Reactogenicity Adverse Events: Collection, Analysis, and Reporting Process in Vaccine Clinical Trials

Tulin Shekar

Merck & Co., Inc., 2015 Galloping Hill Rd., Kenilworth, NJ 07033

Abstract

Vaccine reactogenicity is an integral part of vaccine trials. Reactogenicity adverse events are defined as adverse events that are expected and occur soon after vaccination. These adverse events may include pain, redness, swelling or induration for injected vaccines, and systemic symptoms, such as fever, myalgia, headache, or rash. Reactogenicity events provide important information after vaccination, such as educating the vaccine community, including health care professionals, in maintaining confidence in vaccines by promoting vaccination and setting expectations for vaccines regarding what might occur after vaccination.
In this paper, we will provide technical details on how reactogenicity data is collected and analyzed, and we will review CDISC Therapeutic Area Data Standards User Guide for Vaccines for data structure.
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Key Words: Reactogenicity, adverse events, vaccine, data collection, analysis, and reporting

1. Background

Reactogenicity refers to an expected set of reactions that occur shortly after vaccination, and these reactions are generally a response to vaccination. In clinical trials, information on expected signs and symptoms after vaccination is actively collected (solicited). Reactogenicity events can include injection-site pain, redness, and swelling or induration at the injection site, as well as systemic symptoms such as fever, myalgia, or headache.

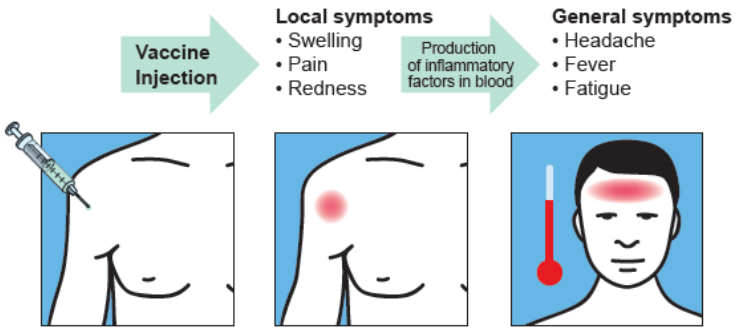

Figure 1: Vaccine injections and reactogenicity

Factors that can influence the reactogenicity can be extrinsic and intrinsic factors. They can be age, gender, race/ethnicity, body mass, general health, and pre-existing immunity, and vaccine administration and composition factors, such as route and site of administration, injection technique, type of antigen, vaccine formulation, and type of adjuvant.

2. Reactogenicity Data for Vaccine Development

Key requirements for OVRR (Office of Vaccine Research and Review) reactogenicity data submission (official release of guidance was on April 2018 and updated in October and December 2019):
(1) Provides technical specifications for the contents of datasets submitted to CBER (Center for Biologics Evaluation and Research), including those for reactogenicity data (solicited events within a prespecified time period);
(2) Necessitates 2 or 3 entries of the same event to be linked during data collection;
(3) Requires reactogenicity data to be stored in the following SDTM (Study Data Tabulation Model) domains:

FACE (Findings About): Daily event records recorded on the eVRC
CE (Clinical Event): Global event records recorded on a separate CE eCRF
AE (Adverse Event): Global event records recorded on the AE eCRF IF the reactogenicity event (1) extends beyond the assessment interval OR (2) becomes serious during the assessment interval.

2.1 Reactogenicity Datasets Based on OVRR Guidance

Reactogenicity data should be represented primarily in the clinical event (CE domain) with details in the findings about clinical event (FACE domain). Daily participant records are represented in findings about clinical event (FACE) domain (flat data model – includes records for days event did not occur or missed entries).

Solicited events also require reporting on AE CRF (requires linkage of CE domain to AE domain) that are solicited events meeting SAE criteria, solicited events continuing beyond the assessment period, solicited events that are part of another diagnosis, specific requirements for data points included in CE and AE domains (eg, reactogenicity category), and calculation of duration for CE linked to AEs.

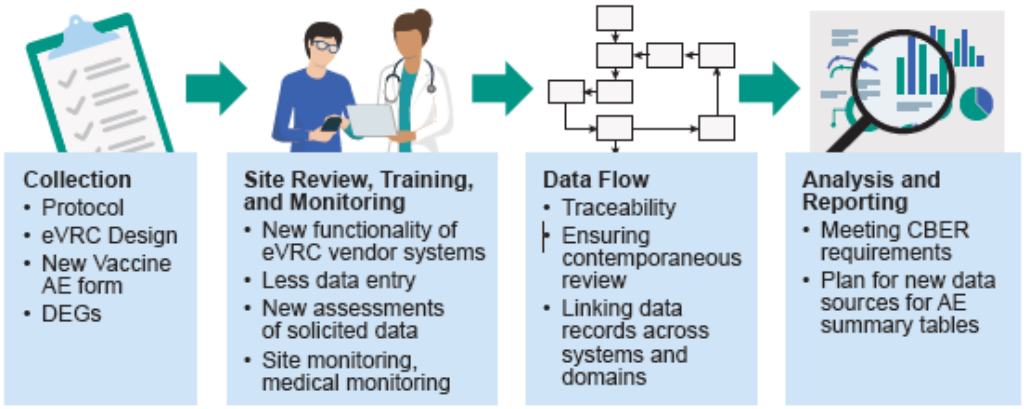

Figure 2. End-to-End flow of reactogenicity data in order to comply with OVRR guidance

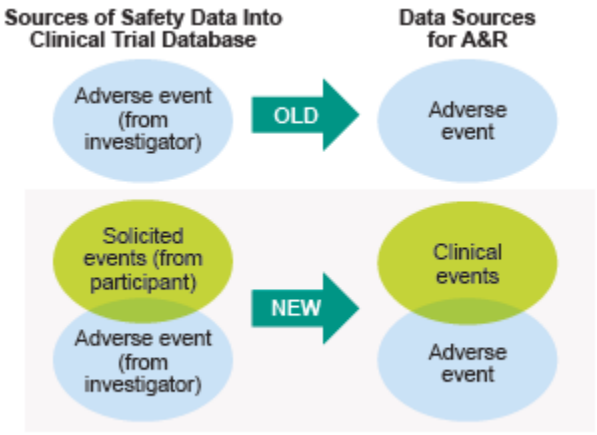

Figure 3. Summary: Old (pre-OVRR) vs New (post-OVRR)

3. Reactogenicity Data Collection

Table 1 summarizes the end-to-end from study design and analysis and reporting impact of the new guidance and collection of the reactogenicity data.

Table 1: End-to-End Full Adoption for Reactogenicity Data Summary

Study Design	Data Collection and Flow	Oversight and Monitoring	Analysis and Reporting
• Consider solicited systemic events to collect • Protocol to define solicited and unsolicited adverse events and include how solicited events are collected and assessed differently from other adverse events • Paper or electronic vaccine report card	• eCOA vendor • New site assessment entry in collector • New inform eCRFs • Significant changes to data flow and storage	• Changes in site monitoring • Changes to medical monitoring • Impact on Global Safety's review of nonserious adverse event (no changes to SAE reporting)	• Impact on safety summaries (including AE summary table) in CSRs and CTDs • Impact to submissions • Impact on label statements

4. Challenges with Reactogenicity Data

Summary of OVRR key elements for submission of safety data for vaccine trials is shown in Table 2.

Table 2: OVRR Key Elements Beyond Reactogenicity

Section	Key Elements
3.1 Reactogenicity	• If you intend to report data based on recall (and not obtained from the diary), please minimize bias by including a reconstructed data flag in supplemental CE using QNAM = RECON ("**reconstructed data**")…
	• **CMCAT** to differential prevention vs treatment if analgesic/ antipyretic used for prevention or treatment of pain and/or fever associated with vaccine administration • Additional flag for analgesic/antipyretic administration (Y/N) on CE
	• **Telephone contact** to be used to ensure diary reporting compliance and/or ascertain any unsolicited AEs is considered a study visit
3.2 Unsolicited AEs	• Unsolicited AEs should be represented in the AE domain regardless of when they occur • New requirements to collect reference time points. • FAAE domain to be used to report day-to-day information • RELREC with CM, PR, HO, DD if corresponding variables in AE marked "yes"

Key components of reactogenicity data include new eCRF designed specifically to support studies submitting to OVRR, data flow changes, required enhanced investigator training, and some adjustments to analysis reporting needs to be made, which are listed below:

- **Modality of administration** of vaccine report card (paper vs electronic) greatly impacts database requirements (eCRFs used, data flow requirements)
- **Electronic VRC (eVRC)**; multiple systems for sites to access to review and enter safety data
- **eVRC structure** impacts the way participants report information
- **Lack of clarity** in OVRR and TAUG CDISC requirements – contradictions between standards and new requirements
- **Sponsors** will adopt requirements differently
- **Contradiction** within AE definition with the introduction of participant-based reporting
- **Timing** for site review is critical (contemporaneous review and end of assessment period review)
- **Impact** on ex-US Health Authority submissions and Label statements
- **eCOA vendor** capabilities, strategy, and considerations

5. Analysis and Reporting

Below are the summaries of reactogenicity data proposed based on the review of the analysis plans available online:

- The frequencies of subjects who provide diary cards by vaccine group and collection method
- For each solicited adverse event, the frequencies of subjects with valid data presented by vaccine group and time point: 30 min, day 1-3 (with and without the 30-minute interval), day 4-7, and day 1-7 (with and without the 30-minute interval)
- Treatment groups were compared on the distribution of highest reactogenicity grades (0,1,2,3,4), post any vaccination and post each vaccination
- Reactogenicity compared between vaccines using 95% confidence intervals provided using Miettinen and Nurminen method for the difference in proportions
- Injection site erythema and injection site swelling are reported by size using counts and percents
- Injection site pain and other solicited systemic AEs were reported using the severity grading (mild, moderate, severe) using counts and percents
- Solicited systemic adverse events summarized using the “relatedness to vaccine” using counts and percents

Below is one of the example summary table for the reporting of VRC data.

Table 3. Example of Key Summary Table

	Treatment 1		Treatment 2		Difference in %	
	n	(%)	n	(%)	Estimate (95% CI)	*P*-value
Subjects in population	**xxx**		**xxx**			
With one or more solicited complaints	xx	(xx.x)	xx	(xx.x)		
With no solicited complaints	xx	(xx.x)	xx	(xx.x)		
Solicited injection site complaints	**xx**	**(xx.x)**	**xx**	**(xx.x)**		
Injection site erythema	xx	(xx.x)	xx	(xx.x)	xx.x (xx.x, xx.x)	x.xxx
Injection site pain	xx	(xx.x)	xx	(xx.x)	xx.x (xx.x, xx.x)	x.xxx
Injection site swelling	xx	(xx.x)	xx	(xx.x)	xx.x (xx.x, xx.x)	x.xxx
Solicited systemic complaints	**xx**	**(xx.x)**	**xx**	**(xx.x)**		
Arthralgia	xx	(xx.x)	xx	(xx.x)	xx.x (xx.x, xx.x)	x.xxx
Fatigue	xx	(xx.x)	xx	(xx.x)	xx.x (xx.x, xx.x)	x.xxx
Headache	xx	(xx.x)	xx	(xx.x)	xx.x (xx.x, xx.x)	x.xxx
Myalgia	xx	(xx.x)	xx	(xx.x)	xx.x (xx.x, xx.x)	x.xxx

6. Conclusion

Safety data submitted to agency for vaccine clinical trials should include reactogenicity data (ie, a set of prespecified AEs collected within a prespecified timeframe, often referred to as solicited AEs or reactions), unsolicited AEs, medically attended adverse events (MAAEs), and death. Team involved in analysis and reporting of the vaccine clinical trials should be familiar with the regulatory guidance. FDA and company regulatory communications are key for successful submission of reactogenicity data and analysis.

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