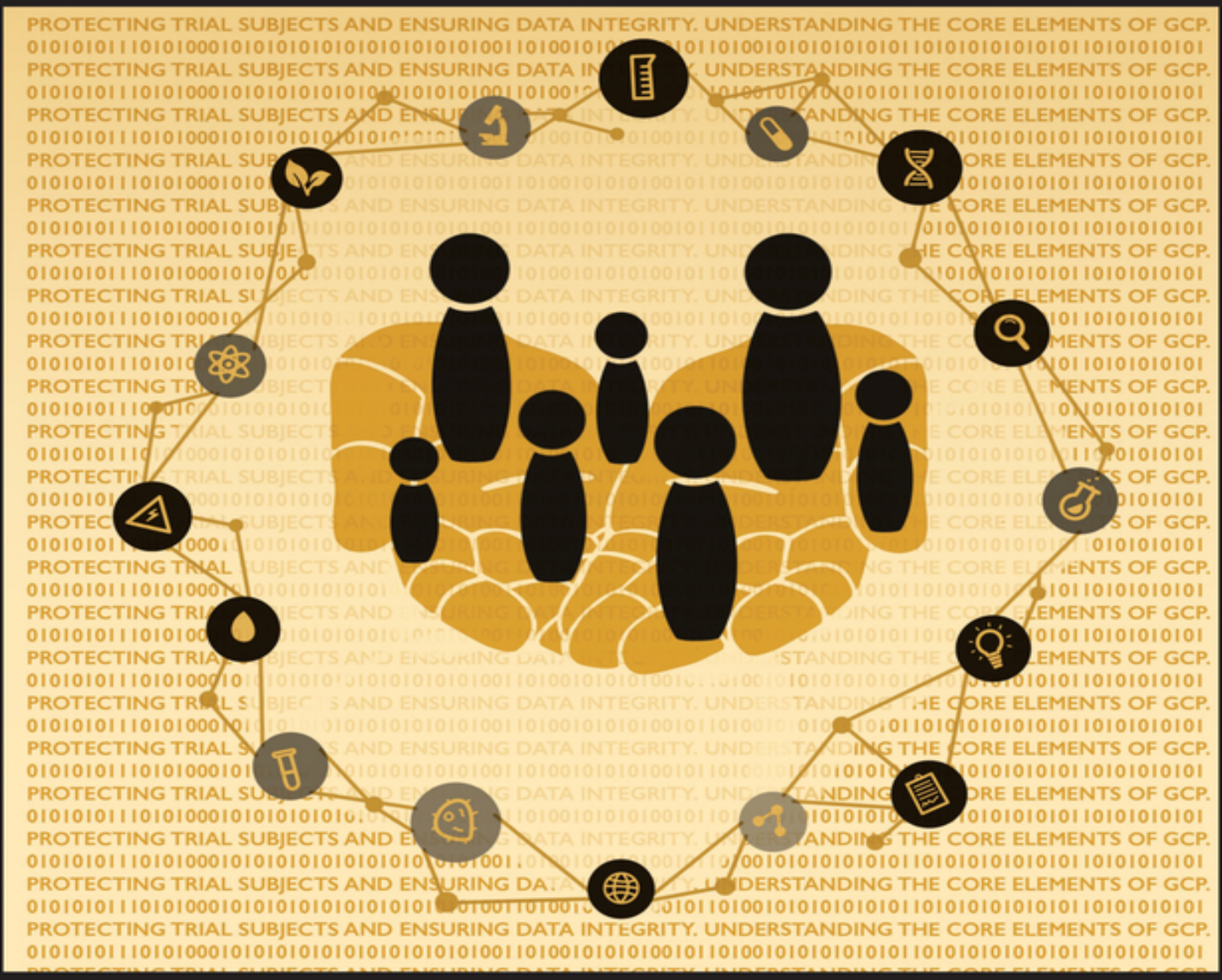
The Fundamentals of Clinical Research

A Universal Guide for Implementing Good Clinical Practice

P. Michael Dubinsky • Karen A. Henry



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Preface

Goal

Since 1996 the emergence of the good clinical practice (GCP) framework for the conduct of clinical trials, more than any other requirement or guidance, has served as a singular reference point for performing trials in humans in conformance with ethical and regulatory expectations. Certainly GCP is mentioned and described in all clinical trial texts, manuscripts, papers, and presentations, and it has moved beyond the role of guidance and become law in a number of global regions and countries: the GCP guidance document developed and published by the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has been adopted into law in both the European Union (EU) and Canada, and the World Health Organization has developed a set of GCPs for its constituency. For medical device products, the ISO standard 14155 was revised in 2011 and now serves as the GCP reference point for device-related clinical research. That step eliminated the need for clinical investigators studying medical devices to debate whether they should be following the ICH-GCP that was targeted at pharmaceutical drug studies. As a result, GCP has become the universal language of trials that involve human subjects.

GCP provides a framework for clinical trial professionals to work within and guidance in how to abide by their local, national, and/or regional regulatory requirements. In turn, regional and national regulatory authorities integrate GCP into their clinical trial regulations, adopt it to their existing regulations, or call their regulations GCP. The regulatory

authorities have established requirements that govern the conduct of trials, and these requirements represent the baseline for compliance. That said, much of the interpretation of the requirements is left to the trial sponsor, investigator, and clinical teams.

The authors, based on their experience both on the job and as teachers, recognize that a comprehensive and integrated understanding of the clinical trial process, with a firm grasp of the fundamental concepts, is vital to improving the quality and outcomes of clinical trials. Both seasoned and novice clinical research professionals wish to obtain a complete overview of the industry and would benefit from learning the fundamentals of clinical research. The comprehensive overview we present in this text will give professionals insight into why they do what they do and provide an integrated understanding of the various disciplines and stages of clinical research. This vantage point allows for judicious application of GCP in practice.

