Types of outcomes in clinical research

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PRACTICAL SCENARIO

In a randomized trial evaluating the efficacy of a new drug for pulmonary arterial hypertension (PAH), patients were randomly assigned to receive the new drug or a placebo. The primary composite outcome was the time to the first PAH-related event (worsening of symptoms, initiation of treatment with prostanoids, lung transplantation, or atrial septostomy) or to death. Secondary outcomes included changes in the 6-minute walk distance (6MWD) and adverse events.

DEFINITIONS

Outcomes (also called events or endpoints) are variables that are monitored during a study to document the impact that a given intervention or exposure has on the health of a given population. Typical examples of outcomes are cure, clinical worsening, and mortality. The primary outcome is the variable that is the most relevant to answer the research question. Ideally, it should be patient-centered (i.e., an outcome that matters to patients, such as quality of life and survival).

Secondary outcomes are additional outcomes monitored to help interpret the results of the primary outcome: in our example, an increase in the 6MWD is inversely associated with the need for lung transplantation. They can also provide preliminary data for a larger study. For example, a preliminary trial that uses 6MWD as the primary outcome may include mortality as a secondary outcome if the power of the study to detect a difference in mortality is low. Although investigators may be tempted to monitor several outcomes, the effort and cost to monitor various outcomes may be prohibitive. Therefore, it is essential to decide which outcome(s) to monitor (Table 1).

Surrogate outcomes are biomarkers intended to substitute for a clinical outcome, for example, 6MWD as a marker of disease severity in PAH. Surrogate outcomes are typically continuous variables and occur earlier than does the clinical outcome, reducing costs, study duration, and size. Surrogates are commonly used as the primary outcome in phase I and II clinical trials. However, they may lead to false interpretations of the efficacy of the intervention if the surrogate is not a very good predictor of the clinical outcome.

Composite outcomes are made up of multiple variables. In our practical scenario, the primary outcome was composed of several clinical outcomes related to disease progression. Using composite outcomes has the advantage of increasing the power of the study when each of the events is rare and when events are competitive (patients who die cannot have a lung transplant). However, the interpretation of results can be misleading: if the intervention reduces the occurrence of the composite outcome, it does not necessarily mean that it reduces the occurrence of all of its components.

IMPORTANT CONSIDERATIONS

- The study outcomes should be stated *a priori* (before the researcher looks at the results) in order to avoid the risk of drawing false conclusions by testing every possible variable until one is statistically significant.
- The sample size calculation should be carried out to detect a clinically relevant effect of the intervention on the primary outcome, although calculations can also be made for secondary outcome variables, which may increase the sample size but also increase trial validity.
- More importantly, the choice of the most suitable outcome should be based on the research question and the corresponding hypothesis.

Table 1. Types of outcomes.

Outcome	Patient-centered	Composite	Surrogate
Asthma	Asthma control (questionnaire)	Hospitalization or a > 20% decline in asthma control	FEV_1, peak flow, eosinophils
PAH	2-year survival	Lung transplantation or death	6MWD, PASP
ARDS	Hospital survival	Time to extubation or tracheotomy	PaO_2/FiO_2 ratio, ventilator-free days

PAH: pulmonary arterial hypertension; 6MWD: six-minute walk distance; and PASP: pulmonary artery systolic pressure.

RECOMMENDED READING

1. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013;369(9):809-18. https://doi.org/10.1056/NEJMoa1213917
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