ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

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Objectives

1. *Define Adverse Events (AE), Serious Adverse Events (SAE), and Unanticipated Problems (UP)*
2. *Understand how to assess, grade and document AEs, SAEs, and UPs*
3. *Understand reporting obligations and reporting deadlines*
4. *Practice determinations using case examples*

Adverse Event (AE) definition

HHS (OHRP Guidance 2007) – BUMC policy

"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"

Serious Adverse Event (SAE) definition

HHS (OHRP Guidance 2007) – BUMC policy

Serious Adverse Event (SAE) is any adverse event that

1. *results in death;*
2. *is life-threatening (places the subject at immediate risk of death from the event as it occurred);*
3. *results in inpatient hospitalization or prolongation of existing hospitalization;*
4. *results in a persistent or significant disability/incapacity;*
5. *results in a congenital anomaly/birth defect; or*
6. *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 (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).*

FDA AE definitions

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

Adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

FDA AE definitions

Serious Unexpected Suspected adverse reaction (SUSAR) is defined as an unexpected serious adverse event that is determined to be at least possibly related to a study medication.

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

Unanticipated Problem (UP) definition

HHS (OHRP Guidance 2007) – BUMC policy

OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets all of the following criteria:

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 possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); 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.*

Intersection of AE, SAE, and UP

AE, SAE, and UP examples

AE:

During an RCT designed to test the effects of Chantix to promote abstinence from nicotine, one of the study participants reported having passive thoughts of suicide. This is a known risk of the medication that was described in the consent. The participant was assessed by the study PI and was determined to not be at risk for suicidal behavior.

SAE:

During an RCT designed to test the effects of Ozempic vs. Zepbound to reduce the risk of non-fatal heart attacks and stroke among patients with obesity, one of the study participants was admitted to the hospital after having a stroke. The participant has risk factors for stroke including obesity and hypertension. Stroke is not a known risk of either Ozempic or Zepbound.

AE, SAE, and UP examples

UP and AE:

During an RCT designed test the the preventive effect of esketamine on postpartum depression in patients undergoing cesarean section, the pharmacy order was entered incorrectly and the participant received twice the expected dose of medication due to this error. The participant experienced intense hallucinations and feelings of depersonalization. Hallucinations and depersonalization are known side effects of the drug.

AE, SAE, and UP examples

UP but not an AE or SAE:

An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors. The data are stored using a in a university-based server that meets all of the security standards of the institution. The university experienced a ransomware attack and it is suspected that this study data was compromised.

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Adverse Event Monitoring Responsibilities

- ✓ Research team members should be aware of what adverse events are and the importance of adherence to ongoing monitoring and reporting in ensuring participant safety.
- ✓ Specific team members, with appropriate training, licensure, and per the Delegation of Authority log, may also have additional responsibilities including per-protocol monitoring, assessing, and reporting.
- ✓ The PI is ultimately responsible for all adverse event monitoring and reporting, including oversight of those with delegated responsibilities.

BUMC SOP: **Adverse Event Monitoring, Assessing, Documenting, and Reporting**

Adverse Event Monitoring Procedures

- ✓ AEs should be monitored and reviewed from time of consent to final data collection.
- ✓ AEs should be followed to a final outcome in accordance with protocol requirements.
- ✓ Research teams should have a process for capturing and monitoring both solicited and unsolicited AEs.
- ✓ The frequency of monitoring and what is monitored should follow the protocol and Data Safety Monitoring Plan (DSMP)
- ✓ The research team is expected to develop workflows to meet AE monitoring requirements

BUMC SOP: **Adverse Event Monitoring, Assessing, Documenting, and Reporting**

Adverse Event Monitoring
Solicited vs. unsolicited

Solicited:
- ✓ Questions that target specific possible symptoms of interest
- ✓ General questions about changes in health symptoms
- ✓ Assessment that is conducted as part of study visits (lab, BP, ECG)

Unsolicited:
Events that are not directly solicited regardless of how they were disclosed
- ✓ Medication assessment reveals some OTC medication – implies AE that should be assessed
- ✓ Events documented in the electronic medical record
- ✓ Reports of health symptoms in conversation with any team member

BUMC SOP: **Adverse Event Monitoring, Assessing, Documenting, and Reporting**

Adverse Event
Documentation requirements

Requirements
- ✓ Key dates associated with the event (onset, recorded, follow-up, resolution, reporting obligations)
- ✓ Relevant medical history if appropriate for event
- ✓ Plan for medical or clinical follow-up if appropriate for the event
- ✓ Assessment of the event as
  - Seriousness
  - Severity
  - Relatedness
  - Expectedness

CRRO Best practice AE assessment form:
https://www.bumc.bu.edu/crro/files/2023/09/CRRO-Tool_Adverse-Event-Form_9122023.docx

BUMC SOP: **Adverse Event Monitoring, Assessing, Documenting, and Reporting**

Adverse Event Grading
Seriousness

Does the AE qualify as a Serious Adverse Event?