We have designed this text to be used as source material in educational settings such as university courses and as a training aid for the clinical research industry. Our goal is to provide a universal working reference for all of the players in clinical trials: an educational resource that integrates the fundamentals of clinical research for working individuals, clinical research students, or any curious person. By “working individual,” we mean everyone from the novice to the seasoned clinical research professional in academia, industry, or a regulatory environment. From a practical viewpoint, this text has been written to address the regulatory, scientific, administrative, business, and ethical considerations of clinical research trials within a GCP framework. It describes how to implement clinical research to meet research, regulatory, and ethical objectives, such that the process succeeds the first time and does not need to be repeated.

Scope of this Book

Clinical research has reached global proportions. This text will not attempt to touch on each individual country, but rather will look at global regions and nations, such as the EU and the United States, which set the pace for the implementation of GCP worldwide. We have aimed to give perspective to each element of GCP from as many vantage points as we can, and have expanded our discussion of the elements of GCP to include regulatory, scientific, technological, site investigator, sponsor, quality, and IRB viewpoints, as appropriate.

We have focused the scope of our clinical research discussion on trials involving humans in a biomedical context. From an investigative product/test article perspective, the text favors pharmaceutical drugs since they are associated with the majority of clinical trials. Biological products fit into the same niche. We have also addressed medical devices, though we recognize that despite the similarities in areas such as regulatory controls in the United States, there is a plethora of differences. While we cannot discuss all of these differences, we have highlighted some of the most significant ones.

How to Use this Book

This text is divided into sections that contain relevant chapters on the history of GCP, drug development in the regulatory environment, the GCP framework, GCP for the individual clinical trial, and quality in clinical trials. Each chapter builds on a key GCP concept and contains chapter objectives, content, a summary, and a set of knowledge check questions so that the reader can self-check their learning and comprehension. The ICH-GCP Guidelines serve as the glossary of terms and definitions. Plates

visually summarize the content for certain chapters, and the reader is also able to cross-reference details in pertinent chapters from the plates. Figures, tables, and other illustrations also enhance the text materials.

