

Eliminating Unnecessary Review of Offsite Adverse Event (Expedited IND Safety) Reports: Departmental Collaboration Leading to Institutional Position

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Abstract

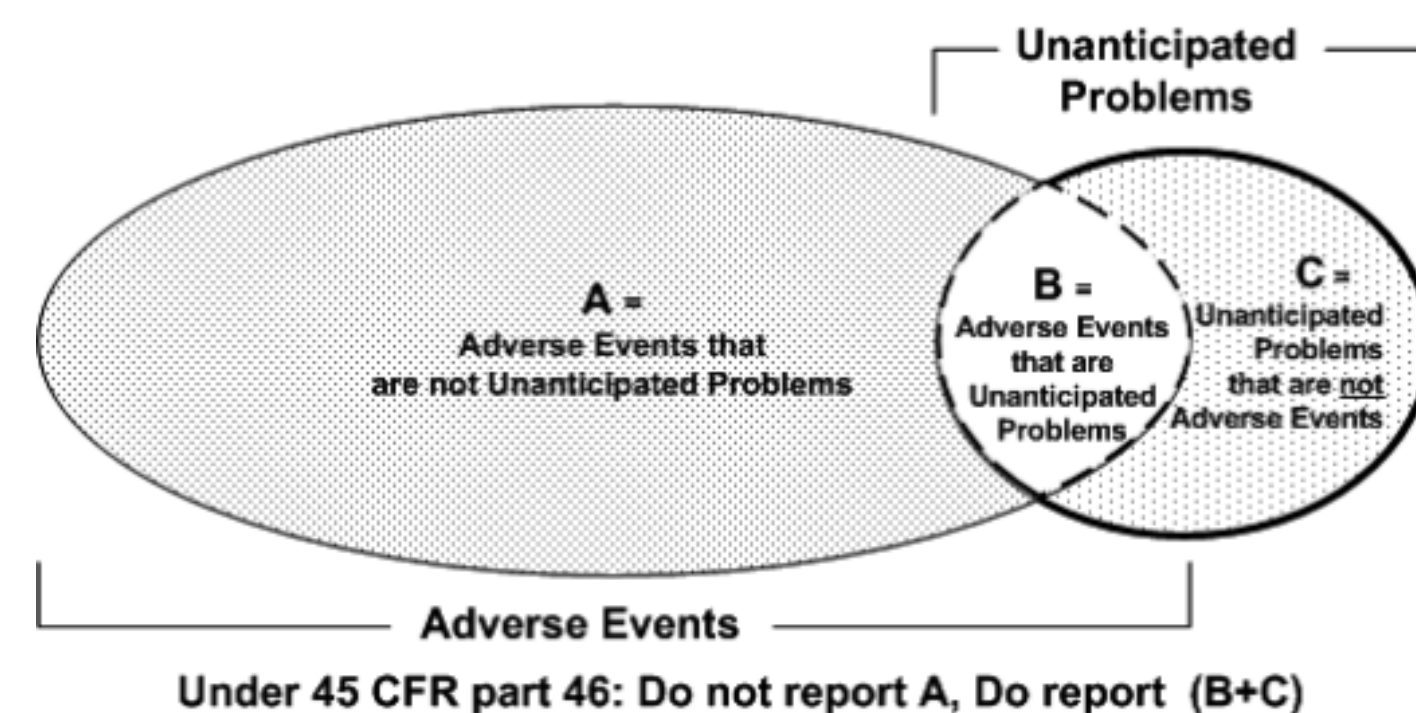
FDA Guidance indicates the sponsor is responsible for evaluating individual safety reports, assessing significance, performing aggregate analysis, and communicating actionable concerns to sites. OHRP has taken the position that it is neither useful nor necessary for reports of individual adverse events (AEs) in subjects enrolled in multicenter studies to be distributed to all investigators or IRBs [Unanticipated Problems (UPs)]. Individual AEs should be reported to investigators and IRBs after the sponsor has made a determination that the events meet specific criteria and are deemed actionable at the site. Sponsors and sites have not yet reached consensus on the process for distribution of individual reports. Most sponsors send all safety reports regardless of assessment and including those lacking action at the site. The University of Pennsylvania, Perelman School of Medicine (PSOM)'s Office of Clinical Research and the Abramson Cancer Center Clinical Research Unit (ACC CRU) have adopted an approach intended to limit administrative burden associated with unnecessary event report reviews.

