

Good clinical practice (GCP): A universal call for ethics in biomedical research

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Abstract

Today, the principles of good clinical practice (GCP) form such an integral part of the development of new medicines that they could easily be taken for granted. Yet, the road to a universal code of ethics in human experimentation is paved with tragedies which have only gradually led to tightened rules on human experimentation. Awareness of the historical roots of GCP helps explain that GCP, rather than representing a seemingly endless series of regulations, finally provides an international ethical and scientific quality standard designed to protect the rights and safety of individuals consenting to participate in clinical trials and to ensure the integrity and credibility of clinical research data. For medical writers, familiarity with the principles of GCP, which in the European Union are now a legal obligation, is an essential prerequisite for providing documentation in compliance with the ethical and scientific principles of GCP: not only are medical writers expected to frame clinical research into a language that enables independent assessors to evaluate the methodological validity of a study and the safety and efficacy of a given drug, they also compose documents that may be instrumental in assuring the rights and safety of clinical trial participants.

Keywords: Good clinical practice (GCP), Medical writing, Ethics in human research

The decision to allow a new medicinal product to enter the market can have far-reaching consequences for millions of patients around the world. Today, the development of a new medicine is so inextricably linked with the concept of good clinical practice (GCP) that it is hard to believe that GCP has only been around for about 20 years.

Historical perspective

The realisation that it is important both to thoroughly assess medicinal products before

allowing them to be marketed and to safeguard the interests of those healthy individuals or patients in whom new products are first assessed was nurtured by a series of tragedies – caused either by a lack of ethical judgement, a lack of awareness, or a combination of both.

First directive on informed consent, Prussia 1891

The advances in science in the late nineteenth century were accompanied by an increased demand for experimentation in human subjects. Human experiments were mainly carried out in hospitalised patients or prisoners and without their consent. In 1891, the public controversy about the ethics of such practices caused the government of the Kingdom of Prussia to pass a directive decreeing that tuberculin for the treatment of tuberculosis ‘must in no case be used against the patient’s will’.¹ Nine years later, the first regulations regarding non-therapeutic research in Western medicine were passed.¹

The Neisser case and the first detailed directive on informed consent of 1900

In 1898, the German Albert Neisser, professor of dermatology and venereology, published the results of studies designed to find a cure for syphilis. He inoculated serum from patients with syphilis into patients who had been hospitalised for other reasons. When some of the ‘vaccinees’, most of whom had been prostitutes, actually contracted syphilis, Neisser claimed that their infection was a result of their professional activity. In response to the public outcry triggered by the case, the Prussian parliament, assisted by a scientific commission composed of leading German experts such as Rudolf Virchow, in 1900 issued the first directive in history to require unambiguous consent of the subject after proper information given by a physician, the *Richtlinien für Wissenschaftliche Experimente* (Guidelines for Scientific

Experiments).¹ These guidelines may be the first reported regulatory document applicable to the field of human experimentation and recognising the need for the protection of vulnerable populations.²

Guidelines for new therapy and human experimentation of 1931

Continued criticism of unethical human experimentation caused the government of the Weimar Republic to issue detailed *Richtlinien für Neuartige Heilbehandlung und für die Vornahme Wissenschaftlicher Versuche am Menschen* (Guidelines for New Therapy and Human Experimentation) in 1931. These guidelines clearly differentiated between therapeutic and non-therapeutic research and, on some counts, included regulations that were even stricter than those contained in the Nuremberg Code of 1947 or the Declaration of Helsinki of 1964. For example, human experiments in dying patients were absolutely prohibited.¹ Thus, contrary to common belief, the concept of informed consent had developed long before World War II and was introduced not at the instigation of the research community but by government authorities.

