Intercurrent events in clinical research: 
the norm, not the exception

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PRACTICAL SCENARIO
A pulmonary and critical care team designed a randomized controlled clinical trial (RCT) to evaluate the efficacy and safety of a new drug vs. standard of care on reducing the number of hospitalizations due to COPD exacerbations within one year among adult patients. Both interventions (new drug and standard of care) required daily inhaler use throughout the follow-up period; therefore, daily adherence was monitored. Importantly, researchers anticipated a nonpreventable problem related to longitudinal studies: participants could die due to common comorbidities, which constitutes an intercurrent event.

INTERCURRENT EVENTS
In RCTs, intercurrent events are defined as events that occur after treatment initiation and either affect the ability to measure the intervention of interest or prevent the occurrence of an outcome over follow-up (Figure 1). Adverse events that lead to study arm crossover or discontinuation of the assigned treatment are considered intercurrent events, because they prevent the continuation of the assigned intervention. Since these events impact the interpretation of study results, we must consider them when defining the research question, study design, and analysis.

COMPETING EVENTS—WHEN THE OUTCOME CANNOT OCCUR
Competing events are a particular type of intercurrent events; they prevent the study outcome from occurring.(1) In our example, participants who died due to other reasons and prior to a hospitalization due to a COPD exacerbation could no longer experience the study outcome. Consequently, death determines that the risk of a COPD exacerbation-related hospitalization for these participants is zero. Therefore, when calculating the measure of effect, such as risk difference or risk ratio between the two study arms, we must be careful when interpreting the results, because part of the effect of the new intervention when compared with the existing one may be explained by how and/or if the intervention affected the competing event.

CENSORING EVENTS—WHEN THE OUTCOME CANNOT BE MEASURED
Competing events can also be defined as a censoring event in some settings. Censoring events are those that may prevent investigators from measuring the outcome, as opposed to preventing it from happening. For example, when participants move to another geographical area and follow-up is interrupted, investigators cannot determine whether those participants were hospitalized, died for other reasons, or remained outcome-free. Censoring

Figure 1. Illustration of different intercurrent events that may happen over follow-up in a controlled trial (or in an observational study). Each identification (ID) represents the path followed by a different participant.

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relies on the assumption that participants who were lost to follow up (censored) share similar measured and unmeasured demographic and clinical characteristics with those who remained in the study. This assumption is called the "independent censoring assumption", and it requires extensive expertise on the topic of interest to evoke it.\(^1\)

In our example, defining death due to other causes as a censoring event would require that we conceptualized this event as preventable by study design (just as loss to follow-up) and assumed that those who died are demographically and clinically comparable to those who remained in the study. Similarly, having a lung transplant could be considered a competing event, because lung transplant patients no longer have COPD and thus cannot be hospitalized for COPD exacerbations. However, treating lung transplant as a censoring event could be reasonable in some settings.\(^2\)

Careful consideration of the impact of intercurrent events on study results is necessary when designing analytical approaches in order to provide accurate and reliable results to inform patient care and health policies.

**KEY POINTS**

- Identify all potential intercurrent events that can occur over follow-up when designing RCTs or longitudinal observational studies
- Clear definitions of intercurrent events help refine research questions
- Identify data that need to be collected longitudinally to account for intercurrent events
- Facilitate result interpretation and implications
- Report frequency (absolute and relative numbers) of intercurrent events across the variable
- Consult with an expert when conducting longitudinal studies with competing events

**REFERENCES**

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