SESUG 2020 Paper 153

Analysis and Reporting of Reactogenicity Events in Vaccine Clinical Trials

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ABSTRACT

Reactogenicity events are usually the primary endpoint, in terms of safety, in vaccine clinical trials. They are pre-specified adverse events that are commonly known to be associated with a vaccine. These events are usually recorded within 60 minutes of vaccination, and each day through 7 days following any vaccination for most killed and recombinant vaccines. For most live vaccines, the event monitoring period is 14 or more days. There is also a telephonic interview or questionnaire follow-up period of at least 30 days for live or killed vaccines. The Case Report Forms (CRF) are designed to accommodate daily recording of these events during the predefined observation period. These reactogenicity events are classified as local or systemic reactions. Examples of local reactions include erythema, induration, pain, and tenderness. Examples of systemic reactions include fever, headache, and vomiting.

Data is captured either by the severity level (mild, moderate, and severe) or numerically, for example daily temperature is recorded then at the analysis level, severity of fever is calculated based on predefined ranges. Since data collection of reactogenicity event is more or less standard across vaccine clinical trials, we propose some of the common ways of analysing and reporting data with supporting table shells. A table shell is a standard terminology in clinical trials which defines the required analysis and reporting format for the regulatory submission. For each table shell, we will add tips and tricks for programming and add a statistical interpretation.

INTRODUCTION

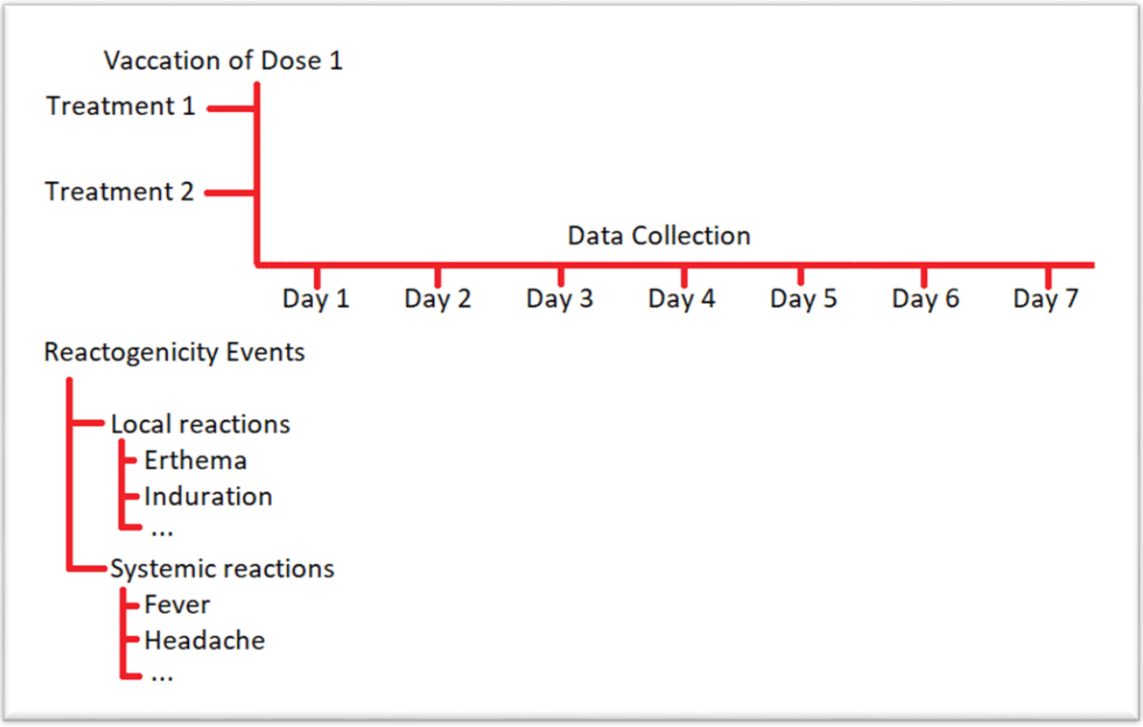
Reactogenicity events are usually the primary endpoint, in terms of safety, in vaccine clinical trials. They are expected adverse events that are commonly known to be associated with a vaccine. It is important to understand the expected symptoms as it can give the participant a better understand of what to expect.

