

Safety Information and Unanticipated Problems Reporting

Quorum
REVIEW IRB



Objectives

This presentation will address the following issues:

- What events must be promptly reported to the Quorum Review institutional review board
- When and how such events must be reported
- Why it is important to promptly report certain reports to the Board
- How to report serious events, major protocol deviations and other significant unanticipated problems to Quorum Review IRB.

Investigators confront a variety of events that may be reportable to the sponsor of the research or the IRB / REB

Unrelated adverse events

Major protocol deviations

Expected adverse events



Minor protocol deviations

Minor adverse events

New safety information

Significant adverse events

Unanticipated Problems

Sponsors and IRB / REBs have different regulatory reporting requirements

Sponsor

- Regulations require sponsors to monitor **all** adverse events (AEs) experienced by a study's participants.

IRB /REB

- Regulations require an IRB/REB to develop procedures to ensure prompt reporting of “unanticipated problems involving risk to human subjects or others.”

Sponsors monitor all adverse events experienced by a study's participants

- Sponsors monitor minor, serious, expected, unexpected, related and unrelated AEs
- Sponsor perform data analysis and trending for the study
- Sometimes sponsors delegate data monitoring to a separate entity, such as a data safety monitoring board (“DSMB”)
- Sponsors must report their findings at least annually to the FDA

Investigator reporting requirements to sponsors and IRB / REBs are different

Sponsor

- Investigators generally must report ***all adverse events*** to the sponsor of the clinical trial.
- The investigator's reporting requirements are set forth in the protocol for the study.

IRB / REB

- Investigators must report ***all unanticipated problems involving risk*** to human subjects or others to the IRB/REB.

The definition of an unanticipated problem involving risk is left to the IRB / REB

- The regulations do not provide a definition for “unanticipated problems involving risk”
- IRB / REBs must establish their own definition and procedures for investigators to report unanticipated problems involving risk

Quorum's definition of an unanticipated problem

- An unanticipated problem involving risk is an unexpected event that:
 - Potentially increases risk to participants or others;
 - Adversely affects the rights, safety or welfare of the participants; or
 - Adversely affects the integrity of the study
- The investigator's judgment is needed to identify an unanticipated problem involving risk

