Peer reviewed article

Quality requirements in clinical studies: a necessary burden?

Marc Salzberg, Emilie Müller

Basel University Hospitals, Basel, Switzerland

Summary

Drug development has continued to progress over the past decades and the processes involved have become more complex. The basis for these changes include advances in substance analysis and production, targeted drug development and defined guidelines for the conduct of clinical trials. The aim of standardised quality requirements is to generate scientifically sound data in clinical trials while observing strict ethical rules.

The conduct of clinical trials is governed by internationally established Good Clinical Practice (GCP) guidelines [14]. For the protection of human beings directly involved, framework conditions must be established as guidelines to accompany the research process. At the same time, these regulatory requirements enable a quality criteria standard to be defined. However, those regulations form a major challenge for clinical study centres, since they affect current clinical practice considerably.

The objective of this paper is, on the one hand, to clarify the historical background relating to the development of clinical trials and the corresponding legal guidelines, on the other hand, to discuss consequences for clinical practice.

Key words: quality requirements; clinical studies; Good Clinical Practice

Historical development of clinical trials

Trials to evaluate or demonstrate the benefit and risk of medical interventions date back to very early stages in the history of medicine. In general, these involved unsystematic, relatively unscientific studies with sometimes entirely subjective and extravagant problem statements, with the result that the studies were without practical relevance. Up until the end of the 1940s, as a rule studies were not conducted using control groups and often no test hypotheses were established [1]. There were, however, isolated studies which may be viewed as early milestones in clinical research, such as the study by Lind (1753) on the treatment of scurvy, which even then was designed according to modern, scientifically based methods [2].

The essential difference from the clinical trials of the last 50 years was the lack of scientific standards in terms of planning, conduct and publication of clinical trials. For medical practice, this meant that treatments were only considered effective if unequivocal effects were observed despite a scientifically dubious conception of the study design (e.g. lack of randomisation, blinding and control groups), as for example with the use of penicillin. On the other hand, as a result of the somewhat informal study methods, there was the risk of establishing therapies which unfavourably affected the benefit-risk ratio [2].

The importance of clinical trials

The aim of clinical trials is to establish whether a specific intervention produces the intended outcome. Since the results from preclinical use generally cannot be extrapolated to use in humans, there is the need to test new substances in volunteers or patients before licensing their widespread use. This means that individual patients are offered new therapies or those not previously tried in the current form. The general aim must be the highest possible statistical power with the least possible stress to humans and animals from experimental conditions [3].

No financial support declared.

Clinical trials are divided into four phases. Phase I corresponds to the first use of the test substance in humans and serves to determine the ideal dosage and to test the tolerability and toxicity of the drug. In phase II, the tolerability is tested on a broader basis and the efficacy evaluated. In phase III, the test substance is compared with the so-called standard therapy for the disease concerned in terms of efficacy and tolerability. Finally, phase IV defines the further development of drugs that are already commercially available. The results of clinical trials are therefore not "proven" in the sense of a logically causal relationship of mathematical theorems, but rather the probability of existence of a suspected causality is studied in terms of relative efficacy.

The relevance of a study depends essentially on its design, careful implementation and the statistically "clean" analysis of the recorded data [4]. The effects of an intervention on a disease can also be studied by means of meta-analyses of studies [5].

Patients benefit to varying degrees from participation in a study. Inclusion is ethically acceptable if individual benefit to the study participant may be expected or hoped for as a result. In oncology, this applies both to patients for whom, owing to the advanced stage of their disease, no other treatments are available, and to patients who do not (or no longer) respond to standard therapy [6]. In addition, more recent drugs or treatment methods are only available for patients in a study context because they have either not been authorised for marketing by the authorities or are only reimbursed to a limited extent by health insurance companies.

Treatment according to a study protocol frequently requires the conduct of additional studies, more careful monitoring and shorter recruitment intervals. This implies that a qualitatively higher standard of treatment may be assumed in general for study patients. The close monitoring means that patients are probably best protected and cared for in the context of clinical trials [6].

Demands on clinical trials

Legal requirements for an important sub-area of drug development can be illustrated by the situation in the USA, since regulatory requirements were developed there at a very early stage to protect the rights of consumers and study participants. The death of several patients following the administration of study medications led to the recognition that the necessity of proving the *safety* of active substances by scientific methods was the most important aspect of clinical trials [7].

A further decisive step towards drug safety was necessitated by the birth deformities caused by thalidomide in Europe. This resulted in the USA in drug manufacturers having to fulfil specific requirements *before* launch on the market. These requirements were tailored to the demonstration of *efficacy* in addition to safety. In this way, the conditions under which a drug might achieve suitability for marketing were defined for the first time.