Opinion of the Authors

The authors of this text have a combined approximately 76 years of experience working in various areas of clinical research, as well as approximately 25 years of experience as part-time instructors in university-sponsored classrooms and online courses of study designed to introduce students to the clinical research industry. They have also developed some of the educational and learning materials that make up these university-sponsored courses. This text is written from their individual viewpoints as they have interpreted and applied the GCP Guidelines. Except for direct references to the ICH E6 (R2) Guideline or other sources, all statements are the opinions of the authors.

The authors would like to thank Kay Ranganathan for introducing them to the instructional arena for clinical research; their esteemed colleagues for their review of the manuscript; and their families for their patience and support through the times when writing this book got in the way of family life.

About the Authors

P. Michael Dubinsky has more than 40 years of experience in the field of GxP quality and compliance in government and industry. He has worked with the FDA and as a regulatory consultant for private corporations. He was also an Instructor in the areas of clinical trial compliance, regulatory audits, and quality at the University of California Berkeley Extension Programs.

Karen A. Henry has worked as a clinical research professional since 1990. She has expertise in regulatory medical writing, standards and processes, trial management and monitoring, biostatistics, and data management. She is also a Lead Instructor for the Certificate Program in Clinical Research Conduct Management at the University of California Berkeley Extension Programs.

About the Authors

This book is accompanied by a companion website.

www.wiley.com/go/dubinsky/clinicalresearch

This website includes:

- Solutions to the Problems
- Further References Section

Protocol Synopsis and Schedule of Trial Activities Template

Part I
Good Clinical Practice History

1
History

P. Michael Dubinsky

GCP Key Point

Good Clinical Practice might be termed a cultural approach to applying ethics and integrity to human biomedical clinical trials with investigational products.

1.1 Introduction

This chapter will briefly outline the history of biomedical clinical trials from the standpoints of regulatory oversight and ethical expectations and the emergence of good clinical practice (GCP).

1.2 Objectives

The objectives of this chapter are to:

- Provide an outline of legislation, events, and circumstances which provide the background and history for the development of the ICH GCP Guideline E6 R2.
- Offer thoughts and points of view on why the GCP mindset emerged among the global regions most involved in pharmaceutical drug development occurred.

1.3 Chronology

If you research the history of GCP, you will find that it is aligned with the events which form the stepping stones on the pathway of clinical trial regulation. The best known events involve abuses of humans during medical experimentation and the subsequent legislative and regulatory initiatives to prevent the recurrence of those abuses. The following events, policies, and legislation stand out.

- 1902 – The Biologics Control Act [1] is enacted by the US Congress requiring licensing of vaccines, serums, and similar products. The legislation was prompted by the distribution of a contaminated batch of diphtheria antitoxin contaminated with tetanus which killed 13 children. This legislation eventually became part of the Public Health Service Act and serves as the primary regulatory control for the same group of products which now includes cell therapies and many biotechnology-derived products.
- 1906 – The Food and Drugs Act [2] is passed by the US Congress and gives the Federal Government control over misbranded or adulterated drugs.
- 1938 – The US Congress enacts the Federal Food, Drug and Cosmetic Act (FFDCA) [3] in part due to the Elixir of Sulfanilamide [3] episode in which 107 deaths occurred. The new law required proof of safety prior to marketing and drew cosmetics and therapeutic devices into the regulatory scheme.
- 1949 – The Nuremburg Code [4] is born out of the criminal trials of Nazi researchers who conducted unethical experiments on humans during WWII. The Code is a set of 10 points that establishes a foundation for voluntary consent of research subjects as well as

most of the key ethical principles which emerge in subsequent documents.

