Title:	Policy Number: BC-IRB-411
REPORTING ADVERSE EVENTS INCLUDING SERIOUS ADVERSE EVENTS, UNANTICIPATED PROBLEMS, PROTOCOL DEVIATIONS, VIOLATIONS, or EXCEPTIONS, AND NONCOMPLIANCE POLICY	**Page:** 1 of 7
SPONSORED BY: Sponsored Programs and Research Committee	**Issued for:** All BayCare, including without limitation: Bartow Regional Medical Center BayCare Alliant Hospital BayCare Hospital Wesley Chapel Mease Countryside Hospital Mease Dunedin Hospital Morton Plant Hospital Morton Plant North Bay Hospital South Florida Baptist Hospital St. Anthony's Hospital St. Joseph's Hospital Winter Haven Hospital
Original Issue Date: 6/2023 **Review Dates:** **Revision Date:**	
Approved by: Keri Eisenbeis, SVP Corporate Relations/Chief of Staff **Signature:** Keri Eisenbeis	

This policy is developed as a guideline to address general circumstances. There may be certain instances in which the exercise of professional judgment and/or discretion by the healthcare provider warrants taking other actions.

This **REPORTING ADVERSE EVENTS INCLUDING SERIOUS ADVERSE EVENTS, UNANTICIPATED PROBLEMS, PROTOCOL DEVIATIONS, VIOLATIONS, or EXCEPTIONS, AND NONCOMPLIANCE POLICY** applies to BayCare Health System, Inc., and any of its affiliated entities, including those entities listed above (collectively, "**BayCare**").

Scope:

BayCare Human Research Protection Program when submitting a reportable event to BayCare Health System-Institutional Review Board (BCHS-IRB) including when BCHS-IRB is not the IRB of record.

Purpose:

To outline the BCHS-IRB requirements for reporting adverse events and unanticipated problems that occur during the course of a research project.

- Unanticipated problems or adverse events can occur in any type of research (medical or social/behavioral/educational research). Some events are expected (e.g., lightheadedness during blood collection), while others are unexpected (death or theft of devices containing Protected Health Information (PHI)).
- Events vary in seriousness and the extent to which they are related to the research. Reporting serious adverse events and unanticipated problems facilitates protection of research participants by allowing investigators and the BCHS-IRB to determine whether the event/problem necessitates changes to minimize risk, keeping the risk/benefit ratio favorable, for the fully-informed participants.

Definitions:

Unanticipated problems involving risks to subjects or others: Any incident, experience, or outcome that meets all of the following criteria:

- Is 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
- Is related or possibly related to an individual's participation in the research
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, social, economic, legal, or informational harm) than was previously known

Related or possibly related to the research: An event is considered related to the research if, 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).

Adverse event: Any untoward or unfavorable occurrence in a research participant that is associated with the participant's involvement in the research. An adverse event encompasses physical, psychological, social, economic, legal, or informational harms. It may or may not be directly related to the individual's participation in the research.

Serious adverse event: Any adverse event associated with the individual's participation in research that meets any of the following criteria:

- Results in death
- Is life threatening (places the subject at immediate risk of death from the event as it occurs)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the individual's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition
- Results in a breach of confidentiality that is damaging to the participant's rights, employment, financial standing, or reputation
- Causes significant psychological, social, economic, or legal harm to the participant or others

Unexpected problem/adverse event: Any adverse event occurring in one or more participants when the nature, severity, or frequency is not consistent with either:

- the known or foreseeable risk described in (a) the protocol-related documents (i.e., the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document) and (b) other relevant sources of information (e.g., product labeling and package inserts); or
- the expected natural progression of any underlying disease, disorder, or condition of the individuals(s) experiencing the adverse event and the individual's predisposing risk factor profile for the adverse event.

Unanticipated adverse device effect (UADE): For studies of medical devices, the investigational device exemption regulations define an unanticipated adverse device effect as any serious effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Anticipated problem/adverse event: Any foreseen or expected problem/event that was described in the IRB approved research protocol, any applicable investigator brochure, and/or the current IRB-approved informed consent document.

Reportable Event: A type of event that requires reporting to the IRB within five working days: The investigator follows the process (with an associated IRB form) to report any problem or event or other act or omission to the IRB that, in their opinion, is an unanticipated problem involving risks to subjects or others.

IRB of Record: A reviewing IRB that assumes IRB responsibilities for another organization and is designated to do so through an approved Federalwide Assurance (FWA) on file with the Office for Human Research Protections (OHRP).

Federalwide Assurance (FWA): A formal, written, binding attestation in which an institution commits to the Department of Health and Human Services (DHHS) that it will comply with applicable regulations governing research with human subjects.

Procedure:

A. Investigator Reporting Requirements and Timelines for Reporting to the BCHS- IRB when the BCHS-IRB is the IRB of Record

1. **Investigators promptly report to the BCHS-IRB:**
   - any *serious adverse event* that is related or possibly related to the research; or
   - any event that meets the definition of *an unanticipated problem*.

"Prompt" reporting means *within five business days* of an occurrence or *within five working days of the principal investigator becoming aware of an occurrence*.

