BU Clinical & Translational Science Institute (CTSI)

Research Professionals Network Workshop Series

REPORTING ADVERSE EVENTS (AE), SERIOUS ADVERSE EVENTS (SAE) AND UNANTICIPATED PROBLEMS (UP)

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Objectives

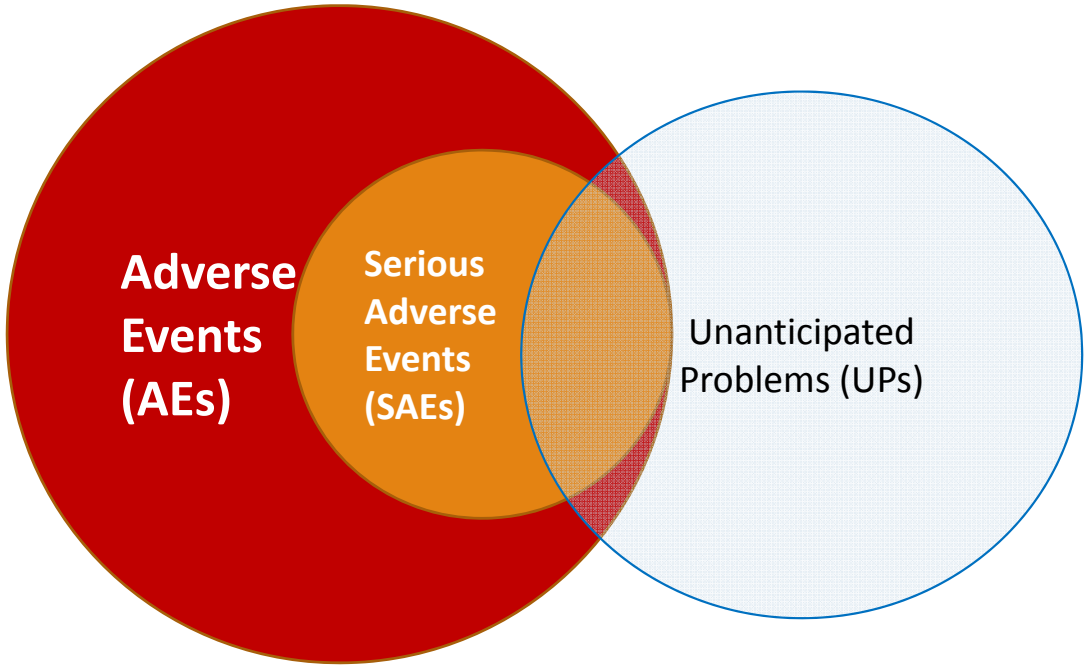
1) To be able to define an adverse event, serious adverse event, and an unanticipated problem
2) To understand how to document adverse events
3) To identify when an adverse event is reportable and to whom
4) To submit a reportable event to BUMC IRB via INSPIR II portal

Definitions

ADVERSE EVENT (AE)

SERIOUS ADVERSE EVENT (SAE)

UNANTICIPATED PROBLEM (UP)


Adverse Events (AEs)
Serious Adverse Events (SAEs)
Unanticipated Problems (UPs)

Where do definitions come from?

- International Conference on Harmonization, Good Clinical Practice (ICH GCP)
- BMC/BU Medical Campus Institutional Review Board (BUMC IRB)
  - Policies document: http://www.bumc.bu.edu/ohra/hrpp-policies/
- With industry sponsor, defined in clinical protocol

Which definition(s) should I follow?

- Are you using local BUMC IRB? If yes, follow BUMC IRB definitions & reporting guidelines
- Are you using a central IRB? If yes, follow their definitions & reporting guidelines
- Does your study have an industry sponsor? Follow sponsor's definitions per clinical protocol.
- Do you have an industry sponsor, but using BUMC IRB? Follow both sponsor and BUMC IRB definitions and reporting guidelines.

Adverse Event (AE)

BUMC IRB definition

Adverse Event (AE) is 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.

Example: A participant who has just given informed consent and completed screening assessments, but has not been randomized yet. The participant leaves the study visit and then gets in a car accident on the way home.

Would this be an AE? If so, why would it be important to record this as an AE?

