ADAPTIVE TRIALS AND ELECTRONIC ADHERENCE MONITORING

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The classic approach to decision-making in clinical research is the randomized controlled trial (RCT). Patients are assigned at random to treatment conditions according to sample sizes that are determined *a priori* by power calculations. The data are not analyzed until the end of the study, at which time assignment codes are broken. Most clinical trials employ the intent to treat (ITT) strategy, which involves retaining all patients enrolled in the trial to its end. Decisions about efficacy are made on completion of the trial. Due to the cost and time involved in recruiting and processing subjects, size determination is critical. It is done by a pre-trial power calculation. Unfortunately, this calculation relies on parameters that are rarely available during the study of new drugs –within-subject variability and magnitude of experimental effect.

Estimates of experimental effect are derived from previous experience with the subject matter. In the case of Investigational New Drugs (INDs), there is often little such experience on which to draw. If the IND belongs to a well-studied class of drugs, reasonably accurate estimates may be available, but this is the exception rather than the rule. Generally, researchers simply make educated guesses about this parameter.

Within-subject variability is complicated. Empirical research can be viewed as the optimization of a signal-to-noise ratio. The signal is the desired therapeutic effect and the noise the myriad sources of within-subject variability. In clinical research the latter variability is complex.

Because of the many sources of noise and the generally poor estimates of magnitude of effect, clinical trials pose a dilemma for their designers. In this approach the study methodology, including sample size, must be specified *a priori,* and cannot be changed once the trial has commenced.Since power increases with sample size, the use of large samples gives the best chance of demonstrating a statistically significant treatment effect. However, large samples are expensive to obtain due to the difficulty of recruiting and processing large numbers of subjects. Since power calculations require an estimate of the magnitude of effect, and since this value is generally quite subjective, the research designer essentially guesses about a value that will determine the sample size anticipated to give the best chance of detecting a therapeutic effect if one exists. At the time of trial implementation, then, the researcher is committed to a process that may or may not be the most effective way of testing the effectiveness of an IND.

Statisticians have long recognized the problems associated with launching protracted trials that do not allow for intra-trial correction. Delays in getting important drugs to market and keeping patients on ineffective protocols for longer than necessary are two examples. However, due to a combination of statistical advances in gaming theory, the application of such advances to the area of clinical research, and increasing pressure on regulatory bodies to speed up the drug approval process, there is a move toward the use of adaptive clinical trials. This can be described broadly as the use of methodologies that allow modification of research protocols in real time according to pre-established criteria. On the basis of data obtained during the early stages of the trial the protocol can be modified to optimize early rejection of ineffective INDs and earlier approval of effective drugs.

Unfortunately, nothing comes without a cost. First, there are statistical arguments that question the validity of adaptive methodologies. Since clinical research is generally an inexact science, these arguments may be more philosophical than of practical significance. However it is impossible to ignore the fact that decisions must be made regarding each adaptation, and each such decision carries the risk of a Type I error (false positive). The more adaptations, the greater the risk. Second, and more troublesome, is that the adaptations to be used in an adaptive clinical trial must still be specified *a priori*, only now the number of estimates of the magnitude of effect is greater (one for each adaptive step), compounding the problem as compared to trials requiring only one such estimate. The accuracy of the outcome will still only be as good as the effect estimates. Within-subject variability remains a problem, and to this is added the inflated risk of Type I errors (false positives).

This leads us back to the issue of patient non-adherence with medication regimens. This is a major source of within-subject variability and one that to this point largely has been ignored. In classic designs, monitoring medication adherence can control for a significant part of the within-subject variability, resulting in more powerful designs. Applying electronic compliance monitoring (ECM©) to the multiple stages of adaptive trials can have a compounding positive effect, as at each level of adjustment there will be a greater chance of making the correct statistical decision. In this way regulatory approval of effective INDs will be quicker, as will rejection of ineffective drugs with, in both cases, large cost savings.

Adherence monitoring can be used to:

- Provide motivational feedback to patients during a trial
- Adjust trial data by statistical means
- Guide patient assignment adaptations in adaptive trials.

The FDA, through its Critical Path initiative[1], has expressed an interest in the application of new tools to clinical trials. Clearly adaptive trials and medication adherence monitoring should be an integral part of this process.

[1]http://www.fda.gov/oc/initiatives/criticalpath/