

Outcome Measure Considerations for Clinical Trials Reporting on ClinicalTrials.gov

What is an Outcome Measure?

An outcome measure is the result of a treatment or intervention that is used to objectively determine the baseline function of a patient at the beginning of the clinical trial. Once the treatment or intervention has commenced, the same instrument can be used to determine progress and efficacy. Outcome measures normally stem from overarching goals and aims. Outcome measures should be measurable, which indicates that they are assessed by a numerical value.

ClinicalTrials.gov Outcome Measures Classification

One way to classify your outcome measures is distinguishing into three groups: primary, secondary, and exploratory. *Primary and secondary outcomes are required by law to be analyzed and reported in ClinicalTrials.gov if any data was collected for the outcome.* The primary and secondary endpoints should be pre-specified, meaning they are determined before the start of the trial. *We recommend that you do not include exploratory outcome measures as they are optional.*

- a. **Primary Outcome Measure:** defined by ClinicalTrials.gov as “the outcome measure(s) of greatest importance specified in the protocol, usually the one(s) used in the power calculation. Most clinical studies have one primary outcome measure, but a clinical study may have more than one”. The Primary outcome measures are the main reason why you are conducting your study.
- b. **Secondary Outcome Measure:** defined by ClinicalTrials.gov as “an outcome measure that is of lesser importance than a primary outcome measure but is part of a pre-specified analysis plan for evaluating the effects of the intervention or interventions under investigation in a clinical study and is not specified as an exploratory or other measure. A clinical study may have more than one secondary outcome measure”.
- c. **Not required to report results on ClinicalTrials.gov:**
 - a. **Other Pre-Specified Outcome Measure:** defined by ClinicalTrials.gov as “any other measurements, excluding post-hoc measures, that will be used to evaluate the intervention(s) or, for observational studies, that are a focus of the study”.
Exploratory Endpoints fall into this category
 - b. **Post-Hoc Outcome Measures** refers to outcomes that are specified AFTER the trial has started.

Considerations When Selecting Study Outcomes

1. **Number of Primary/Secondary Outcome Measures:** Listing a large number of outcome measures may increase the chance of encountering issues when fulfilling the ClinicalTrials.gov reporting requirements. All primary and secondary outcomes should have complete and accurate data when possible. Even if the endpoints are later deemed to not be clinically relevant or only have limited data, they must still be analyzed and reported on if ANY data is collected for that outcome. Consider outcomes that are clinically relevant, achievable, and address realistic research questions.
2. **Secondary vs Exploratory:** Consideration should be given to whether a secondary endpoint may be better identified as an exploratory endpoint. Appropriate secondary endpoints often are used to demonstrate additional effects after success on the primary endpoint or to provide evidence that a particular mechanism underlies a demonstrated clinical effect. If an outcome is only being used to frame future research or explore new hypotheses, it may be better classified as exploratory. Exploratory endpoints may also include clinically important events that are expected to occur too infrequently to show a treatment effect.

3. **Outcome Measure Description:** What information is being collected and how it is being collected needs to be pre-specified for all primary and secondary outcomes. If a scale, grading method, device, etc. is being used to evaluate an outcome, it should be pre-specified. Verbs frequently used to describe aims should not be used to describe outcome measures such as “to determine”, “to assess”, and “to validate”.

Example 1: Instead of having the outcome be ‘to evaluate response rate’, it should instead be something like ‘response assessed using Response Evaluation Criteria for Adverse Events (CTCAE 4). Response is evaluated with the use of MRI or CT scan.’

Example 2: Instead of “measure of blood pressure”, it should be instead “change in systolic blood pressure from baseline at week 12”.

4. **Outcome Measure Time Frame:** The specific time point(s) and overall duration of evaluation must be specified in this section. If the outcome’s overall time duration can only be represented qualitatively (e.g. until the time of disease progression), a specific numeric measure should then be included at the time of results reporting. This could be something like the median duration of follow-up or the range of follow-up times.

Example 1: In the protocol, you may specify that response is evaluated after the end of every 28-day chemotherapy cycle (\pm 7 days), until the time of disease progression, for up to two years. You may report this in the time frame field on CT.gov as ‘baseline, end of every two 28-day cycles, up until disease progression (maximum of two years)’. If there was not a specific endpoint cap you may instead say ‘baseline, end of every two 28-day cycles, up until disease progression, median duration of follow-up of 18 months’.

Example 2: Time frame should specify at which time points the outcome measure data were collected: “change in systolic blood pressure was calculated at Week 12 minus baseline”.

5. **Appropriate Quantitative Parameter for Each Outcome:** Outcome measures *cannot be reported as free text, graphs, or qualitative information*. It is allowed for the outcome measure to involve qualitative information, but it must also be able to be reported in a quantitative/numeric fashion. Bear in mind that outcome measures that you might normally report as qualitative (eg. graphs, images) for publishing purposes will need to be transformed into quantitative data for results reporting in ClinicalTrials.gov. Each quantitative outcome measure also needs to include an appropriate measure of dispersion.

