



A technical introduction to the basic requirements of clinical trials

Wolfgang Kuchinke, PhD; Professor Christian Ohmann

Hospital pharmacists have an important role in clinical trials, whether as part of the ethics committee, as supplier of the study medication or in the investigation team that carries out the trial. Here we look at the whole world of requirements needed to conduct a clinical trial.

The necessity for clinical trials

A wide spectrum of clinical research exists, covering, amongst others, clinical trials on medicinal products and medical devices, surgical trials, trials with psychotherapy, nutritional studies, physiological studies and epidemiology studies. The most rigorous form of clinical research of a medicinal product or a particular treatment is the double-blinded randomised clinical trial. It is not possible to do research on humans without it, because it is the only way to determine if a medicinal product is both safe and effective. Clinical trials are often used to test new medicines or vaccines, but can also be used to investigate new combinations of existing treatments, or to compare new treatments with accepted treatments. Clinical trials are necessary because animal models and cell culture tests cannot completely be transferred to humans. Until a well-designed clinical trial has been carried out, we simply do not have enough evidence to know if a treatment is both effective and safe for patients. In fact, the increase in patients with chronic diseases and infections, the growth in novel biomedical products that have to be tested and the challenges of personalised medicine have increased the demand for clinical trials.

The requirements for clinical trials

Before a clinical trial can be started, and this applies especially to clinical trials on medicinal products that have to be conducted in a GCP (Good Clinical Practice) compliant way, a multitude of requirements have to be implemented. Requirements for the conduct of clinical trials are laid down in a number of inter-

national guidelines, the most important are: ICH-GCP E6 [1], Directive 2001/20/EC (the Clinical Trials Directive) [2] and Directive 2005/28/EC [3]. These guidelines require that a number of prerequisites have to be fulfilled before the clinical trial can start; they define roles and specify reporting obligations during and at the end of the trial. This is so because ethical considerations must play a prominent part in clinical tests with humans. A thorough knowledge of the regulatory requirements and their ethical background is therefore a prerequisite for every researcher participating in clinical trials.

Requirements for the set-up of a clinical trial

Once the purpose and objectives of the clinical trial have been formulated a trial protocol has to be created. The protocol describes objectives, design, methodology, statistical considerations, and the organisation of a clinical trial. The content and structure of the trial protocol is determined by the ICH GCP E6 guideline [1]. A Trial Master File (TMF) and an Investigator Site File (ISF) have to be prepared, to be gradually filled with study documents during the course of the trial. An Investigator's Brochure contains important efficacy and safety details the investigators and other clinical staff should know before administering the test product to humans. For data collection a special form, the Case Report Form (CRF), has to be prepared. Storage, distribution and the management of the test substance, the Investigational Medicinal Product (IMP), has to be planned, including the generation of a drug inventory log, temperature log,

etc. Procedures for the import of laboratory data and a process for dealing with laboratory values must be in place. To ensure the quality of the execution of a clinical trial standard operating procedures (SOPs) have to be in place and staff should be trained. SOPs are written instructions to achieve a uniform and standardised performance of all clinical trial functions. SOPs should be authorised, reviewed at regular intervals and their versions must be controlled.

Hospital pharmacists have an important role in all drug trials, even more so in investigator-initiated clinical trials, whether as part of the ethics committee, as supplier of the study medication or in the investigation team that carries out the trial. To provide the IMP, the pharmacy has to maintain a system for IMP reception, logging storage and dispensation. Pharmacy staff may review the study protocol and assess the feasibility of the study and the work undertaken by the pharmacy department. Thus pharmacy clinical staff may participate in the investigator meetings, to explain use and storage conditions of the IMP. Study medication must be manufactured in accordance with Good Manufacturing Practice and labelled according to specific requirements [4]. Other possible tasks are inventory control, drug accountability, study product disposition, product expiration review, on-site destruction and chain-of-custody documentation.

