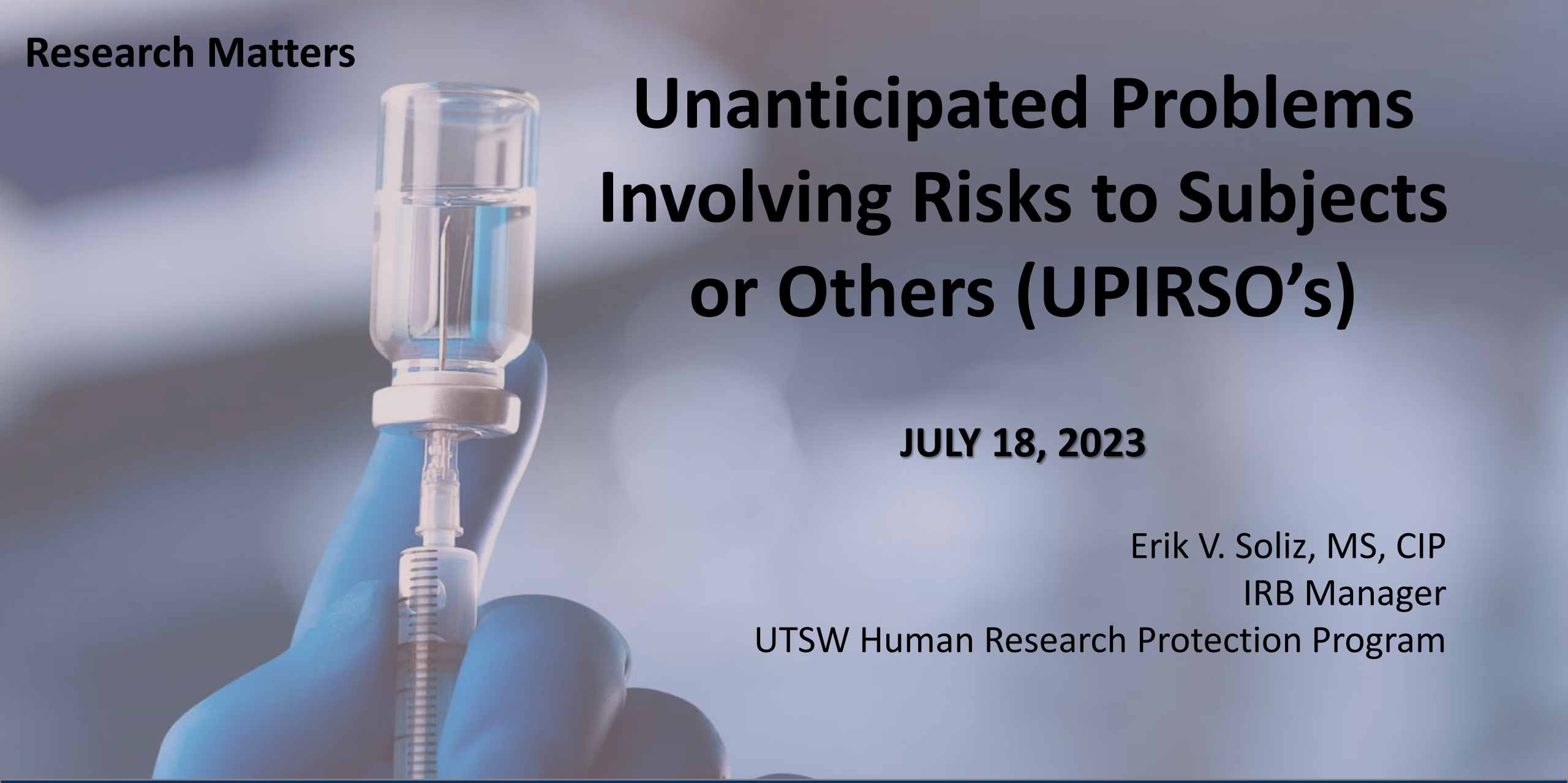
Research Matters



Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO's)

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WHAT WE WILL COVER

- Define Unanticipated Problems
- Define Adverse Event and Non-AE Event
- Define UPIRSO & UADE
- Reporting of AE/Non-AE and UPIRSO & UADE
- AE/Non-AE and UPIRSO & UADE Examples
- Questions?

