Adverse Event Information: Introduction

Results Database Train-the-Trainer Workshop

August 2021

Results Information Submission

42 CFR Part 11 – Subpart C

§ 11.48 – What constitutes clinical trial results information?

42 CFR 11.48(a) applies to applicable clinical trials required to register and with a Primary Completion Date on or after January 18, 2017 (effective date).

Results information consists of:

- Participant flow
- Demographic and baseline characteristics
- Outcomes and statistical analyses
- Adverse event information
- Protocol and statistical analysis plan
- Administrative information
- Additional clinical trial results information for applicable device clinical trials of unapproved or uncleared device products

What Are Adverse Events?

"A table of anticipated and unanticipated serious adverse events grouped by organ system, with number and frequency of such event in each arm of the clinical trial."

From: FDAAA 801, Sec. 282(j)(3)(I)(iii)(I)

What Are Adverse Events?

"A table of anticipated and unanticipated adverse events *that are not included in the [Serious Adverse Events] table* . . . that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system, with number and frequency of such event in each arm of the clinical trial."

From: FDAAA 801, Sec. 282(j)(3)(I)(iii)(II)

Adverse Event Data Tables

42 CFR 11.48(a)(4)

Information for completing three tables summarizing anticipated and unanticipated adverse events collected by arm or comparison group

1) All serious adverse events
2) Adverse events, other than serious adverse events, that exceed a frequency of 5 percent within any arm of the clinical trial
3) All-cause mortality

What Is Included in Adverse Events?

Methods for collecting adverse events

- Time Frame
- Adverse Event Reporting Description
  - If adverse event information collected in the clinical trial is collected based on a different definition of "adverse event" and/or "serious adverse event"
  - Can also be used to clarify the analysis population, if necessary
- Source Vocabulary Name for Table Default
  - Standard terminology, controlled vocabulary, or classification and version from which adverse event terms are drawn, if any
- Collection Approach for Table Default
  - The type of approach taken to collect adverse event information, whether systematic or non-systematic

Time Frame	From the beginning to the end of the study (Week 78 plus extended safety follow-up, with an average duration of 96 weeks).
Adverse Event Reporting Description	
Source Vocabulary Name for Table Default	MedDRA (Unspecified)
Collection Approach for Table Default	Systematic Assessment

What Is Included in Adverse Events?

- For each of the three tables
  - Adverse Event Arm/Group Information
    - Arm/Group Title and Arm/Group Description
  - Total number of participants affected and at risk, by arm/group
- For serious and other adverse events
  - Descriptive term for the adverse event
  - Organ system associated with the adverse event
  - Number of participants affected by each adverse event
  - Number of participants at risk for each adverse event, if different from the total

Arm/Group Title	Rituximab 1000 mg + Prednisone	Placebo + Prednisone
Arm/Group Description	Participants received rituximab 1000 mg intravenously (IV) on Days 1, 15, 168, and 182. Participants also received an initial dose of prednisone (0.5, 0.75, or 1.0 mg/kg orally once a day) with tapering beginning at Day 16 for 10 weeks to a dose of ≤ 10 mg/day. Participants also received acetaminophen 1000 mg orally and diphenhydramine 50 mg orally prior to study drug infusion.	Participants received placebo intravenously on Days 1, 15, 168, and 182. Participants also received an initial dose of prednisone (0.5, 0.75, or 1.0 mg/kg orally once a day) with tapering beginning at Day 16 for 10 weeks to a dose of ≤ 10 mg/day. Participants also received acetaminophen 1000 mg orally and diphenhydramine 50 mg orally prior to study drug infusion.

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events	5%	
	Rituximab 1000 mg + Prednisone	**Placebo + Prednisone**
	Affected / at Risk (%)	Affected / at Risk (%)
Total	164/169 (97.04%)	85/88 (96.59%)
Blood and lymphatic system disorders		
Anaemia †A	6/169 (3.55%)	7/88 (7.95%)
Cardiac disorders		
Palpitations †A	9/169 (5.33%)	3/88 (3.41%)
Tachycardia †A	10/169 (5.92%)	3/88 (3.41%)
Endocrine disorders		
Cushingoid †A	7/169 (4.14%)	6/88 (6.82%)
Eye disorders		
Conjunctivitis †A	4/169 (2.37%)	6/88 (6.82%)
Dry Eye †A	6/169 (3.55%)	5/88 (5.68%)
Vision Blurred †A	3/169 (1.78%)	5/88 (5.68%)
Gastrointestinal disorders		
Abdominal Discomfort †A	10/169 (5.92%)	5/88 (5.68%)
Abdominal Pain †A	12/169 (7.1%)	7/88 (7.95%)
Abdominal Pain Upper †A	12/169 (7.1%)	5/88 (5.68%)
Constipation †A	15/169 (8.88%)	8/88 (9.09%)
Diarrhoea †A	30/169 (17.75%)	12/88 (13.64%)
Dyspepsia †A	8/169 (4.73%)	7/88 (7.95%)
Gastrooesophageal Reflux Disease †A	13/169 (7.69%)	7/88 (7.95%)
Nausea †A	44/169 (26.04%)	24/88 (27.27%)
Toothache †A	7/169 (4.14%)	5/88 (5.68%)
Vomiting †A	24/169 (14.2%)	11/88 (12.5%)

Similarities between Publications and ClinicalTrials.gov

Publication (Table 2)

Table 2. Adverse events in the safety population*

Adverse event	Placebo (n = 88)	Rituximab (n = 169)
Any treatment-emergent SAE	32 (36.4)	64 (37.9)
Any treatment-emergent SAE reported in ≥5% of patients		
Cardiac disorder	5 (5.7)	5 (3.0)
Infections and infestations	15 (17.0)	16 (9.5)
Gastrointestinal disorders	7 (8.0)	8 (4.7)
General disorder	5 (5.7)	7 (4.1)
Musculoskeletal and connective tissue disorders	5 (5.7)	9 (5.3)
Neutropenia	0 (0)	6 (3.6)
Any study drug–related treatment-emergent SAE	8 (9.1)	13 (7.7)
Any infusion-related AE	34 (38.6)	74 (43.8)
First infusion	26 (29.5)	46 (27.2)
Second infusion	14 (16.5)	29 (17.6)
Third infusion	7 (10.0)	23 (16.3)
Fourth infusion	4 (5.9)	25 (18.5)
Any infusion-related SAE	15 (17.0)	16 (9.5)
Any treatment-emergent infection-related SAE	15 (17.0)	16 (9.5)
Any treatment-emergent infection-related SAE reported in ≥2% of patients		
Lower respiratory tract and lungs	4 (4.5)	5 (3.0)
Bacterial	4 (4.5)	4 (2.4)
Abdominal and gastrointestinal	4 (4.5)	2 (1.2)
Sepsis, bacteremia, viremia, and fungemia NEC	3 (3.4)	2 (1.2)
Death	1 (1.1)	4 (2.4)

* Values are the number (%). SAE = serious adverse event; NEC = not elsewhere classified.

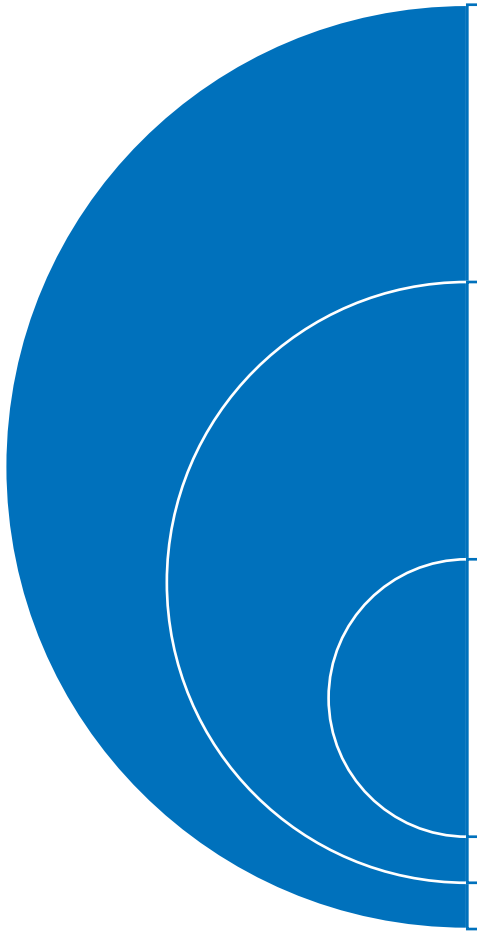
ClinicalTrials.gov

▼ **Serious Adverse Events**

	Placebo + Prednisone	Rituximab + Prednisone
	Affected / at Risk (%)	Affected / at Risk (%)
Total	32/88 (36.36%)	72/169 (42.6%)
Blood and lymphatic system disorders		
Cardiac Failure †A	0/88 (0%)	1/169 (0.59%)
Haemolytic Anaemia †A	0/88 (0%)	1/169 (0.59%)
Lymphophenia †A	0/88 (0%)	1/169 (0.59%)
Neutropenia †A	0/88 (0%)	6/169 (3.55%)
Pancytopenia †A	1/88 (1.14%)	1/169 (0.59%)
Thrombocythaemia †A	0/88 (0%)	2/169 (1.18%)
Thrombocytosis †A	0/88 (0%)	1/169 (0.59%)
Cardiac disorders		
Angina Pectoris †A	0/88 (0%)	1/169 (0.59%)
Cardiac Arrest †A	0/88 (0%)	1/169 (0.59%)
Cardiac Failure Congestive †A	0/88 (0%)	1/169 (0.59%)
Cardiomyopathy †A	0/88 (0%)	1/169 (0.59%)
Coronary Artery Disease †A	1/88 (1.14%)	1/169 (0.59%)

Adapted from: Merrill JT, et al. *Arthrit Rheum*, 2010 and NCT00137969

Best Practices



Report summary data at the end of the study.	• Not real-time adverse event reporting while the study is ongoing
Report Serious Adverse Events and Other (Not Including Serious) Adverse Events in separate tables.	
Report data in accordance with the procedures for data collection described in the study protocol.	• Use the Adverse Event Term Additional Description to describe the methods, as needed.