These events are usually recorded within 60 minutes of vaccination, and each day through 7 days following any vaccination for most killed and recombinant vaccines. For most live vaccines, the event monitoring period is 14 or more days. There is also a telephonic interview or questionnaire follow-up period of at least 30 days for live or killed vaccines.

REACTOGENICITY EVENTS

The Case Report Forms (CRF) are designed to accommodate daily recording of these events during the predefined observation period. These reactogenicity events are classified as local or systemic reactions. A local reaction occurs at the point of the injection. Examples of local reactions include erythema, induration, pain, and tenderness. A systemic reaction affects the entire body. Examples of systemic reactions include fever, headache, and vomiting. Data is captured either by the severity level (mild, moderate, and severe) or numerically, for example daily temperature is recorded then at the analysis level, severity of fever is calculated based on predefined ranges.

Display 1 illustrates the flow of how reactogenicity events are captured in a typical trial. In this paper we review previous vaccine clinical trials and summarize how reactogenicity events are captured and reported. We also propose a limited number of table and figure shells with a description of each that can be used in vaccine clinical trial on need basis.



Display 1: Reactiogenicity Flow Diagram

LITERATURE REVIEW

Below are 5 examples from published vaccine studies that collected reactogenicity events. Details on the reactions and the tables and/or figures that the authors reported are summarized.

1. Immunogenicity and safety of Fluzone® intradermal and high-dose influenza vaccines in older adults ≥65 years of age: A randomized, controlled, phase II trial (Tsang 2014)

This study was a phase II, randomized, controlled trial conducted in the US. Subjects received a single dose of an influenza vaccine, four arms in older adults was compared to a single arm in young adults. Older adult subjects were double-blinded. Solicited systemic reactions (fever, headache, malaise, myalgia, and chills) and solicited injection-site reactions (pain, erythema, swelling, induration, ecchymosis, and pruritus) were recorded by subjects on diary cards for up to 7 days following vaccination. The authors reported a single table outlining overall safety results, the number and percentage of subjects with at least one event and the 95% CI. They also reported two figures for solicited systemic and injection-site reactions by severity for each vaccine group. The text focused on the differences in proportion among vaccine groups, the severity of the solicited reactions and the duration, and the most common reaction.

2. Immunogenicity and safety of a quadrivalent meningococcal tetanus toxoid-conjugate vaccine (MenACYW-TT) in healthy toddlers: a Phase II randomized study (Vesikari 2020)

This study was a Phase II, randomized, active-controlled, open-label trial conducted in Finland. Toddlers received a single dose of a meningococcal vaccine and were randomized to one of two vaccine groups. Solicited injection site (tenderness, erythema, and swelling) and systemic reactions (fever, vomiting, abnormal crying, drowsiness, loss of appetite, and irritability) were reported on a diary card between Day 0 and 7. The authors reported a single table outlining overall safety results, the percentage of subjects with at least one event and

the 95% CI. They also reported the percentage of subjects with at least one grade 3 reaction. No figures were included. The text focused on the severity of the solicited reactions, and the onset and duration of the solicited reactions.

3. Immunogenicity and safety of the AS04-HPV-16/18 and HPV-6/11/16/18 human papillomavirus vaccines in asymptomatic young women living with HIV aged 15-25 years: A phase IV randomized comparative study (Folschweiller 2020)

This study was a phase IV, randomized, controlled, observer-blind study conducted in Brazil, Estonia, India, and Thailand. Two HPV vaccines were compared among young women living with and without HIV, three doses were given. Solicited adverse events that occured within 7 days were recorded on a diary card, after each vaccine dose. The authors did not report a table but reported a figure of the percentage of subjects, and 95% CI, experiencing a local (pain redness, and swelling) or general (arthralgia, fatigue, gastrointestinal symptom, headache, myalgia, rash, fever, and urticaria) symptom overall and for high grade, by vaccine group. The text focused on the most common reaction and the most common grade 3 reaction.