How do AEs come up during study?

AEs *usually* come from:

- Physical complaint (headache, chest pain, etc…), either reported during an Adverse Event assessment or unprompted participant report
- Abnormal, clinically significant vital signs
- Abnormal laboratory results
- Hospitalization/ER visit
- Abnormal electrocardiograms (ECGs)
- Suicidality assessment (e.g. Columbia Suicidality Severity Rating Scale (C-SSRS))
- Other?

Adverse Event

"So I guess this probably counts as an adverse event."

Serious Adverse Event (SAE)

BUMC IRB definition

Serious Adverse Event (SAE) is any adverse event that

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient 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 (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).

Serious Adverse Event

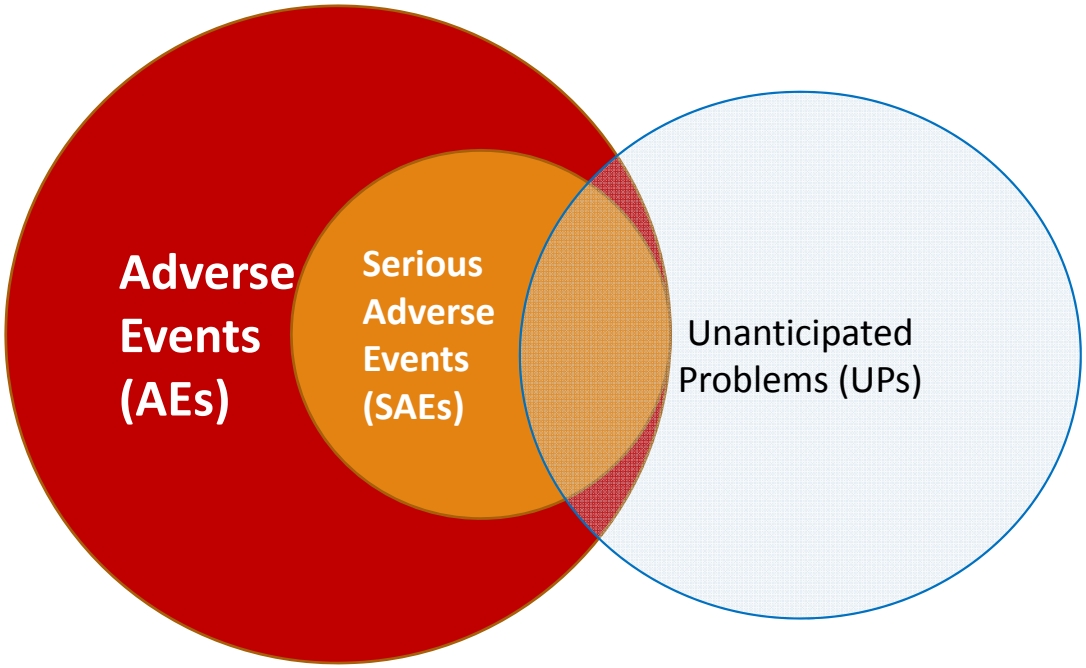
"I suppose this probably counts as an adverse event."

Unanticipated Problem (UP)

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

1. 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; AND
2. is 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.

How are these definitions interrelated?



Not all AEs are SAEs, but all SAEs are AEs.

An AE can be an UP without being a SAE.
AEs can be both UPs and SAEs.
Not all SAEs are UPs.

Some UPs are not AEs.

