1. PURPOSE

1.1. This procedure establishes the process to manage Reportable Events submitted to the IRB that are Non-Compliance, Unanticipated Problem Involving Risks to Subjects, Serious Adverse events or other Miscellaneous items.

1.2. The process begins when the IRB office receives the reportable event via myIRB.

1.3. The process ends when the executive reviewer has determined that no further action is needed or has referred the submission to the full board.

2. POLICY

2.1. Federal regulations require prompt reporting to the IRB, appropriate institutional officials, the head of sponsoring Federal department agency, if any, and OHRP and/or FDA must be reported within 30 days. For VA approved research, investigators are also required to comply with VA reporting requirements per Policy on IRB-01 as the NFSG/VA Medical Center Affiliate IRB (HRP-193).

- Any serious or continuing non-compliance with the Federal Regulations, or requirements, determinations, or policies and procedures of the IRB,
- Any unanticipated problems involving risks to subjects or others, and
- Any suspension or termination of IRB approval

2.2. Non-Compliance Pertaining to Human Subject Research:

2.2.1. Non-compliance: any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with Federal Regulations, state law, university policies and/or requirements, determinations, or policies and procedures of the IRB. Non-compliance may range from minor to serious, be unintentional or willful, and may occur once or several times. The seriousness of non-compliance will be evaluated on a case-by-case basis.

2.2.2. Serious non-compliance: any action or omission in the conduct of oversight of research involving human subjects that may affect the rights, safety and/or welfare of research participants, increase risk or decrease benefits to subjects, and/or compromise the integrity or validity of the research.

2.2.3. Continuing non-compliance: is a pattern of failing to follow Federal Regulations, state law, University Policies, and/or requirements, determinations, and/or policies and procedures of the IRB. Continuing non-compliance is assessed by the number of incidents during the course of a given protocol or across a number of protocols (for the same investigator) and whether the same non-compliant action or activity was repeated or a variety of noncompliant actions or activities occurred.

2.3. Unanticipated Problems Involving Risk to Subjects or Others and Adverse Events:

2.3.1. Federal Regulations [46.103(b)(5)(i) and 56.108(b)(1)] require that unanticipated problems involving risk to subjects or others be promptly reported to the IRB, appropriate institutional officials, and any supporting department or agency head and OHRP and/or FDA. Although the regulations do not define unanticipated problems, OHRP (2007) published guidance on unanticipated problems. Reportable events under FDA regulations include a subset of unanticipated problems (serious, unexpected and related adverse events).

For Unanticipated problems involving risk to subjects or others and adverse events involving research at the VA, the IRB will refer to the applicable requirements outlined in VHA Handbook.

2.3.2. Unanticipated Problem (UPR): any incident, experience, or outcome that meets all of the following criteria:

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

(2) related or the relationship to the participation in the research is “more likely than not”: based on study interventions, the reporting investigator or the sponsor determines that a reasonable possibility exists that an outcome may have been caused or influenced by the study event in question (e.g., administration of a study drug); no plausible alternative cause/influence was present; and

(3) 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. Events that do not cause detectable harm or adverse effects to subjects or others may still represent unanticipated problems (OHRP Guidance, 2007).

Both risks to subjects and risks to other individuals (e.g., research personnel, subjects’ family members) are included in the concept of UPRs. Risks may reflect any type of potential harm (e.g., physical, psychological, social, economic). Other problems that are unanticipated and indicate that subjects or others are at increased risk, but that are not caused by research procedures may also be considered UPR.

2.3.3. Adverse Event: 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.

2.3.4. Unexpected Adverse Event: Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is not consistent with either:

(1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

(2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event.

2.3.5. Expected Adverse Event: any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is consistent with:

(1) the known toxicities and side effects of the research procedures;

(2) the expected natural progression of subjects’ underlying diseases, disorders, and conditions; and

(3) subjects’ predisposing risk factor profiles for the adverse events.
2.3.6. The relationship to participation in research is “more likely than not”: Any reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research, and there is not a more plausible reason for the event.

2.3.7. **Serious Adverse Event**: Any adverse event that results in death for all local subjects and non-local deaths (considered by the local PI or project Study Chair to be related or the relationship to study participation is “more likely than not”), is life-threatening, results in inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, results in a congenital anomaly/birth defect, or based upon appropriate medical judgment, may jeopardize the patient or subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above.

   (1) **Internal Adverse Event**: adverse events experienced by subjects enrolled by the investigator(s) at that institution

   (2) **External Adverse Event**: adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.

2.3.8. **Unexpected Adverse Drug Experience (21 CFR 312)**: any adverse event, the specificity or severity of which is not consistent with the current investigator brochure or the investigational plan (protocol, consent form). In addition, known adverse events may occur more frequently than expected.

2.3.9. **Unanticipated Adverse Device Effects (21 CFR 812)**: any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if 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.