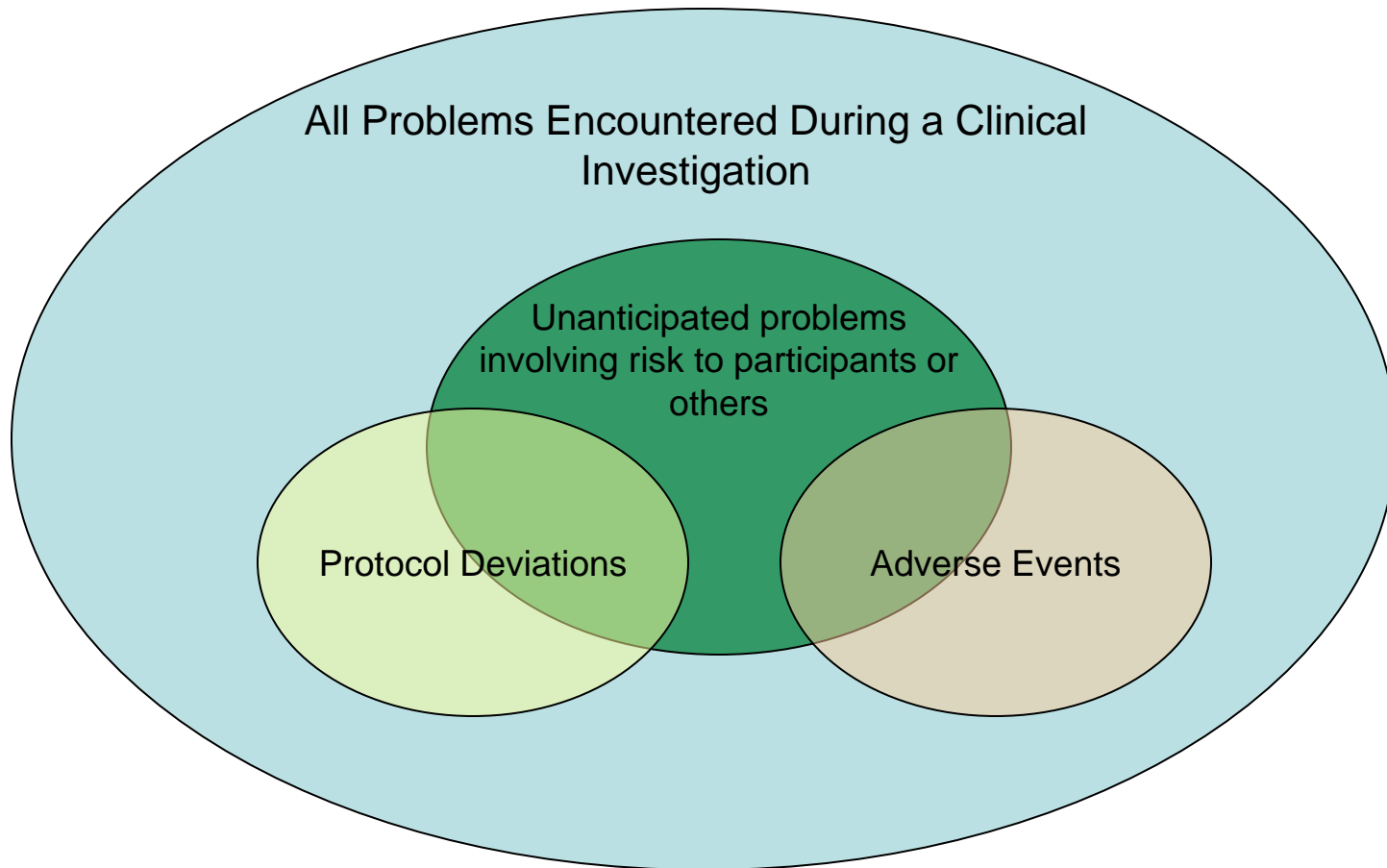
Prompt reporting of unanticipated problems allows the IRB / REB members to decide whether:

- The risk/benefit ratio of the study is still acceptable in light of this new information
- Modifications should be made to the study to minimize risk to participants
- Participants should be informed of potential risks or findings
- The study should be suspended or terminated

Quorum's policy regarding reportable events

- Quorum's position is that unanticipated events that possibly involve risk are reportable events that must be reported promptly to the IRB / REB
- A reportable event must be reported ***within 10 business days*** of the investigator becoming aware of the event
- Reportable events must be reported using Quorum's report forms.

Report only unanticipated problems involving risk to participants or others



What events to report

- Serious Adverse Events
- Major Protocol Deviations
- Other reportable events as defined by Quorum (including new safety information and significant unanticipated problems)

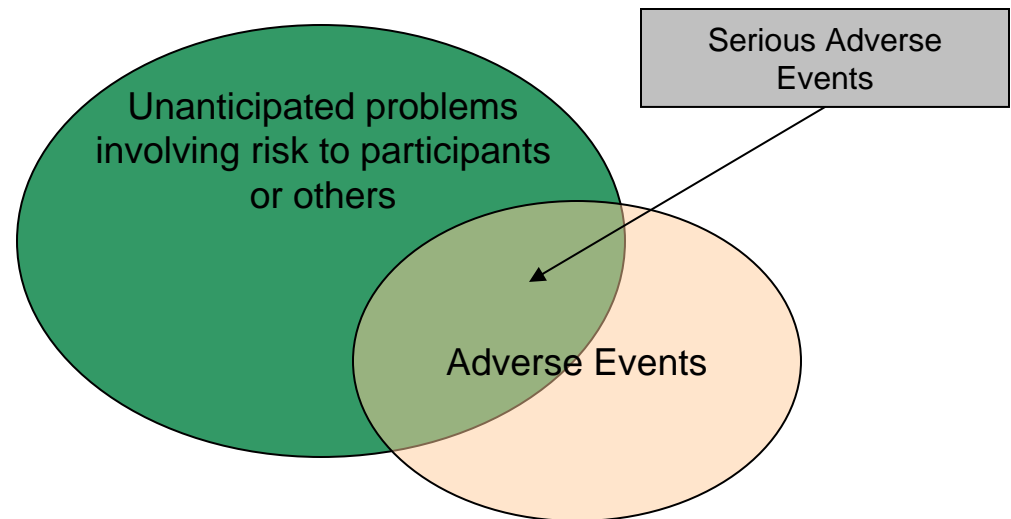
What events to report...a closer look

- ***Serious Adverse Events***
- Major Protocol Deviations
- Other reportable events as defined by Quorum (including new safety information and significant unanticipated problems)