4. Safety and tolerability of cell culture-derived and egg-derived trivalent influenza vaccines in 3 to <18-year-old children and adolescents at risk of influenza-related complications (Diez-Domingo 2016)

This study was a phase III, randomized, non-comparative, observer-blind study conducted in Spain and Italy. Children at risk of influenza-related complicated were enrolled to one of two influenza vaccine groups to receive two doses. Solicited local (tenderness, erythema, induration, and ecchymosis) and systemic reactions (change in eating habits, chills, diarrhea, irritability, sleepiness, vomiting, and fever) were recorded on a diary card within one week of each vaccination. The authors reported four tables regarding solicited reactions. One was an overall table that reported the number and percentage of any solicited reactions, local, and systemic by vaccine group after each dose and overall. The remaining tables, separated by three age groups, reported the number and percentage of symptom by severity and vaccine group. No figures were included. The text focused on the overall incidence of solicited reactions and the difference in incidence after the first dose compared to the second dose. The authors also focused on the severity of the solicited reactions, with emphasis on severe reactions, and the most commonly reported reaction.

5. Repeated administration of a reduced-antigen content diphtheria-tetanus-acellular pertussis and poliomyelitis vaccine (dTpa-IPV; *Boostrix*™ IPV) (Knuf 2010)

This study was a phase IV, non-randomized, open-label study conducted in Germany. Subjects were healthy children who received a booster vaccination for pertussis. Solicited local symptoms (pain, redness, and swelling) and general symptoms (fever, headache, fatigue, and gastrointestinal) were collected using a diary card for 4 days after vaccination. The authors reported a single table of local reactions of the number and percentage of participants with any and grade 3. The table was separated by two age groups and the percent difference was calculated between these age groups. The authors also included a figure of the percentage of subjects, and 95% CI, experiencing a local and general symptom overall and grade 3. The text focused on the most common reaction and the incidence of grade 3 reactions.

TABLE SHELLS

Reactogenicity data was simulated assuming two treatment groups. Severity was reported within 60 minutes of vaccination and Day 1 through Day 7. Systemic reactions were decreased appetite, diarrhoea, fever, irritability, abdominal pain, headache, cough, and vomiting. The

same logic would apply to local reactions. The data assumed one dose (priming dose) but the results can be repeated for multiple doses. For multiple doses, the incidence of reactogenicity events is usually lesser than the first dose. When considering the population, it is recommended to consider participants who took the vaccination associated with the reactogenicity data, e.g. those who took the second dose.

In the examples below, 60 minutes summaries are considered in Section 1 only. For the remaining sections, only Day 1 to Day 7 are summarized. The results are summarized by treatment group, but total summaries can be included. Confidence intervals are from the Clopper-Pearson interval and p-values are based on the Fisher's Exact Test but any appropriate statistical method can be applied. For the illustration purpose, the tables include results from only any reaction and decreased appetite, the remaining symptoms would be similar.

SECTION 1: OVERALL SUMMARY OF SYSTEMIC REACTIONS

This is an overall summary of systemic reactions. The value 'N' corresponds to the population size and 'x' corresponds to the number of participants. Day 7 is equivalent to within 7 days, it can either include or exclude the 60 Min evaluation. In this example, Day 7 excludes the 60 minutes evaluation, so the reactions only fall in one timepoint. This summary provides a general overview of the incidence of the reactions. We can also determine which reaction occurred most frequently. This summary is considered the primary safety endpoint. The 95% CIs and p-values are used to test for treatment differences.

If the investigator is interested in looking at the number of events, then this can be included in the format as x (%), E, where 'E' is the number of events. Suppose there are 672 events in the treatment group for any reaction within Day 7, then we can say there are 672 events reported in 87 (34.8%) participants in the treatment group and it would e written as 87 (34.8), 672 in the table.

