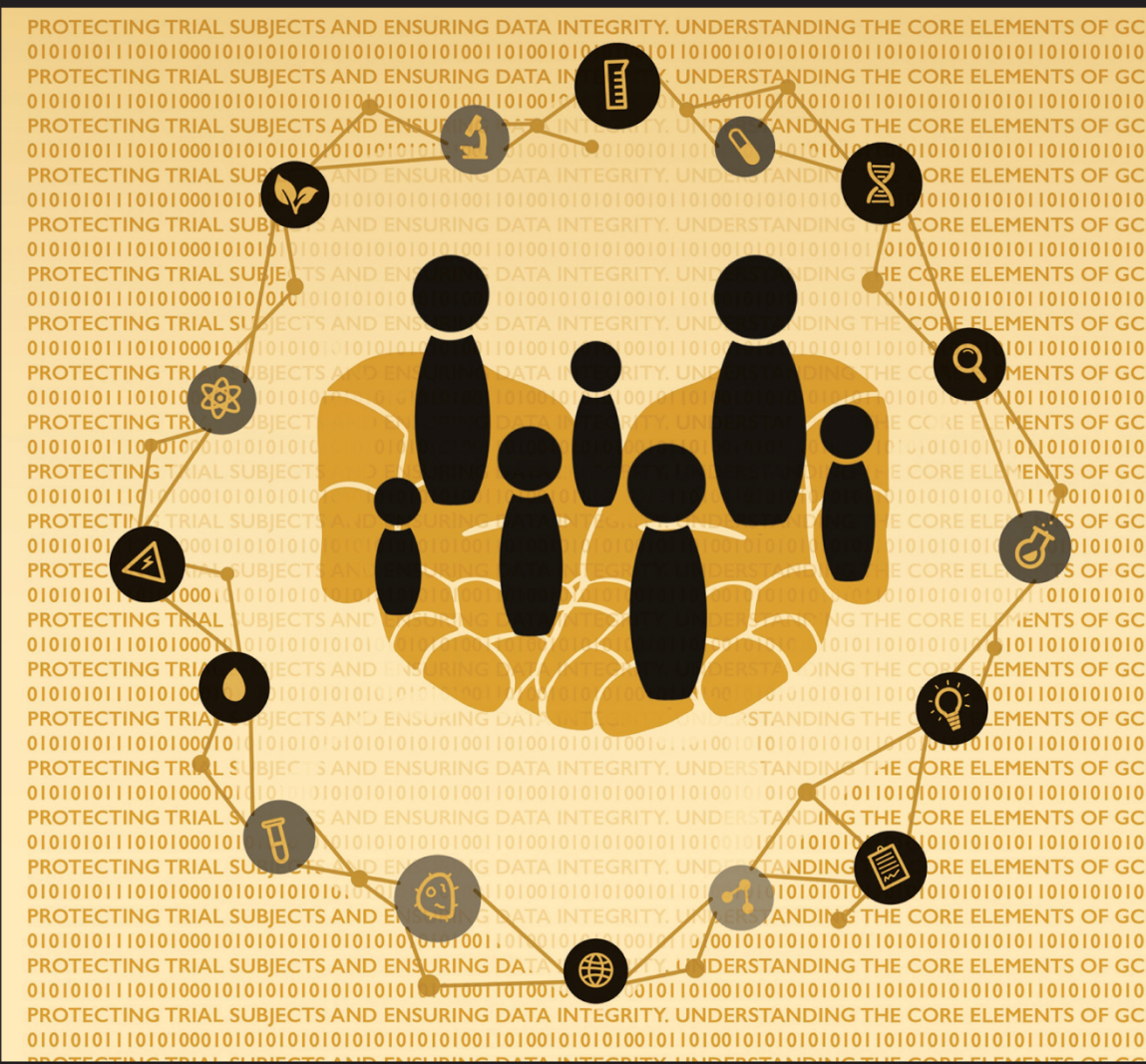
The Fundamentals of Clinical Research

A Universal Guide for Implementing Good Clinical Practice

P. Michael Dubinsky • Karen A. Henry



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Contents

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 Companion Website

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

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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 industry trade associations. It therefore had the best of both regulatory thinking and for-profit science. The newly born organization moved quickly to develop and propose a number of key guidelines which would benefit the entire pharmaceutical industry. GCP was one of the efficacy guidelines defining approaches to clinical trial activities. Others included clinical safety for Drugs Used in Long Term Treatment (E1) and general considerations in clinical trials (E8).