Regulations

Department of Health & Human Services (HHS)

- *(45 CFR 46.103(a)).* Ensuring **prompt reporting of unanticipated problems** to the IRB, appropriate institutional officials, any supporting department or agency head (or designee), and OHRP. The purpose of prompt reporting is to ensure that appropriate steps are taken in a timely manner to protect other subjects from avoidable harm.

- *45 CFR 46.103(b)(5)* Require written procedures for ensuring prompt reporting to the IRB…**unanticipated problems involving risks to subjects or others** with this policy or the requirements or determinations of the IRB…

Food and Drug Administration (FDA)

- *21 CFR 312.53(c)(1)(vii), Requires the Investigator to promptly report to the IRB all changes in the research activity and all* **unanticipated problems involving risks to human subjects or others**

- *21 CFR 812.3(s))* IDE regulations require reporting of **unanticipated adverse device effects (UADE)** to the IRB

- *21 CFR 56.108(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1)* ***Any unanticipated problems involving risks to human subjects or others***

What are Unanticipated Problems?

In the conduct of research, there may arise types of incidents, experiences, and outcomes.

- Unexpected
- May be related or unrelated
- Unanticipated problems may or may not be adverse events.
- Unanticipated problems may involve an increased risk of harm to participants
- Unanticipated problems may not involve actual harm to participants

What are Adverse Events (AEs)?

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 or not serious
- Physical and psychological harms
- Commonly occur in biomedical research
- Occasionally occur in social and behavioral research
- May be a UPIRSO

What are Non-Adverse Events?

- Can be related or unrelated
- These events may also suggest that the research places subjects or others at a greater risk psychological, economic, or social harm than was previously known or recognized
- Non-adverse events are those that do not involve a reaction to a study drug
- Do not involve physical harm
- May be a UPIRSO

What are Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)?

Unanticipated problems, in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure (IB), protocol, or informed consent document), AND

2. Definitely or probably related to participation 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.

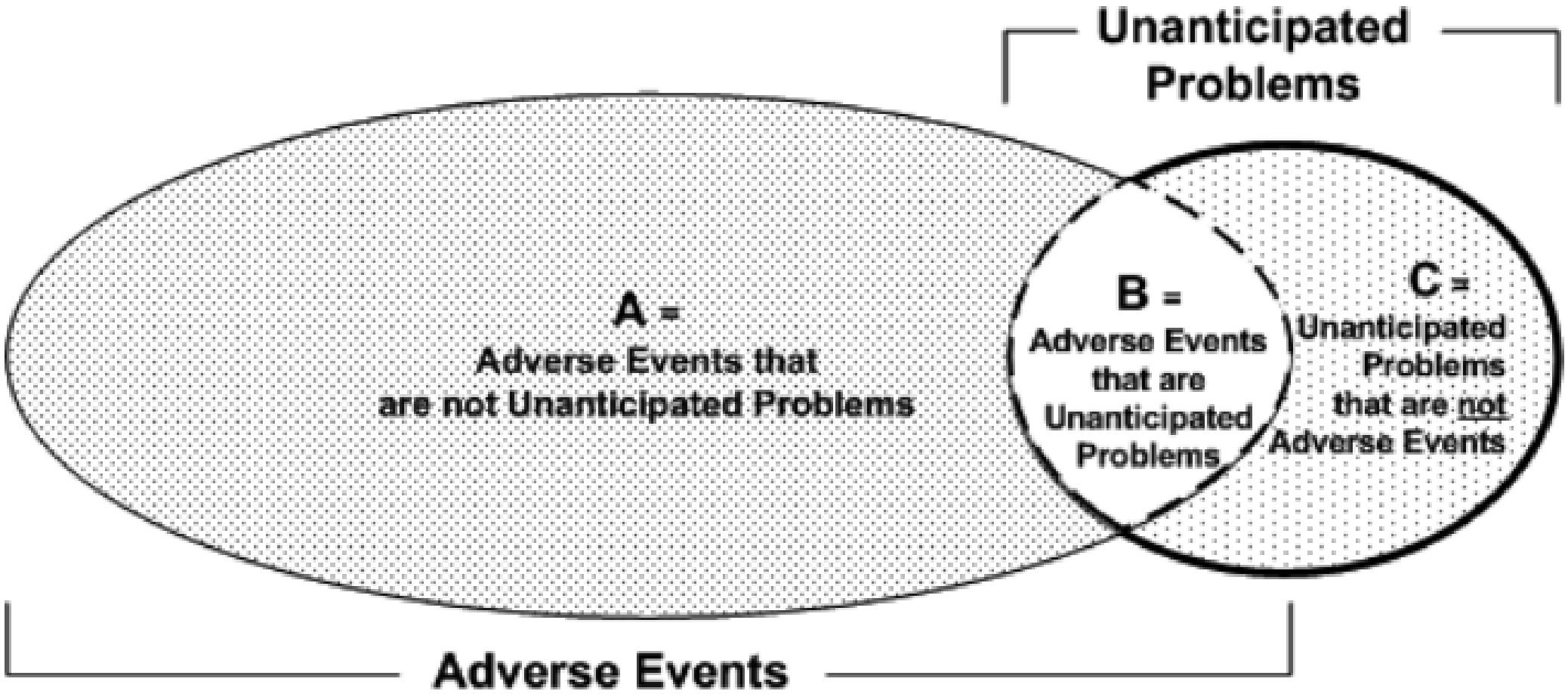
NOTE: Any incident, experience, or outcome meeting this criteria will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