Serious Adverse Event (SAE) is any adverse event that

1. *results in death;*
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4. *results in a persistent or significant disability/incapacity;*
5. *results in a congenital anomaly/birth defect; or*
6. *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*

Adverse Event Grading
Severity

What is the impact on functioning, need for intervention?

Mild - Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities

Moderate - Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment.

Severe - Event results in significant symptoms that prevents normal daily activities; may require hospitalization or invasive intervention.

Adverse Event Grading Severity

What is the impact on functioning, need for intervention?

Life threatening - Life-threatening consequences; urgent intervention indicated

Death – Participant death

Common Terminology Criteria for Adverse Events (CTCAE)

- NCI Common Terminology Criteria for Adverse Events (CTCAE) provides a grading guidelines for health changes observed during a study.
- Includes common terms and thresholds for severity grading
- Participants may have adverse events that are detected by health assessments (vitals, labs etc.) that would be hard to grade without CTCAE
- Adverse event can include worsening of a health condition that was present before enrollment.

Adverse Event Grading Severity

Example grading of laboratory results

Table 1. CTCAE Criteria for Clinical Laboratory Adverse Events

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
ALT elevated	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AST elevated	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Total bilirubin elevated (bilirubinemia)	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN
Hypernatremia (elevated sodium)	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences
Hyponatremia (low sodium)	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences

Adverse Event Grading Relatedness

Is the AE a known effect of intervention or other study procedure?

Is there some temporal relationship between a study intervention or procedure and the onset of the AE?

Is there a clear cause of the AE that is not related to study interventions or procedures?

Does the AE presentation look similar to published data about this AE as a response to the intervention or procedure?

Does the AE respond to discontinuation and/or rechallenge?

Adverse Event Grading Relatedness

Unrelated - The temporal sequence of the AE/SAE onset relative to study interventions or procedures is not reasonable, or there is another obvious cause of the AE/SAE.

Unlikely - There is evidence of exposure study interventions or procedures, but there is another more likely cause of the AE/SAE.

Adverse Event Grading Relatedness

Possible - There is evidence of exposure to study interventions or procedures, the temporal sequence of the AE/SAE onset relative to exposure is reasonable, but the AE/SAE could have been due to another equally likely cause.

Probable - There is evidence of exposure to the study interventions or procedures, the temporal sequence of the AE/SAE onset relative to exposure is reasonable, and the AE/SAE is more likely explained by the exposure than by any other cause.

Definite - There is evidence of exposure to the study interventions or procedures, the temporal sequence of the AE/SAE onset relative to exposure is reasonable, the AE/SAE is more likely explained by the exposure than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the study interventions or procedures.

Adverse Event Grading Expectedness

Expected - Known effect or event based on prior experience (published data, consent, or investigational brochure) or condition under study

Unexpected - The event 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, investigators brochure, or informed consent document); and
(b) the characteristics of the subject population being studied;

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Reporting requirements
AE, SAE, UP

Know your responsibilities
- Sponsor and protocol requirements
- IRB requirements – Local and cede review
- FDA requirements - IDE or IND

Follow best practice guidelines - Record AE data in a summary log in real time to help identify actionable findings

CRRO best practice tool for logging AE data:
https://www.bumc.bu.edu/crro/files/2023/09/CRRO-Tool_Adverse-Event-Log_9122023.docx

Participant ID	1-2 Word Description	Relatedness	Expectedness	Severity	Seriousness	Prompt Reporting Required
		☐ Definite ☐ Possible ☐ Unrelated	☐ Unexpected ☐ Expected	[Insert options]	☐ Not Serious ☐ Serious	BUMC/BMC IRB: ☐ Yes ☐ No [Insert Authority]: ☐ Yes ☐ No [Insert Authority]: ☐ Yes ☐ No
		☐ Definite ☐ Possible ☐ Unrelated	☐ Unexpected ☐ Expected	[Insert options]	☐ Not Serious ☐ Serious	BUMC/BMC IRB: ☐ Yes ☐ No [Insert Authority]: ☐ Yes ☐ No [Insert Authority]: ☐ Yes ☐ No

BUMC IRB Reporting requirements
Adverse and Serious Adverse Events

BUMC IRB reporting requirements
- Comply with reporting requirements specified in the protocol (e.g., report to the sponsor) and comply with required reporting to the FDA.
- Submit a summary report of all Adverse Events (including SAEs) that are NOT Unanticipated Problems to the IRB at the time of the continuing review and at study closure.
- A formal report by a data safety monitor satisfies the requirement for a summary report. The summary must include an analysis of whether the pattern of events, in total, suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm), based on their nature or frequency of occurrence.