Quorum's definition of a Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is an adverse event that, in the investigator's judgment is

- Serious,
- Unanticipated, and
- At least possibly related to the study product or device



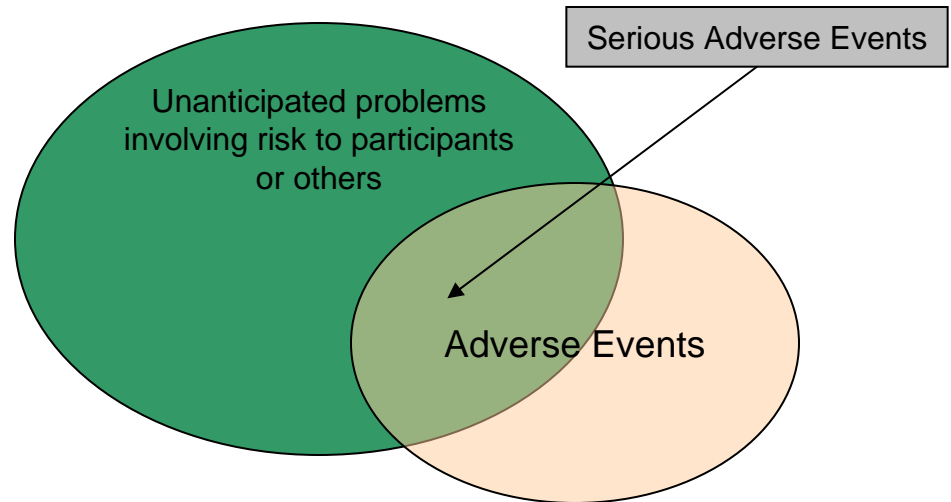
What makes an SAE serious?

In the investigator's judgment it...

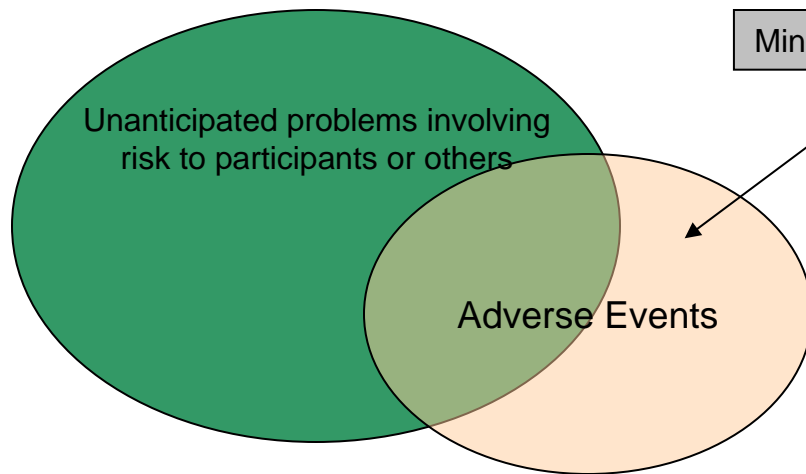
- Results in death
- Is life threatening (places the participant at immediate risk of death)
- Results in persistent or significant disability/incapacity (a substantial disruption of the participant's ability to conduct normal life functions),
- Results in, or prolongs an existing, inpatient hospitalization
- Is a congenital anomaly/birth defect, or
- Jeopardizes the participant or requires intervention to prevent one of the outcomes listed above

Quorum's policy on reporting serious adverse events to the IRB / REB

- An investigator should report to the IRB / REB all serious adverse events that occur at his or her site.