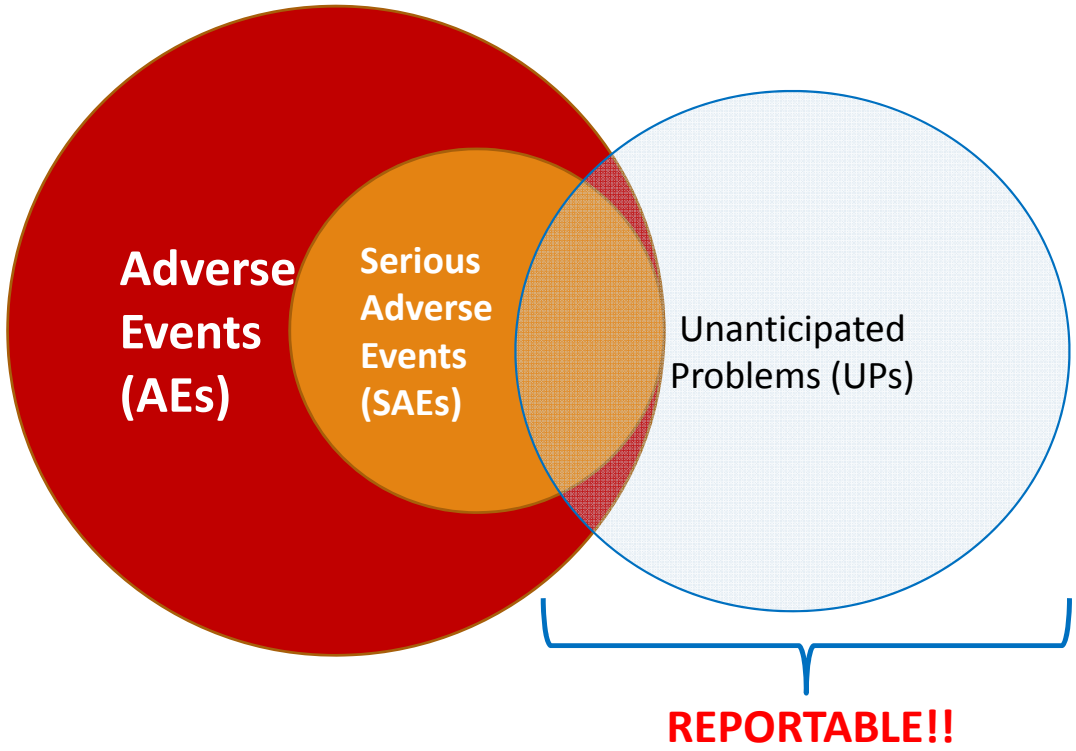
Reporting

ADVERSE EVENTS

SERIOUS ADVERSE EVENTS

UNANTICIPATED PROBLEMS

When is an AE a reportable event?

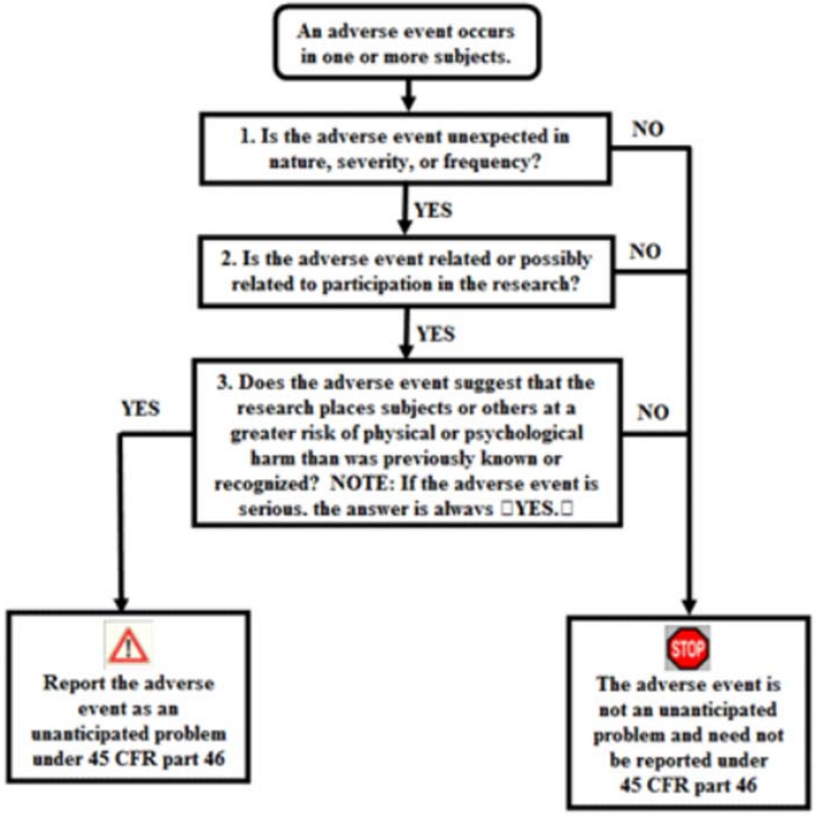


REPORT to BUMC IRB when an AE meets all 3 criteria to be an Unanticipated Problem

If an AE is an UP, it must be reported to BUMC IRB within 2 days of the investigator *learning of* the incident if fatal or life threatening, or within 7 days otherwise.

