ARGUMENTS FOR PHASE III ADHERENCE MONITORING

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Inertia is difficult to overcome. When IMC introduced the Med-ic® electronic compliance monitor (ECM) in 2002 it represented the potential for a revolution in clinical trials. No less eminent a statistician than Bradley Efron, Professor of Statistics and Biomedical Data Sciences at Stanford, predicted:

> "***At some point, perhaps not in the far future, it will seem as wrong to run a clinical trial without adherence measurement as without randomization.***"
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> Bradley Efron, *Statistics in Medicine*, Vol. 17, 249-250 (1998)

Of course this idea was not immediately accepted. Although nearly everyone agrees that patient non-adherence is a huge problem, many involved in clinical research were resistant to the idea and much of that resistance was not rationally based. Many rejected the idea simply on the basis of what they perceived as additional cost. With the new generation of Med-ic adherence monitors cost is no longer a reason to ignore non-adherence. The positive effect of adherence monitoring on clinical trial economics is clearly demonstrated by IMC's ROI Calculator, putting this argument to rest.

While ECM has been used increasingly in clinical trials over the last few years, this has largely been as an-add on to already-designed studies or as REMS. However, *post hoc* analysis is not the optimal use for ECM data. The best use is to monitor patient adherence during clinical trials and provide targeted education and motivational feedback ("coaching") during follow up visits with the clinical research monitor (CRM). This use is just coming online, as it needs to be incorporated early in the trial planning process.

With the economic argument out of the way, resistance to adherence monitoring is still seen in the form of concerns about generalization from the trial sample that is "coached" by the CRMs using ECM data, to the population of patients that will be taking the drug post approval. The argument is that the results are not generalizable unless the commercially available drug also incorporates identical adherence coaching or, conversely, that trial subjects are equally non-adherent to the target population.

There are several parts to the answer to this concern. First, science does not progress by ignoring problems for which there is consensual validity. There is simply no logical argument to support ignoring a known problem, especially one that can be measured and addressed.

Second, the current situation without ECM is that anything less than perfect adherence introduces error variance into a trial's statistical analyses. This undermines the ability of the trial to assess accurately the drug's effectiveness in an adherent population. This in turn creates a safety issue where, during commercialization, dosing schedules will be based on under estimates of the drug's efficacy (i.e. higher doses will be prescribed). This places fully adherent post-approval patients, who are always encouraged to be 100 percent adherent, at risk for toxicity. In the interest of safety, every effort should be made to ensure trial subjects are maximally adherent. After all, the instructions to post approval patients always advise full, not partial, adherence.

The idea that clinical trial subjects should be as adherent as possible is not a foreign concept, as it has support in the literature[1]. In addition, CRMs do "coaching" in one form or another during most clinical trials. Just seeing a subject weekly in a research setting differentiates that subject from the target

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

population, which will not have such follow up. Pill counts, medication diaries, and blood samples can all result in “coaching” that will not be continued when the drug reaches the target population. If a patient following up with a CRM has not completed their diary, the CRM will likely engage in a form of “coaching”. For most trials this “coaching” is highly scripted. Scripting can also be used with ECM, where adherence data can be shown to the patient in graphic form along with standardized motivational counselling about the need to take the medication on schedule. This feedback can also be completely automated or delivered by an app, structuring the “coaching” to ensure that all subjects, both treatment and control, get the same message. This ultimately increases the accuracy of assessing the drug’s effectiveness.

“Better the devil you know than the devil you don’t”

Unattributed proverb

One thing is well-known – patient adherence decreases over time. Consistent motivational counselling will result in improved mean adherence for the duration of the trial. At the end of the trial two things will have occurred: mean adherence will have improved due to the “coaching” effect and adherence will be less variable, as highly non-adherent outliers will have derived more benefit from “coaching” because they initially had more room for improvement. The investigator also has a known adherence baseline for the population of interest to use in transitioning to commercialization.

Without adherence monitoring the situation is more confusing. Although the investigator knows (or should at least suspect) that some subjects are non-adherent, the magnitude of the non-adherence is unknown. In this scenario there is no systematic “coaching” to motivate non-adherent subjects to improve, and outliers remain wild cards that contribute disproportionately to error variance. At the end of the study the investigator does not have an adherence baseline to guide the transition to commercialization. Generalization from clinical trial to commercial application will be safer and more predictable when the data are based on intra-trial motivational counselling using targeted education based on adherence data.

In addition, ECM may detect biases that might otherwise go unnoticed. If a placebo group is consistently more adherent than a treatment group it may be due to a subtle side effect of the drug. Conversely, if the treatment subjects are more adherent they may have broken the blinding by noticing a therapeutic effect or, possibly, a positive side effect such as mild euphoria. In either case, the effect might be subliminal and not noticed by the subjects.

Adherence data can have a significant effect on the power of a research design. Such data might be covaried out in the statistical analyses to give a more accurate assessment of treatment effectiveness. Similarly, ECM can identify non-adherent outliers, justifying their omission from primary analyses or the use of strategies to estimate missing data points. If a trial population has a wide range of non-adherence, subjects can be stratified on this variable and treated as an additional factor in *post hoc* analyses.

Tim Cook’s recent suggestion that Apple will disrupt clinical research with its health initiatives is very likely to be true, and adherence data will be an important part of these initiatives.