HOW CAN Med-ic® HELP WITH THE PHASE 2 GO/NO GO DECISION?

Michael Petersen and Allan Wilson

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.

Med-ic is a medication event monitoring system in the form of a smart blister package. As an add-on to a phase 2 clinical trial, Med-ic-generated data can be highly effective in the *post-hoc* analyses leading up to the go/no go decision regarding a move to phase 3. Once the phase 2 objectives of establishing safety and tolerability, determining dose range, and possibly noting early signs of efficacy have been achieved, a decision to move to phase 3 involves the commitment of considerable 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.

As an example, perhaps you end up with data from your phase 2 trial that do not convincingly argue for "go" or "no go". 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, for instance 90 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 adherence or, worse, poor adherence-induced bias?

Consider the example of a trial of an anti-hypertensive drug. Primary outcome analyses show a modest blood pressure reduction overall but no significant difference between the treatment and comparison groups. The logical conclusion is that the drug is not differentially effective. However you had wisely utilized the Med-ic compliance monitor and you now turn to compliance data. There was a wide range of compliance (43 to 90 percent) averaging 65% across groups. When the primary measures are corrected for noncompliance there is a significant difference between those treatment subjects who took the medication as 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 serious consideration for a move to phase 3.

Med-ic generated data can be used for *post hoc* (after the trial has concluded) analyses of outcome data either by covariance analysis (in an effort to find meaningful differences between subject groups) to correct for compliance-related error, or by stratifying (sorting) subjects by compliance level. In this way compliance-related bias that would not be evident from the

primary outcome analyses may be detected, providing support for critical “go/no go” decision-making.

In the case of good subject compliance, decisions based on primary outcome analyses can be made with confidence. But one wouldn’t be able to predict accurately subject compliance *a priori* (before the trial starts). Where subject compliance is highly variable it Med-ic generated adherence data could be crucial in “unmasking” treatment effects that would otherwise go undetected. If compliance is systematically poorer for a treatment group than for a 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 positive effects (planned or otherwise as, for example, mild euphoria) and being motivated by this.

Conclusion: ***Electronic compliance monitoring is an invaluable tool to support phase 2 “go/no go” decision-making***.