Table 1: Overall Summary of Systemic Reactions Following Priming Dose Within 7 Days by Timepoint and Treatment Group – Safety Population

		Treatment N=250		Placebo N=250		
Systemic Reactions	**Timepoint**	**x (%)**	**95% CI**	**x (%)**	**95% CI**	**p-value**
Any Reaction	60 Min	12 (4.8)	(2.50, 8.23)	4 (1.6)	(0.44, 4.05)	0.0722
	Day 7	87 (34.8)	(28.91, 41.06)	75 (30.0)	(24.39, 36.09)	0.2932
Decreased Appetite	60 Min	8 (3.2)	(1.39, 6.21)	4 (1.6)	(0.44, 4.05)	0.3818
	Day 7	82 (32.8)	(27.02, 39.00)	70 (28.0)	(22.53, 34.01)	0.2848

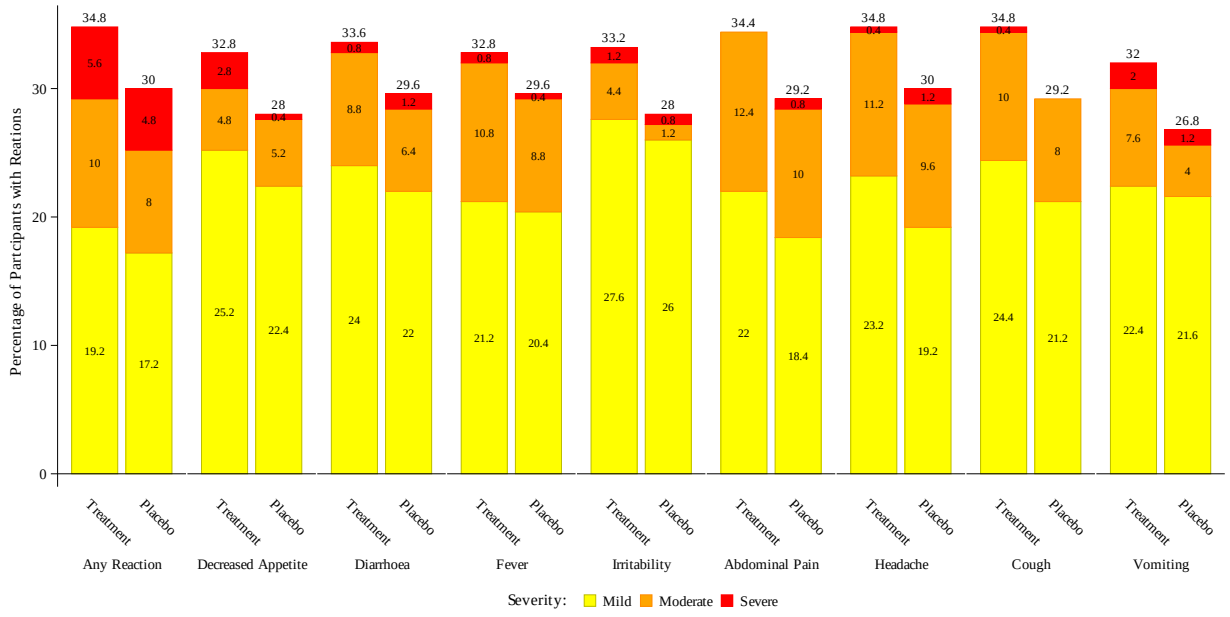
SECTION 2: REACTIONS BY SEVERITY

This summary looks at the distribution of severity for each reaction. Maximum severity within 7 days is considered. This table is considered as a primary table. The primary interest is severe events but some investigators may be interested in moderate and severe events. From this table we can determine how many participants had severe events and the reaction with the most number of severe events. Although not calculated here, a p-value can also be used to compare the severity distribution between treatment groups. The figure illustrates the results in the table and should be consistent. Figures are usually a graphical representation of an existing table.

Table 2: Systemic Reactions Following Priming Dose by Maximum Severity and Treatment Group – Safety Population

		Treatment N=250		Placebo N=250		
Systemic Reactions	**Severity**	**x (%)**	**95% CI**	**x (%)**	**95% CI**	**p-value**
Any Reaction	Any Severity	87 (34.8)	(28.91, 41.06)	75 (30.0)	(24.39, 36.09)	0.2932
	Mild	48 (19.2)	(14.51, 24.64)	43 (17.2)	(12.74, 22.46)	
	Moderate	25 (10.0)	(6.58, 14.41)	20 (8.0)	(4.95, 12.09)	
	Severe	14 (5.6)	(3.10, 9.22)	12 (4.8)	(2.50, 8.23)	
Decreased Appetite	Any Severity	82 (32.8)	(27.02, 39.00)	70 (28.0)	(22.53, 34.01)	0.2848
	Mild	63 (25.2)	(19.94, 31.06)	56 (22.4)	(17.39, 28.08)	
	Moderate	12 (4.8)	(2.50, 8.23)	13 (5.2)	(2.80, 8.73)	
	Severe	7 (2.8)	(1.13, 5.68)	1 (0.4)	(0.01, 2.21)	

