Outcome Measures and Statistical Analyses: 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

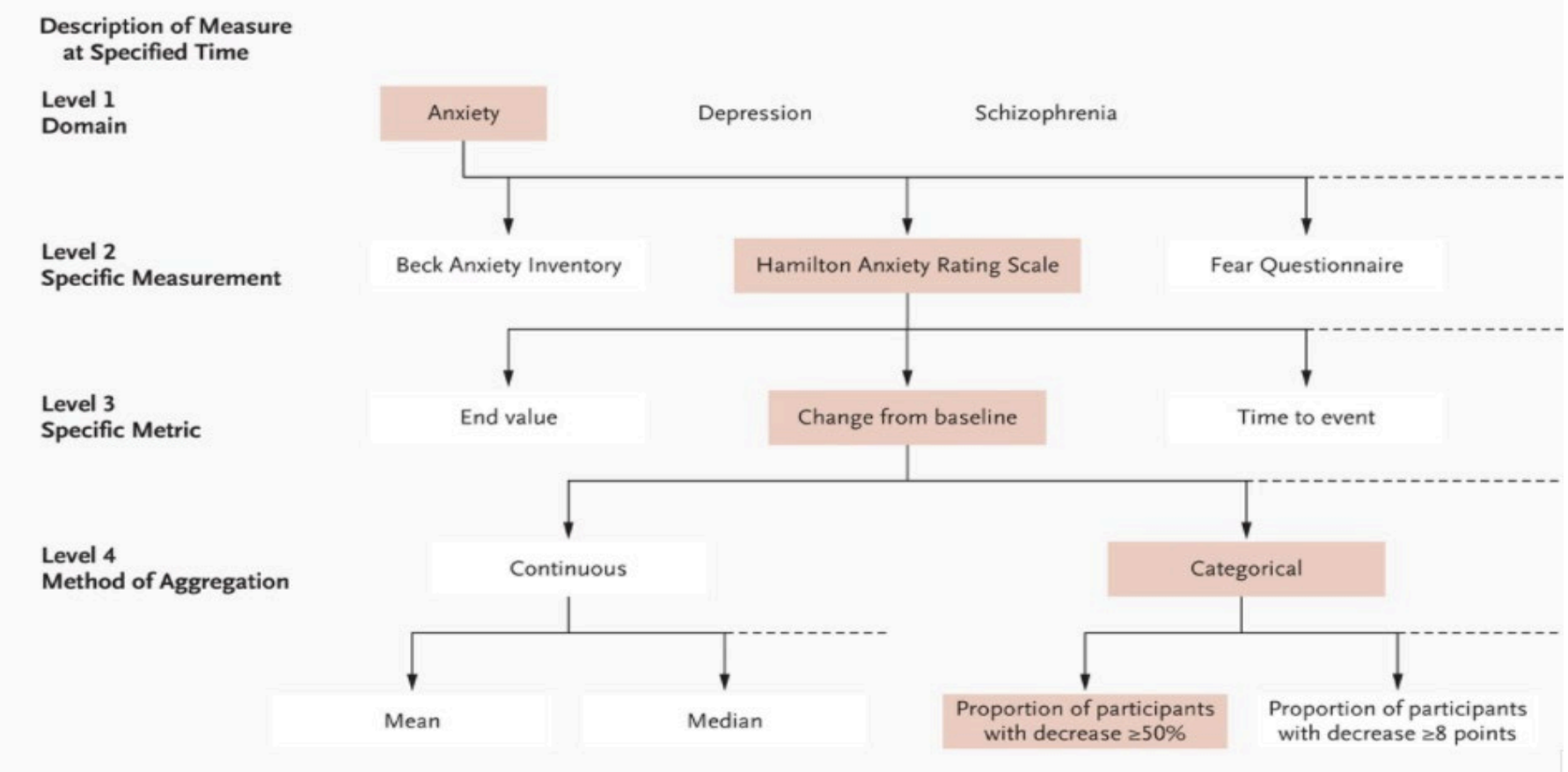
What Are Outcome Measures?

"... a table of values for each of the primary and secondary outcome measures for each arm of the clinical trial ... including the results of scientifically appropriate tests of the statistical significance of such outcome measures."

From: FDAAA 801, Sec. 282(j)(3)(C)(i)

Outcome Measures: Conceptual Framework

Four Levels of Specification in Reporting Outcome Measures



Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. *N Engl J Med*, 2011; 364:852-860.

