Med-ic® and the PHASE 2 GO/NO GO DECISION?

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One of the most critical decision points during drug development is to make a phase 3 go/no go decision after a phase 2 proof of concept trial is conducted.

Hong, S and Shi, L. *Stat Med* 2012, *31*, 831.

Patient compliance data can be highly effective in phase 2 *post hoc* analyses leading up to the go/no go decision regarding a move to phase 3. Once the phase 2 objectives of assessing safety, tolerability and effectiveness have been met, the question is whether or not to proceed to phase 3 with its considerable resource requirements.

This multifactorial decision, generally made by balancing the current condition of a development organization's portfolio, the future cost of development, the competitive landscape, and the expected safety and efficacy benefits of a new therapy, needs to be a good one.

Sabin T et al. *Stat Biopharm* 2014; *6*(1), 67.

As an example, perhaps you end up with data from your phase 2 trial that do not convincingly argue either for "go" or "no go". Safety does not appear to be an issue and pharmacokinetics are known, but support for effectiveness is equivocal as you were only able to test a small number of subjects. On the one hand you are not able to argue convincingly for continuing, but on the other hand the data do not clearly support abandoning the drug. Although your pill counts suggest 85 percent subject compliance, you know there is strong evidence in the literature that it is more likely to be 50 or 60 percent. Could the equivocal results be the result of poor patient compliance or, worse, poor compliance-induced bias?

How does the use of Med-ic smart blister packages change the picture? Consider the example of a phase 2 trial of an anti-hypertensive IND. Primary outcome analyses show a modest blood pressure reduction overall but no significant difference between the IND and the comparison drug(s). The logical conclusion is that the IND is not differentially effective. However you had wisely utilized Med-ic and you now turn to the compliance data. There was a typically wide range of compliance (43 to 78 percent[1]) averaging 55% across groups. When the primary measures are corrected for noncompliance there is a significant difference between those treatment subjects who took the medication as

1. Osterberg L and Blaschke T. Adherence to medication. N Engl J Med 2005, 353, 487-497.

prescribed and the placebo plus non-compliant treatment subjects. Where the primary data might suggest abandoning the drug, Med-ic adherence data analysis shows that it really deserves further investigation.

Med-ic generated compliance data can be applied in a number of ways. Covariance analysis can be used to adjust primary outcome measures for compliance to see if there is a compliance effect. Subjects can also be stratified by compliance levels (eg: top 50%/bottom 50%) and *post hoc* analysis (eg: ANOVA) used to determine if there is a compliance by treatment interaction. In this way compliance-related effects that would not be evident from the primary outcome analyses may be detected, providing important input to critical "go/no go" decision-making.

In the case of good overall subject compliance, decisions based on primary outcome analyses can be made with confidence. Unfortunately, subject compliance cannot be predicted accurately *a priori* with the exception of a few populations known to be poorly compliant. The more variable the compliance rates the more useful the Med-ic generated data are in "unmasking" treatment effects that would otherwise go undetected.

Compliance data can also detect treatment bias. If compliance is systematically poorer for a treatment group than for a placebo or comparison group it may indicate subtle side effects that might otherwise go unreported. Conversely, if compliance is higher for a treatment group it may indicate that those subjects are detecting a positive effect (planned or otherwise as, for example, mild euphoria) and being motivated by this.

The goal of clinical trials should be 100% compliance with the medication regimen, something we know is rarely achieved. With this goal in mind, the highest and best use of electronic compliance monitoring is to allow CRMs to detect poor compliance early in the trial and correct it through education and motivational counselling a follow-up visits. Analysing the trend of compliance over time will demonstrate the degree to which such interventions are effective in the treatment population of interest.

The cost of equipping a phase 2 trial with Med-ic is quite modest and, if incorporated from the outset, can actually reduce the cost of the trial (see the Med-ic ROI calculator).

The conclusion:

Electronic compliance monitoring can play an invaluable role in phase 2 "go/no go" decision-making with up-front costs that are minimal compared to the return on investment.