- 1962 – The Kefauver–Harris Drug Amendments to the FFDCA [5] required that drugs must demonstrate efficacy as well as safety and the investigational new drug (IND) application as we know it today is launched in the regulations. One of the driving forces behind these legislative amendments to the FFDCA was the thalidomide tragedy of 1961 when newborns suffered severe birth defects. The FDA's IND regulations followed circa 1963.
- 1964 – The Declaration of Helsinki [6] takes the ethical principles for conducting research on humans to a new level through the efforts of the World Medical Association.
- 1965 – The US National Institutes of Health proposed that their research involving humans be examined by an impartial panel of peers to ensure ethical integrity. By 1971 the Public health Services' policy of ethical review for human research was expanded to include Department of Health Education and Welfare research however the policy was not well enforced. In 1974. Regulations requiring group ethics review were published and the term institutional review board was born [7].
- 1972 – The US Public Health Service's Tuskegee Syphilis Study [8], which began circa 1932, is publically exposed for its deficiencies and ethical failures.
- 1974 – The US Congress reacts to the Tuskegee study episode by enacting the National Research Act [9] (National Research Act 1974) which establishes the National Commission for the Protection of Human

Subjects of Biomedical and Behavioral Research (National Commission).

- 1976 – the US Congress is provided a report [10] from the General Accounting Office which reported that based on a special survey of sponsor and investigator inspections 74% failed to comply with legal requirements pertaining to informed consent, drug accountability, adherence to protocol, record accuracy, and availability as well as the appropriate supervision by the clinical investigator. This report prompts Congress to recommend that FDA undertake adequate monitoring / inspection programs of clinical trial sponsors, investigators, and institutional review boards.

> "the Food and Drug Administration (FDA) is not adequately regulating new drug testing to insure that human subjects are protected and the test data is accurate and reliable."

- In 1979 the Belmont Report [11] is published by the National Commission and joins the Nuremburg Code and Declaration of Helsinki as a fundamental policy document describing the application of ethical principles such as respect for persons, beneficence, and justice in the conduct of behavioral and biomedical research involving humans.

- 1980s – Global regions, countries with mature drug regulatory systems such as Japan, the European Union (EU), and the United States, as well as global health

authorities, e.g. World Health Association, independently establish or enhance regulations and guidelines governing the conduct of human clinical trials. Harmonization of requirements for drug approval is championed by many.

- 1990 – The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [12] is founded by the regulatory authorities and pharmaceutical associations of Japan, the United States and the European Union.
- 1996 – The ICH guidance GUIDELINE FOR GOOD CLINICAL PRACTICE E6 (R1) [13] (ICH E6(R2) is finalized. It remains the gold standard for the design, conduct, recording, and reporting of clinical trials involving human subjects. Note – It was revised in 2016 to (R2).
- 2004 – The EU Clinical Trial Directive 2001/20/EC [14] becomes effective and EU member states must move to adopt it into their legal requirements. The Directive sets universal requirements for clinical trials including approval by an ethics committee, harmonization of technical requirements through participation in the ICH, and application of GCPs in the conduct of human trials.

The verification of compliance with the standards of GCP and the need to subject data, information, and documents to inspection in order to confirm that they have been properly generated, recorded, and reported are essential in order to justify the involvement of human subjects in clinical trials.

- 2011 – The International Standards Organization (ISO) in conjunction with its standard setting partners publishes the medical device version of the GCP requirements in the form of the standard ANSI/AAMI/ISO 14155 Clinical investigation of medical devices for human subjects – GCP [15] (ISO 14155-2011). 14155 Represents the medical device version of the ICH GCP standard for pharmaceuticals. This publication solidified the application of GCP expectations for human clinical trials in essentially all investigative (unapproved) articles intended for the cure, mitigation, or treatment of disease and injury in man.

This chronology does not however speak directly to the driving forces that were in play as the events unfolded and the progress towards an international acceptance of GCP as a standard was underway.

1.4 The Emergence of the ICH and Its Guidelines

GCP as we know it today was born not just out of tragic episodes in human experimentation such as the Tuskegee Syphilis Study and the abuses of Nazi researchers in the WWII concentration camps. It was very much a work-product of the for-profit drug industry which needed harmonized standards to facilitate the marketing application process among the world's primary producers and consumers of pharmaceuticals. An additional motivation for the ICH concept was to remove duplicative testing which would reduce the exposure of humans to investigational medicinal products, unnecessarily. Viola!, the emergence of the ICH. The ICH was born out of collaboration between the regulatory authorities and