HOW GCP KILLED GOOD CLINICAL PRACTICE

It is a truth not universally acknowledged that no sooner the introduction of a new regulation in possession of a logical rationale than it is wont, rapidly and progressively, to become more bureaucratic and completely divorced from the original intent.

(With Apologies to Jane Austen)

And what better example of the truth of this dictum than the way in which GCP is applied. The objectives, when GCP started to be introduced in earnest in the 1980s, were clear and rational: to ensure the safety of clinical trial subjects and the integrity of the data. Since then the requirements have been expanded, codified and harmonised, but the underlying objectives are unchanged.

What *has* changed in the interim is that the process, rather than the outcome, has become the primary objective, with the focus on GCP-related procedures rather than the logical overall conduct of the clinical trial. The reason for this is that the GCP machine is often left the control of people for whom obsessional risk-avoidance at any cost is their primary objective, and whose distortion of the benefit to risk ratio goes unchallenged.

This would be all very well if the result justified the means, but in fact the cumbersome, tortuous, and mindless approach now adopted by most companies serves only to waste time, use vital resource and cripple budgets without improving either the safety of trial subjects or the quality of the data. Furthermore, as the requirement for more safety data and for robust outcome studies grows, few biotech or medium-sized pharma companies will have the necessary budget, which will stretch the resources of even the wealthiest companies.

The irony of all this is that it is completely unnecessary, and largely the result of inexperience, lack of knowledge, fear and (especially) poor training and management. The consequence is a vicious spiral, starting with someone adding a few unnecessary embellishments ("just to be on the safe side") which are then mindlessly repeated and expanded ("because this is how we do things") until they become enshrined as a non-existant "regulatory requirement" ("because this is what the FDA/EMA wants!!").

Most of the problem could be eliminated if everyone involved in the clinical trial process were to learn these 4 simple lessons:

1 *The more objectives in the protocol and the more irrelevant data you collect the, the longer it will take, the more errors you will have and the less likely it will be that you get a clear answer.*

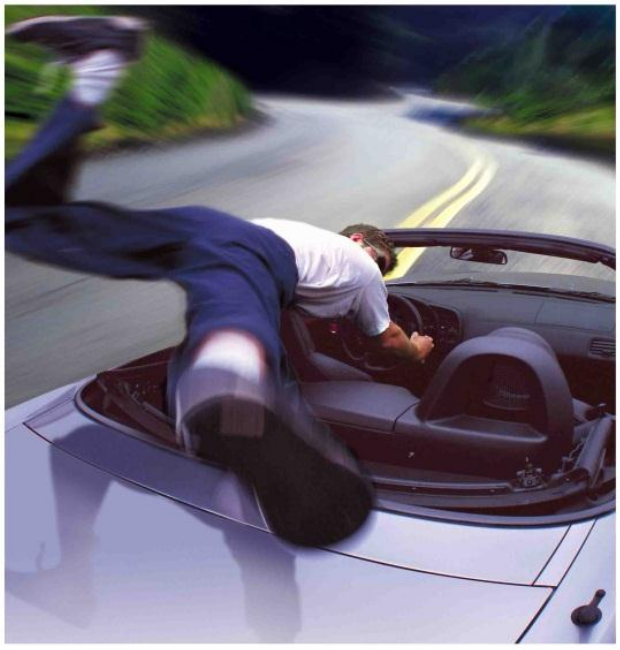
The validity of a study is not directly proportional to the amount and frequency of data collection. On the contrary, the usefulness of a study is directly related to the intelligent collection of relevant data at appropriate times.

The lemming-like rush to collect copious non-essential laboratory data, details about concurrent medication, and clinical observations results in the following:

- time-wasting and abuse of trial subjects;
- time-wasting and frustration on the part of investigators;
- incomplete data;
- a cumbersome and unwieldy data capture instrument (DCI, whether electronic or paper)
- poorly completed DCIs;
- delay in DCI completion;
- inevitable random, meaningless shifts in lab results, all of which will be mulled over obsessionally;
- a multiplicity of errors;
- the inevitable costly round of queries (in which everything is queried at well over $100 each time) resulting in further delays and investigator frustration.