What is an Unanticipated Adverse Device Effect (UADE)?

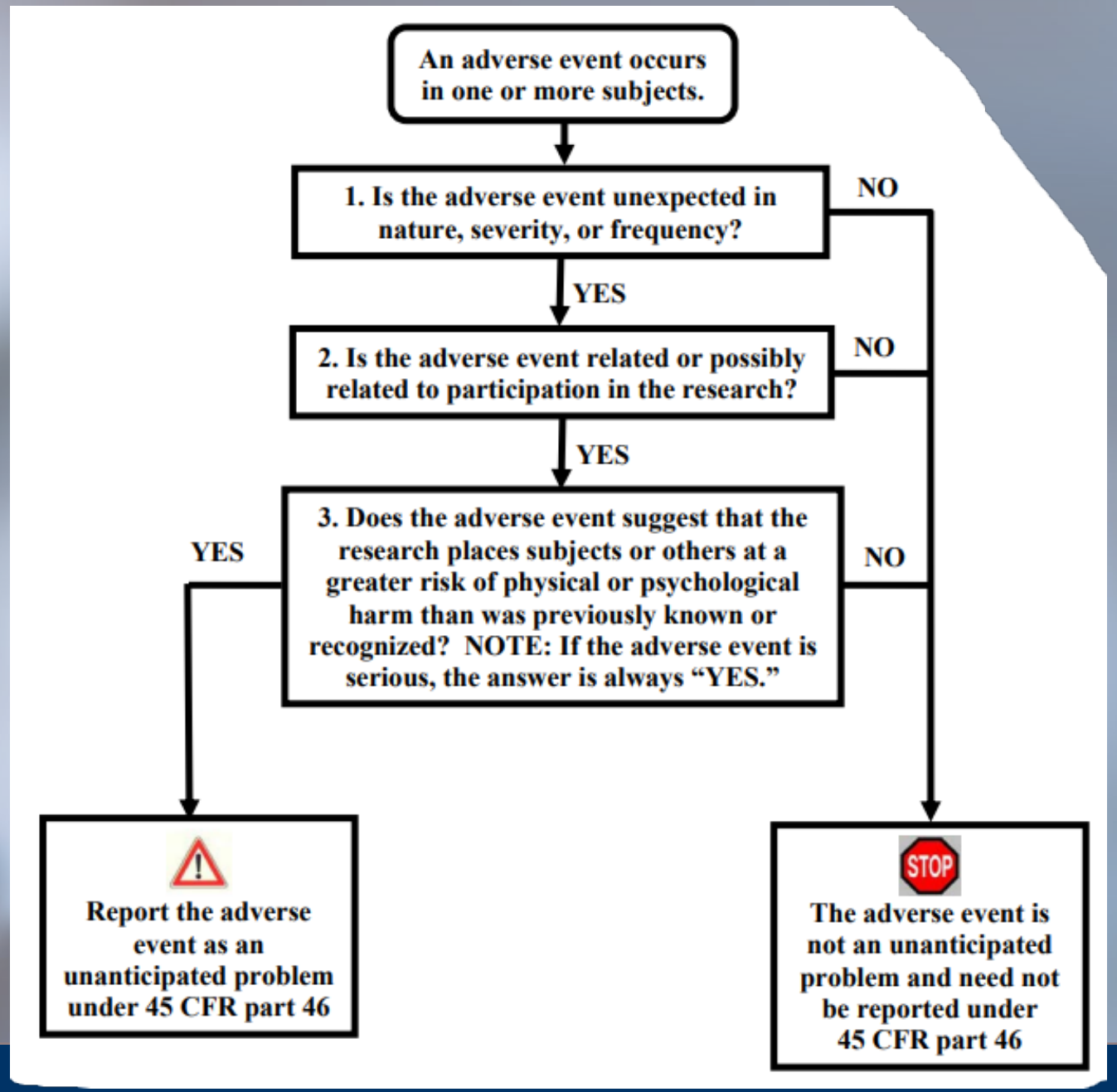
Unanticipated Adverse Device Effect - UADE:

