Dredging in the Dirt

WHY DO CLINICAL TRIAL SPONSORS ACCEPT DIRTY DATA AND WHAT CAN BE DONE ABOUT IT?

Imagine that this is the process for buying a custom-finished car.

You agree the specification with the dealer, sign a contract and pay a substantial deposit. In addition you may have to pay a fee of 20% to 40% of the cost of the car for 'overheads'. In anticipation of your purchase you have hired a mechanic, who makes regular visits to the car manufacturer to ensure that the work is being carried out according to specification. Frequently the visits are futile, as essential staff or information is missing. Finally the day comes to take possession of the car. Your mechanic goes to collect the car, only to find that certain bits and pieces (such as the steering wheel, the odd spark plug and left front door) are either missing or have not yet been fitted. Gathering up all the pieces available, your mechanic pays in full for the car, brings everything home and completes the less-than-perfect assembly.

Though no sane person would accept the above scenario when buying a car, that is precisely what most clinical trial sponsors accept from most of their investigators. Sponsors pay investigators and their staff, or the institutions in which the investigator works, or both, to produce clean data according to an agreed protocol. Sponsors hire qualified staff to monitor and detect errors or omissions in the case record forms during the study, pay substantial sums correcting errors which make their way into the database and then pay more qualified staff to correct errors remaining at the end of the study. Investigators are usually paid in full, irrespective of the quality of the data they provide. For example, in a study to assess how patients would use an auto-injector, one paternalistic investigator decided that patients couldn't possibly cope so he injected them himself. The affiliate general manager insisted on paying in full, because "we mustn't upset our customers".

Objective drug development depends entirely on accurate data, and the responsibility for accurate data rests entirely with the investigator ("The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the case record forms and in all required reports" ICH-GCP [4.9.1]), a concept that often comes as a surprise when pointed out. This responsibility is rarely enforced, yet the consequences of dirty data can be

SO WHO IS TO BLAME?

Unequivocally, the sponsors. Though taking money and then failing to deliver according to an agreement is reprehensible (at best), reality dictates that if we, as sponsors, aren't getting what we need it is up to us to do something about it. There are many sponsor-related causes for poor study conduct and dirty data that can be addressed to help investigators; key among these are over-complicated and poorly written protocols resulting in over-complicated and poorly designed case record forms, inexperienced sponsor staff, and a lack of education of investigators and study coordinators.

For today I would like to address the issue of education. Traditionally studies are preceded by the infamous 'investigator meeting', a non-descript event during which elements of the protocol, the case record form and GCP are covered inadequately in too short a time to a less than attentive audience whose attention span is assumed to be superhuman. Each of the elements is important enough to warrant a dedicated meeting; at the same time one of the most important elements is missing. The missing element is 'how to carry out a clinical trial'.

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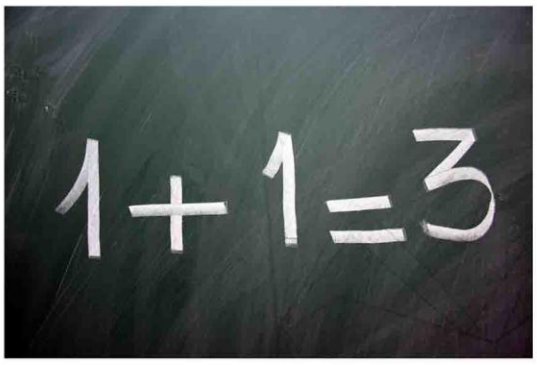
There is an implicit assumption, among investigators and sponsors alike, that physicians have a genetically acquired ability to run clinical trials. Nothing could be further from the truth. The clinical trial process is a specialty of its own which requires experience and understanding to be carried out properly. Whilst there are certainly investigators whose experience and professionalism could teach much to the pharmaceutical industry, these investigators are few and far between. As Dr Temple, of the FDA, remarked on an investigator training video: "The qualities that make a good physician are not necessarily the qualities that make a good investigator".

As in all professions there is a minority of physicians, with the arrogance associated with lack of insight, which believes it knows it all. Most physicians, however, welcome the opportunity to learn more and become more desirable as investigators. This has been proved in an initiative to educate investigators that is described later. Where sponsors claim to provide clinical trial education, it tends to centre entirely on GCP. And that is the problem. To continue the car analogy, learning GCP is to clinical trial conduct what learning the Rules of the Road is to driving a car. Both are essential, but learning GCP no more enables a physician to carry out a study properly than learning the Rules of the Road enables someone to drive a car safely. In each case practical, hands-on learning and experience are needed.

At some time in the future a global, all-encompassing, foolproof, remote electronic system will change the way in which data are capture accurately in real time, and the educational approach as described today may become redundant. Until then education to ensure a full understanding of the clinical trial process, which is generic and applicable to all studies, should be provided to all who intend to carry out clinical trials. This education should be completed separately, before discussing the specifics of a given study.

Proof of the benefits of this approach is, as always, best shown by the outcome. Over the three-year period before Pharmacia became defunct a stand-alone educational programme, encompassing the broader elements of the clinical trial process, was provided to over 9000 physicians and study coordinators in 44 countries. In a relatively short time this approach (in combination with other initiatives) resulted in a significant fall in both the error rate and the need for routine monitoring visits. This benefit, incidentally, was only one of many, including the reduction of clinical conduct times (phases II and III, all indications) by 35%.



Sponsors can continue expensively to dredge in the dirt to uncover the data vital to the success of their projects, or can take the time to ensure that an adequately educated and prepared investigator pool provides data of the expected quality.

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