If an AE is not a UP, it is reported to IRB at the annual progress report/continuing review.

Determining Whether an Adverse Event is an Unanticipated Problem



A note about terminology

When a sponsor says to "report as an AE," they may actually be referring to *documenting* the AE…

- In the CRF
- In the database/eCRF

9.5.4 Reporting of Adverse Events, Serious Adverse Events, and Other Events of Interest

Adverse Events (AEs) and Serious Adverse Events (SAEs) have specific reporting procedures as listed in Appendix 1 and Appendix 2.

9.5.4.1 Reporting of Adverse Events

OVERVIEW

All AEs observed during the study will be reported on the Adverse Events/Side Effects Case Report Form (AE CRF) and in the REDCap data system. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study Informed Consent Form through the last visit. Serious AEs will be collected for 30 days after the last dose following early termination or at the Follow-up Visit, whichever comes later.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an AE should be reported as an AE on the CRF.

It is the responsibility of the local investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

It is the responsibility of the local investigator to review the results of the movement ratings scales: AIMS, BAS, and SAS each time they are completed and to determine if a result constitutes an AE.

It is also the responsibility of the local investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE.

Documentation of Adverse Events

Documentation Type	Purpose	Location
Adverse Event Assessment Form	To assess for presence of AEs in individual research participant	CRF/study binder
Note-to-File	To provide additional info via short narrative about the AE	CRF/study binder
Supporting documentation (e.g. medical record)	Additional source documentation of the AE	CRF/study binder *make sure to de-identify first!
Adverse Event Log	To track all AEs that happen throughout the course of the study	Submit to BUMC IRB at Continuing Review (annually)
Serious Adverse Event Form	To document details of SAE and any follow-up procedures.	Fax/email to sponsor within specified time period. File in participants' CRF/study binder

Adverse Event Assessment Form

ADVERSE EVENTS/SIDE EFFECTS FORM

Instructions: Record adverse events reported by the patient that are either new or ongoing. Severity of the adverse event or side effect may have varied over the rating period; please record the highest severity rating possible.

Serious Adverse Events (SAEs) and Immediately Reportable Events (IREs) must also be reported, immediately, on the SAE form.

Definitions:
Mild adverse event: Awareness of sign, symptom, or event, but easily tolerated.
Moderate adverse event: Discomfort enough to cause interference with usual activity and may warrant intervention.
Severe adverse event: Incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.

Ask the following questions for each commonly reported adverse event listed below:	**Code:** **0** = Absent **1** = Mild **2** = Moderate **3** = Severe			
1. **NAUSEA:** Have you had any problems with nausea?	0	1	2	3
2. **VOMITING:** Have you had any vomiting?	0	1	2	3
3. **SIALORRHEA:** Have you had any problems with excessive saliva or drooling?	0	1	2	3
4. **DRY MOUTH:** Have you had any problems with dry mouth?	0	1	2	3
5. **CONSTIPATION:** Have you had any problems with constipation?...moving your bowels?	0	1	2	3
6. **ORTHOSTATIC FAINTNESS:** Have you had any problems with lightheadedness or fainting when you get up from sitting down or lying in bed?	0	1	2	3

Ask the patient if he/she has any other complaints or problems to report and record responses below (if any). Assess each for expectedness, severity, and relatedness:					
20. **ADVERSE EVENT:**	**Expected** **Unexpected**		**Mild**	**Moderate**	**Severe**
	Definite	**Probable**	**Possible**	**Not likely**	**Not related**
21. **ADVERSE EVENT:**	**Expected** **Unexpected**		**Mild**	**Moderate**	**Severe**
	Definite	**Probable**	**Possible**	**Not likely**	**Not related**

Note-to-File

NOTE TO FILE

PI:

Date:
Subject ID: **1833-4**
Study Visit #: Stage 2—Month 3

On the morning of Monday we received the blood lab results for participant 1833-4 from his Stage 2—Month 3 visit. I brought the Study MD to review the results and make a determination regarding the clinical significance of results that were out of range. It was noted that one of the out of range values for the participant was his level of uric acid which was high (9.1 mg/dl). While Dr. did not feel that the result was clinically significant and required urgent care or removal of the subject from the study, she recommended that the PCP of the participant be contacted as to this lab abnormality. The same morning, the PCP was contacted by me, and notified of the result, in addition to the PI. Any subsequent medical intervention or additional clinical care the participant requires due to this issue will be noted in the case report form in a follow up note to file.

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Adverse Event Log

Log template downloaded from CRRO website: http://www.bumc.bu.edu/crro/regulatory/regulatory-binder/

[1]SAE Classification: AE is an SAE if it meets any of the criteria below:		[2]Severity Grade	[3]Unanticipated problem: If AE meets all three criteria below report to IRB within 2 days
Results in death	Results in disability or incapacity	1-Mild AE (not requiring treatment)	1. Unexpected in terms of nature of severity.
Life threatening	Congenital anomaly/birth defect	2-Moderate AE (resolved with treatment)	2. Related/possibly related to the research.
Requires/prolongs hospitalization	Medically important event	3-Severe AE (inability to carry on normal activities/required professional medical attention)	3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.
		4- Severe: life-threatening or disabling AE	
		5-Death	

Internal AE/UP Report Tracking Log

This log tracks assessment and reporting of internal AEs. AEs should be assessed for seriousness, severity, whether or not they are expected, and whether they are related. From this information, a determination of expedited reporting can be made. Events that are serious (OR pose a greater risk of harm than was previously known or recognized), at least possibly related to the research, and unexpected are Unanticipated Problems (UPs) and must be reported within two days to the BUMC IRB. The sponsor may have different reporting requirements. Other events (non-UPs) should be reported to the IRB at the time of the progress report. If the study is monitored by an outside independent monitoring committee then their report(s) will suffice instead of an AE summary at the time of the progress report. Investigators monitoring their own studies may use this log to submit to the IRB at the time of progress report. Please refer to the BU AE Reporting policy at: http://www.bumc.bu.edu/Dept/Content.aspx?DepartmentID=293&PageID=9923.

Ptp ID	Date AE	AE description	SAE?[1] (y/n)	Relationship with study intervention, per MD (i.e. *Definite, Probable, Possible, Unlikely*)	Expected? (y/n)	Severity Grade[2]	UP?[3] (y/n)	Date reported to sponsor (if applicable)	IRB reporting (expedited for UPs, vs. progress report)

Sheet1 Sheet2 Sheet3

(Serious) Adverse Event reporting form

9.5.4.2 Reporting of Serious Adverse Events

OVERVIEW

All SAEs and events of interest, regardless of their relationship to study treatment, must be reported to the Coordinating Center within 1 business day from the date the local investigator becomes aware of the event.

Deaths and life-threatening events should be reported immediately by telephone to the Coordinating Center. The immediate report should be followed up within 1 business day by emailing or faxing the completed SAE CRF.

Preliminary SAE CRFs should be followed as soon as possible by detailed descriptions, including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

To whom do you report AEs/SAEs/UPs?

BUMC IRB, or the IRB of record

The study sponsor/coordinating center

The FDA

Keep in mind that different entities may have different (though usually similar) reporting criteria, timeframes, forms and/or processes.