- 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

Determining Which AE's are Unanticipated Problems?

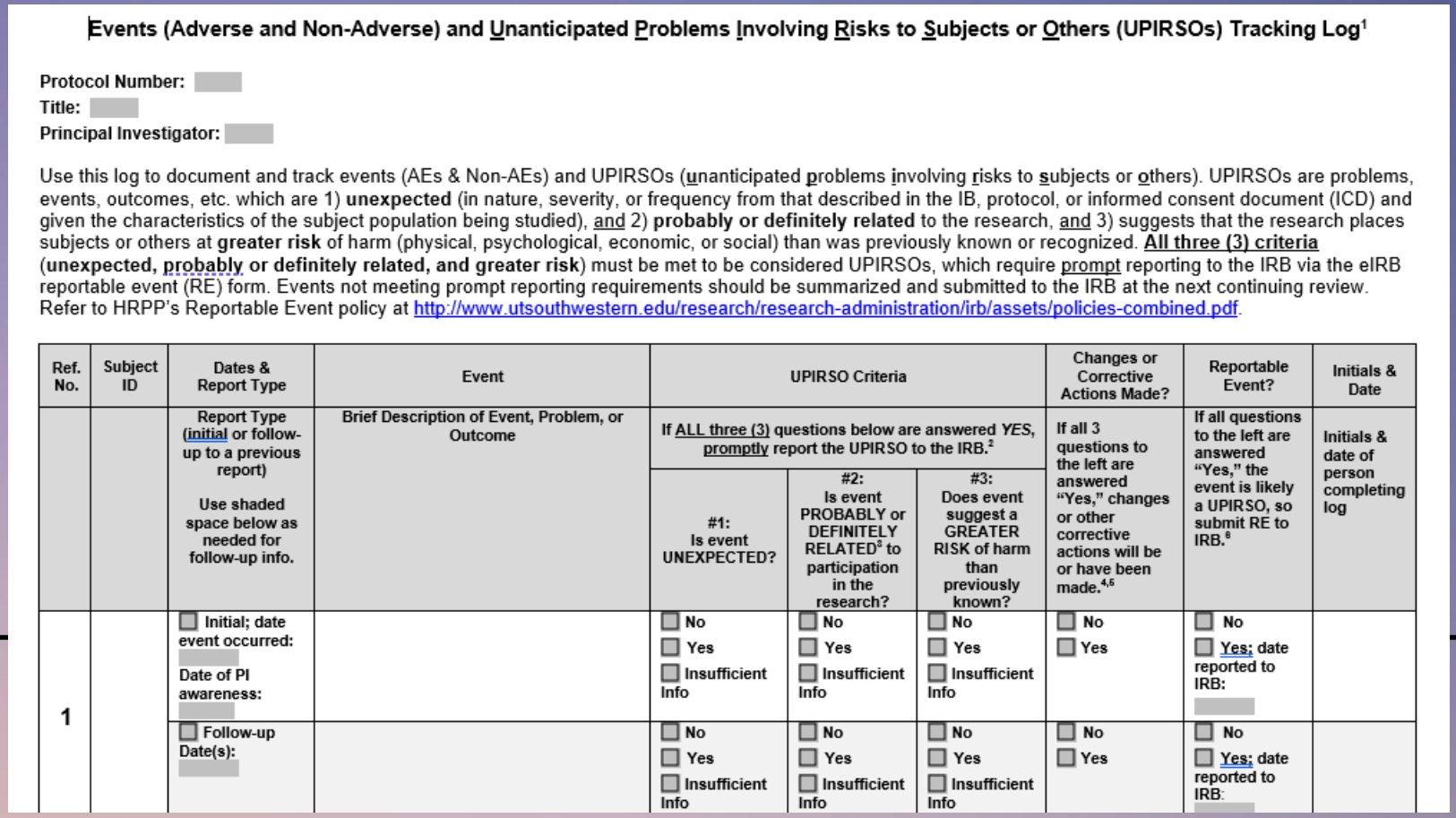


How to determine whether an adverse event is unanticipated?



