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Making Sense of Biostatistics: Stopping Rules

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> You got to know when to hold 'em, know when to fold 'em,
> Know when to walk away and know when to run.
>
> – The Gambler

Kenny Rogers could have been writing the charter for a data and safety monitoring board (DSMB) in a clinical study. Allow me to explain. Consider a randomized clinical trial to compare two medications. There is a clear outcome variable, say 90-day survival, and a reasonably complete list of potential side effects. Also, the sample size is adequate to detect an anticipated difference in outcomes 90% of the time. Under what circumstances might the trial be stopped before enrolling all the planned subjects and following them for 90 days? These circumstances would be specified in the charter of the DSMB or a similar group.

In general, a DSMB examines the data at intermediate time points to see how the trial is going and advise the study sponsor whether to proceed. Formally, the DSMB can say either, "Keep doing what you're doing, everything looks good" or "Stop! There are some issues to be addressed." The "Stop!" order can be given for three reasons:

- **Fold 'em.** The DSMB has determined that outcomes in one arm of the trial are significantly worse than in the other arm. The better treatment should not be denied to subjects randomized to the inferior arm.
- **Walk away.** Preliminary analysis indicates that even if the trial goes to completion, it is highly unlikely that data yet to be collected will support an analysis that shows a statistically significant difference between the two treatments. Better to quit now and save money.
- **Run away.** The DSMB has determined that subjects in one arm of the study are experiencing serious adverse events at a significantly higher level than in the other arm, and the study must be stopped to avoid additional harms. Or, there are safety issues with both arms of the trial.

Statistical analysis of data at intermediate time points can be quite complex. For example, a difference in outcome for just a few subjects can swing a test result from significant to non-significant; for this reason the α-value (alpha value) for an early test is usually set very low, e.g., 0.001. (α is the probability of making a type 1 error, that is, the probability of accepting a false positive result.) α-Levels for later analyses may be set at progressively higher values; however, the sum of the alphas should not exceed the predetermined value for overall statistical significance, generally 0.025 for one-sided tests and 0.05 for two-sided tests. (Distributing α-values over the various analysis points is called "α spending." A general technique for specifying α-levels at intermediate analysis points was described by O'Brien and Fleming in 1979.[1])

DSMBs are frequently reluctant to suggest stopping a trial at an early stage, even if an analysis shows $p<0.001$, and this reflects justified skepticism that initial results that look definite may in fact be a statistical fluctuation.[2] Finally, there are ethical reasons not to stop a trial early, even though stopping early to make a new treatment available might benefit subjects in the inferior treatment arm or even the general population. For example, allowing the study to continue might reveal additional information about serious side effects of the new drug that are not yet revealed.

There is a vast literature on stopping rules. Two excellent treatments of the subject are readily accessible to the non-statistician.[3,4]

References

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