Reporting AEs to BUMC IRB

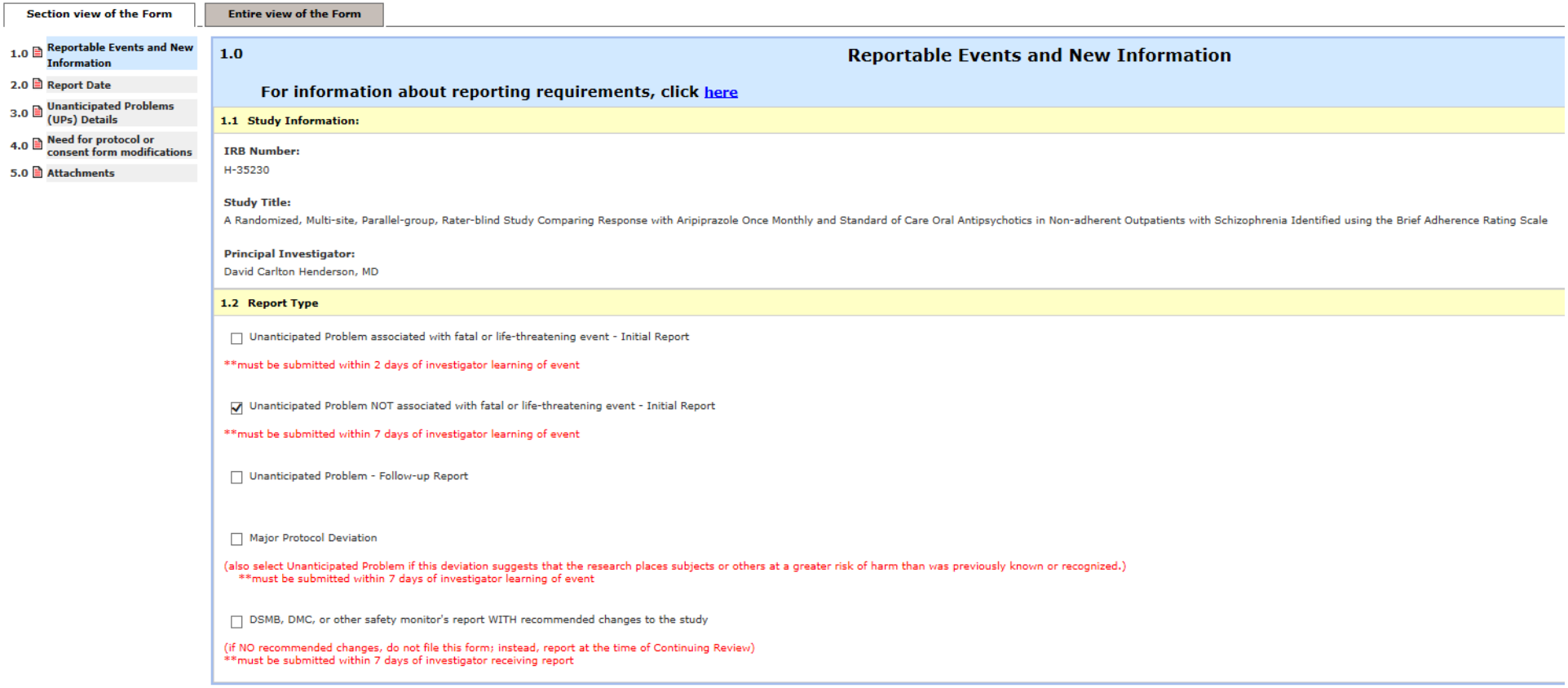
Protocol Items

Protocol Items
Study Application
Informed Consent ▸
Other Study Documents ▸

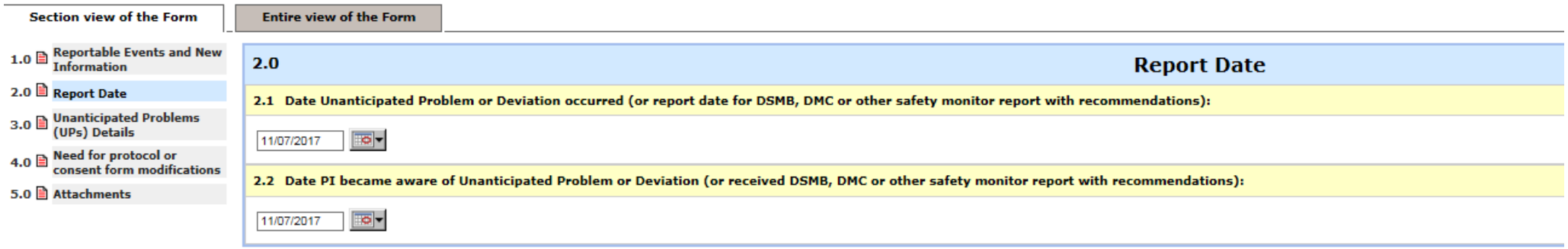
Submission Forms

Available Forms
Change Request and Amendments
Continuing Review Submission Form
Final/Closure Report Form
Initial Review Submission Form
Internal Study Personnel Changes
Protocol Exception Form
Reportable Events and New Information Form

