**NEWS IN DEPTH**

**Q&A: Rajeshwari Sridhara, Robert Temple on Trial Design**

Adaptive and enrichment clinical trials come with pluses and pitfalls for researchers

As part of its longstanding quest to improve options for clinical trials, the U.S. Food and Drug Administration issued draft guidance on enrichment strategies for clinical trials in December. The document complements draft guidance on adaptive design for clinical trials issued in 2010. Robert Temple, MD, deputy director for clinical science in the agency’s Center for Drug Evaluation and Research, and Rajeshwari Sridhara, PhD, division director in the Office of Biostatistics, played lead roles in developing both documents. They spoke with Cancer Discovery’s Suzanne Rose about trends in trial design for oncology drugs.

**What is meant by adaptive design? Enrichment design?**

**Temple:** An adaptive design allows you, in a formal way, to look at the data at an interim point in the trial and modify some aspect of the trial. For example, if the population in your clinical trial isn’t as sick as you expected, you could increase the sample size because the number of people who progress or die is lower than you thought it would be.

The possibility of taking interim looks and dropping doses that don’t increase the response rate, with appropriate statistical correction, is another kind of adaptive design.

**What can you do in early studies is far more flexible than in a study intended to be a definitive trial. We’re very worried about alpha error—the possibility that you find a beneficial effect that really isn’t there—in the definitive trial.**

**Sridhara:** Enrichment means selecting the study population in which you are most likely to see a benefit, if one exists.

**What types of selection are used for enrichment?**

**Temple:** There are 3 basic kinds. One is noise reduction. If you are testing a drug, you could screen people to see whether they will take it. There’s no point in randomizing people to the trial if they will not take the drug.

The second kind is prognostic enrichment—you try to find people who are going to have a lot of the events of interest. If you’re doing a trial of adjuvant therapies to see whether you can prevent recurrent, metastatic breast cancer, you want to enroll people who are likely to develop metastases, so you look for people who have genetic predictors for that.

The third type—and this has the cancer world very excited—is predictive enrichment. If you can find people who respond to a particular therapy and enter only them into the trial, you don’t expose people who can’t respond to a potentially toxic therapy—and you get a dramatic response rate. A classic example of this is Herceptin [trastuzumab; Genentech/Roche].

**Can enrichment and adaptation be combined?**

**Temple:** Yes. Suppose you start your trial, take a planned look at the data at 6 months, find a genetic predictor of response, and discover that only people with this marker responded. You can adapt the rest of the study and only enroll people with that marker. You’d have to analyze all the patients in the trial or only the newly randomized ones, and in most cases, you’d have to make a statistical correction, but the increase in sensitivity and efficiency would be vast in comparison.

**What are the disadvantages of these trial designs?**

**Temple:** The worry for more adventurous adaptive designs is the same worry you always have when you look at data many ways: multiplicity, leading to an increased error rate. Let’s say the overall study doesn’t show anything, so you have a large group of people who are at risk. If you modify the analysis to look at only those patients, you’d have to make a substantial statistical correction, and the correction might not even be credible. You could, of course, do the next study in people over 60. Although one cannot engage in what is often called data dredging, it does make sense to look in the data for subgroups that behave differently. There’s nothing wrong with this, but you have to adjust your statistical analysis to be sure you don’t increase the alpha error.

**Sridhara:** These studies may bring in operational bias, which can arise when people who know the interim results unconsciously influence the study. Also, changing the trial design based on such results is risky.

**What are the limits on findings from these trials?**

**Temple:** One is that if you study an enriched population, you may not know as much as you’d like to about the nonenriched population. Might they also respond to the drug?

**Sridhara:** With respect to adaptive design, the question is whether there is a planned way of looking at the data and adjusting for looking at the data multiple times. We should be able to say that the results are not due to chance.

**What oncology drugs have been approved on the basis of adaptive trials?**

**Sridhara:** Many. For instance, for metastatic, castration-resistant prostate cancer, we approved Xtandi [enzalutamide; Astellas Pharma/Medivation] based on interim analysis of overall survival.

**What else should researchers keep in mind?**

**Sridhara:** They should consult regulators about the best design, and statisticians familiar with that design.