Human experiments during World War II and the Nuremberg Code of 1947

However strict these pre-war regulations, they were unable to prevent some of the worst atrocities ever to be performed under the cloak of medical research. The Doctors' Trial, one of the subsequent Nuremberg Trials held in the US occupation zone from 1946 onwards, brought to light the gruesome experiments performed during World War II in huge numbers of Jewish prisoners, members of the Roma population, mentally or physically disabled Germans, and prisoners of war. One category of experiments was performed with a view to advancing the survival of German military personnel and included freezing, transplant, infection, and mustard gas experiments in prisoners. Another sought to advance the racial goals of the Nazi ideology using medical experiments in twins as well as artificial insemination and sterilisation studies, all performed with a view to creating a master race. These experiments left thousands of victims physically and mentally mutilated, dead, or killed for the purpose of post-mortem measurements.³

The final judgement of the Doctors' Trial passed in 1947 enumerated a set of 10 principles of what the trial's medical expert witnesses, Drs Leo Alexander and Andrew Ivy, and the trial's judges and prosecutors considered legitimate medical

research, derived from the natural law of all people.² These 10 points were to make up the Nuremberg Code.⁴ As Grodin put it, 'Medical ethics would forever be changed after the Holocaust'.²

Declaration of Geneva of 1948

Spurred by the revelations of the Doctors' Trial and details about the terrifying human experiments performed by the Japanese Army at the biological and chemical warfare research Unit 731 in China during World War II, the idea of establishing an international medical organisation setting ethical guidelines for physicians across the world was born in the House of the British Medical Association in 1945, a popular meeting place for doctors from all the allied nations during the war. In 1947, the World Medical Association (WMA) was founded. Among its first activities was the drafting of a modernised version of the ancient Oath of Hippocrates, which was adopted by the General Assembly of the WMA in 1948 as the Declaration of Geneva.⁵ Also inspired by the horrors of World War II, the idea for a position paper on recommendations guiding physicians in biomedical research involving human subjects was born in 1953. Before the adoption of this guidance document – which would come to be referred to as the *Declaration of Helsinki* – another disaster was to shake the world of medical research.

Thalidomide disaster

Thalidomide had been developed in the 1950s as an anticonvulsant drug. Early trials showed it to be unsuitable for this purpose but indicated that it had sedative properties. It was first marketed in Germany in 1957 as an over-the-counter drug considered safe even for use during pregnancy, and it was also found to be a highly effective anti-emetic alleviating morning sickness.⁶ By 1960, thalidomide was sold throughout Europe and South America, in Canada, and in many other parts of the world.⁷

By about the same time it had become clear that long-term use of the drug was associated with peripheral neuritis. The British Medical Journal in 1960 published a letter by Leslie Florence⁸ about peripheral neuritis in four of his patients, further nurturing FDA medical officer Frances Oldham Kelsey's long-held suspicion about thalidomide's safety. Although Germany was already witnessing an increase in teratogenic deformities in children born to mothers who had used the drug during pregnancy, no link with thalidomide was established until 1961,⁹ when, in response to reports by

the German paediatrician Hans-Rudolf Wiedemann and the geneticist and paediatrician Widukind Lenz, the drug was finally taken off the market by the German health authorities.⁸ By that time, thalidomide had caused the deaths of more than 2000 children and serious birth defects in about 10 000 children,⁹ most of them in West Germany. At the time, drugs were tested in rodents only, and because they were thought to be incapable of passing the placenta, were not tested for teratogenic effects.¹⁰ In the wake of the thalidomide disaster, many countries introduced stricter assessment, approval, and monitoring procedures for new medicinal products.

Declaration of Helsinki of 1964

The Declaration of Helsinki – the first significant effort by the medical community to regulate research in human subjects that had been on the agenda of the WMA since after World War II – was finally adopted in 1964. It expanded on the principles of the 1947 Nuremberg Code and linked them to the 1948 Declaration of Geneva – but may also have had much to do with the devastating effects of thalidomide on thousands of babies. Among its general principles are that ‘medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights’, and that the goal of generating new knowledge ‘can never take precedence over the rights and interests of individual research subjects’. Consistent with the mandate of the WMA, the Declaration of Helsinki addresses the medical profession only.¹¹

Guidelines for GCP by the World Health Organization of 1995

Four years after the adoption of the Declaration of Helsinki, the World Health Organization (WHO) convened the Scientific Group on Principles for Clinical Evaluation of Drugs in 1968 and charged it with formulating principles for the clinical evaluation of drug products.¹² In 1975, WHO formed another Scientific Group responsible for drawing up relevant guidelines. The reports that resulted from this work formed the basis for the WHO guidelines for GCP for Trials on Pharmaceutical Products published in 1995,¹³ which in turn found their way into the 1996 guideline for Good Clinical Practice E6 by the International Conference on Harmonisation (ICH)¹⁴ or the international standard EN ISO 14155:2011, Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice published in 2011.¹⁵

