Whose Responsibility Is It? A Sponsor-Investigator's Guide to Reviewing External Safety Reports

Michele Lowe, BS, CCRC; Elizabeth Cunningham, MS, CCRP
Barbara Ann Karmanos Cancer Institute

Background

In August 2017, the Clinical Trials Office (CTO) at the Barbara Ann Karmanos Cancer Institute (KCI), an NCI-Designated Comprehensive Cancer Center, released a policy on External Safety Reports (ESRs) stating that KCI would no longer review, acknowledge, or retain ESRs for industry-sponsored trials that did not have implications for the conduct of the study [e.g., requires a change to the protocol, informed consent form (ICF), or Investigator's Brochure (IB)]. While this dramatically cut down on the work for these studies, this policy did not address how to handle ESRs for studies where one of our principal investigators (PI) holds the investigational new drug application (IND) and is required to comply with both the sponsor and investigator responsibilities included in 21 CFR Part 312. As such, ESRs have been inconsistently processed for our investigator-initiated trials (IITs).

Goals

Ensure our investigators were following all applicable regulations by:

1) Understanding our responsibility as a Sponsor-Investigator (SI) to review ESRs and;
2) Defining a formal, centralized review process for ESRs received for IITs.

Solutions and Methods – Goal 1

After thorough review of FDA guidance documents, the CFR, and other sources, we determined SI responsibilities as defined in Figure 1.

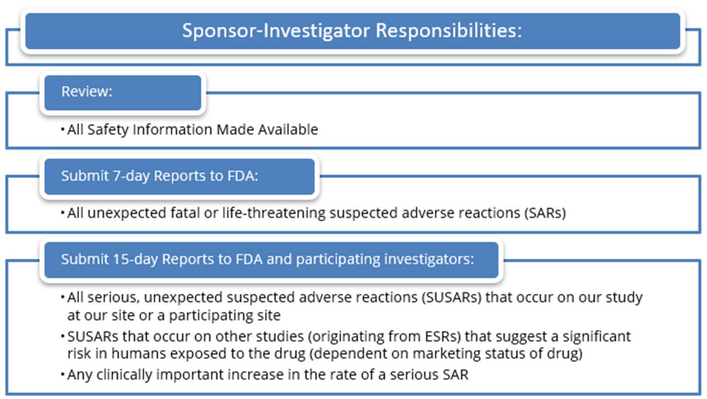


Figure 1: Sponsor-Investigator Responsibilities for Safety Reviews/Submissions

Solutions and Methods – Goal 2

In May 2023, the CTO started reviewing all incoming ESRs for open to accrual IITs to ensure timely expedited reporting of any 7-day reports to FDA. The ESRs previously received were reviewed and an aggregate analysis spreadsheet was created for each investigational agent (IA) to record and track all ESR events. A CTO Administrative Assistant was enlisted in August 2023 to review the incoming reports and maintain/update the aggregate analysis spreadsheets with new ESR details.

In June 2023, the KCI Data and Safety Monitoring Committee (DSMC) agreed to serve as our IIT safety committee by acting as our aggregate analysis reviewer for IIT ESRs. At their monthly meeting, the DSMC reviews ESRs received in the previous month, compares the events to the risk profile in our local protocol/ICF, and determines if any changes may need to be made (see Figure 2). This recommendation is shared with the PI, who makes the final decision to update the ICF and/or share the new risks with study participants. The PI would also ensure any ESRs that necessitate a local change are submitted to FDA and any participating investigators within 15 days of the DSMC meeting.

AER#	Report Date	Verbatim Term	Unexpected	Investigator/ Reporter Causality	Company Causality	Term Included in 09/28/23 ICF	Changes to ICF Required	Comments	DSMC Chair Initials
2023KPT001778	12/26/23	Febrile Neutropenia	Yes	Yes	No	Decrease in neutrophils	No		
2023KPT001779	12/11/23	Febrile Neutropenia	No	Yes	Yes	Decrease in neutrophils	No		
2023KPT001779	12/11/23	Tumor Lysis Syndrome	Yes	Yes	No	Tumor lysis syndrome	No		
2023KPT001779	12/11/23	Urinary Tract Infection	No	No	No	Urinary Tract Infection	No		
2023KPT001779	12/11/23	Circulatory Collapse	Yes	No	No	Low blood pressure	No		
2023KPT001779	12/11/23	Dyspnea	No	No	No	Shortness of Breath	No		
2023KPT001779	12/11/23	Cardiac Failure	Yes	No	No	N/A	No	No impact on patient safety	
2023KPT001821	12/6/23	Pneumonia	Yes	Yes	Yes	Pneumonia	No		

Figure 2: KCI DSMC ESR Review Table

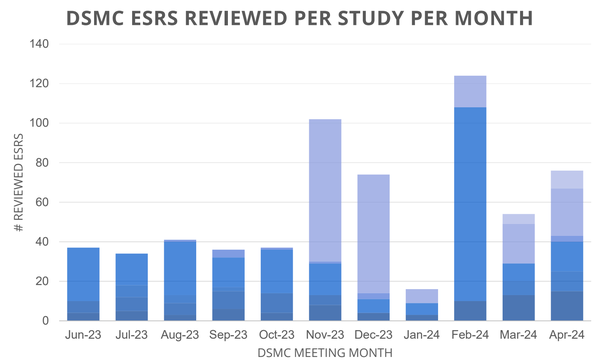
Lessons Learned/Future Directions

Moving forward, the DSMC will start reviewing ESRs at the time of accrual to ensure no backlog occurs. We will formalize an official policy for this process by December 2024. The KCI Data and Safety Monitoring Plan will also be amended to include reviewing IIT ESRs as an official responsibility of the KCI DSMC.

This process has been complicated by the differing ways pharmaceutical companies distribute ESRs. In the future, we would also like to implement a centralized electronic location/database to locally store ESRs and aggregate analysis data.

Results

A backlog of 559 ESRs comprising 892 events for six different IAs were reviewed to create the initial aggregate analysis spreadsheets. As of April 2024, the KCI DSMC has reviewed 631 ESRs containing 754 unique events, and two local changes have been recommended/made. 42 ESRs have been submitted to FDA and one ESR was distributed to participating investigators.



We have received positive feedback from our investigators and the DSMC after instituting this process.

Additionally, tracking these ESRs also gave us a unique opportunity to see how well pharmaceutical sponsors are following the regulations for distributing ESRs to participating investigators. Only 57% of the ESRs included an event that met the criteria for a SUSAR and needed to be distributed to investigators, and only one ESR was received that indicated a change would occur to the safety profile of the investigational agent based on the event.

References

- 21 CFR Part 312
- FDA Guidance for Industry: Sponsor Responsibilities - Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies
- FDA Guidance for Industry: Safety Reporting Requirements for INDs and BA/BE Studies