

Chapter 2. Good Clinical Practice

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I. INTRODUCTORY REMARKS

GCP, Good Clinical Practice, is an international set of ethical and quality standards that applies to medicinal trials in humans. Compliance to these standards provides the health authorities as well as the general population with assurance of the integrity of trial subjects and the validity of the data generated. It is important to stress that these standards *de facto* relate to research; in fact a more appropriate title would be Good Clinical *Research* Practice. These standards have been in effect for many years pertaining to all trials intended to generate data for marketing authorisation procedures whether it be new medicinal products or a line extension for an already marketed product. As a general rule, academic research involving already marketed products and not intended to generate results for marketing authorization purposes has been exempt from these rules. As more general attention and political focus is given to quality assurance and to the autonomy of the individual within health care systems, these standards are getting more attention world-wide; Within the EU, these rules, as of May 1st 2004, pertain to *any* medicinal trials in humans, including those involving already marketed drugs and trials performed without industry engagement. This represents a serious challenge to the academic independent drug related research, as systems to assure GCP compliance must be developed, which in turn requires allocation of appropriate resources.

I.1 History

The first documents describing some quality recommendations for the design of clinical trials in humans can be dated back to USA, where Harry Gold from Cornell University Medical School published two influential papers *Conference on Therapy* in 1946 and again in 1954. The emergence of the thalidomide disaster around 1960 further served to justify the need for formal guidelines and procedures for clinical trials with new medicinal products. Throughout the 60's and 70's guidelines were refined and implemented throughout the world. These were, unfortunately, far from being easily comparable due to differences in approaches to clinical trials, mainly between USA, Japan and Europe. It became obvious that some sort of international consensus on this issue was overdue in order to promote mutual recognition of clinical trials and marketing authorization procedures. The result was the birth of the current guidelines that in effect are known as ICH (*International Conference on Harmonization*)-GCP.

I.2. GCP concepts

In order to give a better understanding of the principal GCP concepts, some key definitions are given below:

Sponsor

A person, institution, company or organization which takes responsibility for the initiation, management and/or financing of a clinical trial. Note that the sponsor does not necessarily finance the study. Sponsor and investigator may be identical in which case the term (surprise) *sponsor-investigator* is used.

Investigator

A person who is responsible for the trial conduct at the trial site. If multiple investigators are involved at a trial site, a *principal* investigator must be appointed.

Monitoring

The act of overseeing a clinical trial to ensure that it is conducted recorded and analysed according to the trial study plan, standard operating procedures, GCP and regulatory requirements.

SOP, Standard Operating Procedure

A set of written detailed instructions to achieve uniformity of the performance of a given function.

Audit

An independent examination of all trial related activities and documents in order to determine if the trial was conducted, recorded and analysed according to the trial study plan, standard operating procedures GCP and regulatory requirements. The audit procedure is independent of the monitoring procedure.

II. GCP IN CLINICAL RESEARCH

The ICH-GCP guideline specifies, in rather general terms, how to design, conduct, record and report a clinical trial in accordance with GCP standards. In order to comply with this, it is the responsibility of the sponsor, or sponsor-investigator, to ensure that a set of standard operating procedures is written. An important point is that the guideline explicitly states that the level and intensity of the GCP monitoring process is specified by the sponsor according to the complexity of the study: size, purpose, design, blinding, outcome measures etc. These standard operating procedures form the basis of the central element of GCP-compliance: the monitoring process. The monitoring process must be conducted by individuals possessing documented skills of GCP monitoring, and, obviously, the monitors cannot be directly involved in the study otherwise.

II.1. The monitoring process

The monitoring process is the fundamental aspect of GCP compliance. This systematic process is based on study-specific SOP's, and serves to document that the study complies with GCP standards. There are three phases of this process some core issues of which are listed below. Please note that this is not an exhaustive listing.