The past has shown that legal requirements may be seen as the result of inadequate mechanisms of self-control on the part of the pharmaceutical industry and investigators. Careful monitoring of work in terms of conformity with rules and specifications of Good Clinical Practice (GCP) therefore appears sensible to pre-empt further legal refinements. By adhering to quality-based principles and methods, responses in the form of relevant legislation may be averted. In this sense, regulatory requirements may be interpreted as useful and effective preventive measures [7, 8].

The aim of the GCP recommendations issued by the International Conference on Harmonization is to define standards for the ethical, scientific and technical quality of clinical trials on drug substances, diagnoses and therapies. This concerns in particular:

- the protection of participants in clinical trials (including patient information and informed consent, approval of the study by ethics committees and national authorities, and monitoring of adverse events);
- the credibility and authenticity of the data obtained and results (transparency/comprehensibility of the clinical trial by means of archiving and documentation, quality control and assurance);
- the establishment of responsibilities associated with clinical drug trials.

In addition, it must be possible to ensure that studies comply with legal and "corporate policies" [7] and explicitly deceptive procedures (e.g. inclusion of non-existent patients, reporting of incorrect data) should be prevented [9].

Over the last few years, GCP has been increasingly implemented as a result of the efforts of the relevant authorities, the pharmaceutical industry and the study centres. The detailed requirements of GCP concerning the conduct and reporting of clinical trials should facilitate the mutual recognition of study data by the regulatory authorities.

The GCP Guidelines have acquired the nature of normative specifications, even if the text is not formulated in binding terms: "[…] the guidelines *should* be followed when generating clinical trial data that are intended to be submitted to Regulatory Authorities and *may* be implied to other clinical investigations […]" [9]. The member states of

the ICH consist primarily of the rich industrialised countries, so that GCP can therefore only be binding in those countries. Regulatory authorities in ICH countries nowadays only accept GCP studies, so that the other countries should also adhere to these guidelines.

GCP guidelines should ensure that strict ethical rules *(Declaration of Helsinki and its amendments)* in the conduct of clinical trials are observed, that these trials are conducted in accordance with high standards of quality and that authentic, scientifically verifiable and reliable data are the result of such studies [10, 15]. In order to be able to meet these requirements, the establishment of quality assurance measures is essential.

In addition to the definition and establishment of standards (Standard Operating Procedures; SOP), there is the (self-) inspection of the required quality standards (quality control, QC) and external quality assurance (QA) by inspections and audits or monitoring [11, 12].

In order to avoid or minimise errors in the conduct of clinical trials, standardisation of work procedures and their routine use must be implemented. Standardisation is defined as "production of the same or similar conditions ... (and the) establishment of standards and norms including standard values" [13]. This standardisation of specifications, known as standard operating procedures (SOPs), in the form of manuals serves in the first place to improve and guarantee quality. In addition, it ensures a more rapid and unproblematic study procedure by the description and definition of all individual steps.

What is the impact of these rules on the conduct clinical studies in daily practice? Patient care in clinical practice is now confronted with an increasing degree of bureaucracy topped by the need to have an eye on the study sponsors' internal procedures. In many cases the latter is the real problem, namely the room for interpretation of GCP by pharmaceutical companies. Insufficient education of trial staff in this field intensifies the problem.

Examples for GCP and protocol violations occur for instance with the Patient Information and Informed Consent. The patients' signature might only be obtained after enrolment or at least not before study-related procedures are undertaken due to the nature of clinical routine. The signature, randomisation and initiation of therapy are done the same day for the same reason. Excessively lengthy patient information prospectuses, often 8 to 15 pages long, are crying to be rendered comprehensible, in contrast to GCP.

Further examples of GCP compliance problems relate to study project management: forms are not filed in the correct place, CVs of all hospital staff involved in the study are needed, instances of residents seeing a patient once and taking medical decisions without supervision. A pre-study visit by the sponsor is needed before a trial initiation visit can occur; the first meeting is obsolete in our eyes, if the sponsor and centres/investigator have been working together for many years and know each other well.

From under- to over-regulation: for clinical practice a better balance between desirable and feasible demands should be discussed between the partners, obviously without damaging the implementation of GCP.

Discussion

The positive effects on the protection of study participants and the scientific quality of the data recorded are undisputed. The regulatory steps are comprehensible and desirable in terms of establishing an internationally recognised standard and enhancing the quality of medical interventions. For clinical practice, however, this means that studies are becoming more time-consuming, complex and expensive. The increasing demands on the GCP compliant conduct of studies require an increased adaptation of know-how and manpower in the study centres.

Under these conditions, the question arises as to how hospital centres should organise themselves in the area of clinical trials in future. Academic centres have the on-going task of maintaining or improving the quality of the medical care of their patients. The benefit of new interventions, however, can only be evaluated by intensive research. Participation in the conduct of clinical trials is therefore unavoidable. It provides contact with the most recent state of research and increases the quality of care of patients. For patients, participation in clinical trials offers access to potentially better treatments and more recent methods which are not (yet) available on the open market.