Specification of Outcome Measures in the Protocol

	2011 Analysis	2017 Analysis
Level	Primary OMs (% Total) n = 100	Primary OMs (% Total) n = 101
1 – Domain (only)	36%	0%
2 – Specific Measurement	25%	12%
3 – Specific Metric	26%	43%
4 – Method of Aggregation	13%	45%
Included Specific Timeframe	63%	94%

Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. *N Engl J Med*, 2011; 364:852-860.
Zarin DA, Tse T, Williams RJ, Rajakannan T. *N Engl J Med*, 2017; 376:383-391.

What Is Included in the Outcome Measures?
42 CFR 11.48(a)(3)

For each primary and secondary outcome measure:

- Outcome Measure Arm/Group Information (Arm/Group Title and Arm/Group Description)
- Analysis Population Information
  - Number of Participants Analyzed
  - Number of Units Analyzed
    - If the analysis is based on a unit other than participants, a description of the unit of analysis (e.g., eyes, lesions, implants)
- Analysis Population Description
  - If Number of Participants Analyzed or Number of Units Analyzed differs from the number of human subjects or units assigned to the arm

▼ Analysis Population Description

Intent-to-treat (ITT) population

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.
Overall Number of Participants Analyzed	169	88
Measure Type: Number Unit of Measure: Participants		
MCR (excluding PCR)	21	14
PCR	29	11
Nonclinical Response (NCR)	119	63

Results from: NCT00137969

What Is Included in the Outcome Measures?
42 CFR 11.48(a)(3)

- Outcome Measure Information
  - Name of the specific outcome measure, including any categories in which outcome measure data are aggregated
  - Description of the metric used to characterize the specific outcome measure
  - Time points at which the measurement was assessed
  - Outcome Measure Type (Primary, Secondary, Other Pre-specified, or Post-Hoc)
  - Measure Type and Measure of Dispersion/Precision
    - Same modifications as described for similar elements in the Baseline Characteristics
  - Unit of Measure
- Outcome Measure Data

1. Primary Outcome

Title	Number of Participants Who Achieved a Major Clinical Response (MCR), Partial Clinical Response (PCR), or Nonclinical Response (NCR) Defined by British Isles Lupus Assessment Group (BILAG) Scores Over The 52-week Treatment Period
Description	The BILAG Index measures clinical disease activity in Systemic Lupus Erythematosus (SLE). A single alphabetic score (A through E) is used to denote disease severity for each of the 8 domains. The global BILAG score is the sum of a converted numerical score (A=9, B=3, C=1, D=0, E=0) over 8 domains. MCR = participants who achieved BILAG C scores or better at 24 weeks, maintained this response without developing a flare to 52 weeks, and did not experience a severe flare from Day 1 to Week 24; PCR = participants who achieved BILAG C score or better at 24 wks and maintained response without a flare for 16 consecutive weeks, or maximum of one BILAG B score at 24 weeks and maintained response without a flare to 52 wks, or maximum of 2 BILAG B scores at 24 wks without development of BILAG scores of A or B until Week 52 if the baseline BILAG score was 1A+>=2Bs, or>=2 As, or>=4 Bs, or participants who enrolled with scores of severe disease and did not achieve a single BILAG B at Month 6.
Time Frame	From baseline to 52 weeks

Outcome Measure Data

Analysis Population Description

Intent-to-treat (ITT) population

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.
Overall Number of Participants Analyzed	169	88
Measure Type: Number Unit of Measure: Participants		
MCR (excluding PCR)	21	14
PCR	29	11
Nonclinical Response (NCR)	119	63

What Are Statistical Analyses?

Results of scientifically appropriate tests of statistical significance of primary and secondary outcome measures (limited to statistical analyses that rely on submitted outcome measure data)

- Prespecified in the protocol and/or statistical analysis plan and performed on the outcome measure data (excludes statistical analyses considered exploratory)
- Made public by the sponsor or responsible party prior to the date on which clinical trial results information is submitted for the primary outcome measures
- Conducted on a primary outcome measure in response to a request by the U.S. Food and Drug Administration prior to the date on which clinical trial results information is submitted for the primary outcome measures

What Is Included in the Statistical Analyses?