Tracking AE's & UPIRSO's

- Adverse Events and UPIRSO's should be tracked
  - Help with prompt reporting of unanticipated events and reporting adverse events at the time of continuing review
  - To assist with local data safety monitoring



Events (Adverse and Non-Adverse) and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) Tracking Log[1]

Protocol Number:
Title:
Principal Investigator:

Use this log to document and track events (AEs & Non-AEs) and UPIRSOs (unanticipated problems involving risks to subjects or others). UPIRSOs are problems, events, outcomes, etc. which are 1) **unexpected** (in nature, severity, or frequency from that described in the IB, protocol, or informed consent document (ICD) and given the characteristics of the subject population being studied), and 2) **probably or definitely related** to the research, and 3) suggests that the research places subjects or others at **greater risk** of harm (physical, psychological, economic, or social) than was previously known or recognized. **All three (3) criteria (unexpected, probably or definitely related, and greater risk)** must be met to be considered UPIRSOs, which require prompt reporting to the IRB via the eIRB reportable event (RE) form. Events not meeting prompt reporting requirements should be summarized and submitted to the IRB at the next continuing review. Refer to HRPP's Reportable Event policy at http://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combined.pdf.

Ref. No.	Subject ID	Dates & Report Type	Event	UPIRSO Criteria			Changes or Corrective Actions Made?	Reportable Event?	Initials & Date
		Report Type (initial or follow-up to a previous report) Use shaded space below as needed for follow-up info.	Brief Description of Event, Problem, or Outcome	If ALL three (3) questions below are answered *YES*, promptly report the UPIRSO to the IRB.[2] #1: Is event UNEXPECTED?	#2: Is event PROBABLY or DEFINITELY RELATED[3] to participation in the research?	#3: Does event suggest a GREATER RISK of harm than previously known?	If all 3 questions to the left are answered "Yes," changes or other corrective actions will be or have been made.[4,5]	If all questions to the left are answered "Yes," the event is likely a UPIRSO, so submit RE to IRB.[6]	Initials & date of person completing log
1		☐ Initial; date event occurred: Date of PI awareness:		☐ No ☐ Yes ☐ Insufficient Info	☐ No ☐ Yes ☐ Insufficient Info	☐ No ☐ Yes ☐ Insufficient Info	☐ No ☐ Yes	☐ No ☐ Yes; date reported to IRB:	
		☐ Follow-up Date(s):		☐ No ☐ Yes ☐ Insufficient Info	☐ No ☐ Yes ☐ Insufficient Info	☐ No ☐ Yes ☐ Insufficient Info	☐ No ☐ Yes	☐ No ☐ Yes; date reported to IRB:	

Tracking AE's & UPIRSO's

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  - Help with prompt reporting of unanticipated events and reporting adverse events at the time of continuing review
  - To assist with local data safety monitoring

Ref. No.	Subject ID	Dates & Report Type	Event	UPIRSO Criteria			Changes or Corrective Actions Made?	Reportable Event?	Initials & Date
		Report Type (initial or follow-up to a previous report) Use shaded space below as needed for follow-up info.	Brief Description of Event, Problem, or Outcome	If ALL three (3) questions below are answered *YES*, promptly report the UPIRSO to the IRB.[2]			If all 3 questions to the left are answered "Yes," changes or other corrective actions will be or have been made.[4,5]	If all questions to the left are answered "Yes," the event is likely a UPIRSO, so submit RE to IRB.[6]	Initials & date of person completing log
				#1: Is event UNEXPECTED?	#2: Is event PROBABLY or DEFINITELY RELATED[3] to participation in the research?	#3: Does event suggest a GREATER RISK of harm than previously known?			
1		☒ Initial; date event occurred: 06/01/2023 Date of PI awareness: 06/21/2023	Anaphylactic shock	☐ No ☒ Yes ☐ Insufficient Info	☐ No ☒ Yes ☐ Insufficient Info	☐ No ☒ Yes ☐ Insufficient Info	☐ No ☒ Yes	☐ No ☒ Yes; date reported to IRB: 06/24/2023	ES
		☐ Follow-up Date(s):		☐ No ☐ Yes ☐ Insufficient Info	☐ No ☐ Yes ☐ Insufficient Info	☐ No ☐ Yes ☐ Insufficient Info	☐ No ☐ Yes	☐ No ☐ Yes; date reported to IRB:	

