

GCP101
Good Clinical Practices OR
“Why we do What we do the Way we do it“
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INTRODUCTION

Good Clinical Practices are at the very core of our industry. Since this presentation section of Industry Basics is new this year, I thought it appropriate to start out with a discussion of Good Clinical Practices. No matter what our job description, whether we are SAS programmers, Data Managers, Statisticians, Clinicians or Administrative Personnel, GCPs should be basic to every task we perform. The object of this presentation is to cover the history of GCP including what we did wrong initially and how the need for GCP came about. And, most importantly, what has been done to ensure that Good Clinical Practices are at the heart of everything we do.

WHAT ARE GOOD CLINICAL PRACTICES?

Good Clinical Practice is defined as follows by the Institute for the Advancement of Clinical Research:

“Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials. GCP provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are respected and protected.”

The importance of GCP should be obvious. Even the Hippocratic oath, which all medical doctors are bound by, was initiated back in Ancient Greece with the underlying sentiment of “do no harm”. However, history has shown us that this has not been the case and that there needs to be careful regulation when one life is being placed into the hands of another.

The idea of consumer protection is not unique to clinical trials. In fact, it was addressed as far back as 1906 with the Food and Drug Act of that year which prohibited the manufacture of “adulterated” food or drugs after it was found that “embalmed” beef was sent to the soldiers fighting the Spanish-American war. This also prevented the over-the-counter sale of elixirs that contained harmful or lethal drugs. An example of this was “Kopp’s Baby’s Friend” which contained large doses of *morphine*. This 1906 initiative was followed by the Food, Drug and Cosmetic Act of 1938 but there was still no real controls that applied to the manufacture and testing of drugs on human subjects. This became painfully evident a few years later.

WHAT HAPPENS WHEN GOOD CLINICAL PRACTICES ARE NOT FOLLOWED?

The first well-known violation of the premise of GCP occurred during World War 2 and culminated with the Nuremburg Doctors Trials of 1946. Experiments were performed on concentration camp internees to obtain information that would be useful to the German military. These experiments included exposure to chemical and biological agents resulting in the death of many. When this information became public knowledge to the world, the men behind this, the Nuremburg Doctors, were charged with murder and torture. Fifteen were found guilty and seven were sentenced to death. As a result of this the Nuremburg Code was adopted.

Summary of principles of the Nuremburg code:

- Informed consent of volunteers must be obtained without coercion
- Studies involving humans should only be performed after a related animal study
- Anticipated results should justify the experiment
- Only qualified scientists should conduct experimental research
- There should be no expectation of death or disabling injury as a result of the study

Despite the adoption of the Nuremberg code in 1947, another stunning example of the lack of good clinical practices was found in the “Tuskegee Study of Untreated Syphilis in Negro Males”. This study was sponsored by the US Public Health Service (predecessor of the CDC) and was designed to study effects of untreated syphilis on black males. Although penicillin became the standard of care for syphilis in 1943, the subjects in this study continued untreated since the study represented a “never again opportunity”. Although this study actually began in 1932 and was supposed to end within one year, it actually went on for the next ten years without review and the public was unaware of it until 1972 when an expose was written in the Atlanta Constitution.

Now, with this second travesty fresh in the public mind, the principles of GCP were ripe for being reworked as shown in the following initiatives:

- 1962 – The Kefauver-Harris Amendment to the Food, Drug and Cosmetic Act (Thalidomide)
- 1964 – The Declaration of Helsinki
- 1966 – UPHS IRB and Informed Consent Regulations
- 1979 – The Belmont Report
- 1981 – DHHS/FDA regulations for human subject research
- 1990 - The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
- 1991 – Common Rule
- 1995 – National Bioethics Advisory Committee
- 1999 – Data Safety Monitoring Boards (DSMBs)
- 2000 – Office of Human Research Protection
- 2001 – International Standard Organization (ISO)
- 2005 – Pan American Health Organization (PAHO). “GCP Document of the Americas”
- 2006 – World Health Organization (WHO) “Handbook for Good Clinical Practices” and Guideline for Implementation

Today, Good Clinical Practices in clinical drug trials is a federal and, indeed, a universal mandate. The International Conference on Harmonization (ICH) leads the way in the effort for universal cooperation. The identification of “13 Principles of GCP” was/is a major achievement of ICH and carries through to all other international GCP guidelines.