Based on the ‘ethical principles which have their origin in the Declaration of Helsinki’, the WHO guidelines for GCP extended these principles to apply not only to physicians, but to all parties involved in clinical trials – from sponsors, investigators, site staff, and contract research organisations to ethics committees, regulatory authorities, and clinical trial participants.^{14,15}

Guideline for Good Clinical Practice E6 by the ICH of 1996

In 1996, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) passed its guideline for Good Clinical Practice E6, based in part on the guidelines drawn up by the WHO.¹⁶ Although both guidelines share the same content, an important difference is that the ICH guideline for Good Clinical Practice E6 was drawn up as a regulatory standard with the express purpose of harmonising the technical requirements for the registration of medicinal products across the three main ICH regions, i.e. the USA, Japan, and Europe, whereas the WHO guidelines for GCP are intended as an educational tool for regulatory agencies in countries where no other guidance exists.

In Europe, efforts at harmonising regulatory requirements had dated back to the 1980s, as the then European Community started to move towards the development of a single market. In 1990, in response to increased globalisation, the ICH was established to bring together the regulatory authorities and pharmaceutical industry of Europe, Japan, and the USA to achieve ‘greater harmonisation to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner’.¹⁶ ICH harmonisation efforts are summarised in guidelines developed in a step-wise approach, from consensus building in Step 1 to adoption of the guideline in Step 4 and implementation in each of the three ICH regions in Step 5.¹⁷ Guidelines are divided into four categories, with quality, safety, and efficacy guidelines reflecting the three criteria for approving and authorising new medicinal products and multidisciplinary guidelines covering cross-cutting topics (Figure 1).

The benefits of ICH range from reducing duplication of testing and reporting, providing guidance on the preparation of regulatory documents, such as clinical study reports, use of a harmonised submission dossier format, i.e. the common technical document, or the creation of a joint medical terminology, i.e. Medical Dictionary for Drug



Figure 1: Four categories of ICH guidelines. Source: <http://www.ich.org/products/guidelines.html>.

Regulatory Affairs (MedDRA) – all designed to streamline the dossier compilation and review process across regions and getting high-quality, safe, and effective medicinal products to patients in a more timely fashion. The ICH guideline for Good Clinical Practice E6 is part of the efficacy category of ICH guidelines.¹⁶

Principles of GCP

In brief, the principles of GCP are designed ‘to ensure that clinical research participants are not exposed to undue risk and that the data generated from the research are valid and accurate’.¹⁴ They are intended to be applied during all stages of drug development and specify standards for designing, conducting, recording, and reporting clinical trials.

- In terms of *study design*, GCP requires a written study protocol describing the trial’s objectives, design, methodology, and statistical considerations, an investigator’s brochure summarising the available clinical and non-clinical data on the investigational product, scientific soundness and feasibility, and bias-reducing measures such as randomisation and blinding.
- In terms of *study conduct*, GCP requires approval of the study by both independent ethics committees and regulatory authorities, compliance with the protocol, freely given informed consent, data confidentiality, adequate medical care for subjects experiencing adverse events or adverse drug reactions, product accountability, adequate qualification and training of all study personnel, and appropriate resources.

- In terms of *recording standards*, GCP requires that case report forms be completed accurately and in agreement with the patient records, reliable data handling, security systems preventing unauthorised access to the data, internal audits overseeing the conduct of the trial, and adequate management and archiving strategies for study files.
- In terms of *reporting*, GCP requires adverse events, interim and final reports, and monitoring, audit, and inspection reports to be compiled and archived.

Importantly, the principles of GCP ‘may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects’.¹⁶ The 13 core principles as enumerated in the ICH guideline for Good Clinical Practice E6 are given in Box 1.

Box 1: Thirteen core principles of GCP as spelled out in the ICH guideline for Good Clinical Practice E6

1. *Ethical principles*. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirement(s).
2. *Favourable benefit–risk profile*. Before a clinical trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A clinical trial should be initiated and continued only if the anticipated benefits justify the risks.