Before study initiation the monitor visits each investigation site to verify that

- Sponsor and investigator responsibilities are properly described
- Relevant authorizations are present
- Written informed consent is acceptable
- The investigation site realistically can provide the specified number of subjects within the specified time-frame
- Procedures for handling of trial medicine and laboratory tests are present
- Source documents are specified

During the trial, the monitor visits the trial sites to verify that

- The trial is performed and documented as planned
- Informed consent is given from every participant
- In- and exclusion criteria are fulfilled
- Data are correctly recorded and are in accordance with the specified source documents
- Corrections in the case report form (CRF) are properly performed and documented
- Serious adverse event are handled correctly

After the trial is completed the monitor verifies that

- Trial medicine is accounted for in detail
- The trial database is properly secured and validated
- Trial documents are filed and stored properly

In effects this means that quite a number of SOP's must be developed and maintained. A standard operating procedure must exist for all items and procedures below:

- Protocol
- Informed consent
- Investigators brochure

- Case Report Form (CRF)
- Trial medication
- Adverse events
- Protocol amendments
- Monitoring
- Monitor's report
- Monitor qualification
- Filing
- Audit
- Handling of documents
- Structure and approval of SOP's

All monitor's visits must be accompanied by a written report describing what was monitored, the outcome of the monitoring process, including errors and deviations, and initiatives to correct the latter. For the individual researcher this likely represents an insurmountable task and flexible systems to handle GCP in independent academic drug research must be developed.

II.2. A Danish example

In Denmark a public GCP monitoring service has been organised, and a brief overview is given here for inspiration: The first public GCP initiative was taken back in 1995 at the University of Aarhus. Anticipating the implementation of the aforementioned EU directive, it was estimated that about 80 independent academic drug trials in humans were initiated every year in Denmark. A coordinated activity and initiative has resulted in the presence of three GCP-units in Denmark, which are all situated around medical schools and universities. The GCP-units are partly funded by the Government; we are estimating that, having reached steady-state, about 20 full time monitors will be employed, and that a total budget would linger around USD 2 million. The three units work closely together and have agreed upon identical SOP systems, and apply identical principles of services: Smaller trials, typically trials in Ph.D. projects, are monitored free of charge, while larger trials must account for factual GCP-costs, if more than 100 hours of service is required. Despite initial skepticism from researchers this system has so far proven manageable, but the full scale test still waits, at the time of writing, the implementation of the EU directive.

II.3. Challenges and perspectives for independent academic drug research

The challenge is to assure compliance with GCP standards, while not consuming an insurmountable amount of resources, which would cripple the independent academic clinical drug research. It is here that one must recall that the guidelines are general specifications of GCP standards. However, the translation into factual procedures, and the specific way these are implemented leave some room for breathing and interpretation. The approach that the pharmaceutical industry and most CRO organisations have taken is meticulously detailed and very resource consuming. This is understandable, as they cannot afford to have a large pivotal phase III trial be subjected to scrutiny, or even rejection, by health authorities due to a GCP related issue. Hence, the industry developed GCP concept is designed to account for a worst case scenario. So as GCP seems to enter an era were the principle is likely to become applicable to any drug related research in humans, it is really up to all of us, as independent academic clinical researchers, to influence the way that GCP is implemented. There is no denying that implementation of GCP in academic research programs *will* assimilate some of our scarce funding. However, it is the opinion of this author, that we should welcome many of the principles covered by GCP. Quality in performance and respect for patient's integrity is imperative for the thrust on which the very existence of any health care system relies, and there are simply no valid arguments to exclude research related activities from these principles. And, if we make our opinion and experience heard it is my belief that it is possible to reach an interpretation of the

GCP guidelines which satisfies this principle and still allows for a fruitful continuation of independent drug research.

III. REFERENCES

The current ICH-GCP guideline can be viewed (among many sites) at the European Medicines Agency's homepage: www.emea.eu.int/pdfs/human/ich/013595en.pdf.

The FDA has an entire homepage with plenty of easily accessible information: <http://www.fda.gov/oc/gcp/default.htm>.