The 13 Principles of Good Clinical Practice as Defined by ICH

- **Principle #1:** Trials 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 the applicable regulatory requirement(s).
- **Principle #2:** Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- **Principle #3:** The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
- **Principle #4:** The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
- **Principle #5:** Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
- **Principle #6:** A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.
- **Principle #7:** The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
- **Principle #8:** Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- **Principle #9:** Freely given informed consent should be obtained from every subject prior to clinical trial participation.

- **Principle #10:** All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
- **Principle #11:** 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)
- **Principle #12:** 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.
- **Principle #13:** Systems with procedures that assure the quality of every aspect of the trial should be implemented.

About fifteen years later, the World Health Organization (WHO) came up with its own list of Principles of Good Clinical Practices that borrows heavily from ICH:

The 14 Principles of Good Clinical Practice as Defined by WHO

- **Principle #1: Ethical Conduct**
Research involving humans should be scientifically sound and conducted in accordance with basic ethical principles, which have their origin in the Declaration of Helsinki. Three basic ethical principles of equal importance, namely respect for persons, beneficence, and justice, permeate all other GCP principles.
- **Principle #2: Research Described in a Protocol**
Research involving humans should be scientifically justified and described in a clear, detailed protocol.
- **Principle #3: Risk Identification**
Before research involving humans is initiated, foreseeable risks and discomforts and any anticipated benefit(s) for the individual trial subject and society should be identified. Research of investigational products or procedures should be supported by adequate non-clinical and, when applicable, clinical information.
- **Principle #4: Benefit-Risk Assessment**
Research involving humans should be initiated only if the anticipated benefit(s) for the individual research subject and society clearly outweigh the risks. Although the benefit of the results of the trial to science and society should be taken into account, the most important considerations are those related to the rights, safety, and well being of the research subjects.
- **Principle #5: Review by IEC/IRB**
Research involving humans should receive independent ethics committee/institutional review board (IEC/IRB) approval/favourable opinion prior to initiation.
- **Principle #6: Protocol Compliance**
Research in humans should be conducted in compliance with the approved protocol.
- **Principle #7: Informed Consent**
Freely given informed consent should be obtained from every subject prior to research participation in accordance with national culture(s) and requirements. When a subject is not capable of giving informed consent, the permission of a legally authorized representative should be obtained in accordance with applicable law.
- **Principle #8: Continuing Review/Ongoing Risk-assessment**
Research involving humans should be continued only if the benefit-risk profile remains favourable.
- **Principle #9: Investigator Qualifications**
Qualified and duly licensed medical personnel (i.e., physician or, when appropriate, dentist) should be responsible for the medical care of trial subjects, and for any medical decision(s) made on their behalf.
- **Principle #10: Staff Qualifications**
Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s) and currently licensed to do so, where required.

- **Principle #11: Records**
All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
- **Principle #12: Confidentiality and Privacy**
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).
- **Principle #13: Good Manufacturing Practice**
Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice (GMP) and should be used in accordance with the approved protocol.
- **Principle #14: Quality Systems**
Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Though defined by two different international organizations, we can see what is at the very core of Good Clinical Practices by both ICH and WHO. The rights and safety of the study subject are of first and foremost importance.

WHAT IS THE CURRENT REGULATORY ENVIRONMENT FOR CLINICAL TRIALS?

