# ARGUMENTS FOR PHASE lll COMPLIANCE MONITORING

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Inertia is difficult to overcome. When IMC introduced the Med-ic® electronic compliance monitor (ECM) nearly a decade ago it represented the potential for a revolution in clinical trials. No less eminent a statistician than Bradley Efron, Professor at Stanford and inventor of bootstrap resampling for statistical simulation, predicted:

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

Of course it was not initially accepted as such. Although nearly everyone agreed that patient noncompliance was 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 compliance monitors cost is no longer a reason to ignore noncompliance. The positive effect of compliance monitoring on clinical trial economics is clearly demonstrated by IMC's ROI Widget, 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 most powerful use is to monitor patient compliance during clinical trials and provide targeted education and motivational feedback ("coaching") during follow up visits with the CRM. This use is just coming online as it needs to be incorporated into trial planning from the outset.

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

There are several parts to the answer to this concern. First, science does not progress by ignoring problems such as noncompliance 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 compliance introduces error variance into a trial's statistical analyses. This undermines the ability of the trial to assess accurately the drug's effectiveness in a compliant population. This IN TURN creates a safety issue where, during commercialization, dosing schedules will be based on under estimates of the drug's efficacy (ie: higher doses will be prescribed). This places fully compliant post-approval patients at risk for toxicity-related problems. In the interest of safety, every effort should be made to ensure trial subjects are as compliant as possible. After all, the instructions to post approval patients advise full, not partial, compliance.

The idea that clinical trial subjects should be as compliant as possible is not a foreign concept, as it has support in the literature[1] [2]. 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 population, which will not have such follow up. Pill counts, medication diaries, blood samples, *etc,* are all common activities that can result in "coaching" that will not be continued when the drug reaches the target population. If a patient following up with the CRM has not completed his or her diary, the monitor will likely engage in a form of "coaching". For most trials this "coaching" is highly scripted. Scripting can also be used with ECM, where compliance data can be shown to the patient in graphic form along with standardized encouragement to take the medication on schedule. This feedback can even be completely automated or delivered by an app, structuring the "coaching" to ensure that all subjects, both treatment and control, get the same motivational feedback to be more compliant. 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 deteriorates over time. Consistent motivational counseling will result in asymptotically increasing mean compliance for the duration of the trial. At the end of the trial two things will have occurred: mean compliance will have improved due to the "coaching" effect and compliance will be less variable as highly noncompliant outliers will have derived more benefit from "coaching" because they initially had more room for improvement. The investigator has a known baseline of compliance in the population of interest to use in transitioning to the commercial application.

Without compliance monitoring the situation is more confusing. Although the investigator knows (or should at least suspect) that subjects are noncompliant, the magnitude of the

[1] Czobor P, Skolnick P. The secrets of a successful clinical trial: compliance, compliance and compliance. Mol Interv 2011, 11(2): 107-110.

[2] Smith DL. Patient nonadherence in clinical trials. TIRS 2012m 46(1): 27-34.

noncompliance is unknown. In this scenario there is no systematic "coaching" to motivate noncompliant subjects to be more compliant, and outliers remain wild cards that contribute disproportionately to error variance. At the end of the study the investigator does not have a compliance 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 counseling using targeted education based on compliance data.

In addition, subtle biases that might otherwise go unnoticed may be detected by ECM. If a placebo group is consistently more compliant than a treatment group it may be due to a subtle side effect of the drug. Conversely, if the treatment subjects are more compliant 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 result in verbal reports by the subjects.

Compliance data can have a significant effect on the power of a research design. Such data might be covaried out in the primary statistical analyses to give a more accurate assessment of treatment effectiveness. Similarly, ECM can identify noncompliant 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 noncompliance, 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 compliance data will be an important part of these initiatives.