The need for 'Good Clinical Practice' in health care research

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Abstract

Randomised controlled trials form the foundation for 'evidence-based-medicine', but the results of such research can be relied upon only if it was conducted according to principles and standards collectively referred to as 'Good Clinical Practice' (GCP). The GCP was established as a basis both for the scientific and ethical integrity of research involving human subjects and for generating valid observations and sound documentation of research findings. It provides a framework for clinical investigators and pharmaceutical companies to conduct clinical trials according to similar rules and regulations, to ensure clinical research is consistently performed to high ethical and scientific standards and an assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. Thus the GCP protects the rights, safety and well-being of subjects and ensures that investigations are scientifically sound and advance public health goals.

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Introduction

The practice of medicine today is driven by evidence: data derived from published, peer-reviewed reports, many of which come from randomised controlled clinical trials.[1] In the past 30 years, the number of clinical trials has increased, consistently with the increase in the number of new drugs, devices and treatment strategies.[2] Published research usually alters clinical practice and a few landmark clinical trials have resulted in major changes in medical practice.[3] The increasing number of trials generated a need to ensure that participants in clinical trials are protected and that the data reported are valid.[4] As a result, a standard international guideline named Good Clinical Practice was developed by the World Health Organization in the mid-1990s for this purpose.[5,6]

What is Good Clinical Practice (GCP)?

Good Clinical Practice (GCP) is a set of guidelines that must be followed when conducting clinical trials to ensure that the rights and wellbeing of the trial participants are protected and that the data generated in the trial is valid.[5,6] It is an international ethical and scientific quality standard for designing, conducting, performance monitoring, auditing, recording, analysing and reporting on clinical trials that involve human participants.[5,6] The guidelines were developed in the mid-1990s in order to provide clinical trials with a unified standard across the European Union, Japan and the United States, and to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

History of Good Clinical Practice

The guideline for Good Clinical Practice was developed in reaction to events or tragedies.[5,6,7,8,9,10] For instance, between the 1950s and 1960s, thousands of children were born with phocomelia (seal limbs).[10] This condition was then linked to the administration of thalidomide for the treatment of morning sickness. Another example comes from the Tuskegee trial.[4] This study, which included men with syphilis, was sponsored by a government health agency. In the trial, some of the participants were given treatment and the others had no treatment. The untreated patients fared poorly and a significant number of patients died. These patients were not given any information and no permission was sought to withhold treatment. The investigators also had no clear endpoints. This resulted in litigation and financial settlements, and a public apology from a very senior government official in an international news network.[4] Another famous example was 'The Harvard Fraud' of the 1980s.[10] In this incident, a prominent senior researcher based at a reknowned institution trained and tutored a student. The student fabricated the study data, which was discovered because the data were 'too clean' The student was terminated from the institution and his licence was withdrawn. The outcome for the senior researcher and the institution included a written public apology, a retraction of papers and great embarrassment resulting from the questioning of the credibility of their past and future work.[10] At the same time, the pharmaceutical industry was experiencing problems obtaining marketing authorisation for drugs in different countries.[11] It was thought that this could be avoided by having a common clinical trial practice guideline. These events highlighted the worldwide need for a single, global, worldwide standard for the conducting of clinical trials, regardless of region, study design or study phase. [10]

For whom is Good Clinical Practice intended?

The GCP guideline is intended for all research, including:

- all types of sponsors, including private, government, university or industry
- all study designs, including randomised clinical trials (RCTs)

- double-blinded, open-label or comparator
- all study phases, including Phase I to Phase IV trials and
- all investigational products, including new drugs, new indications, biomedical devices, new methodology or new surgical techniques[5,6]

Principles of Good Clinical Practice and its importance

The World Health Organization Good Clinical Practice consists of 14 principles.[5,6]

Principle 1

Research involving humans should be scientifically sound and conducted in accordance with basic ethical principles, which have their origin in the Declaration of Helsinki. The basic ethical principles include respect for persons, beneficence, non-malevolence and justice, which permeate all other GCP principles.[5,6] The importance of these ethical principles is that they ensure that each individual is treated as an autonomous individual and is given the opportunity to choose what shall or shall not happen to him/her.[8] On the other hand, it also protects vulnerable subjects. For instance, vulnerable groups such as children, prisoners, handicapped or mentally disabled people, or people who are disadvantaged economically or educationally may not be unduly coerced into research.[11] These ethical principles also ensure that each research design is sound and that investigators are competent to conduct research and to safeguard the welfare of the subjects.[4] It also requires research to exhibit 'fairness', meaning that the research should not be offered to only some patients or select only 'undesirable' persons for risky research. Thus, these ethical principles safeguard both the able and vulnerable groups.