Prior to the commencement of a trial the approval of a Competent Authority (CA) and a positive vote of an Ethics Committee must be obtained. CAs have

For electronic archiving over longer storage periods, data migration strategies may be necessary to guarantee readability.

the power to regulate, including the authority to conduct inspections at investigator sites. The Ethics Committee is an independent body, consisting of healthcare professionals and non-medical members, whose responsibility is to protect the rights, safety and well-being of human subjects involved in a trial by expressing an opinion on the trial protocol, the suitability of investigators and the adequacy of site facilities. Any clinical trial on a medicinal product requires a clinical trial authorisation (CTA) from the CA in the EU Member State in which the trial is being carried out. The CTA application form and accompanying guidance documents can be obtained from the EMEA website. Before completing the CTA application a EudraCT number must be obtained from the EudraCT website [5]. There are also guidelines available concerning the pharmaceutical data required in a CTA [6]. According to the European Directive 2001/20/EC a clinical trial may be undertaken only if an insurance coverage exists. As no common European coverage is available, an insurance certificate must be obtained from each country participating in the clinical trial.

Requirements during the conduct of clinical trials

To support the conduct of clinical trials a framework consisting of recruitment, randomisation/blinding, data management, adverse event, and serious adverse event reporting and monitoring must be in place. In the first step patients are screened for participation and checked against inclusion criteria. The current recruitment rate of adult patients into clinical trials is low. On average, only up to 3–5% of newly diagnosed cancer patients are enrolled into clinical trials. Improved patient enrolment presents

one of the largest opportunities to eliminate common delays in clinical trials; however, recruitment for a clinical trial is a very complex, multilevel process [7]. It is an important requirement for the clinical trial to achieve the projected number of patients, to meet the required sample size for convincing statistical power. The patient that meets the inclusion criteria will be randomly assigned to a particular treatment (randomisation) to either the new medicine, a medicine that is considered standard therapy, or a placebo. Using randomisation and blinding neither the patient nor the investigator knows which treatment is applied. In order to be included in a trial the patient has to give an informed consent to participate. It is required that the patient information included in the informed consent is comprehensive and easily understandable and should include any risks associated with the trial. All participants entering the clinical trial have their human rights as a person guaranteed, their personal data is protected and patients can withdraw their informed consent at any time without any consequence.

Already a large number of clinical trials use electronic data capture (EDC) with a browser-based electronic CRF. For this purpose, an infrastructure consisting of EDC software, web server, application server and a clinical database have to be set up. Before entering data in the electronic CRF investigators have to be trained in using them. Electronic CRFs contain specially designed plausibility checks in addition to a query system to guarantee the quality of collected data. Every data management system used in clinical trials has to be system validated. A guiding principle is therefore: ‘perform no clinical trial with an invalidated system’. System validation is a method

to provide documented evidence that the system operates in the intended way and is compliant with GCP and other regulations. Data access control, regular data backups and database archiving have to be conducted.

The requirements for monitoring activities, like initiation visits, monitoring visits during the trial and close-out visits, are part of the quality control of clinical trials. The monitor focuses on those trial data and study information that are essential for an assessment of trial participant’s safety, well-being and rights, as well as for data quality to achieve the primary and secondary trial objectives. Therefore, data and supporting documents have to be accurate and presentable for inspections, informed consent and data privacy requirements have to be observed, and prevention for fraud and misconduct in clinical trials must be in place.

Enabling faultless adverse events reporting in clinical trials is one of the most important requirements. Especially two events: serious adverse reactions and suspected unexpected serious adverse reactions need special attention and must be reported within a fixed period. The sponsor (in conjunction with investigator) is responsible for the ongoing safety evaluation of the IMP.

Requirements at the end of clinical trials

After the database is closed, data collected is sent to the sponsor or leading investigator for analysis with a series of statistical tests. Commercial trials aim at marketing authorisation, investigator-initiated trials are targeted to improve scientific evidence about interventions. Results of randomised clinical trials should be reported according to the CONSORT statement [8]. In addition, medical journal editors have defined requirements for clinical trial registration as a prerequisite for publication of trials in journals. Trial registration can be done for example at ‘Clinical Trials.gov’ [9]. The end of a clinical trial

should be notified to both the CA and the Ethics Committee.