If applicable, reporting follows the requirements and timelines set forth in data safety and monitoring plans that are in place for the research.

NOTE:

Immediate Risk of Serious Harm

If the problem poses an immediate risk of serious harm to a participant or others, it is reported immediately but no longer than 24 hours to IRB.BCHS@baycare.org.

Federally Funded or Supported Research
Some federal agencies require investigators to report adverse events or unanticipated problems to the agency within specified timeframes—immediately in certain instances. Investigators need to be aware of these requirements.

Medical Devices and New Drugs
For research on medical devices, an unanticipated adverse device effect (UADE) is reported to the IRB and the sponsor as follows:

- Submit a report of a UADE to the sponsor and the reviewing BCHS-IRB as soon as possible but no later than 10 working days after the investigator first learns of the event.
- Sponsors immediately conduct an evaluation of a UADE and report the results of the evaluation to the US Food and Drug Administration (FDA), all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect.

Investigators conducting clinical investigations of drug or biological products under an investigational new drug (IND) application or investigational medical devices under an FDA Investigational Device Exemption (IDE) are to report certain types of adverse events and unanticipated problems to the sponsor and/or FDA.

B. Relationship between Adverse Events and Unanticipated Problems

1. An unanticipated problem is by definition 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.

   Examples of reportable unanticipated problems (which may or may not be adverse events) include, but are not limited to:

   - A breach in confidentiality resulting from disclosure of confidential information or from lost or stolen confidential information that may involve risk to the subjects or others
   - Complaint of a participant or family member that indicates an unanticipated risk
   - Harm or risk of harm to research staff
   - Laboratory or medication errors that may involve potential risk to the individual or others
   - Disqualification or suspension of investigators
   - Accidental or unintentional change to the IRB-approved protocol that involves risks or has the potential to recur
   - Deviation from the IRB-approved protocol without prior IRB review to eliminate apparent immediate hazard to a research participant
   - A deviation from the IRB-approved protocol that increases risk or affects the participants' rights, safety, or welfare
   - Newly discovered information (publication in literature, a safety monitoring report, a revised investigator's brochure, interim results, or other finding) that indicates a change in the risk/benefit ratio of the research

2. An adverse event is reported (whether or not it is serious) if it meets the definition of an unanticipated problem (i.e., unexpected, related to the research, suggests increased risk of harm to subjects or others). In general, the following types of adverse events are considered to be unanticipated problems that must be reported to the IRB:

   - Single occurrence of a serious, unexpected event that is strongly associated with the research
   - Multiple occurrences of an adverse event that, based on aggregate analysis, is determined to be an unanticipated problem. The series of adverse events represents a signal that the adverse events were not 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)
   - 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

C. Reporting Unanticipated Problems, Protocol Deviations and Noncompliance to the BCHS-IRB When the BCHS-IRB is the IRB of Record

1. Report unanticipated problems to the BCHS-IRB using the Adverse Event Report Form in eIRB within five working days after discovery of their occurrence. The BCHS-IRB makes the final determination as to whether an incident constitutes an unanticipated problem.
2. Report noncompliance and protocol deviations using the Protocol Deviation Report Form within five working days after discovery of their occurrence.
3. The BCHS-IRB makes the final determination as to whether an incident constitutes serious noncompliance

D. BCHS-IRB Process for Handling Reported Problems

1. Upon review of the report, the BCHS-IRB Chair(s) (a) determine if the report includes the necessary information, (b) perform an initial evaluation, and (c) consult with appropriate individuals (e.g., physician consultant, other BCHS-IRB members, etc.) if necessary.
2. If, in the judgment of the BCHS-IRB Chair(s), participants or others may be at immediate risk of harm and there is insufficient time to wait for review by the convened BCHS-IRB, the BCHS-IRB Chair(s) requires the principal investigator to suspend the study pending review by the convened BCHS-IRB.
3. If participants or others are not at immediate risk, the report is scheduled for review at the next meeting of the convened IRB.
4. The convened BCHS-IRB determines whether the incident constitutes an unanticipated problem involving risks to subjects or others and specifies any corrective actions. Corrective actions may include, but are not limited to the following:
    - Acknowledgement/acceptance without further recommendation
    - A request for further clarification or a corrective action plan from the investigator
    - Changes in the protocol (e.g., additional tests or visits to detect similar events in a timely fashion changes to the confidentiality measures employed in the study, changes to inclusion/exclusion criteria)
    - Changes to the informed consent document(s)
    - Notification to enrolled subjects and/or re-consenting when appropriate
    - A change in frequency of continuing review
    - Further inquiry into other protocols utilizing particular dietary supplements, devices, or procedures in question
    - Additional training for investigators and/or research team members
    - Monitoring of the research procedures or informed consent process
    - Referral to other organizational entities
    - Suspension or termination of BCHS-IRB approval for the study; and
    - Post-approval monitoring or other monitoring actions deemed appropriate by the BCHS-IRB.
5. If the BCHS-IRB acknowledges/accepts the report and deems that no further follow-up is required, the BCHS-IRB team notify the Principal Investigator (PI) of the review outcome.
6. If the committee requests clarification(s), additional information or revisions to the approved protocol, the BCHS-IRB team notifies the PI of the need for additional information and/or changes.
7. Adverse events or unanticipated problems that involve deviations from the IRB-approved protocol are reviewed in accordance with the BCHS-IRB Review of Protocol Deviations and Noncompliance.
8. If the BCHS-IRB determines the problem/event to be an unanticipated problem involving risks to subjects or others, the BCHS-IRB team reports the BCHS-IRB's determination to federal agencies or sponsors in accordance with federal regulations. The BCHS-IRB staff reports the BCHS-IRB's determination to the Institutional Official.