Investigators do not need to report minor, expected, or unrelated adverse events to the IRB / REB



Examples of adverse events not reportable:

- A minor headache, even if probably caused by the study drug
- A worsening of the underlying disease condition, if such worsening was expected
- A MedWatch report that, in the PI's judgment, reports a risk that is probably not related to the PI's study

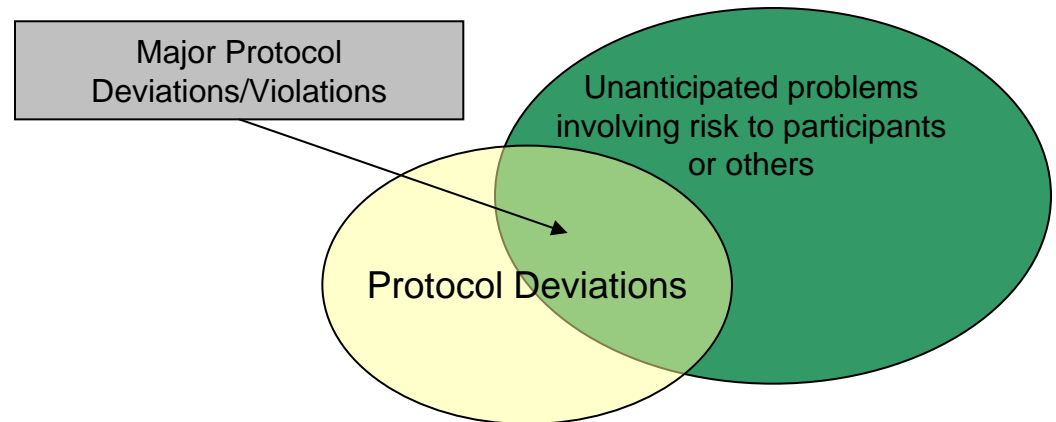
What events to report...a closer look

- Serious Adverse Events
- ***Major Protocol Deviations***
- Other reportable events as defined by Quorum (including new safety information and significant unanticipated problems)

Quorum's definition of a Major Protocol Deviation / Violation

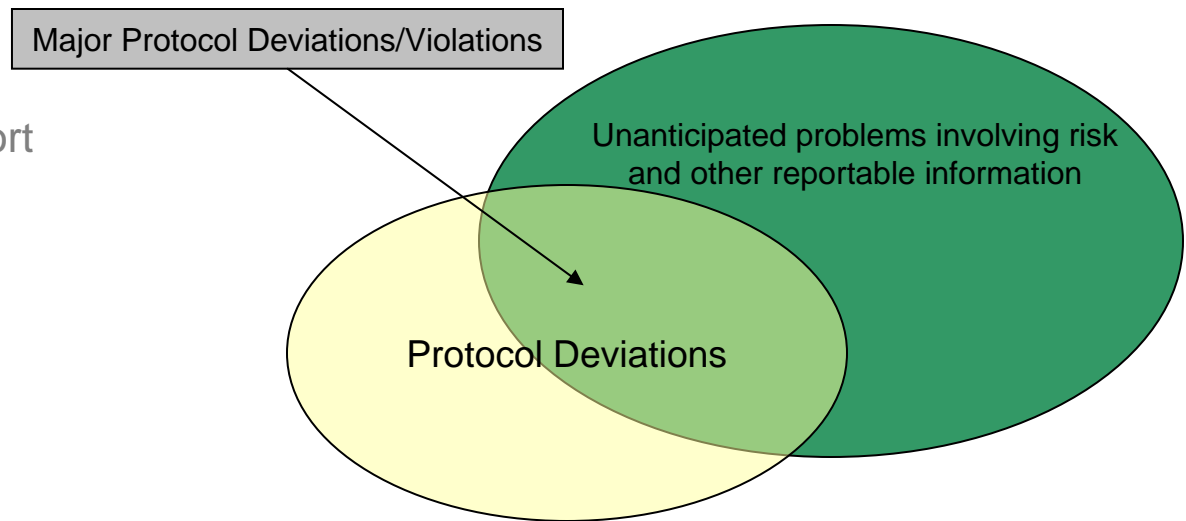
A Major Protocol Deviation, is a deviation that in the investigator's judgment:

- Increases risk to one or more participants;
- Adversely affects the safety, rights or welfare of one or more participants; or
- Adversely affects the integrity of the study



Quorum's policy on reporting Major Protocol Deviations to the IRB / REB

An investigator should report to the IRB / REB all Major Protocol Deviations/ Violations that occur at his or her site.