2 *Knowledge of GCP is not synonymous with (or a substitute for) expertise in clinical trial conduct.*

The answer to the question: "Do you train your investigators and their staff?" is inevitably "Yes, we do GCP training." The equivalent approach would be to give people driving licenses only on the basis of their having read the Rules of the Road, and without any practice whatever in driving a car, or awarding medical degrees purely on the basis of having memorised the Hippocratic oath and read a few textbooks.



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Knowing the regulatory requirements for conducting a trial ethically, safely and credibly is essential, but it is only one part of the trial process. Equally important is expertise in clinical trial conduct, which investigators tend to believe they have acquired by divine right. However, to quote the FDA's Dr. Robert Temple: "The qualities that make a great physician are not necessarily the qualities that make a great investigator".

Given that most investigators and their staff have never had formal training in how to conduct clinical trials, and that the propagation of bad practice from one study to another is the norm, as evidenced by the poor quality of data (for which the investigator has sole responsibility), it should be clear that the emphasis on GCP alone is a costly liability.

3 *Source Document Verification (SDV) has a logical basis but is not an end in itself.*

The purpose of SDV is to help in ensuring the accuracy of data and to minimize fraud by providing an auditable link between the study CRF and the patients' medical records. It is therefore an important and integral part of the clinical trial process. Unfortunately SDV has now become virtually the full-time obsession of Clinical Research Associates (CRAs), who tend to view it as synonymous with clinical trial monitoring.

The result of this obsession is that virtually all drug development companies (and therefore virtually all CROs, who follow blindly) insist on 100% verification of all data for all patients. Far from being a requirement, this approach, coupled with the mindless associated activities aimed at complying with non-existant regulations, ensure expenditure of time, effort and money at the expense of equally important activities and without significant improvement in outcome.

As bad, or worse, is the obsession in trying to ensure that all data in the CRF appears in the medical records, despite the fact that for some data the CRF itself is the source document. The ultimate expression of this approach is where the DCI is copied and added to the patients' medical records. The ultimate consequence of the blinkered rush to unnecessary double entry (with attendant transcription errors) is to clutter the medical records with information of no value to the physician or the patient, to the possible detriment of medical care.

4 *Clinical study monitoring is about site management, and involves much more than just Source Document Verification.*

The essence of good site management is preparation, so that a study can run smoothly and time can be spent addressing unforeseen issues. However, the traditional approach to site management and to trial monitoring is the reverse, and quality control (trying to correct mistakes) outweighs the almost non-existant quality assurance (preventing mistakes).

Classically investigators and their staff are given some study-specific training and some GCP training. Rarely, if ever, are investigators trained in the important operational aspects of clinical trials.

The rot therefore sets in from the start. It is perpetuated by the traditional approach to monitoring. With good site training routine monitoring should be reduced to a minimum, with the effort being concentrated where most needed, including areas which are now almost completely ignored by monitors, such as patient recruitment.

Instead monitoring is reduced to a meaningless round of 6-weekly visits, irrespective of what is going on at the site. The most important element of the timing of a monitoring visit is that it should be in anticipation of, or in immediate response to, an unforeseen problem. By waiting until the 'routine' visit, festering or unknown issues may cause delays or even threaten the integrity of a trial.

In summary, the way in which GCP is understood and applied not only subverts its original intent but has resulted in a clinical trial process which has become progressively more bureaucratic, time-consuming, cumbersome and expensive without adding any value whatever to the outcome. A reassessment of GCP practices is essential if the conduct of complex development programmes is to remain feasible.

Mike Tansey is a Managing Partner of CDDI. He has extensive international experience in all phases of drug development across a wide range of therapeutic areas. He has held positions in Hoechst, Glaxo, Rhone-Poulenc Rorer, and Pharmacia as CMO & SVP Medical Development. Since 2003, Mike has worked with more than 14 biotech companies and CROs in the USA and Europe. With a track record of involvement in over 40 regulatory submissions worldwide, Mike can provide expertise in both strategic and hands-on operational project management.

Contact Mike at CDDI | +1 908 720 7354 | mike.tansey@cddi.co