Category: Trial Recruitment and Study Conduct - Work in progress

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

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1. Background
In August 2017, the Karmanos Cancer Institute (KCI) Clinical Trials Office (CTO) released a policy regarding External Safety Reports (ESRs) stating that KCI would not review or acknowledge ESRs for industry-sponsored studies that did not have implications for the conduct of the study [e.g., requires a change to the protocol, informed consent form (ICF), or IB]. However, the policy did not address ESRs for studies where a local investigator holds the Investigational New Drug (IND) application and is required to comply with both the sponsor and the investigator responsibilities under Part 312. As a result, ESRs have been inconsistently processed for our investigator-initiated trials (IITs).

2. Goals
To ensure our investigators were complying with all applicable regulations by 1) understanding our responsibility as a Sponsor-Investigator (SI) to review ESRs and 2) defining a formal review process for ESRs received for IITs.

3. Solutions and Methods
After review and consultation of the Food and Drug Administration (FDA) regulations and guidance documents, we determined SI's are responsible for:

- Reviewing all safety information available to them
- Submitting applicable ESRs to FDA and participating investigators

In May 2023, the CTO started reviewing all incoming ESRs for open to accrual IITs to ensure timely expedited reporting 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.

In June 2023, the KCI Data and Safety Monitoring Committee (DSMC) agreed to serve as our entity for aggregate analysis of IIT ESR data. 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. This recommendation is shared with the principal investigator, who makes the final decision to update the ICF and/or share the new risks with study participants.

4. Outcomes
A backlog of 559 ESRs comprising 892 events for six different IAs were reviewed to create the initial aggregate analysis spreadsheets. As of February 2024, the KCI DSMC has reviewed 501 ESRs containing 738 events, and two local changes have been recommended/made. Thirty-seven 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.

5. Lessons Learned and Future Directions
Moving forward, we would like to start reviewing ESRs at the time a study opens to accrual to ensure no backlog occurs. We are hoping to formalize an official policy by December 2024. The KCI Data and Safety

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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 store ESRs and aggregate analysis data.

Figure

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		
2023KPT001978	12/13/23	Weight Loss	No	Yes	Yes	Weight Loss	No		
2023KPT002265	12/11/23	Colitis	Yes	Yes	Yes	Infection	No		
2023KPT002311	12/20/23	Weakness	No	N/R	Yes	Weakness	No		
2023KPT002311	12/20/23	Diarrhea	No	N/R	Yes	Diarrhea	No		
2023KPT002311	12/20/23	Death	Yes	Yes	No	Death	No		

Figure 1: KCI DSMC External Safety Report Review Table