It is important to note that in establishing the ICH approach the industry and regulators did not attempt to cut corners or somehow create a shortcut bypassing

a structured process. Instead the ICH framework has become a model for sound business accomplishment while operating in a transparent and efficient manner. Inclusion of interested parties was encouraged and while the founding members remain in place as the governing entity, participation by other global regions and countries has been fostered and encouraged as observers and as part of global cooperation. Canada, Brazil, China and Australia to name a few participate in ICH meetings and workgroups.

In 2015 the ICH took several steps to solidify its organizational presence and expand its influence. It established itself as an association under Swiss law and it invited regulators and industry counterparts from Switzerland, and Canada to join as full members. It also adopted a name change – The International Council for Harmonization – and continues to grow and prosper today.

Notwithstanding the harmonization mission of the ICH, implementation of guidelines such as GCP even among the founding members of the ICH has not been identical. The European Union and Japan have adopted the GCP guideline into their legal requirements for the conduct of clinical trials. The United States has not, however, done so. The reasons for this difference in adoption of the GCP, as well as other ICH guidelines, lie primarily in the legal system supporting the regulatory framework. For example the United States has had in place regulations governing new drug studies since the early 1960s including requirements associated with informed consent. Modifying those regulations to integrate or adopt the GCP guideline would have been a monumental task. In addition, the system in place to modify/change regulations is a cumbersome one which would encounter difficulties and complexities in keeping up with the technology changes that can more efficiently be processed by a nongovernmental entity such as the ICH.

Without doubt, the US FDA agrees with the ICH GCP guidance, they helped write it! The manner in which the FDA has integrated GCP into its regulatory scheme provides a good example of harmonization with its ICH counterparts as well as demonstrating its support and approval for the application of GCP for human clinical trials.

FDA in a 2004 Federal Register Notice of Proposed Rulemaking (NOPR) [16] to adopt GCP in 21 Code of Federal Regulations (CFR) 312.120 as a reference point for the acceptance of foreign clinical studies not conducted under an IND. At the time, the criteria in 21 CFR 312.120 called for foreign clinical studies to be conducted in accordance with the ethical principles in the Declaration of Helsinki. In reviewing the Preambles to both the NOPR and the 2008 Final Rule [17] it is apparent that the FDA wanted to demonstrate its support and agreement with GCP but was grappling with adopting GCP as a document into law because it would pose administrative difficulties from a procedural and regulatory standpoint. The end product is that FDA removed the reference to the Declaration of Helsinki, which itself had become problematic from several policy standpoints

and substituted GCP as the criteria for acceptance of data generated in studies not conducted under an IND. They even devised a set of 11 specific pieces of information that should be described as evidence that GCP was followed during the course of the human clinical trial. It was a win for the FDA and a win for GCP.

Contemporaneous with the development of the ICH GCP was the development of a set of GCP expectations by the World Health Organization [18]. Subsequent to the publication of the ICH GCP, a number of countries has published its own version by modifying the standard to include requirements that fit their regulatory model.

In the next Chapters we will outline the regulatory environment within which GCP is enabled.

1.5 Summary

The advent of the GCP Guideline and its adoption as a global reference for the conduct of human biomedical clinical trials is a story that emerges from a number of business and regulatory objectives that came together in the early 1990s. The chronology of regulatory legislation, historical incidents, and ethical policy development listed earlier formed the backdrop for the success of the ICH organization. It is noteworthy that GCP stood out as a key early guideline development project. Protection of trial subjects and the assurance that data can be trusted were central themes for regulators and the pharmaceutical drug manufacturers were keen to find the protocols which would have a universal appeal. The story of the ICH in general and the development of GCP in particular is one where everyone was a winner.

