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

Allan Wilson and Michael Petersen

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

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.

For example, perhaps you end up with data from your phase II 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 adherence, you know there is strong evidence in the literature that it is likely to be nearer 65 percent. Could the equivocal results be the result of poor patient adherence or, worse, poor adherence-induced bias?

How does the use of Med-ic® smart blister packaging change the picture? Consider the example of a phase II 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 adherence data. There was a typically wide range of adherence (43 to 78 percent[1]) averaging 55 percent across groups. When the primary measures are corrected for non-adherence there is a significant difference between those treatment subjects who took the medication as prescribed and the placebo plus non-adherent treatment subjects. Where the primary data might suggest abandoning the drug, Med-ic® adherence data show that it merits further investigation.

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

In the case of good overall subject adherence, decisions based on primary outcome analyses can be made with confidence. Unfortunately, subject adherence cannot be predicted accurately *a prior* with the

1. Osterberg L and Blaschke T. Adherence to medication.NEJM 2005, 353, 487-497.

exception of a few populations known to be poorly adherent. The more variable the adherence rates, the more useful the Med-ic® data are in "unmasking" treatment effects that might otherwise go undetected.

Adherence data can also detect treatment bias. If adherence is systematically poorer for the treatment group than for the placebo or comparison group, it may indicate subtle side effects that might otherwise go unreported. Conversely, if adherence is higher for the 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 percent adherence with the medication regimen[2], something that is rarely achieved. With this goal in mind, the highest and best use of electronic adherence monitoring is to allow clinical research monitors (CRMs) to detect poor adherence early in the trial and correct it through education and motivational counselling at follow-up visits. Analysing the trend of adherence over time will demonstrate the degree to which such interventions are effective in the treatment population of interest.

The cost of equipping a phase II trial with Med-ic® smart blister packaging is quite modest and, if incorporated from the outset, can significantly reduce the overall cost of the trial (see the Med-ic ROI Calculator)

The conclusion:

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

[2]Czobor P, Skolnick P. The secrets of a successful clinical trial: Compliance, Compliance, and Compliance. *Mol. Interv*, 2011, *112*, 107-110.