Report only Major Protocol Deviations to the IRB / REB

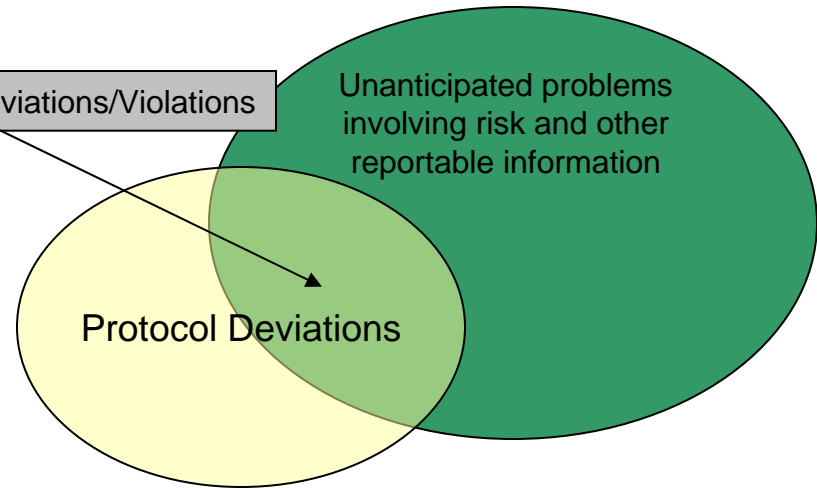
Major Protocol Deviations/Violations

Unanticipated problems involving risk and other reportable information

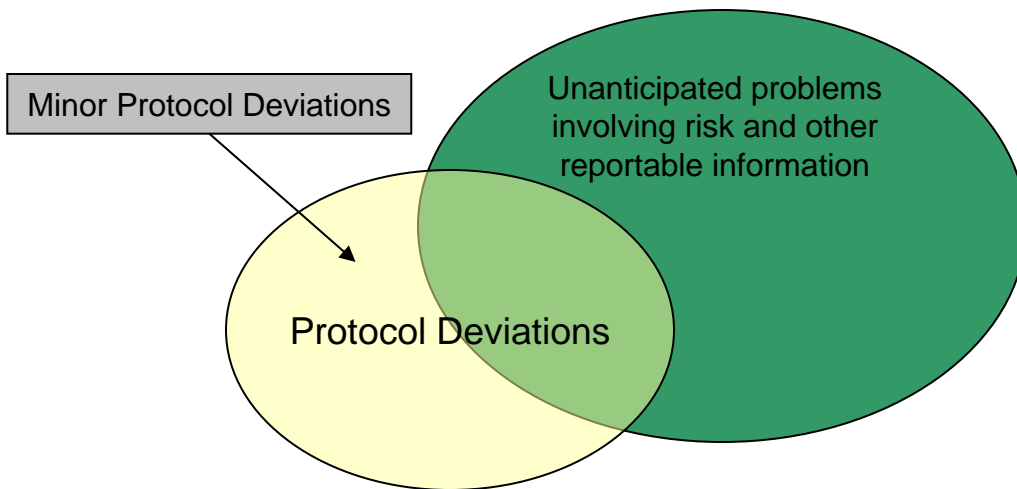
Protocol Deviations

Examples of Major Protocol Deviations:

- Significant dosing error
- Study procedures initiated before informed consent
- Failure to perform laboratory test



Don't report minor protocol deviations or violations to the IRB / REB



Examples of minor protocol deviations:

- Insignificant delay in performing study procedure (i.e. minor window violation)
- Failure to initial every page of a consent form
- Participant failure to return study diaries

What events to report...a closer look

- Serious adverse events
- Major protocol deviations
- ***Other reportable events as defined by Quorum (including new safety information and significant unanticipated problems)***

