigator or their designee will send the completed form and initial study protocol to the HRPD staff at the IRB email inbox (IRB@balladhealth.org).

ii. After the approval of the reliance:

1) The Principal Investigator is responsible for providing the Ballad Health IRB with information concerning the Relying Organization and the Relying Organization's site-specific documents (consent/HIPAA form(s)), subject contact material(s), etc., according to policy) at the time of original

submission within IRBNet requesting approval of the addition of the Relying Organization.

2) The Principal Investigator is responsible for communicating determinations with and ensuring that study-related information from the Ballad Health IRB is received by the Relying Organization.

3) The Principal Investigator is responsible for providing the Ballad Health IRB with information concerning study status for the Relying Organization at the time of continuing review in accordance with Ballad Health IRB's Continuing Review policy.

4) The Principal Investigator is responsible for submitting to the Ballad Health IRB modification to the study on behalf of the Relying Organization.

5) The Principal Investigator is responsible for submitting events that occur at the Relying Organization that meet the definition of a Reportable Event to the Ballad Health IRB in accordance with Ballad Health IRB's Adverse Events policy.

l. HRPD Staff Responsibilities

i. Ballad Health HRPD leadership or their designee(s) will evaluate the request for Ballad Health to serve as the reviewing IRB for a Relying Organization and either approve or not approve of the research affiliation or reliance to serve as the IRB of Record.

m. If the IRB of Record request is approved, the HRPD staff:

i. Proposes the type of reliance agreement to be used to the Relying Organization. Examples of types of reliance agreements are an IRB Authorization Agreement or Smart IRB Authorization Agreement.

ii. Documents the use of a Smart IRB Authorization Agreement (through a Determination Letter, Exhibit, Acknowledgement Letter, etc.) or obtains signatures from the Institutional Officials at Ballad Health and the Relying Organization for a single-study IRB Authorization Agreement, if applicable.

iii. Emails a signed copy of the IRB Authorization Agreement or documentation of the use of a Smart IRB agreement to the Principal Investigator named on the Ballad Health IRB application. This email will:

1) Include the IRB operations, leadership staff, and the HRPD team (cc'd)

2) Provide the Relying Organization's Principal Investigator's name and email address and an alternative contact's name and email address. This allows the Relying Organization's PI and contact to receive IRB notifications from IRBNet.

3) Instructs the Principal Investigator to complete the Study Locations section of the IRBNet application and upload the IRB Authorization Agreement or documentation of the use of a Smart IRB agreement.

4) Note: In some research studies that have previously been approved by the IRB, the Principal Investigator may need to submit a modification to

complete the Study Locations section and to upload the IRB authorization Agreement or documentation of the use of a Smart IRB agreement.

iv. The following text is used (or modified) in the IRB minutes or notification to document acceptance of Ballad Health IRB serving as the IRB of Record for a Relying Organization:

1) The Committee/Reviewer accepts the appointment of Ballad Health IRB as the IRB of Record for the Relying Organization (name of organization), and notes receipt of the fully executed IRB Authorization Agreement.

v. If the IRB of Record request is not approved:

1) The IRB Manager (or designee) will inform the Principal Investigator or student (when applicable) of the determination not to approve the affiliation or reliance and the reason/s why.

n. Record Keeping:

i. IRB Authorization Agreements must be kept in the Researcher's IRBNet file and available to OHRP, FDA, or assessors upon request.

ii. The IRB maintains a copy of the IRB Authorization Agreement.

iii. IRB Authorization Agreements are retained per IRB Record policy.

iv. Upon study closure or study termination, by the Principal Investigator, Ballad Health IRB, or Relying Organization, the IRB Authorization Agreement will be considered inactive, and the document will be archived according to the Closure of an IRB Approved Protocol.

o. Termination of IRB Authorization Agreements:

i. The IRB Authorization Agreement becomes effective on the date of the last signature on the agreement or when the documentation of reliance (through a Determination Letter, Exhibit, Acknowledgement Letter, etc.) is completed.

ii. The IRB Authorization Agreement shall continue for the duration of and until the cessation of the Principal Investigator's or the Relying Organization's participation in the research study.

iii. Either the Institution's IRB or the Relying Organization may terminate the agreement in the event that any party's FWA is suspended, terminated, or expires.

52. Program Evaluations

a. Program evaluations involve a systematic collection and analysis of information about the effectiveness of the program in order to make judgments about the program, improve program effectiveness, and/or inform decisions about future program development. These evaluations may involve various methods of human interaction such as surveys, interviews, and the analysis of documents and background information. If the intent of these projects is to inform a particular program about that program's effectiveness and needs rather than to contribute to generalizable knowledge, they are not considered research. As long as the

survey, interview, analysis of documents, and background information do not include any of the PHI-18 identifiers.

b. An exemption to the PHI-18 restriction can be requested by submitting the proposed survey, interview form, and other items that are needed to be reviewed to the IRB@balladhealth.org email address. The items allowed to be waived through an exception, must have the wording "optional" next to them are Name and Work / School Email address.

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8. 45 CFR Part 46, Subpart D
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10. 45 CFR Part 160
11. 45 CFR Part 164
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13. 21 CFR Part 50
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15. 21 CFR Part 56
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17. 21 CFR Part 312
18. 21 CFR Part 314
19. 21 CFR Part 512
20. 21 CFR Part 600

21. 21 CFR Part 807

22. 21 CFR Part 809

23. 21 CFR Part 812

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26. Food, Drug & Cosmetics Act, Section 530

27. Belmont Report

28. OHRP Assurance Information

29. OHRP IRB Registration

30. OHRP Policy Guidance

31. Code of Federal Regulations, Title 45 Public Welfare, Parts 164 Health Insurance Portability & Accountability Act of 1996

32. OHRP and FDA, Institutional Review Board (IRB) Written Procedures Guidance for Institutions and IRBS, May 2018

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46. 5 USC § 552a

47. HHS, Federal Policy for the Protection of Human Subjects, 82 F.R. 12 (Jan. 19, 2017)

48. OHRP Continuing Review Guidance (Nov. 10, 2010)

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54. National Bioethics Advisory Commission, Research Involving Persons with Mental Disorders That May Affect Decision-Making Capacity (December 1998).

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56. OHRP Compliance Activities: Common Findings and Guidance #3, #45, #65

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Vice President, Chief Academic Officer, Ballad Health Date

Executive Vice President, Chief Physician Executive	Date