Compliance Data in Clinical Research

PEER REVIEWED

There is a great deal of emphasis on streamlining the regulatory process to get important drugs to subjects who need them expeditiously. This is of increasing importance because of the trend to personalised drug development and the realisation that classic randomised clinical trials are becoming prohibitively expensive. Whereas in the search for "blockbuster" drugs, recruiting a few hundred subjects for a trial was manageable, this is no longer the case for drugs to treat rare disorders. It is simply too costly to seek out and process these less prevalent subjects.

Strategies to get investigational new drugs (INDs) approved more rapidly (and cheaply) abound. These include vaguely-described easing of regulatory requirements, accelerated approval, use of surrogate endpoints, patient registries and adaptive trials. While on the absolute scale these are all methodologically inferior to classic randomised ITT (intent to treat) methodologies, on the larger stage they offer considerable potential for addressing rare disorders.

So why are such alternative strategies not in widespread use? Fear of the unknown inhibits their adoption. The classic research paradigms have a long history with the FDA and EMA, so researchers have confidence that, if they do things a certain way, a predictable regulatory response will follow. However, with innovative strategies there is no such history. Although regulators encourage their use, they do not give specific guidelines, and nobody wants to be the early adopter who has an expensive study turned down because of methodological innovation. Thus, changes in strategy are slow.

There is another way to expedite the approval process, and it can be used with both classic trial designs and alternative strategies. It is based on an idea that is older than research itself. Hippocrates, *circa* 390 *BC*, cautioned his students to 'Keep watch also on the faults of the patients, which often make them lie about the taking of things prescribed'[1]. 2000 years later it is widely accepted that patients and subjects are poorly compliant with medication regimens, and a large volume of literature estimates that 50 to 65 per cent compliance is common[2].

To illustrate the magnitude of the problem, the current US Surgeon-General cites the annual cost of non-compliance in its broadest sense to US healthcare as between $100 and 200Bn[3], and other estimates are even higher[4]. This is just for the US – the problem is global. A 2003 World Health Organization report opined "Increasing the effectiveness of adherence interventions may have far greater impact on the health of the population than any improvement in specific medical treatments"[5]. In clinical research, the importance of compliance cannot be overemphasised[6], as poor compliance can create a downstream effect that can persist long beyond regulatory approval. Despite the magnitude of the problem, very little effort has been made to address it. Clinicians and researchers alike agree their patients are poorly compliant, yet research and clinical care both proceed as if they were fully compliant.

Research as a Signal-to-noise Ratio

Few research reports mention subject compliance and fewer still make an effort to address it. Research can be viewed as an exercise in optimising a signal-to-noise ratio (S/N) where the signal is the desired therapeutic effect, and the noise all the factors that conspire to obscure the signal.

The therapeutic effect is the variability between treatment groups (SS between groups in (1)) as measured by the primary outcome measure(s). Noise factors such as age, sex, body mass, activity level, gastrointestinal absorption, differences in metabolism, use of alcohol and drugs, use of herbal remedies, and myriad others both known and unknown obscure the therapeutic effect (Figure 1). These are typically lumped together and distributed at random over all subjects to give the SS within groups. The effectiveness of a treatment is evaluated by calculating a S/N such as the F (analysis of variance) or analogous test (1).

Fig. 1. Sources of noise

Various strategies are used to control within group variability in clinical trials, a common one of which is exclusion criteria. In this way the SS within is minimised, increasing the likelihood of detecting a signal. However this addresses only a small part of the noise spectrum and, as shown in Figure 1, a large source of noise is due to subject non-compliance. This is an untapped source of power than can be utilised to increase the efficiency of the drug development process. The terms compliance and adherence are used interchangeably in

the literature. Non-compliance poses a big problem for clinical trials, as poor compliance reduces the accuracy of a trial's data, encouraging inaccurate conclusions about a drug's effectiveness[7]. Generally, this is in the direction of underestimation and may lead to effective medications being abandoned, or approved drugs being commercialised at higher than optimal dosing that increases the chance of side-effects which can in turn prompt subjects to discontinue the drug[8].

Measuring Subject Compliance

Subject self-reports have been used to assess compliance, but there is considerable anecdotal evidence that subjects overestimate their compliance. As an alternative, medication diaries may be used, but these also result in overestimation, frequently being filled out with less than perfect recall while the subject awaits a follow-up visit. By default, pill counts and added pill counts are now widely used in clinical trials.