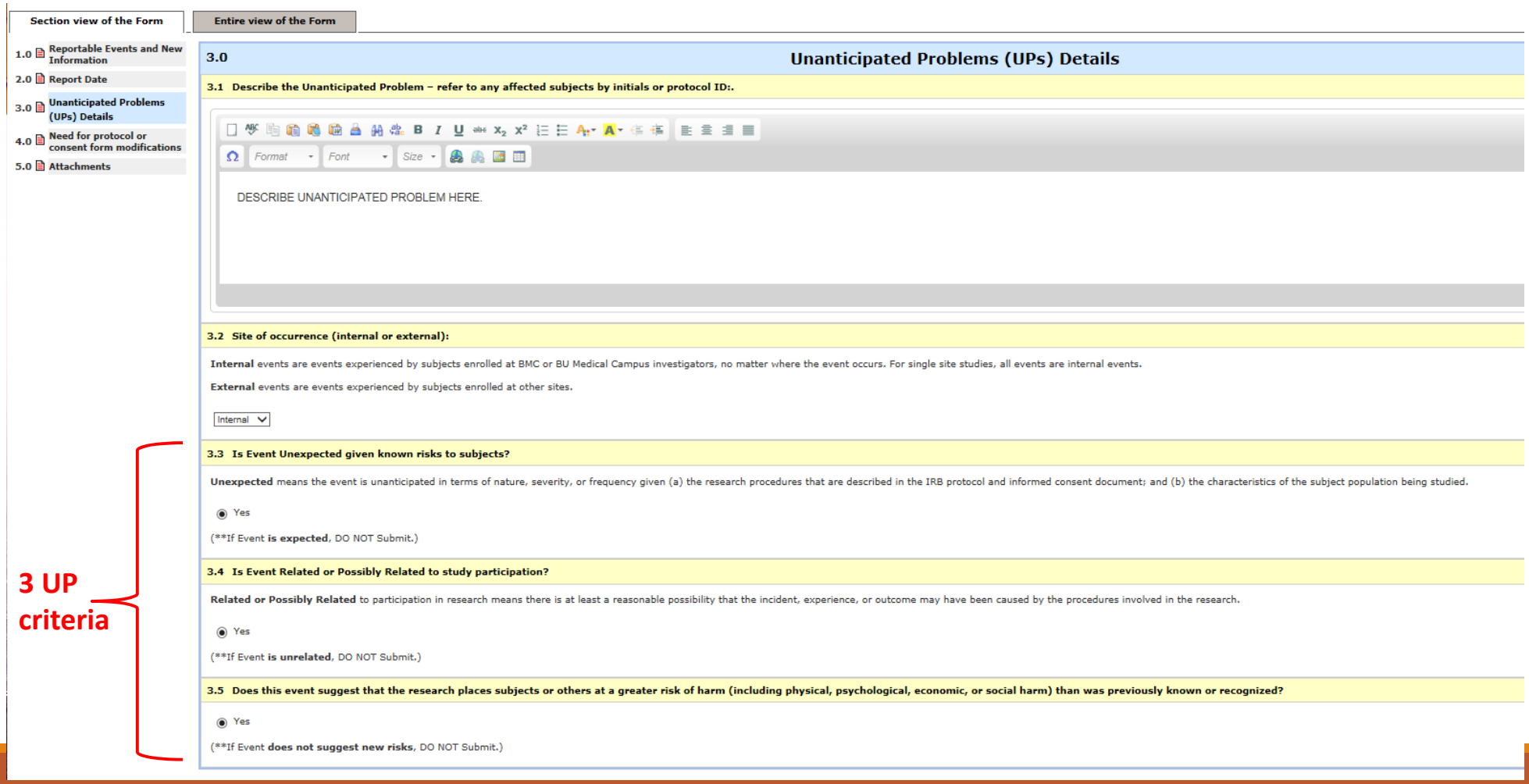
1.0 Reportable Events



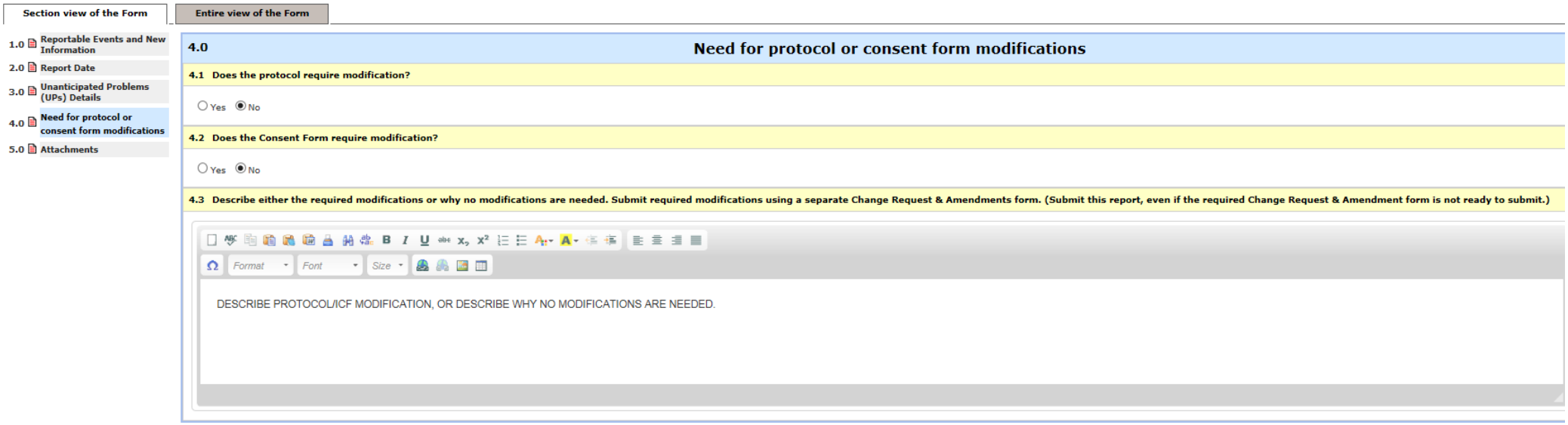
2.0 Report Date



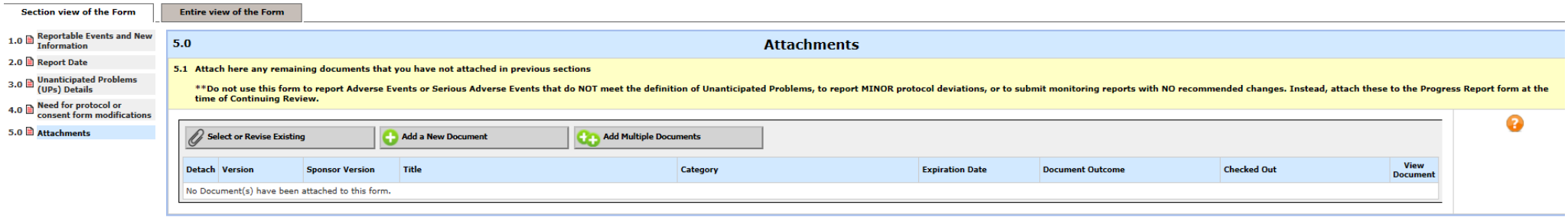
3.0 Unanticipated Problem Details



4.0 Need for protocol/ICF modifications



5.0 Attachments (modified protocol/ICF)



This is confusing!

Yes, it is! Refer back to the BUMC IRB policy, study protocol, Manual of Procedures, etc…

Ask your fellow RAs/coordinators, project/program manager, ask the IRB, ask the CRRO – it is always better to ask than guess!

For More Information

For more information on reviewing and reporting unanticipated problems, visit the Office for Human Research Protections (OHRP) and the Department of Health and Human Services (HHS) webpage

https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html

GROUP EXERCISE