Types of outcomes in clinical research

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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 | FEV1, peak flow, eosinophils         |
| PAH ARDS      | 2-year survival  | Hospitalization or a > 20% decline in asthma control | Lung transplantation or death       |
|               | Hospital survival| Time to extubation or tracheotomy               | 6MWD, PASP                          |

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

RECOMMENDED READING

1. Pulido T, Adzenihko I, Channick RN, Delcroix M, Galié 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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