

Adverse Event Reporting in Clinical Trials: Time to Include Duration as Well as Severity

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Assessing the efficacy of therapy involves a complex interplay between the risks and benefits within particular patient populations. The concept of patient benefit has been well established. Direct patient benefits are typically assessed with regard to patients living longer, living better, or both.

Assessing risks of therapy can be more difficult. To properly assess risks, one must have a clear understanding of risks imposed by the underlying disease and how that risk might be counterbalanced by therapeutic interventions. Acceptable risk profiles of pharmaceuticals used to treat potentially lethal cancers are quite distinct from those associated with treatment of milder conditions such as hypertension or hypercholesterolemia.

By convention, one of the key ways that risks of therapy are conveyed is by using tables that capture frequencies of adverse events (AEs). These AE tables are part of virtually all major clinical trials, and such data are frequently presented in package inserts that accompany regulatory approval. There are many attributes for this system, pioneered by the National Cancer Institute, but the deficits are not commonly discussed.

Current AE tables are restricted to the grade and frequency of events within the trial population, but there is no reporting that allows discernment of either the kinetics or the duration of these events. Thus, the current commonly used AE tabular approach that focuses on frequency has significant deficiencies that impair proper assessment of the risks that occur as a consequence of cancer therapies.

Imagine that a “Drug A” and an underlying disease both are associated with fatigue. Imagine that patients treated with “Drug A” experience moderate (grade 2) fatigue 1 week after starting therapy and that this fatigue persists (continuously) for 1 year. In the same trial, a similar number of patients received placebo. These individuals initially experience no fatigue; however, as their underlying disease progresses, grade 2 fatigue becomes notable during the last month of observation.

If a typical current AE table were to be constructed, both the placebo and “Drug A” might appear to have a similar frequency of the adverse event, and one could reasonably conclude that placebo and “Drug A” had similar fatigue-inducing properties. In truth, however, one group of patients has a persistent drug-induced effect, whereas the other group has suffered transient fatigue consequent to disease progression.

Another example, just for heuristic discussions, would be nausea. After chemotherapy, a transient grade 1 nausea may have little impact on quality of life. However, with an oral medication, a persistent grade 1 nausea that occurs every day for 24 hours a day is very different. Again, in the current tabular AE reporting schema, the adverse event rate would appear to be similar but the actual effects perceived by the patient would be very different.

As clinicians and regulators consider the risk and benefits of therapy, it would be optimal to have a better representation of the AEs profile than currently provided. Perhaps a straightforward solution would be to simply capture the duration of graded AEs in a quantitative fashion. This is distinct from kinetics but would solve some, but not all, problems associated with current AE tables. If the duration of AEs were represented by grade, the current tables would have more complexity, but also more accuracy. For small trials, one could also envision “swimmer’s plots” or “spider plots” for various grades of AEs, similar to those now commonly used to communicate individual duration of responses and time to progression.

Taken together, it is time to reconsider the overly simplistic AE table that served oncology well during the chemotherapy era. Communication of AE duration and kinetics can improve the assessment of risks during clinical trials and ultimately lead to better clinical decision-making.

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