BUMC IRB Reporting requirements Unanticipated Problems

BUMC IRB reporting requirements

- The report of the Unanticipated Problem must be made as soon as possible but no later than **7 calendar days** after the investigator or research staff learns of the incident.
- The submission must describe the Unanticipated Problem and either specify what changes to the research are required or explain why no changes are necessary.
- A separate amendment request must also be submitted for the required changes, but this requirement should not delay the submission of the Unanticipated Problem report.
- Reporting requirement for UP even when review is ceded

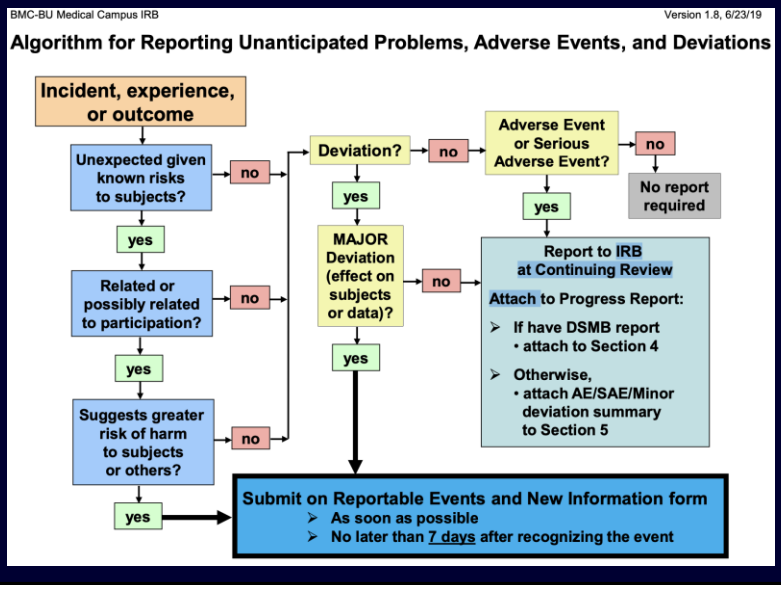
Unanticipated Problem (UP) PI responses

Immediate concern to protect subjects from a NEW RISK

Possible changes might include:

- Suspension of the study (new enrollments and/or all procedures)
- Immediate changes eliminate exposure to new risk
- Change in INC/EXC
- Additional monitoring and/or discontinuation rules
- Revision of consent to describe new risk
- Reconsenting of enrolled subjects to describe new risk

BUMC IRB Reporting requirements graphic algorithm



FDA Reporting requirements IND research (21 CFR 312.32)

SAE reporting

SAEs, whether or not considered drug-related, must be reported "immediately" to the sponsor, with some exceptions. "Immediately" should be defined in the protocol but is typically within 24 hours of first knowledge of the SAE by any member of the research team.

Follow-up reporting:

Any relevant additional information should be submitted without delay, as soon as the information is available but no later than 15 calendar days after the sponsor receives the initial SAE report

Note that if the PI holds the IND, the PI is the "sponsor" and is subject to reporting requirements to the FDA

FDA Reporting requirements
IDE research (21 CFR 812.150)

Unanticipated adverse device effect (UADE) reporting: Unanticipated adverse device effects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

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Case examples

Is it an adverse event?
Is it a serious adverse event?
Can we determine relatedness?
Can we determine expectedness?
Is this an unanticipated problem

Case Example 1

A 68 year old participant enrolled in a comparative effectiveness study evaluating two standard of care knee replacement methods was completing a 6-minute walk test during a follow-up visit. During this test, the participant complained of chest pain and collapsed. The participant had a history of prior cardiac arrest. The study team provided CPR until a code team arrived. The patient fully recovered.

Is it an adverse event? – Yes, cardiac arrest is an untoward event that occurred during the study.
Is it a serious adverse event? – Yes because it was life threatening.
Was the event related?– Probably related because the walk test has this as a known risk.
Was the event expected?– Unclear without more medical record review but given prior heart condition it might be an expected event for the population being studied.
Is this an unanticipated problem – Need more info to determine expected to make this judgement

Case Example 2

A 44 year old participant screening for entry into an RCT for alcohol use disorder was having blood drawn when he began to feel light-headed and lost consciousness. He was seated for the blood draw and the phlebotomist was trained to prevent injury. The subject rested in the clinic until he felt steady and then he continued screening.