- Statistical Analysis Overview
  - Identification of arms compared
  - Type of statistical test conducted
    - Superiority, Non-inferiority, Equivalence, or Other (appropriate for single group or other descriptive analysis)
    - For a non-inferiority or equivalence test, a description that includes the power calculation and non-inferiority or equivalence margin
- One of the following, as applicable:
  - Statistical Test of Hypothesis (procedure used and p-value)
  - Method of Estimation (Estimation Parameter, Estimated Value, and Confidence Interval (if calculated))
  - Other Statistical Analysis (general "other" option if information cannot be submitted using one of the options above)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Group Selection	Rituximab 1000 mg + Prednisone, Placebo + Prednisone
	Comments	Stratified by randomization factors (race and initial prednisone dose)
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.4875
	Comments	One-sided p-value.
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not Specified]

Where Do Outcome Measure Data Come From?

Publication

"At week 52, no difference was noted in major clinical responses or partial clinical responses between the placebo group (15.9% had a major clinical response . . .) and the rituximab group (12.4% had a major clinical response . . .)."

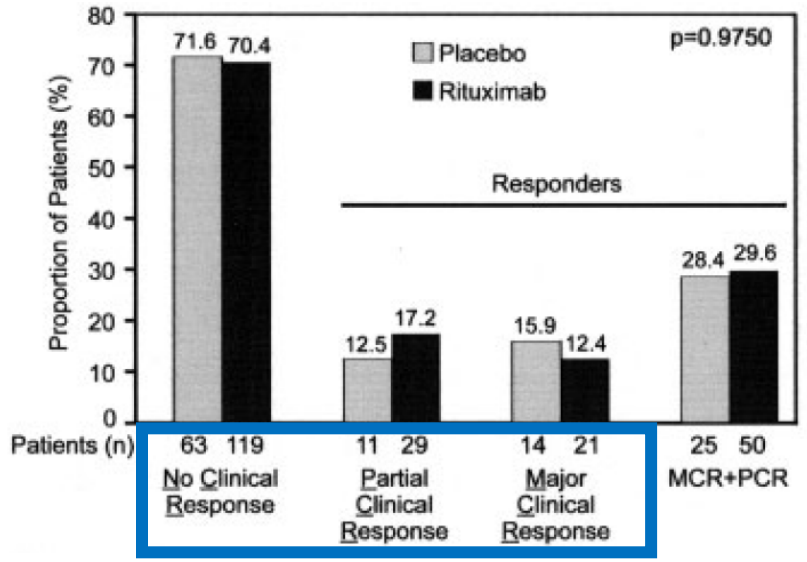


Figure 2A. Proportion of patients experiencing a major clinical response (MCR) . . . at 52 weeks

ClinicalTrials.gov

1. Primary Outcome

Title:	Number of Participants Achieving a Major Clinical Response (MCR), Partial Clinical Response (PCR), or Nonclinical Response (NCR) as Defined by British Isles Lupus Assessment Group (BILAG) Scores Over The 52-week Treatment Period
▸ Description:	The BILAG Index measures clinical disease activity in Systemic Lupus E... If reporting a score on a scale, please include the unabbreviated scale title, the minimum and maximum values, and whether higher scores mean a better or worse outcome.
Time Frame:	Baseline to 52 weeks

▾ Outcome Measure Data ✓

▸ Analysis Population Description

Arm/Group Title	Placebo + Prednisone		Rituximab + Prednisone	
▸ Arm/Group Description:	Participants received placebo intra...		Participants received rituximab 100...	
Overall Number of Participants Analyzed	88		169	
Measure Type: Count of Participants Unit of Measure: participants				
Row Title				
MCR (excluding PCR)	14	15.91%	21	12.43%
PCR	11	12.5%	29	17.16%
Nonclinical Response (NCR)	63	71.59%	119	70.41%

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

Where Do Outcome Measure Data Come From?

Publication

"The time to the first moderate or severe flare was calculated using Kaplan-Meier estimates of the flare-free time after the patient's first disease remission; the median was ~4 months in both groups (P = 0.8979)."