Additional reportable events

- Adverse audit results from a sponsor audit
- FDA Form 483 or Warning Letter
- Suspension or restriction of medical license
- Unfavorable publication in literature
- Unresolved participant complaints
- Incarceration of research participant
- Breach of confidentiality (e.g., loss of study records)
- Problem involving control of study product (e.g., lost shipment of study drug)
- Research personnel misconduct
- Updated product information citing new risks (e.g., revised Investigator Brochure)
- Data Safety Monitoring Board report
- FDA Public Health Advisory
- Early Study termination or marketing withdrawal

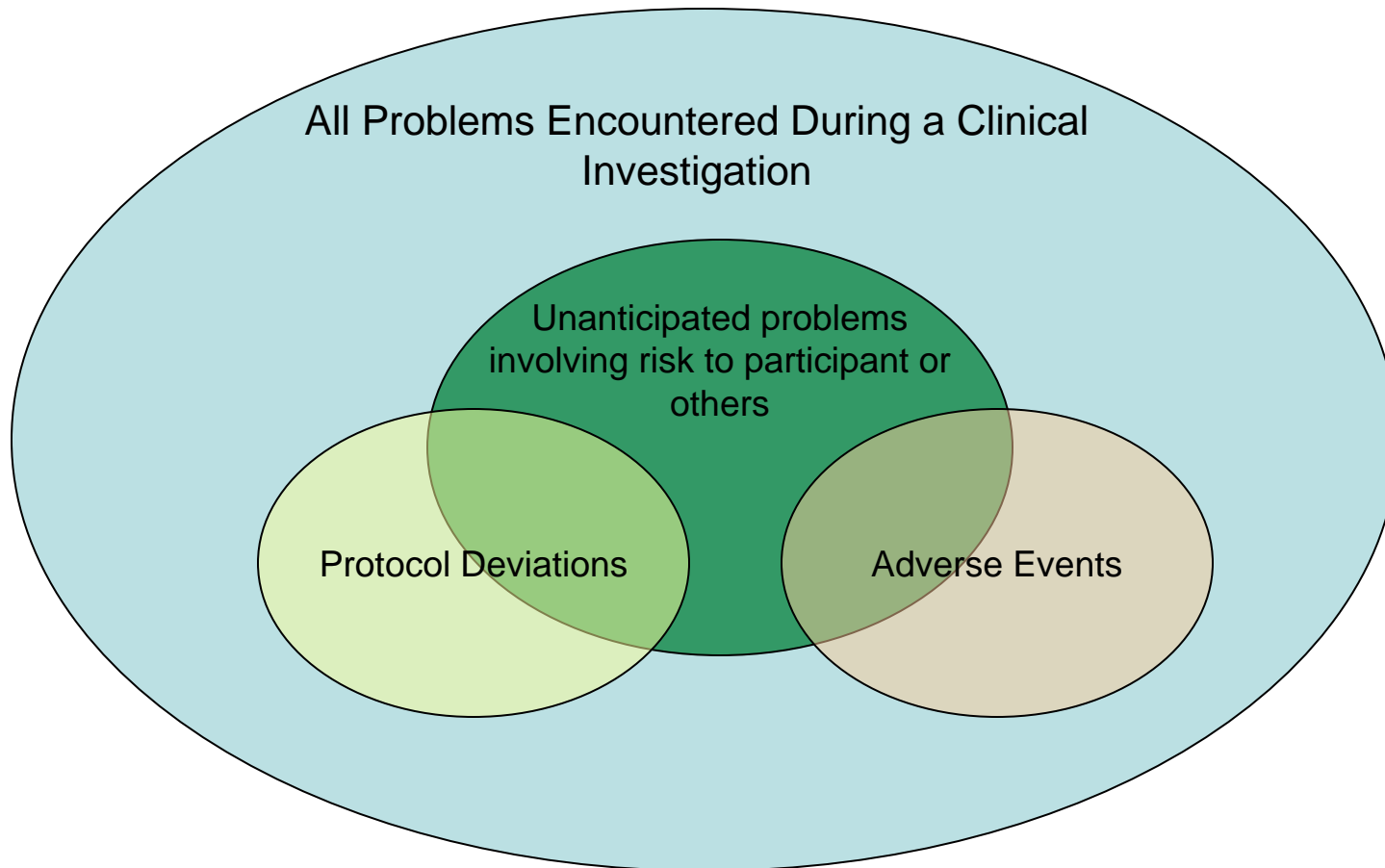
Must an investigator report other events to the IRB /REB?