Reporting of Adverse Events (AE's and Non-AE's)

- Prompt Reporting of AE's or Non-AE's that do not meet the criteria for UPIRSOs to the IRB is NOT required and should be reported at the time of continuing review.

- All non-UPIRSO adverse events should be reported at the time of continuing review in Section 8.0 of the CR Smartform

8.0 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)

Review your study records related to UPIRSOs since the last continuing review to answer the following questions. If other sites are relying on the UTSW IRB, include UPIRSOs from all sites.

* **8.1 Taking into consideration all experiences and safety-related information, have any problems (AE or non-AE) occurred (locally or externally if multi-center) since the last continuing**

● Yes ○ No Clear

* **8.1.1 Are the nature, frequency, and/or severity of the problems unanticipated? (in order to determine frequency, you should consider all AE's and Non-AE's that have occurred since**
Select Yes when there have been unanticipated problems (i.e., events are not listed in protocol or consent form(s); occurred more often or more seriously than expected; or considerin
of the population, occurred more often or were more serious than expected).
Select No when problems have occurred as anticipated (i.e., events are listed in protocol or consent form(s), or considering the underlying condition of the population, the events are e

● Yes ○ No Clear

* **8.1.2 Were any of the unanticipated problems identified in question 8.1.1 at least probably related to the research?**
Answer Yes when there have been unanticipated problems that are probably or definitely related; otherwise, answer No.

○ Yes ● No Clear

Reporting of Unanticipated Problems (AE/Non-AE or UADE)

- Report to the IRB within ***5 days*** of the PI becoming aware of the occurrence using the Reportable Event Form
- All unanticipated problems should also be noted at the time of continuing review in Section 8.0 of the CR Smartform
- This pertains to both unanticipated problems that are adverse events and non-adverse events.
- This includes UADEs

8.0 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)

Review your study records related to UPIRSOs since the last continuing review to answer the following questions. If other sites are relying on the UTSW IRB, include UPIRSOs from all sites.

* **8.1 Taking into consideration all experiences and safety-related information, have any problems (AE or non-AE) occurred (locally or externally if multi-center) since the last continuing review?**
● Yes ○ No Clear

* **8.1.1 Are the nature, frequency, and/or severity of the problems unanticipated? (in order to determine frequency, you should consider all AE's and Non-AE's that have occurred since the study started)**
Select Yes when there have been unanticipated problems (i.e., events are not listed in protocol or consent form(s); occurred more often or more seriously than expected; or considering the underlying condition of the population, occurred more often or were more serious than expected).
Select No when problems have occurred as anticipated (i.e., events are listed in protocol or consent form(s), or considering the underlying condition of the population, the events are expected).
● Yes ○ No Clear

* **8.1.2 Were any of the unanticipated problems identified in question 8.1.1 at least probably related to the research?**
Answer Yes when there have been unanticipated problems that are probably or definitely related; otherwise, answer No.
● Yes ○ No Clear

* **8.1.3 Have the unanticipated and probably related problems been serious or do they suggest a greater risk than previously known?**
Answer Yes when the unanticipated and probably related problems are serious or suggest a greater risk than previously known; otherwise, answer No.
● Yes ○ No Clear

* **8.2 Did you report all UPIRSOs in the past year – even if the IRB determined the event was not a UPIRSO?**
● Yes ○ No Clear

Examples – Adverse Event

Participant 899 experiences an event of cardiac arrest. The consent form, protocol, and investigator's brochure (IB) list cardiac arrest is a risk of the study drug. The Sponsor (industry or sponsor-investigator) assesses that cardiac arrest as related to the administration of study drug.

