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

## Specification of Outcome Measures in the Protocol

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

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

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**
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)

<table>
<thead>
<tr>
<th>Statistical Analysis Overview</th>
<th>Comparison Group Selection</th>
<th>Type of Statistical Test</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stratifed by randomization factors (race and initial prednisone dose)</td>
<td>Superiority or Other</td>
<td>[Not Specified]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statistical Test of Hypothesis</th>
<th>P-Value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.4875</td>
<td>One-sided p-value.</td>
</tr>
</tbody>
</table>

*Method: Wilcoxon (Mann-Whitney)*

*Comments: [Not Specified]*
“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

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**

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.

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.