Below are screenshots that show all the drop-down menu options for each section listed in the Outcome Measure Data Table:

Outcome Measure Data Table

* Measure Type:	<div style="border: 1px solid black; padding: 5px;"> Number ▾ -- Select Measure Type -- Count of Participants Mean Median Least Squares Mean Geometric Mean Geometric Least Squares Mean Number </div>
* Measure of Dispersion/Precision:	

No measure of dispersion is needed for ‘Count of participant’ or other count data. For mean, median, least squares mean, geometric mean, and geometric LSM, dispersion may include:

* Measure of Dispersion/Precision:	95% Confidence Interval ▼
	-- Select Measure of Dispersion/Precision --
	Standard Deviation
	Standard Error
	Inter-Quartile Range
	Full Range
	80% Confidence Interval
	90% Confidence Interval
	95% Confidence Interval
	97.5% Confidence Interval
	99% Confidence Interval
	Other Confidence Interval Level

For the measure type of number, the measure of dispersion should be a confidence interval:

* Measure Type:	Number ▼
* Measure of Dispersion/Precision:	Not Applicable ▼
	-- Select Measure of Dispersion/Precision --
	Not Applicable
	80% Confidence Interval
	90% Confidence Interval
	95% Confidence Interval
	97.5% Confidence Interval
	99% Confidence Interval
	Other Confidence Interval Level

Statistical Considerations for Outcome Measures

The mathematical properties of an outcome measure determine the methodologies and conventions used to analyze and report the results of a study. This section gives a brief summary of these conventions for common types of measurements. Conventions for analysis and reporting for different type of measurements can have important implications for ClinicalTrials.gov reporting so investigators should think carefully about their measures and build specific and well-tailored analysis plans accordingly.

Continuous outcomes such as blood pressure, blood glucose, T-cell count and the like. Continuous outcome measures are easily reportable to Clinicaltrials.gov but there are several considerations to note.

- They are typically reported as a measure of central tendency (mean, median, geometric mean etc...). The measure of central tendency can be of values at a discrete time point (“the median pain score for the treatment group was 9”) or of a change over time (“on average the treatment group saw a 3-point reduction in pain between baseline and follow-up). An investigator should choose the correct measure of central tendency to report based on the distribution of the data. Generally, means are reported for normal or near-normally distributed data and medians or geometric means are reported for skewed data.
- ClinicalTrials.gov requires that investigators include not only measures of central tendency but also a measure of the spread of data in your experiment such as the standard deviations, confidence intervals or interquartile ranges. Standard deviations or confidence intervals should be included when reporting means and interquartile ranges should be included when reporting medians. When reporting confidence intervals, the investigator may need to refer back to any power analysis done prior to the study as this will inform which confidence interval (95%, 90% etc.) would be most appropriate. *Often an investigator will find that they did not include measures of spread in their requests to data analysts.* Once they are informed by Clincialtrials.gov that this is required it can

take considerable time to request this information again.

- Again, graphical depictions of data are not accepted by ClinicalTrials.gov so it is important to consider this upfront and include as much quantitative information as possible. Some other measures to consider reporting are measure of skewedness, kurtosis and tests for normality such as the Shapiro-Wilk test.

Ordinal outcomes such as pain scales, patient satisfaction scales and other Likert-type measures are widely used in clinical research. The considerations for reporting these types of measures are similar for that of continuous data. However, there are some things to keep in mind.

- Clinical scales are often condensed as a summary measure. Sometimes as a mean or sum of a series of questions or transformed to a dichotomous categorical variable. It is important for investigators to be familiar with the conventions for analysis of clinical scales in the literature and be explicit in their definition of outcome measures.
- Clinical scales are sometimes limited in range (consider a 1-5 scale) which can make their analysis as continuous measures tricky. In these cases, investigator should consider alternative methods of analysis such as dichotomization (dummy coding).

Categorical outcomes such as death deserve special consideration. Investigators should be explicit on how these outcomes will be presented.

- The most common presentation of categorical outcomes are proportions, but categorical outcomes may also be presented as counts, or relative measures such as risk ratios and odds ratios. It is important for the integrity of the experiment's design and ClinicalTrials.gov reporting that investigators are very specific when registering their trial in how these outcomes will be measured and presented.
- Measures of dispersion should also be included when reporting proportions or relative measures of effect. Much like the presentation of means, proportions and relative measures of effect should be presented with confidence interval. Again, look to any power analysis that was done for the study to decide which confidence interval level should be used, even though the convention is 95%.
- In certain clinical trials, investigators may wish to follow an outcome such as death out to a time-point years away from the start of the trial. Investigators should consider the feasibility of these timelines and this is a good example of how outcome measures can frame the timeline of an experiment. There are methods available to investigators for dealing with loss to follow-up in longitudinal studies such as reporting relative measures as rate differences or rate ratios with person-time used for denominators. As noted before ClinicalTrials.gov does not accept graphical depictions of data. This can present issues for reporting results for survival analysis which commonly feature a survival curve. Investigators should keep this in mind if a survival analysis is planned and they should consider reporting cumulative probabilities of death during a time period or median survival time. Investigators can also consider calculating a hazard ratio for survival analysis.

Examples:

Results Field	Incorrect Examples:	Corrected Examples:
Outcome Measure Title:	"Efficacy"	"Percentage of subjects that experienced a decrease in [measure: PSA] levels greater or equal to 75% at day 30 post-treatment with [drug]"
	"To assess survival"	"median overall survival"; "number of participants alive at 2 years"
Outcome Measure Time Frame:	"Duration of study"	" 2 years"
		" 5 months"
		" Baseline, day 3, day 5, day 20"
	"30 days after the end of treatment"	"From the start of treatment until 30 days after the end of treatment, up to 2 years"
"Until disease progression"	"From baseline until the time of disease progression, approximately 1 year"	