The trial ends with the archiving of the essential clinical study documents. The TMF shall contain all GCP-essential documents of the clinical trial, including the study database, and must be archived by the sponsor. The ISF contains the essential documents necessary for the investigator to carry out the study, and is archived at the corresponding clinical centre. An archive for clinical study documents must be lockable, must be accessible only by authorised persons and must have appropriate measures to protect documents against water and fire. Electronic documents and data should be archived on durable media in an open standard format which is independent of specific operating systems, applications and special equipment, so that documents can be kept readable for long periods without the original data generating system available. For documents XML, TIFF and PDF and for the database CDISC-ODM [10] are such suitable formats. For electronic archiving over longer storage periods, data migration strategies may be necessary to guarantee readability.

A whole world of requirements

As described here, a multitude of requirements for clinical trials exists. But by meeting them the safety of trial participants and the quality of trial results can be effectively ensured: 'methodological quality is the first ethical requirement in clinical trials' [11]. Trials with high standards of quality met the requirement of reporting ethical issues more frequently than trials with low quality [12]. However, the multitude of requirements constitutes a major challenge for clinical trial centres and investigators, since they affect current clinical practices considerably. To support the academic research community to meet all requirements clinical research units and clinical trial centres at many European universities have been established. In addition, to support international clinical trials enabling access to

The multitude of requirements constitutes a major challenge for clinical trial centres and investigators.

larger populations, the new and EU-funded network European Clinical Infrastructure Network (ECRIN) [13] has been created, which offers services for multinational clinical trials. In this project a certification procedure for ECRIN data centres will be set up to assure GCP-compliant data management on an international level [14, 15].

Authors

Wolfgang Kuchinke, PhD (see photo)
Professor Christian Ohmann
Coordination Centre for Clinical Trials (KKS)
Heinrich-Heine University Duesseldorf
Medical Faculty Blg 14.75
5 Moorenstrasse
D-40225 Düsseldorf, Germany
kuchinkw@uni-duesseldorf.de

References

1. ICH-GCP E6 (R1) Guideline for Good Clinical Practice. [cited 2009 October 18] Available from: www.emea.europa.eu/pdfs/human/ich/013595en.pdf.
2. Directive 2001/20/EC of the European parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official J Eur Commun.* 2001;L21:34-44.
3. Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. *Official J Eur Commun.* 2005;L91:9-19.
4. VOLUME 4, Good manufacturing practices, ANNEX 13, Manufacture of investiga-

- tional medicinal products. Brussels July 2003. [cited 2009 October 18] Available from: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/an13final_24-02-05.pdf
5. <https://eudract.emea.europa.eu/eudract/index.do> [cited 2009 October 18].
6. Committee for medicinal products for human use: Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials (CHMP/QWP/185401/2004), EMEA London 2004. [cited 2009 October 18] Available from: www.emea.europa.eu/pdfs/human/qwp/18540104en.pdf.
7. Ohmann C, Kuchinke W. Meeting the Challenges of Patient Recruitment. *Int J Pharm Med.* 2007;21(4):263-70.
8. Moher D, Schulz KF, Altman DG. The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomized Trials. *Ann Intern Med.* 2001;134(8):657-62.
9. www.clinicaltrials.gov [cited 2009 October 18].
10. www.cdisc.org/models/odm/v1.3/index.html [cited 2009 October 18].
11. Ruiz-Canela M, de Irala-Estevéz J, Martínez-González MA, et al. Methodological quality and reporting of ethical requirements in clinical trials. *J Med Ethics.* 2001;27(3):172-6.
12. Salzberg M, Müller E. Quality requirements in clinical studies: a necessary burden? *Swiss Med Wkly.* 2003;133(31-32):429-32.
13. Demotes-Mainard J, Ohmann C. European Clinical Research Infrastructures Network: promoting harmonisation and quality in European clinical research. *Lancet.* 2005;365(9454):107-8.
14. C Ohmann and the Transnational Working Group on Data Management. Deliverable D10: GCP-compliant data management in multinational trials, ECRIN Paris, 3rd version, 17 June 2008. [cited 2009 October 18] Available from: www.ecrin.org.
15. www.ecrin.org [cited 2009 October 18].