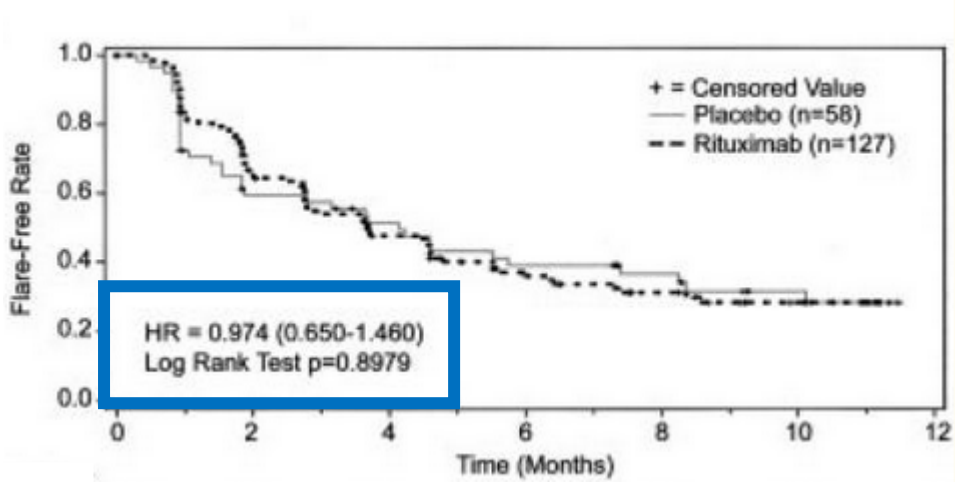


Figure 3B. Kaplan-Meier curve showing the time to moderate/severe flare over 52 weeks. HR = hazard ratio

ClinicalTrials.gov

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Group Selection	Placebo + Prednisone, Rituximab + Prednisone
	Comments	Stratified by randomization factors (race and initial prednisone dose)
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.8979
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.974
	Confidence Interval	(2-Sided) 95% 0.65 to 1.46
	Estimation Comments	[Not specified]

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

Considerations for Terminated Trials

Trial terminated before data are collected for primary and/or secondary outcomes

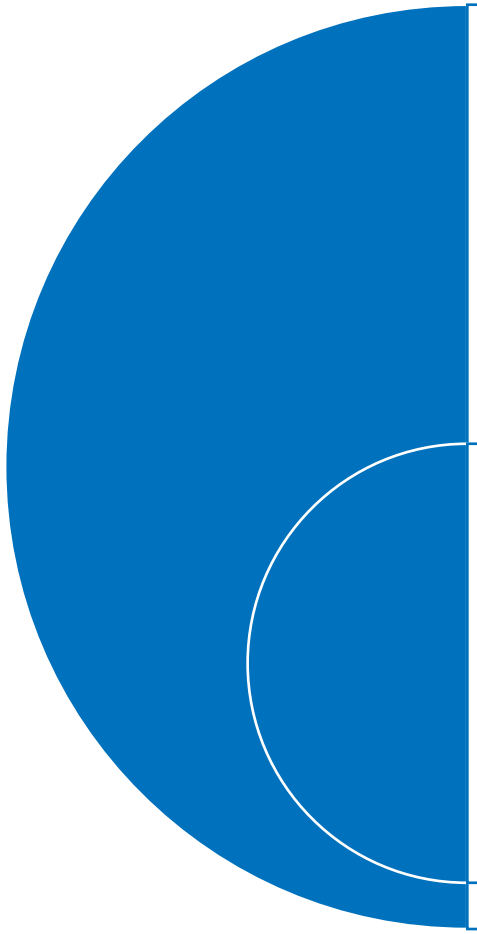
- Specify zero (“0”) for Number of Participants Analyzed.
- Outcome Measure Data are not required to be submitted.
- Participant flow, demographic and baseline characteristics, and adverse event information must still be provided.

Outcome measure data collected, but actual enrollment falls well below target

- Outcome Measure Information and Outcome Measure Data must be submitted.
- Statistical analysis information is not expected to be submitted.
- If there are privacy considerations, 42 CFR 11.54 (waiver) may apply.
  - Waivers are expected to be requested and granted in only a very limited number of situations.

Final Rule, Section IV.C.4. What constitutes clinical trial results information? – § 11.48 (81 FR 65084 - 90)

Best Practices



Use multiple outcome measures to report results for the same measure at different time points.

- Allows for accurate reporting of the analysis population

If the reporting groups are different in the Participant Flow, use the Outcome Measures Arm/Group Title and/or Arm/Group Description to explain why and to relate them to the Participant Flow Arm/Group Title and/or Arm/Group Description.