- **Expected**
- **Related – While this event is related to the study, drug we know it is expected**
- **Report this event at the time of the next continuing review**

Examples – AE UPIRSO

Participant 123 experiences an event of anaphylactic shock. The consent form, protocol, or investigator's brochure (IB) for drug xyz does not list the risk of anaphylactic shock. The Sponsor (industry or sponsor-investigator) assesses that anaphylactic shock as definitely related to the administration of study drug xyz.

- **Unexpected – it is not a risk listed in the consent form, protocol, or IB**
- **Related – definitely**
- **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**
- **Promptly report within 5 business days of the PI becoming aware of the event via an RE submission. And ensure the CR Smartform is consistent with this.**

Examples – Non-AE UPIRSO

Clinical Trial studying "everything" involves payment to participants for time and effort in study participation. An internal audit finds that 20 participants were never paid.

- **Unexpected – Not paying participants is an unexpected event as payment to participants is an expectation of study participation.**
- **Related – definitely related to the research.**
- **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**
- **Promptly report within 5 business days of the PI becoming aware of the event via an RE submission. And ensure the CR Smartform is consistent with this.**

Examples

Clinical Trial studying an investigational device that stimulates the vagus nerve to prevent focal or partial seizures in participants that do not respond to seizure medications. During the research procedure for a participant the device did not execute and in turn did not stimulate the vagus nerve and the participant experiences a seizure.

- **Unexpected – the device failed to execute which is an unanticipated serious problem associated with the device**
- **Related – definitely related to the research.**
- **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**
- **Promptly report within 5 business days of the PI becoming aware of the event via an RE submission. And ensure the CR Smartform is consistent with this.**

Medical Center

HRPP Reportable Event Guidance#

Exception[1] (also called single-subject waiver)

Any change **NOT due to an emergency** that is:
- intentional on part of the investigator; ***or***
- in the investigator's control; ***or***
- not intended as a systemic change; ***or***
- in ***rare instances***, intended as a systemic change, but the change has not yet been IRB-approved

→ **Obtain IRB approval BEFORE implementing** (call if urgent)

Emergency Deviation*

Any change (deviation) without prior IRB approval intended to:
- eliminate an apparent immediate hazard to subjects, ***or***
- for IDE studies only: protect the life or physical well-being of a subject in an emergency[5]

Serious Noncompliance*

Any noncompliance that:
- increases risk of harm to subjects; **and/or**
- adversely affects the rights, safety, or welfare of subjects; **and/or**
- adversely affects the integrity of the data or research (i.e., substantially compromises the integrity, reliability, or validity of the research)

Continuing Noncompliance*

- A pattern of repeated noncompliance (in one or more protocols simultaneously or over time) which continues **after** initial discovery
- Includes inadequate efforts to take or implement corrective or preventive actions within a reasonable timeframe

UPIRSO*[2] (unanticipated problems involving risks to subjects or others)

An event that meets **ALL three (3)** of the following criteria:
1. Unexpected (in nature, severity, or frequency), ***AND***
2. Probably or definitely related to the research, ***AND***
3. Suggests the **research** places subjects or others at a greater risk of harm than previously known or recognized

Complaint*

- Research-related complaint made by subjects or others that affect subjects' rights, safety, or welfare

→ **Report via RE within 5 working days of discovery**

All other research-related events and reports[3]

Includes, but is not limited to:
- Noncompliance events (e.g., deviations) that do **not** meet the UTSW HRPP definition of either serious or continuing noncompliance
- AEs/SAEs that do not meet **ALL 3** UPIRSO criteria
- Events/reports the sponsor wants submitted to the UTSW IRB/HRPP
- Data safety monitoring (DSMB/DMC/DSC) reports
- Other safety reports (e.g., IND/IDE, MedWatch, CIOMS)
- Monitoring/audit reports
- Any other new information since the last IRB/HRPP review

→ **Track, evaluate, and summarize at CR or notice of study closure, whichever comes first[4]**

Prompt Reporting of Unanticipated Problems to the IRB

UT Southwestern Medical Center

Resources

Reportable Events Guidance

HHS AE & UPIRSO Guidance

AE and UPIRSO Tracking Log

FDA AE, UPIRSO, UADE Guidance

Thank You!

- **We'd love to hear your feedback.** We invite you to provide your evaluation of Research Matters and of the Human Research Protection Program.

- Visit: https://ais.swmed.edu/redcap/surveys/?s=3PRJFCFJJW