- An investigator should maintain records (such as logs or line listings) of all adverse events, protocol deviations, etc according to instructions from the sponsor or site monitor
- At the time of periodic site review, the investigator should report to the IRB / REB whether the investigator believes the study or consent form should be modified in light of these events
- Do not submit logs or line listings of minor adverse events, minor protocol deviations, etc. to the IRB / REB.

What if the Sponsor instructs investigators to submit all adverse events to the IRB / REB?

- If Quorum receives a report about an event that is not a reportable event, Quorum generally will issue an acknowledgment of receipt to the site with a reminder that Quorum does not require reporting of such events

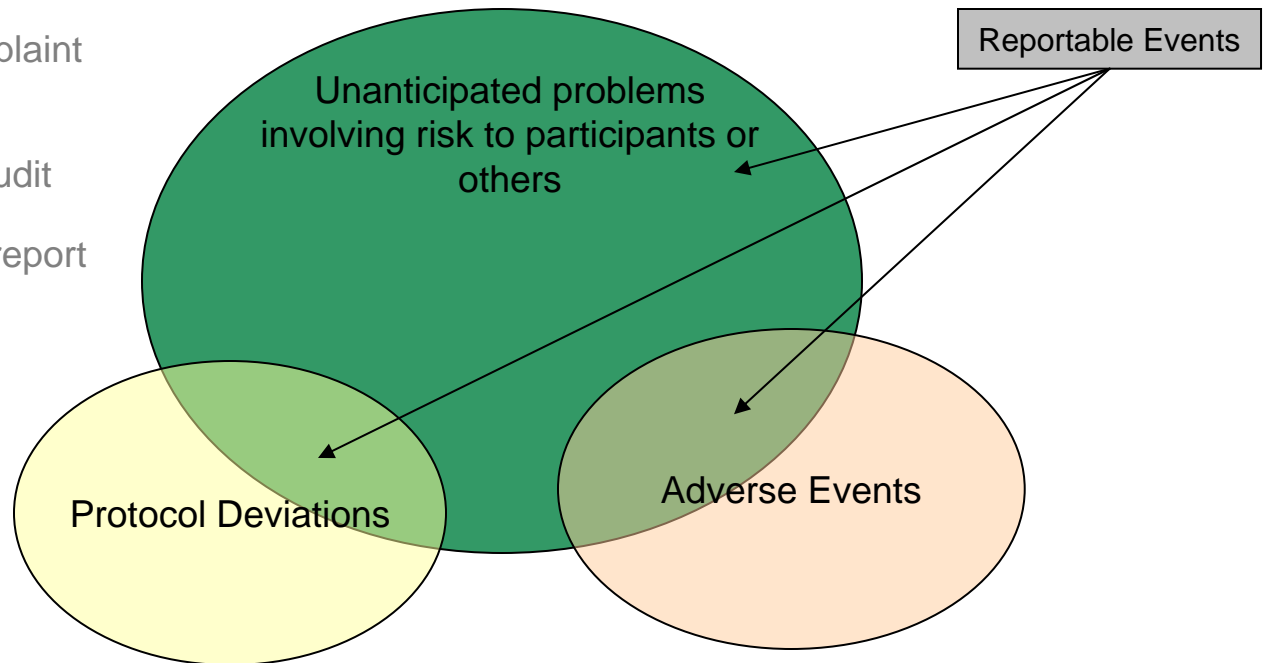
Review: Report only unanticipated problems involving risk



Review: Examples of unanticipated problems involving risk to participants or others that should be reported

Do report these types of events:

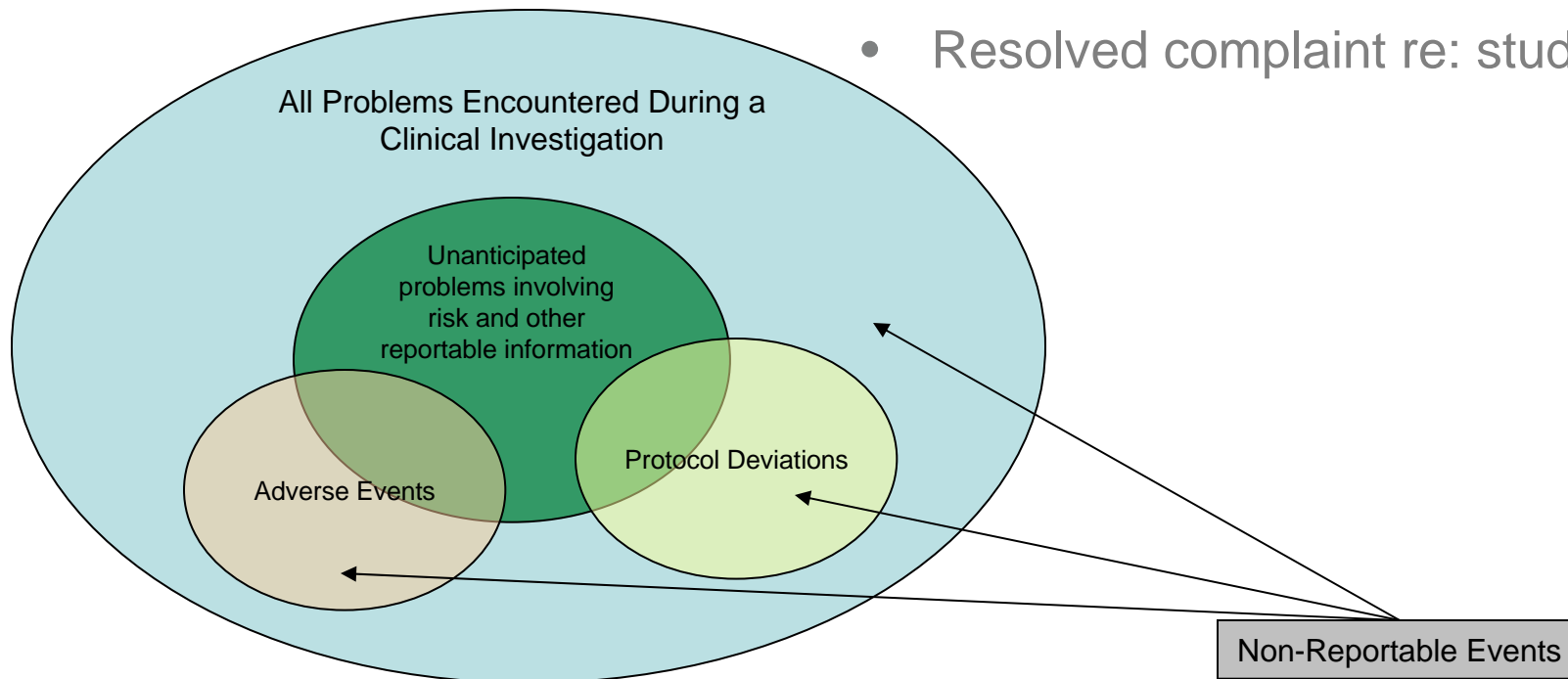
- Serious Adverse Event
- Major Protocol Deviation
- Unresolved research complaint re: participant injury
- Participant incarcerated
- Adverse FDA / Sponsor audit report
- MedWatch of IND Safety report of relevant event



Review: Examples of unanticipated problems not to report to the REB

Don't report these types of events:

- Minor protocol deviation
- Minor adverse event
- Resolved complaint re: study payment



Use Quorum's report forms for reportable events

- **Serious Adverse Event Report** for SAEs
- **Major Protocol Deviation/Violation Report** for major protocol deviations
- **Safety Information and Unanticipated Problem Cover Page** for other reportable events reported by the Sponsor to the investigator (MedWatch Reports, IND Safety Reports, etc.)
- **Unanticipated Problem Report** for additional reportable events reported by the investigator

For more information...

Please link to Quorum's website for more guidance on safety reporting and to find Quorum's reporting forms:

<http://www.quorumreview.com/sites/safety/>