Knowledge Check Questions

1) The emergence of legislative regulatory controls over pharmaceutical drug development and clinical trials was often prompted by:
   a) Protests from university medical students _____
   b) Tragic outcomes from administration of unsafe and/or ineffective drug products_____
   c) Promises made to voters by candidates for political office_____
2) Failure of medical researchers to apply ethical principles has never been a problem that needed solving? True ____ False _____
3) The Belmont Report was authorized by the National Research Act of 1974. True ____ False _____
4) The ICH Efficacy Guideline – GCP – is considered the industry standard for the conduct of human biomedical clinical trials with drug products. It was developed because:

a) Of continuing abuses against study subjects by drug researchers _____
b) The United States, Japan, and the European Union wanted manufacturers in their countries to have a monopoly on drug marketing _____
c) Manufactures and regulatory authorities wanted to establish harmonized standards to facilitate the mutual acceptance of clinical data supporting drug approval_____

5) The ICH headquarters are located in the United States and the organization is under the US FDA. True _____ False _____

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Part II

Drug Development in the Regulatory Environment

2

Regulatory Environment

P. Michael Dubinsky

GCP Key Point
Regulatory authorities along with medical institutions and professional groups form a network of controls which set the boundaries for human biomedical clinical trials thereby ensuring that GCP is followed.

2.1 Introduction

Is it idealistic to think that all clinical research whether commercial, academic, governmental or otherwise will be conducted under ethical guidelines and according to best scientific and professional practices such as GCP? Unfortunately idealism has not always been the guiding force in human biomedical research and along the way governmental and professional oversight has been implemented to ensure that abuses are avoided. This chapter explores the regulatory environment that has evolved to oversee human biomedical clinical trials.

2.2 Objective

To describe the nature and scope of controls that are in place to ensure that human biomedical clinical trials are conducted in a manner which ensures the protection of human subjects participating in them and the scientific integrity of the trial plan. Understanding the nature, scope and reach of the regulatory controls as well as their enforceability is essential to applying the GCP principles.

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2.3 Regulatory Matrix

The regulatory environment within which human biomedical clinical trials are conducted is a matrix composed of: (i) the policies, laws, and regulations which describe the requirements and guidance; (ii) the governmental jurisdictions (Federal, State, Country, Region e.g. EU) which are responsible for implementing the requirements through regulatory authorities; (iii) nongovernmental organizations, e.g. Academic Medical Centers (AMCs), which both sponsor clinical trials and set their own internal standards for how clinical trials will be conducted; and (iv) the professional organizations (e.g. WHO, WMA) which support, define, and interpret the requirements, standards, and guidelines for their professional members.

It is not always clear whether this matrix works together under a planned scenario but the end result is that if a commercial sponsor, medical establishment, or individual practitioner wishes to conduct experimental biomedical studies in humans, that activity receives considerable oversight and review. There are complexities which the regulatory environment matrix introduces to the conduct of clinical trials; therefore it is important to understand the makeup of the regulatory environment. For example conducting trials in conformance with ICH E6(R2) does not guarantee that a trial meets all of the applicable regulatory standards called for by the country or region where the study is performed but it is probable that the use of the those guidelines would ensure that 90% or more of applicable requirements will be met.

Let us begin the examination of the regulatory environment by reviewing each of the four part matrix as depicted in Figure 2.1.

2.4 Laws, Regulations, and Policies

The enforceable requirements governing human biomedical clinical trials are found in the written laws (statutes) and implementing regulations. These laws and regulations, which are based on governmental policies provide the societal backbone for the authorities to regulate and affect control over human biomedical clinical trial activities. The laws are written by the elected legislatures which in the United States is the Congress. Congress is composed of the Senate and House of Representatives. The laws are passed by the Legislature, i.e. Congress and approved by the President and as needed interpreted by the US Supreme Court. Laws however are very high level statements and call for implementing details. Once in place, USA laws are implemented by the executive departments who report to the President. In the United States, the Federal Food Drug and Cosmetic Act (FFDCA) is a primary governing statute and the implementing regulations