In 1986, Aardex marketed the first reliable electronic compliance monitor (ECM) in the form of a vial cap (MEMS®) that recorded opening and closing events as a proxy for medication taking. The MEMS® and, more recently, Information Mediary Corp's eCAP™, have been used extensively since, providing the ability to quantify baseline compliance dynamics and confirming the ineffectiveness of self-reports, medication diaries and pill counts. However simple opening and closing events cannot reliably account for a number of non-compliant scenarios such as the subject taking several or all the tablets from a vial at one time, opening and closing the cap without taking any tablets, or leaving the cap off the vial.

With increasing interest in blister packaging, 2000 saw the first smart blister packages, introduced by both Information Mediary Corp in Canada and Cypak in Sweden, that could monitor medication-taking at the individual dose level. Smart blister packages are now widely available and deployed in clinical trials worldwide. Compliance data are now easy to capture.

This raises the question of what to do with the compliance data. As shown in Figure 1, non-compliance is a large source of noise in the S/N and removing this noise from the denominator would give a larger S/N – the clinical effect would stand out more clearly. This is particularly important where there is a lot of variability within subjects such as in patient registry or natural history studies.

Applying Subject Compliance Data

Power is the ability of a study to detect a real clinical effect (significant S/N). The most effective way of increasing a trial's power is to measure and control for poor compliance, reducing the denominator of the S/N. Power increases with sample size and decreases with noise. The relationship between power, sample size and compliance is shown by the modelling data in Figure 2.

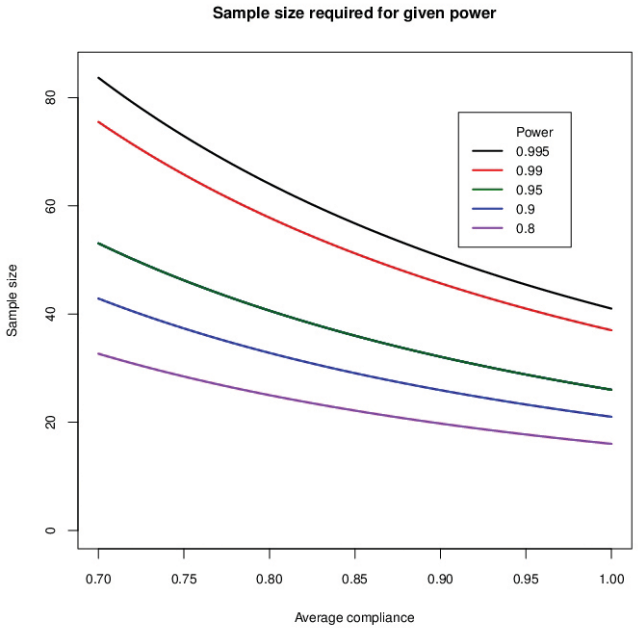

Fig. 2. POWER by COMPLIANCE by N

1) The basic use of compliance data is to give the sponsor confidence that it has done everything to ensure the accuracy of the data. This confidence will flow through to the regulatory agency overseeing the trial. Did the subjects take their medication as prescribed? What was the incidence of non-compliance and was it distributed equally among groups? Were there outliers and could they have distorted the results? Was there missing data? What was done to compensate for missing data? In these roles, compliance data are examined post hoc, documented in an organised way, and used to support the validity of the process that led to the results. In this role compliance data do not affect the primary outcome measures but simply speak to the overall rigour of the trial.

2) Compliance data can be used to screen for problematic compliance prior to enrolling subjects in a trial. Subjects who drop out of a trial or are grossly non-compliant are highly undesirable as they distort the results and conclusions. For ITT trials, this distortion is amplified, and the increasing focus on drugs for rare disorders and the associated difficulty (cost) of recruiting subjects exacerbates the dropout problem and lengthens the regulatory cycle. In short, the ideal trial would see all subjects fully compliant with no dropouts. A brief placebo pre-trial can identify those who are prone to non-compliance and they can either be removed from further consideration or given targeted education to increase their compliance before being enrolled in the study proper.

3) Compliance data can be used to assess the subjects' compliance post hoc. Data mining can throw light on many aspects of subject behaviour and can be tailored to the interests of the sponsor and regulator. For example, a recent ECM-enabled trial found that 40 per cent of

subjects deblistered their medication on at least one occasion, obviating the advantages of blister packaging. Without compliance monitoring, this would have gone undetected. This implicated poor package design (the package was unwieldy and utilitarian) and the subjects did not like carrying it around. As a result, the sponsor switched to a more compact and appealing format for subsequent trials.