3. *Subject rights.* The rights, safety, and well-being of the trial subjects override the interests of science and society.
4. *Adequate supporting data.* The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. *Scientifically sound protocol.* Clinical trials should be scientifically sound and described in a clear, detailed protocol.
6. *Ethics committee oversight.* A trial should be conducted in compliance with the protocol that has received prior institutional review board/independent ethics committee approval or favourable opinion.
7. *Medical care by qualified physician.* The medical care given to subjects, and the medical decisions made on their behalf, should always be the responsibility of a qualified physician or, when appropriate, a qualified dentist.
8. *Qualified personnel.* Each individual involved in conducting a clinical trial should be qualified by education, training, and experience to do their respective task(s).
9. *Informed consent.* Freely given informed consent should be obtained from every subject prior to participation in the clinical trial.
10. *Record-keeping.* All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.
11. *Subject confidentiality.* The confidentiality of records that could identify subjects should be protected – respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. *GMP manufacturing.* Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. *Quality assurance and monitoring.* Systems with procedures that assure the quality of every aspect of the clinical trial should be implemented.

GCP in the European Union

In 2001, the principles of the ICH guideline for Good Clinical Practice E6 found their way into European legislation with the implementation of the Clinical

Trials Directive (i.e. Directive 2001/20/EC) and the accompanying guidance documents. In 2005, the GCP Directive (i.e. Directive 2005/28/EC) clarified the principles of GCP in the European context as required by Directive 2001/20/EC. Directives 2001/20/EC and 2005/28/EC had to be transposed into national law by May 2004 and January 2006, respectively.

Importantly, both directives apply to interventional ‘clinical trials on medicinal products for human use’ only. They do not apply to non-interventional studies, i.e. ‘studies where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation’, nor do they apply to clinical investigations that do not involve medicinal products, such as studies assessing medical devices¹⁷ or other non-pharmacological interventions, such as surgical techniques^{18,19} or diagnostic procedures.²⁰ For clinical investigations involving medical devices, the aforementioned harmonised EU standard EN ISO 14155:2011 provides practical guidance on the conduct and reporting of clinical investigations. Unlike GCP in clinical studies with medicinal products as implemented in Directive 2001/20/EC, therefore, the use of GCP in other areas of clinical research is not mandatory in the European Union (EU).

Ethics is a perpetually evolving subject in the face of a constantly changing social and political environment and rapid development in the fields of science and technology. For example, the year 2013 saw the seventh revision of the Declaration of Helsinki. In July 2012, the European Commission, adopted a proposal for a clinical trials regulation designed to repeal Directive 2001/20/EC,²¹ which is widely considered to have curbed the attractiveness of the EU for conducting clinical trials by introducing unnecessarily tight administrative and regulatory requirements. Between 2007 and 2011, the costs for conducting clinical trials in the EU more than doubled, insurance fees for industry sponsors increased by 800%, and the number of applications for clinical trials dropped by 25%.²² Also, considering that about 24% of clinical trials (with about 67% of enrolled subjects) in Europe are performed in at least two EU member states, an EU regulation, which immediately and simultaneously takes effect in all members states, is likely to more effectively harmonise clinical trial procedures throughout Europe than EU directives, which still have to be transposed into national law and leave considerable leeway as to how the provisions set out in the directive are actually implemented in each member state.

GCP for medical writers?

The ICH guideline for Good Clinical Practice E6 calls for ‘each individual involved in conducting a clinical trial’ to be qualified to do their respective task. According to Directive 2001/20/EC, compliance with GCP not only ‘provides assurance that the rights, safety and well-being of trial subjects are protected and that the results of the clinical trials are credible’ but is also a legal requirement throughout the EU. Therefore, being thoroughly familiar with the principles of GCP is as important for medical writers as for other members of a clinical development team.

For one thing, medical writers are expected to frame clinical research rationales, processes, and data into a language that enables independent assessors and reviewers to determine whether the study results presented are indeed ‘credible’ and evaluate the safety and efficacy of a given medicine. To be able to do so, medical writers need to understand what was done and why. For another, although medical writers are not directly involved in patient care, the documents they write and compile may play an essential role in assuring the rights and safety of healthy individuals or patients participating in clinical research – many of whom may be faced with serious illness and some of the most daunting questions of their lives. In this vein, the principles of GCP – and the historical developments that lead up to their adoption – are a constant reminder that the primary and ultimate purpose of clinical research is to promote health and well-being and to ensure respect for the dignity of all human life.

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