Figure 1: Maximum Severity of Systemic Reactions per Treatment – Safety Population



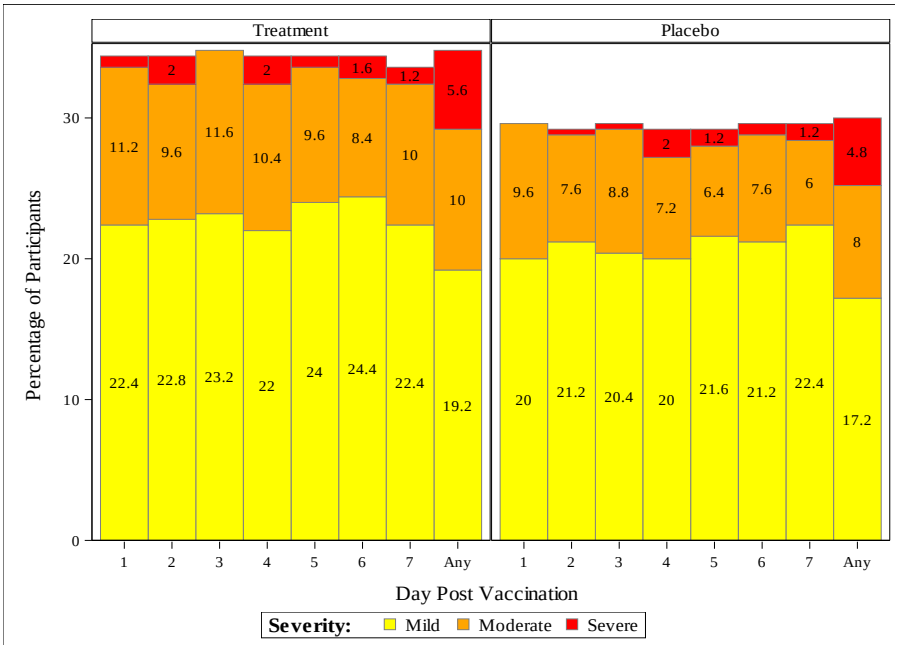
SECTION 3: REACTIONS BY STUDY DAY, SEVERITY AND TREATMENT GROUP

This summary looks at the severity at each day. This summary is viewed as exploratory. The corresponding figure is a more interpretable summary to show how severity changes from Day 1 to Day 7.

Table 3: Systemic Reactions Following Priming Dose by Study Day, Severity, and Treatment Group – Safety Population

			Treatment N=250		Placebo N-250		
Systemic Reactions	**Post-Dose Day**	**Severity**	**x (%)**	**95% CI**	**x (%)**	**95% CI**	**p-value**
Any Reaction	Day 1	Any Severity	86 (34.4)	(28.53, 40.65)	74 (29.6)	(24.01, 35.68)	0.2916
		Mild	56 (22.4)	(17.39, 28.08)	50 (20.0)	(15.22, 25.50)	
		Moderate	28 (11.2)	(7.57, 15.78)	24 (9.6)	(6.25, 13.95)	
		Severe	2 (0.8)	(0.10, 2.86)	0 (0.0)	(0.00, 1.46)	
	…						
	Day 7	Any Severity	84 (33.6)	(27.77, 39.82)	74 (29.6)	(24.01, 35.68)	0.3867
		Mild	56 (22.4)	(17.39, 28.08)	56 (22.4)	(17.39, 28.08)	
		Moderate	25 (10.0)	(6.58, 14.41)	15 (6.0)	(3.40, 9.70)	
		Severe	3 (1.2)	(0.25, 3.47)	3 (1.2)	(0.25, 3.47)	
Decreased Appetite	Day 1	Any Severity	36 (14.4)	(10.29, 19.37)	25 (10.0)	(6.58, 14.41)	0.1714
		Mild	34 (13.6)	(9.61, 18.48)	24 (9.6)	(6.25, 13.95)	
		Moderate	2 (0.8)	(0.10, 2.86)	1 (0.4)	(0.01, 2.21)	
		Severe	0 (0.0)	(0.00, 1.46)	0 (0.0)	(0.00, 1.46)	
	…						
	Day 7	Any Severity	31 (12.4)	(8.58, 17.14)	26 (10.4)	(6.91, 14.87)	0.5738
		Mild	27 (10.8)	(7.24, 15.32)	24 (9.6)	(6.25, 13.95)	
		Moderate	2 (0.8)	(0.10, 2.86)	2 (0.8)	(0.10, 2.86)	
		Severe	2 (0.8)	(0.10, 2.86)	0 (0.0)	(0.00, 1.46)	