4) In accordance with Surgeon-General C. Everett Koop's widely cited: "Drugs don't work in patients who don't take them", subjects can be stratified according to their compliance. For example, a recent study found no significant difference between treatment and placebo groups, auguring poorly for the drug's future. However, when the subjects were divided into tertiles according to compliance, a subsequent analysis showed a highly significant between-group effect for the third of the subjects that actually took the medication (i.e. had a greater than 85 per cent compliance rate). Had subject compliance not been monitored, a promising IND might have been abandoned.

5) If preplanned, ECM data can be used to adjust primary outcome measures for compliance using analysis of covariance or similar adjustment techniques. These are variants of stratification that have more complex inherent advantages and disadvantages.

6) ECM can detect subtle medication-related bias effects that can lead to erroneous conclusions about drug efficacy. For example, subjects in a treatment group might experience mildly euphoric or mildly unpleasant side-effects that control subjects do not. Such subtle effects would typically go unreported by the subjects and might bias the results and confound standard tests of significance. However, differential between-group compliance rates might signal a bias problem.

7) ECM can serve as part of a REMS (risk estimation and mitigation strategy) for trials where non-compliance can have serious consequences beyond those of simple data inaccuracy. Opioids, for example, can result in fatal overdose when taken to excess, and these drugs are often diverted for sale on the street. ECM detects the deblistering that suggests such activities and allows the investigator to implement an intervention strategy.

8) Using ECM may in itself improve subject compliance although this has not been demonstrated due to the ethics of monitoring compliance without informing the subject.

9) The highest and best use of compliance data is to give feedback to subjects about their compliance as they progress through a clinical trial. At follow-up visits, smart packages are scanned and the compliance data reviewed with the subject. Those subjects with less than perfect compliance are targeted for motivational counselling in an effort to improve their compliance for the duration of the trial; those with perfect compliance are encouraged to continue. Standardised motivational techniques are

used to ensure the process does not bias the results that will later flow from the primary outcome measures. While the clinical monitors have access to the compliance data at follow-up interviews, the primary dependent measures remain double-blinded until the study is completed. If treatment and control groups participate similarly in the motivational counselling process, the use of ECM data does not bias the study. To avoid introducing bias, the motivational interviews are semi-structured, with all subjects receiving similar feedback regardless of their level of compliance. The interviews are also timed to avoid the Hawthorne effect. Done properly, this process gives increasing mean compliance over the course of the study, reducing the error variance (noise) and increasing the accuracy of the study results (signal). In statistical terms, the study will have increased power, where power is the ability to detect real differences between treatment conditions. ECM is even more important for adaptive trials due to the increased number of decision points and the consequent inflation of the probability of making erroneous decisions (type I error). If an adaptive trial has five preplanned decision points and decisions are to be made at the 0.05 level, the probability of arriving at one erroneous conclusion is (5 * 0.05) or 25 per cent. Increasing the accuracy of the data by controlling the noise due to non-compliance will minimise this risk.

This argument is even more compelling for the newly legitimised patient registry and natural history studies as means of addressing rare disorders. These studies involve large numbers of subjects with associated high noise levels due to individual differences, so it is more difficult for the therapeutic signal to be seen over the noise. Measuring and controlling for non-compliance is critical if these kinds of study are to give meaningful results.

Return on Investment

Positive return on investment (ROI) occurs with all of the above applications, although for most the ROI will be subjective. Monetising “confidence” in one’s data is difficult. However, for the best use scenario (9), ROI can be calculated. Modelling studies show that for each per cent increase in mean compliance, the calculated sample size (N) can be reduced by two per cent. Since mean compliance tends to be from 50 to 65 per cent, targeted coaching can realistically increase compliance by 10 to 15 per cent. This would allow for a 20 to 30 per cent reduction in the N determined pre-trial from power calculations, without reducing the power of the study to detect real differences between treatments. Cost savings result both from the reduced cost of recruiting and processing the smaller number of subjects, and the reduced time to regulatory approval that gives longer subsequent patent protection. The ROI in this scenario is typically dramatic, as demonstrated by the ROI calculator at http://www.informationmediary.com/roi/roi-calculator. Given the fact that electronic compliance monitoring more than pays for itself in addition to having significant non-monetary value, there is no rational barrier to achieving the prediction of eminent statistician Bradley Efron:

"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."
Bradley Efron, Professor of Statistics, Stanford[9]

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