Is it an adverse event? – Yes, vasovagal response is an untoward event that happened during the study.
Is it a serious adverse event? No, vasovagal response does not meet the SAE definition
Was the event related? Yes, this is a known risk of Phlebotomy
Was the event expected? Yes, we know this to be an expected outcome given phlebotomy
Is this an unanticipated problem No, because it is expected and does not represent an new risk

Case Example 3

A 50 year old participant enrolled in an RCT testing medications for rheumatoid arthritis was stung by a murder hornet while on vacation in Georgia. The participant developed a severe necrotizing infection at the site of the bee sting. The participant was hospitalized overnight for IV antibiotic treatment and fully recovered.

Is it an adverse event? Yes, this is an untoward event that happened during the study
Is it a serious adverse event? – Yes, because it involved hospitalization
Was the event related?- Unsure because arthritis medication might suppress immune function. We need expert medical opinion and review of product brochure to make this determination.
Was the event expected? - Unsure if this is expected until relatedness is determined.
Is this an unanticipated problem – Not enough information to make this determination

Case Example 4

An 18 year old participant enrolled in an RCT testing medications for depression noted worsening depression in week 6 of the trial. The participant had a history of passive suicidality but was frightened by recent increases in the frequency of thoughts about suicide. The study team developed a safety plan and did not judge this subject to be in eminent risk.

Is it an adverse event? – yes, increased suicidal thoughts is a untoward event in the study period.
Is it a serious adverse event? – No, passive SI is common and usually not an emergent risk that is life threatening.
Was the event related? Unsure, need to know more about medication risks to make this determination
Was the event expected? Yes, this is expected given changes in depression are normal for the population being studied.
Is this an unanticipated problem No, because this is an expected event, this does not meet the UP criteria

Case Example 5

A 37 year-old participant enrolled in an COVID-19 vaccination trial developed a moderate allergic reaction that included swelling of their lips 15 minutes after receiving the vaccination. The reaction did not include anaphylaxis. The patient was treated in the emergency department and released later that day.

Is it an adverse event? Yes, allergic reaction is a untoward event in the study period.
Is it a serious adverse event? Unsure, would need medical records from ER to understand if allergic reaction reached the point of being life-threatening.
Was the event related? Yes, this is a known AE of MRNA covid vaccines.
Was the event expected? Yes, given this is a known AE, this is an expected event.
Is this an unanticipated problem No, this does not meet the UP criteria given the event is expected

Case Example 6

Participants enrolled in an RCT to treat cocaine use disorder are given a backpack by the study team as one of the rewards for abstinence in a contingency management intervention. One participant gave this backpack to his partner. His partner was approached by somebody who recognized the unique backpack and asked if she was also in the cocaine study. The partner was not aware that her partner was using cocaine and confronted him about his use of cocaine. The participant called study staff to discuss his distress over the incident.

Is it an adverse event? - Yes, distress is a untoward event in the study period.
Is it a serious adverse event? – No, distress does not meet the criteria of life threatening or other SAE criteria.
Was the event related? – Yes, the event was triggered by something that occurred in the study.
Was the event expected? – No, this is not a known event for the population or study procedures.
Is this an unanticipated problem? – Yes, because this was related, unexpected, and places the subject at risk that was not known before.

Resources

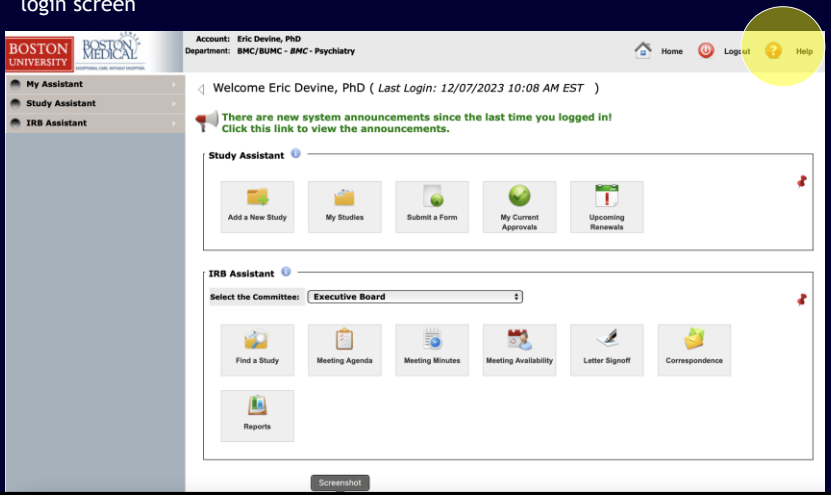
BUMC Clinical Research Resources Office
https://www.bumc.bu.edu/crro/

CRRO Best practice Study Documentation Templates and Tools
https://www.bumc.bu.edu/crro/tools/

NCI Common Terminology Criteria for Adverse Events
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Resources

Institutional Standard Operating Procedures (SOPs) for human research are available within INSPIR by clicking the question mark in the top right of your login screen



Questions