Introduction

Reporting AEs that are not serious, unexpected, and related to the study product creates administrative burdens for all site stakeholders including staff, faculty, and review committee members. The intention of the unified position was to reduce the number of uninformative AE reports being received, processed, and reported, unnecessarily, at the site allowing for focus on informative reports which promotes patient safety. We sought to realize our goal by first provide a framework for those principal investigators conducting clinical trials regarding the processing of external IND safety reports upon receipt from an external sponsor that is consistent with US Food and Drug Administration (FDA) and Office for Human Research Protections (OHRP) regulations.

We chose to take these steps at the current time to realign practice with regulations ensuring the responsibility of analysis and communication of qualifying reports remains with the regulatory sponsor. Our desire was to reduce unnecessary, over reporting, and uninformative reporting at the site level.

Figure 1: Relationship between Adverse Events and Unanticipated Problems:



Methods

We aligned practice for review of events to only those meeting a clear definition for action at the site and those communicated outside of bulk automated systems. A guidance document delineating this best practice was developed, in addition to supportive tools explaining the position; language has also been added to contracts between PSOM and sponsors. Since the position was not specific to oncology programs, and the ACC CRU focuses heavily on sponsored projects, the ACC CRU served as lead in developing the position which could later be applied more broadly across the institution.

Core Tenets:

Principal Investigators are required to receive, review, report (as applicable), and retain external IND safety reports only when the report meets the following criteria:

AE must be:

- Serious or life threatening; and
- Unexpected; and
- Related to the study drug, as assessed by the sponsor; and
- The report must be accompanied by intentional and directed communication from the sponsor that includes the following information:
 - Clear explanation of why the AE has been determined to be an SUSAR or UP
 - Directives and/or actions required of the investigator (i.e., immediate notification to subjects participating, revised consent forms, revised protocol, revised investigator brochure)

Events meeting these criteria fall into categories 'B' and/or 'C' in Figure 1 and would qualify for Investigator review, reporting and retention in the investigator site files (ISF).

Events NOT meeting above criteria are NOT received, reviewed, reported or retained.

Expectations of External Sponsors:

- Directly notify Investigators of UPs and safety information that has implications for the conduct of the research (21 CFR 312.32, 21 CFR 312.55, 21 CFR 812.46, 21 CFR 812.150).
- Succinctly inform investigators of any UPs for which reporting is required, state the proposed action based on analysis of the UP, provide a report in a format sufficient to fully and accurately inform the IRB.
- Make any reports that are required in a dedicated correspondence.
- Provide an explanation of why an event was determined to be an UP and clearly indicate the implications for the conduct of the study.

Key features of the methods included:

- Definitions utilized in position statement are taken from the FDA to ensure consistency and alignment with federal regulations and across industry/site
- Approach and defined processes comply and align with federal regulations and IRB reporting guidelines to ensure both sponsor/site obligations are fulfilled
- Phased implementation, allowing for current practices to remain for active/already established studies yet reduce burden with implementation on new studies

Results

The ACC CRU has seen drastic (nearly complete) reduction in administrative burden as most reports previously received did not include sponsor provided aggregate analysis and/or were not actionable. Actionable events continue to be communicated in alignment with 'Dear Investigator Letters', Protocol Amendments, and/or updates to the Investigator's Brochure. Sponsors have provided generally positive feedback on the position; negative feedback served to present an opportunity for discussion and education. Our confidence has been bolstered by 3 FDA inspections of trials employing the position with no related findings upon review of safety reports/IRB submissions.

Discussion / Future Directions

Sites will gain momentum in pushing back on undesirable, inefficient processes by banding together to communicate a consistent message supported by regulation. Institutions can seek inspiration for broad policy from internal departments as operational workflows and system requirements are realized during the day to day conduct of human subject research. As the ACC CRU continues to improve efficiency through review of process and implementation of new electronic systems, sustained enhanced communication and collaboration with PSOM will afford future opportunity for alignment with institutional policy.

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