Innovative approaches such as pharmacogenomics offer new possibilities for improving study designs and organising them more effectively. The targeted identification of sub-populations enables studies to be focused more specifically. On the one hand, the number of patients per study can thus be reduced and, on the other hand, the probability of benefiting from the test substance is increased accordingly for the individual patient.

As a supplement to the conduct of controlled clinical trials, routinely obtained clinical data should increasingly be analysed scientifically. These data should therefore be amenable to electronic registration.

Further developments in the area of research, new technologies and improvements in medical

documentation will hopefully positively influence the framework conditions under which clinical trials take place. The implementation of quality guidelines and legal requirements in clinical trial practice makes increased demands on know-how and manpower and the state of training of study personnel. Without suitable adaptation combined with professional management, high-quality clinical research work will not be possible in the long-term.

Acknowledgement

We would like to thank Essex Chemie AG, Switzerland for supporting the linguistic revision of the text.

Correspondence:
Dr. med. Marc Salzberg
Universitätskliniken Basel
Klinische Forschung Onkologie
Spitalstrasse 26
CH-4031 Basel
E-Mail: msalzberg@uhbs.ch

References

1 Cleophas TJ. Methods for improving clinical trials. Clin Chem Lab Med 1999;37(11/12):1035–41.
2 Pocock S. Clinical Trials – a practical approach. Chichester/ New York: John Wiley & Sons; 1991.
3 Bothner U, Seeling W, Schwilk B, Pfenninger E, Georgieff M. Klinische randomisiert kontrollierte Studien in der Anästhesiologie gemäss den Qualitätsrichtlinien der guten klinischen Praxis. Teil 1: Grundlagen der Planung. Anasthesiol Intensivmed Notfallmed Schmerzther 1995;30(3):146–54.
4 Buyse M, Staquet M, Sylvester R (eds.). Cancer Clinical Trials – Methods and Practice. Oxford: University Press; 1988.
5 Moher D, Cock D, Jadad A et al. Assessing the quality of reports of randomized trials: implications for the conduct of meta-analyses. Health Technol Assess 1999;3(12):1–98.
6 Tagnon H. Ethical considerations in controlled clinical trials. In: [4]. p. 14–25.
7 Goodson R. Good clinical practices: past, present, and future. Qual Assur 1995:4(1):60–7.
8 Heilman R. Drug development: history, "overview", and what are GCPs? Qual Assur 1995;4(1):75–9.
9 Allen M. Good clinical practice: current state of the art for clinical trial documentation. Med Leg J 1998;66(2):61–4.
10 Poy E. Objectives of QC Systems and QA Function in Clinical research. Qual Assur 1993;4(4):326–31.
11 Lange L, Jaeger H, Seifert W, Klingmann I. Good Clinical Practice I. Grundlagen und Strategie. Berlin, Heidelberg, New York: Springer; 1992.
12 Wood D. Quality assurance in Phase II and III Studies. Qual Assur 1993;2(2):353-8.
13 Ott H, Rohloff A, Seitz O. Standardisierungen von Prüfungsbedingungen am Beispiel von Klinischen Prüfungen mit psychosomatischen und elektrophysiologischen Verfahren. In: [11 b]. p. 175–188.
14 Note for guidance on good clinical practice 1995 (CPMP/ICH/135/95).
15 Declaration of Helsinki 2000. Ethical Principles for Medical Research Involving Human Subjects.

Swiss
Medical Weekly

Official journal of
the Swiss Society of Infectious disease
the Swiss Society of Internal Medicine
the Swiss Respiratory Society

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses

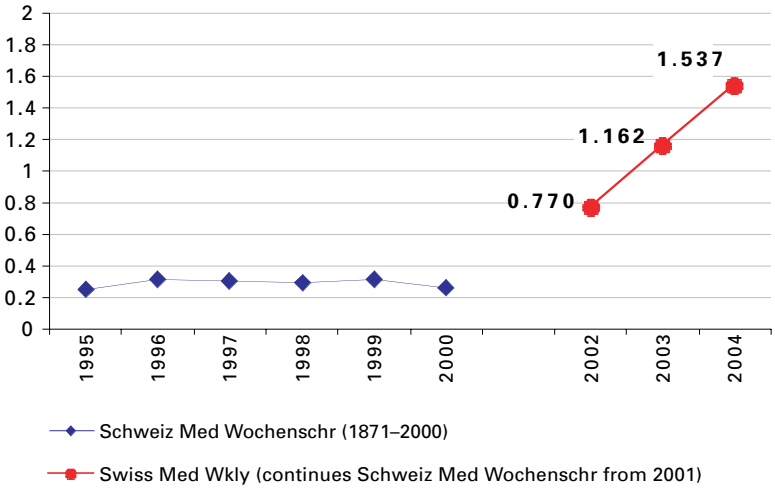
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



EMH FMH Schwabe
Editores Medicorum Helveticorum

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch