
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.

Sponsor-Investigator Responsibilities:

- Review:
  - All Safety information made available
  - Submit 15-day reports to FDA
- Submit 15-day reports to FDA and participating investigators:
  - All serious, unexpected suspected adverse reactions (SUSARs) that occur on our study at our site or a participating site
  - SUSARs that occur on other studies (originating from ESRs) that suggest a significant risk in humans exposed to the drug (dependent on marketing status of drug
  - Any clinically important increase in the rate of a serious SARI

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.

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.

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.

In the future, we would also like to implement a centralized electronic location/database to locally store ESRs and aggregate analysis data.

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