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## Selecting Useful Outcome Measures

### Summary

- Outcome measures assess the effect of the intervention or treatment you are studying.
  - Outcome measures can be defined as primary, secondary, or exploratory.
  - By determining your outcome measures in advance, and categorizing their importance, you can appropriately design your study.
  - Pre-specifying your outcomes and the instruments you plan to use can also help ensure that you do not have incomplete data collection.
  - Concise tables for your readers are a useful method for organizing your outcome measures, instruments, and supporting literature.
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# Selecting Useful Outcome Measures

Hannah Kostan, KerCheng Chen, and Cynthia Cheng, MD, PhD



## Summary

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- By determining your outcome measures in advance, and categorizing their importance, you can appropriately design your study.
- Pre-specifying your outcomes and the instruments you plan to use can also help ensure that you do not have incomplete data collection.
- Concise tables for your readers are a useful method for organizing your outcome measures, instruments, and supporting literature.

## Introduction

An outcome measure is used to verify the effect of the treatment or intervention in a study. In essence, you can categorize outcome measures as primary, secondary, and exploratory. Well-defined outcome measures determine the value of your study. For this reason, it is important to understand what change you are measuring and how that change can most appropriately be measured. If the selected outcome measure is unable to accurately assess the effects of the treatment, then you can lose or misrepresent vital information. By using the study aims to determine the primary and secondary outcomes, as well as listing these measures in concise tables, you will be able to gather important data regarding the effect of a given treatment or intervention.

## What are Primary Outcomes?

A primary outcome encompasses the main focus of the study. In other words, it is defined by what you are directly measuring, therefore you should clearly designate its importance in the protocol. For biomedical research, often primary outcomes have clinical significance, such as blood pressure or depression severity. Choosing outcome measures is one of the initial steps in conducting research, so if you are having trouble choosing your primary outcome measure, it is

useful to consider the reasons why you have chosen the study topic or refer to the grant for which you are applying.

Many clinical studies will only have one primary outcome, but it is acceptable to have more. Often, studies will have one primary outcome per specific aim. Outcome measures are often linked to specific hypotheses, so limiting the number of research study hypotheses can be beneficial, especially when doing so will ultimately lead to a smaller number of primary outcome measures. Having too many hypotheses and primary outcomes can result in an unfocused study, as well as issues with evaluating the differing effectiveness of intervention across all measures. For example, you might hypothesize that administering a new drug will improve digestion, sleep, mood, memory, and hospital readmissions. Including each of these expectations as a primary outcome is challenging because it can be difficult to accurately measure so many primary outcomes, and a reviewer will have a hard time discerning the focus of your study and the ultimate effectiveness of the treatment. Also, having too many outcome measures increases the probability that you will report a false positive in your study. For example, the drug might have a varying effect on each outcome, but it is difficult to obtain accurate, focused results when multiple outcomes are listed. You might find that the drug has a greater effect on hospital readmissions when all primary outcomes are considered, but when considering hospital readmission alone, the drug might have a lesser effect. Therefore, it is best to have a single primary outcome when possible. If you cannot confine your study to a single primary outcome, assigning one outcome per specific aim is a useful guideline to create parsimonious outcomes.

To prevent insufficient data collection, try to choose primary outcomes that are achievable and realistic with consideration of your time frame and budget limitations. It is imperative that all primary outcome measures should have complete data from all enrolled subjects. If incomplete data is collected for a primary outcome, you may need to exclude subjects from analysis, or use imputation methods to fill in the missing data, but these become problematic if there is too much missing data. Furthermore, a large amount of missing data for primary outcomes undermines the credibility of your study.

When you list your outcome measures, the verbiage is important. You should be as specific as possible in your hypotheses. For example, if you state that the primary outcome is “to assess cognitive impairment,” your readers will not have a clear understanding of your expected endpoint. Instead, stating “change in digit symbol coding score from baseline to week 52” is more direct and specific.

## What are Secondary Outcomes?

Unlike primary outcome measures, secondary outcome measures are generally less important outcomes. However, they are still worth measuring and analyzing due to their relation to your

aims. You can include them in your analysis to help tie together all aspects of the study. The guidelines for pre-specifying data collection and timeframe for secondary outcomes are the same as those for primary outcomes. Secondary outcomes should align with the secondary aims of your study and should still evaluate the effect of your treatment or intervention. Often, secondary outcomes may help shed light on the mechanism underlying your intervention's effect on primary outcomes. Studies typically have five to twenty secondary outcomes. While there is no limit to the number of secondary outcomes you choose, it is important to keep in mind that there should still be complete and accurate data for each. You also need to justify them in the study design. This means that they should provide additional information to support the primary endpoint. If your secondary outcomes are not justified, this could result in an unfocused study.

## How Do Secondary Outcomes Differ from Primary Outcomes?

A study sample size is usually based on the primary outcomes, but not the secondary outcomes. That is, the study should enroll enough subjects to have a statistically significant finding for the primary outcome. For pilot studies, though, you may not have an adequate sample size to have adequate study power. In this case, in the statistical analysis and sample power section of your protocol, you would instead acknowledge that your study does not have a sufficient sample size to have statistically significant results for the primary outcomes, but you could mention what sample size you may need to help plan future studies (see the chapter on Statistical Analysis and Power). Also, you need to discuss the primary outcomes in the hypotheses. For the secondary outcomes, you typically do not need to do power calculations and you may not always include every secondary outcome in your hypotheses.