Figure 2: Day Post Vaccination - Safety Population



SECTION 4: ONGOING REACTIONS

The number and percentage of ongoing events at day 7 are summarized. This summary also includes a summary of the maximum severity post day 7. From this table we can understand which reaction is ongoing most frequently and which reaction has the most number of severe events post day 7.

Table 4: Systemic Reactions Following Priming Dose Ongoing at Day 7 by Reaction and Treatment Group – Safety Population

Systemic Reactions	Treatment N=250	Placebo N=250	p-value
Any Reaction			
Ongoing at Day 7	33 (13.2)	12 (4.8)	0.0015
Highest grade:			
Mild	23 (9.2)	9 (3.6)	
Moderate	8 (3.2)	3 (1.2)	
Severe	2 (0.8)	0 (0.0)	
Decreased Appetite			
Ongoing at Day 7	4 (1.6)	0 (0.0)	0.1235
Highest grade:			
Mild	3 (1.2)	0 (0.0)	
Moderate	0 (0.0)	0 (0.0)	
Severe	1 (0.4)	0 (0.0)	

SECTION 5: REACTIONS SUMMARIZED BY ONSET DAY AND DURATION

Onset day summarizes the day the event started. These events are recorded from Day 1 to Day 7, so onset day can only be one of these days. The value 'n' corresponds to the total number of events. This table summarizes which event started the earliest and latest, on average. Duration (days) summarizes the duration of the events. Typically, events that start and stop and start again within 7 days are considered as one event and the duration is calculated as the absolute start and end date.

For example, if an event is mild on day 2 and day 5, but not present on days 3 and 4 and on days 6 and 7, then the duration is 4 days. Events that are ongoing on day 7 will be summarized based on the end date after day 7, so duration can be more than 7 days. Again, the value 'n' corresponds to the total number of events.

Durations that are unusually high, for example more than 20 days, should be flagged as data entry errors as most reactogenicity events last for a shorter number of days. This table summarizes which event lasted the shortest and longest, on average.

Table 5: Onset and Duration (Days) of Systemic Reactions Following Priming Dose by Reaction and Treatment Group – Safety Population

Characteristic	Treatment N=250	Placebo N=250
Onset Day		
Any Reaction		
n (Missing)	672 (0)	577 (0)
Mean (SD)	3.3 (1.51)	3.2 (1.52)
Median	3.0	3.0
Range (Min, Max)	1, 7	1, 7
Decreased appetite		
n (Missing)	82 (0)	70 (0)
Mean (SD)	3.3 (1.59)	3.7 (1.74)
Median	3.0	3.0
Range (Min, Max)	2, 8	2, 8
Duration (Days)		
Any Reaction		
n (Missing)	665 (7)	577 (0)
Mean (SD)	4.6 (2.82)	4.4 (2.33)
Median	5.0	5.0
Range (Min, Max)	1, 11	1, 12
Decreased appetite		
n (Missing)	82 (0)	70 (0)
Mean (SD)	4.2 (2.11)	3.6 (2.20)
Median	4.0	3.0
Range (Min, Max)	1, 7	1, 7

CONCLUSION

Analysis and reporting of reactogenicity events in vaccine clinical trials is inevitable. There are various ways to analyze and interpret reactogenicity data. Based on our experience in vaccine trials, we have attempted to showcase the most frequently used, but not limited, analysis and its reporting format along with a statistical interpretation.

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