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SPECIAL REPORT: Focus on Randomization

Compliance Monitor

Information Mediary Corporation

Power and Return on Investment in Clinical Research

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RANDOMIZATION

Of course we are all aware of the central role played by randomization in the clinical research process. Virtually all clinical research employs this technique. However clinicians are generally surprised to hear that the majority of science proceeds quite nicely without the use of this strategy. The physical sciences get along quite nicely without randomization.

Clinicians are sometimes upset when I tell them randomization is the statistical version of sweeping the dirt under the carpet. The problem with sweeping dirt under the carpet is that it comes at some expense – when the dirt is found the clean-up is usually more difficult. Randomization also comes at some expense, in the form of the requirement for increased sample sizes.

In previous newsletters I have discussed the idea that pharamacotherapy is simply an exercise in optimizing a signal to noise ratio (S/N). The signal is the desired therapeutic effect – resolution of an infection, improved respiration, increased bone density, *etc.* The noise is the concatenation of factors that conspires to obscure the signal. In clinical research, statistical tests are used to assess the significance of the S/N. The widely used analysis of variance or *F*-ratio is an example of such a statistic. In this type of research design, the signal is the difference between the experimental treatment group (S) and a comparison group. This simplest example is where one group of patients receives IND "A" and a second group an identical appearing placebo. The denominator of the S/N is much more complex. There are many sources of noise in the clinical research setting. A few such factors are shown.

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.

B. Efron, Statistics in Medicine, 1998 (17), 249-250.

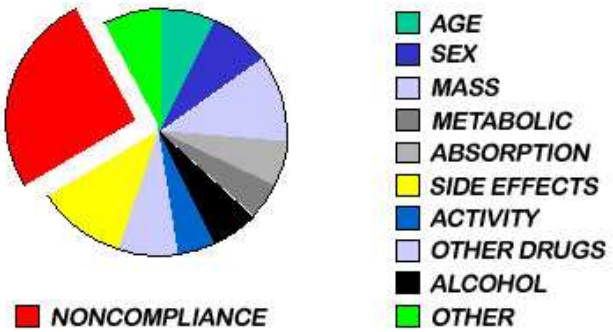

Figure 1

Some, such as the age, sex and body mass of participating subjects, are well understood; others are not. In clinical research, age, sex and body mass are frequently addressed by matching or other strategies designed to control for their ability to obscure the therapeutic effect. Matching ensures that sources of noise will influence the experimental groups (S) equally. This is the most effective way of reducing noise and increasing the S/N (ie: demonstrating clinical efficacy).

Unfortunately, it is not possible to control for all sources of noise. Many are actually unknown, others exert only small effects on the S/N, and yet others are difficult or impossible to measure and thus control. The clinical researcher controls these sources of noise by randomizing patients to the experimental conditions, thus distributing the noise evenly over the treatment groups. To ensure the various sources of noise are distributed homogeneously across the treatment population requires a large number of subjects. The more subjects, the more evenly the noise is distributed. The more evenly the noise is distributed, the more the signal (therapeutic effect) will stand out.

As shown in Figure 1, one well known and relatively large source of noise is patient noncompliance with the medication regimen. There is a burgeoning literature attesting to the problems created by patient noncompliance in both clinical trials and general clinical pharmacy.

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POWER

The relationship between S/N and sample size brings us to the notion of power. The power of a re-search design is its ability to detect reliably a clinical effect – to tease out the signal from the noise. Power is a function of sample size due, in part, to the smearing out of the noise variables by randomization. With larger sample sizes the noise sources are distributed homogeneously across treatment groups, allowing the signal to stand out

more readily. Effectively, larger sample sizes give bigger signals (eg: larger F-ratios, t-statistics, etc.). Larger signals are associated with smaller p values, with p being the probability of making an error in deciding if the S/N represents a true therapeutic effect or simply a statistical aberration (Type II error).

The simplest way to increase the power of a research design is to remove noise from the denominator. Fortunately, patient non-compliance is a large source of noise (the red slice of the pie in Figure 1). Measuring and removing at least some of the noise due to non-compliance increases the power of the design. Electronic compliance monitors such as the Med-ic® ECM™ can measure the subjects' compliance with the medication regimen, allowing it to be minimized in several ways:

1) screening patients for compliance prior to entering them into a trial;
2) screening patients prior to entering them into a trial and targeting education to those with poor compliance;
3) providing intra-trial targeted education and motivation to non-compliant subjects;
4) controlling for non-compliance *post hoc* via analysis of covariance or other statistical means.

Of course each of these techniques has advantages and disadvantages, a discussion of which is beyond the scope of this overview. Each strategy needs to be evaluated in the context of the particular study for which it is being contemplated.

Med-ic® ECM™ : An efficient way of increasing the S/N in clinical trials research.

The bottom line is that removing the noise due to non-compliance is an efficient way of increasing the S/N in clinical trials research. Reducing this source of noise increases the power of any given research design.

WHY BOTHER TO INCREASE POWER?

Measuring and removing any source of noise has a downside. It takes time and costs money to control noise. With patient non-compliance the problem has been simplified dramatically with the Med-ic® ECM™, a device that integrates seamlessly into blister-packaged medication and measures compliance without any effort on the part of the patient.

Increasing the power of a research design in this way gives the clinical researcher two options:

1) reduce sample sizes, or
2) maintain sample sizes and try for "critical experiment" status

Reducing sample sizes saves costs due to running subjects through trials, accelerates the approval process for an IND, and leaves more time on patent to recoup costs and generate revenue. A less tangible benefit is early market entry and penetration.

Critical experiments are studies that demonstrate efficacy so dramatically that the usual approval process is shortened, allowing the IND to enter the market rapidly. This results in the same return on investment arguments described for reduced sample sizes, but may amplify them dramatically.

In summary, the Med-ic® ECM™ obviates the need to sweep the non-compliance dirt under the carpet. Addressing this problem proactively can be shown to offer large return on investment dividends via increased power and S/N ratios.

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About Us

Information Mediary Corporation is dedicated to the convergence of medicine, logistics, high-technology, pharmacology, wireless, e-business and anthroponomy.

IMC's recent flagship Med-ic® and Log-ic™ ECM™ product development efforts underscore this commitment by recognizing and solving important issues Compliance monitoring has been viewed increasingly as a problem in clinical research and clinical pharmacy over the past decade. Prior to the Med-ic® ECM™ Package there was no user friendly, seamless and accurate solution to the problem.

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