OHRP (2005) considers a subset of adverse events to represent unanticipated problems that would need to be reported under HHS regulations including: 1). Adverse events that are serious, unexpected, and related or the relationship to study participation is “more likely than not.”; 2). Serious adverse events that are expected in some subjects, but are determined to be occurring at a significantly higher frequency or severity than expected; and 3). Other unexpected adverse events, regardless of severity, that may alter the IRB’s analysis of the risk benefit ratio of the research, and warrant consideration of substantive changes in the research protocol or informed consent process/document.

2.4. **Events That Require Reporting to the IRB**

DHHS (45 CFR 46) and VA (38 CFR 16) human subjects protection regulations, and FDA (21 CFR 56) IRB regulations require that unanticipated problems involving risk to subjects or others, including a subset of adverse events, be promptly reported to the IRB.

By definition the following unanticipated problems involving risks to subjects or others must be reported to the IRB and may require reporting to FDA, OHRP/DHHS and/or other entities under the Reporting Policy:

1. Incidents, experiences, or outcomes that are unexpected, related or the relationship to study participation is “more likely than not.”, and suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. For unanticipated problems,
the IRB is responsible for determining whether the research places subjects or others at a greater risk.

2. Adverse events that are: serious, unexpected, and related or the relationship to study participation is “more likely than not.” For adverse events, the UF IRB determines relatedness.

3. Unexpected and related adverse events; the IRB determines seriousness.

4. Information security incidents involving any unauthorized use, disclosure, transmission, removal, theft, loss or destruction of research-related protected health information.

2.5. Reporting Requirements of the IRB

Investigators are required to and ultimately responsible for promptly reporting unanticipated problems to subjects or others to the IRB regardless of funding source, study sponsor or type of study.

All adverse events and unanticipated problems that require reporting under UF IRB Policy must be included on the Cumulative Table submitted at continuing review.

Non-adverse events meeting the definition of an unanticipated problem involving risk to subjects or others and/or serious and unexpected adverse events that meet the IRB criteria for expedited reporting must be reported by the Principal Investigator, via myIRB, within five working days of discovery (five working days from notification for off-site adverse events) of the event.

Reporting requirements outlined in VHA Handbook will be followed for VA approved research.

3. RESPONSIBILITY

3.1. IRB staff and Executive reviewers carry out these procedures or ensure they are carried out by other personnel.

3.2. Individuals unsure of a decision in this Policy are to bring new information to higher level official for a determination.

4. PROCEDURE

4.1. Reportable events will be received in the IRB inbox via myIRB. IRB staff will forward the submission to the Chair or Executive Reviewer.

4.1.1. If the Reportable Event is regarding Non-compliance:

4.1.1.1. If the information represents Non-Compliance: Determine whether each Allegation of Non-Compliance has any basis in fact.

4.1.1.1.1. If yes, the assigned reviewer will determine if there were risks to subjects, risks to the integrity of the data, and assess the overall corrective action plan provided by the Principal Investigator.

4.1.1.1.2. If the determination is that the non-compliance is serious or continuing, then the submission will be referred to full board for review. If more immediate action is required, the Chair will be notified and an administrative suspension can be implemented.
4.1.1. If the determination is that the non-compliance is neither serious nor continuing, then the assigned reviewer will document this conclusion and no further action will be required.

4.1.2. If the reportable event is a Serious Adverse Event (SAE) or an Unanticipated Problem:

4.1.2.1. The assigned reviewer will evaluate the risk to the subject and potential risk for subsequent subjects.

4.1.2.2. If the SAE or Unanticipated Problem is unexpected and related to the research it will be referred to the full board for review and a determination, including whether the reported problem is an unanticipated problem involving risk to subjects or others will be made.

4.1.2.2.1. If more immediate action is required, the Chair will be notified and an administrative suspension can be implemented.

4.1.2.3. If the reported SAE or Unanticipated Problem is determined not to be an SAE or Unanticipated Problem, the Chair will acknowledge the report as no further action needed.

4.2. If, in your opinion, the rights and welfare of participants might be adversely affected before the convened IRB can review the information, contact the IRB chair to consider a suspension of IRB approval following the “POLICY: Suspension and Termination by Institution (HRP – 114).”

4.3. If the Reportable Event is miscellaneous information:

4.3.1. Bring the information to the attention of the Assistant Director of IRBs and/or IRB Chair for consideration of whether any immediate actions are necessary to protect the rights and welfare of human subjects.

4.3.2. Assigned reviewer will determine if the information has an impact on subject safety, in which case the reviewer can request that the Principal Investigator submit a revision to the protocol and consent.

4.3.3. Take any additional actions required to resolve any concerns or complaints associated with the reportable event or new information.

4.4. If the reportable event is a subject death related to the study, the Chair will inform organizational officials within 3 days of recognition of the reportable event.

4.5. If the reportable event meets applicable regulatory agency reporting requirements, such reports will be sent by the Institutional Official within 30 days of recognition of the reportable event.

4.5.1. For multicenter projects, only the institution at which the event occurred must report the event.

5. REFERENCES

5.1. 45 CFR §46.103(b)(5)
5.2. 21 CFR §56.108