E. Submitting Reportable Events when BCHS-IRB <u>is not the IRB of Record</u>

Submit reportable events/new information to the Reviewing IRB according to the Reviewing IRB's policies and procedures.
<u>Submit Egregious</u> reportable events promptly to the BCHS-IRB IN ADDITION to the Reviewing IRB.
Examples of egregious reportable events:

Unanticipated Problems Involving Risk to Subjects or Others

Unanticipated Problems Involving Risk to Subjects or Others that involves **BCHS** team members or **BCHS** research subjects are reported to BCHS-IRB office within five working days of becoming aware of the problem or event, in addition to the reporting requirements of the external IRB.
Examples of problems and/or events which may meet Unanticipated Problems Involving Risk to Subjects or Others:

- Any complaint from a subject that indicates an unanticipated risk, or that cannot be resolved by the research team.
- Problems, events, or new information (e.g., from publications, Data and Safety Monitoring Board [DSMB] reports, interim findings, product labeling changes) that, in the opinion of the investigator, may adversely affect the rights, safety, or welfare of subjects or others, or which substantially compromise the research data
- Breach of confidentiality (e.g., unapproved PHI disclosure, a stolen, unencrypted laptop containing subject data and identifiers)
- An unexpected hospitalization - new or prolonged
- An unexpected life-threatening adverse experience

- An unexpected death, not attributed to underlying disease
- A newly developed disability/incapacity - persistent or significant
- An unexpected birth defect/anomaly
- A processing error resulting in a subject receiving a dose of study medication significantly higher than the dose dictated by the IRB-approved protocol, even if the incorrect dosing produces no detectable Adverse Effect (AE)

Protocol Violation/Deviation

Any major Protocol Violation/Deviation that affects the rights and welfare of subjects and others, increases risks to subjects and others, decreases potential benefits, compromises the integrity or validity of the research, or represents willful or knowing misconduct, which involves BCHS team members or BCHS research subjects is considered non-compliance and requires reporting to the BCHS-IRB within five working days of becoming aware of the problem. Follow reporting requirements of the external IRB.

Examples of problems or events which may meet the definition of major Protocol Violations/Deviations (non-compliance):

- Enrolling subjects who did not meet inclusion/exclusion criteria on a greater-than-minimal risk study
- Performing study procedures not approved by the IRB
- Performing study procedures before obtaining informed consent
- Failure to obtain and/or document informed consent
- Use of an unapproved consent document
- Changing the protocol without prior IRB approval except when necessary to eliminate immediate harm to a subject
- Breach of confidentiality (i.e. any occurrence of unapproved PHI disclosure)
- Receipt of incorrect treatment or dose by a subject
- Loss or destruction of samples or data
- Over-enrollment of subjects on a greater-than-minimal risk study
- Unauthorized (i.e. not IRB-approved) persons participating in the conduct of a research study

Investigator Reporting Responsibilities

When an Unanticipated Problem Involving Risk to Subjects or Others and/or major Protocol Violation/Deviation occurs at BCHS, but the BCHS-IRB is not the IRB of Record:

1. The Investigator completes reporting according to the requirements of the external IRB.
2. The Investigator reports the problem or event to BCHS-IRB within five working days of becoming aware of the problem or event by completing the Reportable Event section on the Adverse Event Report form within the BCHS-IRB electronic (eIRB) system.
3. Upon receipt of the external IRB's review and determination regarding the problem or event, the investigator uploads within the eIRB system:
   - A copy of the reviewing IRB outcome
   - A copy of the report submitted to the reviewing IRB

BCHS-IRB Responsibilities

When an Unanticipated Problem Involving Risk to Subjects or Others and/or major protocol violation/deviation occurs at BCHS, but the BCHS-IRB is not the IRB of Record, BCHS-IRB will:

4. Review the submitted Reportable Event form describing the Unanticipated Problem Involving Risk to Subjects or Others and/or major protocol violation/deviation.
5. Communicate as warranted with the designated IRB of record.
6. Notify the BCHS-IRB Committee, BCHS-IRB Chair, BCHS-IRB Institutional Official, and when required, the applicable federal agencies.

Related Policies:

BC-IRB-400 BayCare IRB Composition, Roles and Responsibilities
BC-IRB-405 Requirement for Continuing Review Prior to and After Implementation of the Common Rule

Related BCHS-IRB forms:

Serious Adverse Event Form
Protocol Deviation/Violation Form
BCHS-IRB Letter of reliance to external IRB
BCHS-IRB Aggregate report (to be submitted at study continuing review)