While GCP is a moral principle and obligation, the US has only accepted the ICH Principles of GCP as a “guidance”, the regulatory authorities (FDA) also have clear rules:

- Federal - Code of Federal Regulations
 - o 21 CFR part 50 (FDA) & 45 CFR part 46 (HHS)
 - Federal regulation that governs the use of human subjects in the US
 - Based on the principles found in the Belmont Report of justice, beneficence, and respect for persons
 - Three main provisions
 - Review and approval of research by an IRB
 - Institutional assurance of compliance
 - Informed consent of subjects
 - o (HHS)Financial Administration of Grants and Contracts
 - o Billing for clinical trials (Medicare)
 - o Health Insurance Portability & Accountability Act of 1996 (HIPAA)
 - Mandates secure storage and transmission of health care information in electronic form
 - Standards for Privacy
 - Standards for Security
- State and Local
 - o IRBs
 - o Office of University Counsel/compliance
 - o Financial Conflict of Interest
 - o Policies addressing research misconduct and human subjects research non-compliance

HOW DOES THIS AFFECT ME?

- **Sponsors** - The sponsor of a clinical trial is an individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial. This includes: commercial (pharmaceutical and device) companies, government funding agencies, private foundations, and individuals. Sponsor-investigators – must comply with both sponsor and investigator responsibilities. GCP requires certain direct communications and interactions between the sponsor and the regulatory authority. The sponsor is ultimately responsible for the conduct of the trial.
- **CROs** - A CRO (Contract Research Organization) is a person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of sponsor’s trial-related duties and functions. These duties range from very early pre-clinical responsibilities, to subject enrollment to data collection and analysis.

- **Monitor** – A monitor is an employee of the sponsor (or CRO) who works to oversee the progress of a clinical study through on-site visits and other means to ensure that the study is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP and the applicable regulatory requirement(s). (Quality control)
- **Medical Monitor** - A Medical Monitor (or Medical Expert) is an employee of the sponsor (or CRO) who is readily available to advise on trial-related medical questions or problems. A Medical Monitor can make critical decisions regarding safety of the study participants.
- **DMCs** - A DMC (Data Monitoring Committee) is a committee established by, but acting independent of, the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

ARE BIOSTATISTICIANS AND SAS PROGRAMMERS RESPONSIBLE FOR UPHOLDING GOOD CLINICAL PRACTICES?

How do Good Clinical Practices apply to SAS programmers? Let's discuss this a little further. The positions described above are largely clinical and are mostly applicable during the trial enrollment and treatment phase. Whereas, the work of the statistical programmer takes place largely at the end of data collection intervals defined for the study. Clinical data is collected at pre-defined intervals in a trial for the purpose of analyzing it and presenting it in an understandable, accurate and truthful manner. This data analysis is then presented to either a Data Monitoring Committee, the sponsor organization and ultimately the Food and Drug Administration (for US trials). The data and subsequent analysis must be accurate. This requires strenuous quality control and validation of results as well as documentation of statistical methods. Good Clinical Practices apply because it is our responsibility to ensure the quality of the data and to perform the analysis in the proper way. In virtually all cases, there will be at least two programmers involved, one doing the initial programming and analysis and the second doing an independent quality check which should be as thorough as the effort of the production programmer. This should be done by visual inspection as well as electronic data checks. And, depending upon whether our role is "blinded" or "unblinded", we are also responsible for the confidentiality of the knowledge we have of each subject. So, the answer is a definitive "YES", SAS programmers are accountable for their role in upholding Good Clinical Practices.

CONCLUSION

Many of the principles contained herein are still only a suggested "guidance" and are not technically a law. However, a violation of any of these principles by anyone involved in a clinical trial would be a serious breach. We never want history to repeat itself in the case of the Nuremburg Doctors and we should also always have a serious interest in both the confidentiality of the data as required at a given time as well as the accurate reporting of the data and results of clinical analysis. We are lucky to live in this century when research into new drugs and cures are at an all-time high and someday we may be in the position to be a subject in a clinical trial. That is compelling reason for everyone to keep the principles of good clinical practice on the tip of their tongue at all times.

REFERENCES

"The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guideline for Good Clinical Practice (E6)R1."

"World Health Organization. Handbook for Good Clinical Research Practice (GCP)"

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