## How Do Secondary Outcomes Differ from Exploratory Outcomes?

You can easily confuse secondary outcomes with exploratory outcomes. Since these outcomes have distinct characteristics (e.g., you may not report on the findings of all your exploratory outcomes), it is useful to recognize the differences between the two (see Table 1). Secondary outcomes generally follow a successful primary outcome to show supplementary data, or they are used to verify the mechanism or process behind the effect of the intervention. On the other hand, exploratory outcomes may also be linked to mechanisms, but may often be more speculative, and may not have a high likelihood of showing differences between your study arms. Exploratory outcomes are typically used as a foundation for future studies and new hypotheses.

**Table 1: Examples of Primary, Secondary, and Exploratory Outcomes.**

Type	Specific Outcome	Explanation
Primary	Mean arterial pressure (MAP)	MAP is an important clinical outcome that is often linked to risk of cardiovascular disease or other adverse health outcomes.
Secondary	Systolic blood pressure (SBP), diastolic blood pressure (DBP)	SBP and DBP are components of MAP; the equation is: $MAP = [SBP + (2 \times DBP)]/3$ . Both SBP and DBP are important, but MAP is often viewed as a more comprehensive and useful single outcome, thus MAP could be the primary outcome of a study while SBP and DBP could be secondary outcomes.
Exploratory	Number of capillaries per mm <sup>2</sup> on capillaroscopy	Capillaroscopy can evaluate the microcirculation and provide insights relative to blood pressure risks. This could help inform future studies and hypotheses or provide mechanistic insights.

## Creating Useful Summary Tables

Creating outcome tables is a practical way to keep your outcome measures organized. Tables are reader-friendly and space-efficient, so using them in a report is also beneficial. To begin, you should identify three to five studies that are most relevant to your research, also referred to as key studies (see the chapter on Literature Review). You can then use these studies to start identifying candidate outcome measures and constructing your table. The study titles are placed in the first column, the instruments used in those studies in the second column, and notes and links in the final column. Your table is a convenient tool to use when determining the instruments you want to use in your study. An example table is provided below (Table 2):

**Table 2. Sample Supportive Literature and Instruments.**

Studies	Instruments	Notes/Link
Increased EEG sigma and beta power during NREM sleep in primary insomnia, Kai Spiegelhalder et al., 2012	The Pittsburgh Sleep Quality Index (PSQI)	doi: 10.1016/j.biopsycho.2012.08.009.

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A randomized controlled trial of mindfulness meditation for chronic insomnia, Ong JC et al., 2014	The Pre-Sleep Arousal Scale (PSAS)	doi: 10.5665/sleep.4010
Specific EEG Sleep Pattern in the Prefrontal Cortex in Primary Insomnia, Perrier et al., 2015	Electroencephalogram (EEG)	doi: 10.1371/journal.pone.0116864

Following the creation of this table, you should construct another table for your outcome measures. The first column addresses the specific aim, the second column is the corresponding outcome measure, the third column is the instrument(s) or biomarker you plan to use for that outcome measure, the fourth column defines the type of outcome measure (i.e., primary, secondary, or exploratory), and the final column lists the time point in which you will collect your data for the outcome measure. This outline should be concise and easy to read. An example table is provided below:

**Table 3. Sample Outcome Measures.**

<b>Aim</b>	<b>Outcome Measure</b>	<b>Instrument</b>	<b>Primary/ Secondary/ Exploratory</b>	<b>Timepoint Collected</b>
Aim 1	Sleep onset latency (SOL)	Sleep Diary (CSD)	Primary	Baseline, 6 months, 12 months
Aim 1	Global insomnia symptoms	Insomnia Treatment Satisfaction Scale (ITSS)	Secondary	Baseline, 6 months, 12 months
Aim 2	Alpha wave activity	EEG	Primary	Baseline, 12 months
Aim 2	Cyclical alternative pattern	EEG	Exploratory	Baseline, 12 months

It is often helpful to circulate these tables to other study team members to arrive at a consensus regarding study outcomes prior to writing out a detailed study methods section. In addition, you should include this table in your research plan as it helps to enhance clarity and allows the reviewers to quickly understand what your study will be assessing.

## Conclusion

In order to conduct productive research, you should carefully consider your outcome measures. Understanding the difference between primary, secondary, and exploratory outcomes will allow you to appropriately design your study. When you pre-specify your outcomes and the instruments you plan to use to measure the effect of intervention or treatment, you decrease the probability of collecting incomplete data. A useful method for organizing your supportive literature, outcome measures, and instruments is using a tabular format. These tables and their supporting documents can then be circulated amongst the study team members to reach a consensus, after which you can move forward with designing additional details of your study. Following this system at the beginning of your study design will improve clarity, allow for a parsimonious study design, and reduce the possibility of omitting key data collection once the study begins.

## Overview Resources

1. [https://catalyst.harvard.edu/pdf/regulatory/CTR3\\_OutcomeMeasures.pdf](https://catalyst.harvard.edu/pdf/regulatory/CTR3_OutcomeMeasures.pdf)
  - a. This source is useful because it briefly explains different outcome measures, including ones not mentioned in this chapter, and differentiates between the measures to help us with identification/specification.
2. [https://journals.lww.com/anesthesia-analgesia/Fulltext/2017/08000/Defining\\_the\\_Primary\\_Outcomes\\_and\\_Justifying.45.aspx](https://journals.lww.com/anesthesia-analgesia/Fulltext/2017/08000/Defining_the_Primary_Outcomes_and_Justifying.45.aspx)
  - a. This detailed article goes into a more in-depth discussion of common mistakes made when defining outcome measures, composite endpoints, and how to describe outcome measures in a paper.
3. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3628620/>
  - a. This article is useful primarily because it explains how to pick appropriate outcome measures and when you should test them in your study.

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