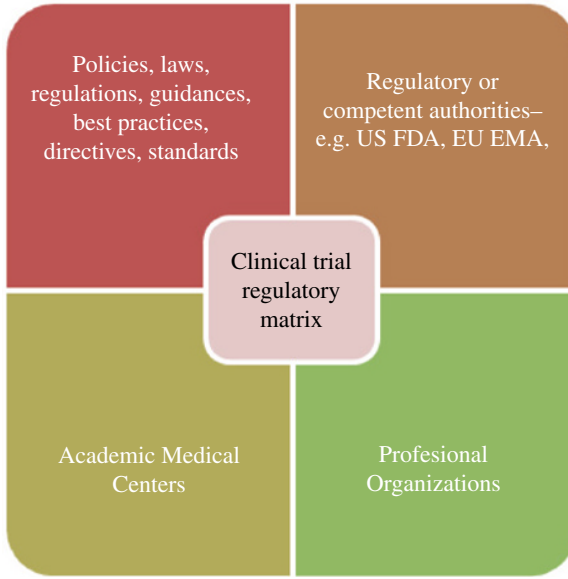

Figure 2.1 The clinical trial regulatory matrix.

are developed/written by staff in the Food and Drug Administration (FDA) which is part of the Department of Health and Human Services (DHHS). The regulations are memorialized in the US Code of Federal Regulations (CFR). Regulations are developed according to the Administrative Procedures Act of 1946 (APA) which calls for agencies such as the FDA/DHHS to (i) keep the public informed of their organization, procedures and rules; (ii) provide for public participation in the rulemaking process; (iii) to establish uniform standards for the conduct of formal rulemaking and adjudication; (iv) to define the scope of judicial review. The rules developed pursuant to the APA have the force and effect of law, i.e. they are enforceable. There are sanctions and penalties if the rules are not followed.

The rules applicable to the conduct of clinical trials in the USA are found in Title 21 of the Code of Federal Regulations. The FDA considers the following Parts to be GCP:

- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure by Clinical Investigators
- 21 CFR Part 56 – Institutional Review Boards (IRBs)
- 21 CFR Part 312 – Investigational New Drug Application (prescription drugs)
- 21 CFR Part 812 – Investigational Device Exemptions (medical devices)

These regulations define the must do ground rules that apply to regulated biomedical research from informed consent to the content of an application for

authorization to conduct the trial in humans. There are additional regulations which have impact on drug development and clinical trials activities such as electronic records, good laboratory practices, and marketing applications.

In addition to the FDA regulations the DHHS has an organizational group titled the Office of Human Research Protections (OHRP) which has responsibility for regulations governing research funded or performed by the federal government. Specifically: 45 CFR Part 46 – Federal Policy for the Protection of Human Research Subjects – "the Common Rule."

The title of the rule speaks for itself in terms of content. It applies to all US Federal government biomedical and behavioral research conducted or sponsored by over 15 Federal department and agencies.

Federal regulations do not stand completely alone in terms of governmental oversight of clinical trial requirements and each of the 50 States has rules which affect one or more aspects of the conduct of clinical trials. For example the age of consent for trial subjects is reflected in State rather than Federal laws. The full nature and scope of the Federal and State requirements will not be covered in this text. The important point is that regulatory requirements may be found in more than one source and sponsors of clinical trials need to be cognizant of them all. ICH E6(R2) 5.1.1 speaks to that expectation.

Another well-known example of the law and regulation framework is that of the European Union. The European Union's approach is a bit different than the USA due to its regional construct but the legal arrangement resembles that of the USA. The European Union currently comprises 28 Member States. There is a central government organization, the European Council (EC) located in Brussels, Belgium. The EC, in conjunction with the European Parliament issues Directives which each of the member states are expected to implement or place into law and regulation within their own country's legislative/governmental system. With regard to GCP the EC issued Directive 20/2001/EC – The Clinical Trial Directive in 2001. In 2005, the EC issued the Good Clinical Practice Directive – 2005/28/EC. These two directives were instrumental in closing several gaps which existed in the regulation of clinical trial activities in the EU member states. These Directives specifically called for ICH E6(R2) to be taken into account in terms of clinical trial regulation. Many people therefore view ICH E6(R2) as essentially a legal requirement in the EU. While changes are underway in several aspects of the regulatory framework established under the two EU Directives they have served as the pillars of regulation for human clinical trials involving pharmaceutical drugs in the EU. Notwithstanding expected changes in other aspects of clinical trial regulation ICH E6(R2) will continue to be the key criteria for conduct of a clinical trial.

It is useful to point out that the regulation of human clinical trials involving medical device products in the European Union is addressed under separate Directives e.g. 93/42/EEC. The overall regulation of medical devices in the European Union is also in the process of change.