Principle 2

The second principle states that research involving humans should be scientifically justified and described in a clear, detailed protocol.[5,6] This means that the research protocol has to be ethically sound and should undergo scientific and ethical review prior to implementation.[12,13,14] The importance of this principle is that it ensures that results are not random and that they were not procured by other methods or means of study, thus ensuring truthful results.[7,14] Clinical trials can also not be justified unless they are capable of producing scientifically reliable results.[11]

Principle 3

The third principle states that, before research involving humans is initiated, the foreseeable risks and discomforts and any anticipated benefit(s) for the individual trial subject and for society should be identified.[5,6] This means that a thorough search of the available scientific information about the investigational product or procedure(s) (including findings from tests on laboratory animals and any previous human experience) is needed before the research can be conducted. This principle takes into account possible harms and benefits.[7] Although the most likely types of harm to research subjects is psychological or physical injury, other potential benefits or risks of harm could be psychological, physical, legal, social or economic in nature.[8] Thus this principle ensures that other possible kinds of harm are not overlooked.

Principle 4

The fourth principle states that 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 benefits 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 wellbeing of the trial subject.[5,6] This means that every medical research project involving human subjects should be preceded by a careful assessment of the predictable risks and burdens in comparison to the foreseeable benefits to the subject or to others.[14,15] This principle ensures the rights, safety and wellbeing of the trial subjects.

Principle 5

The fifth principle states that research involving humans should receive independent ethics committee/institutional review board (IEC/IRB) approval/favourable opinion prior to initiation.[5,6] This means that each research protocol should be submitted for consideration, comment, guidance and, where appropriate, approval to a specifically appointed ethical review committee, which should be independent of the investigator, the sponsor, or any kind of undue influence.[13,15] This principle ensures that ethical standards are not violated, that the rights, safety and wellbeing of human subjects are protected and it provides public assurance of that protection.

Principle 6

The sixth principle states that research involving humans should be conducted in compliance with approved protocol.[5,6] This means that all research should be performed precisely according to the approved protocol. The protocol should be well designed and clearly written, and the investigators should be responsible and personally supervise all study staff and ensure that the staff comply with the protocol. Thus prompt action can be taken in the case of any non-compliance to secure compliance. This is important to ensure that the ethical acceptability of the trial remains valid and to ensure the rights and wellbeing of the subjects.

Principle 7

The seventh principle states that informed consent, given freely, 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 authorised representative should be obtained in accordance with the applicable law.[5,6] This means that no one should be subjected to medical or scientific experimentation without giving free consent.[15] The free consent should contain three elements: information, comprehension and voluntariness, and this is achieved by repetition and explanation, by answering questions from the subjects, and by ensuring that each individual understands each procedure.[11,16] This principle is important, as it avoids unjustifiable pressures that could come from people in positions of authority or who command influence, and also avoids undue influences such as manipulating a person's choice through controlling the influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.[17] Thus it protects the individual's freedom of choice and respects the individual's autonomy.

Principle 8

The eighth principle states that research involving humans should be continued only if the benefit-risk profile remains favourable.[5,6] This means that, during the experiment, the investigator in charge should be prepared to terminate the experiment at any stage if he has probable cause to believe, in the exercise of good faith, superior skill and careful judgement, that a continuation of the experiment would likely result in injury, disability or death to the experimental subject.[18] This is important, as it ensures that appropriate steps to minimise risk are taken in order to identify adverse events early, thus protecting the trial participants.

Principle 9

The ninth principle states that qualified and duly licensed medical personnel (i.e. a 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.[5,6] This means that research on human subjects should only be conducted by scientifically qualified people and under the supervision of a clinically competent medical person.[15] Thus, this principle protects the rights, safety and welfare of trial participants by ensuring access to a reasonable standard of medical care for the study subjects for medical problems arising during their participation in the trial that are, or could be, related to the study intervention. Principle 9 emphasises that the authority or person in charge of responsibility and decision making should be qualified to make and endorse decisions.

Principle 10

The tenth principle states that each individual involved in conducting a trial should be qualified by education, training and experience to perform his or her respective tasks(s) and currently be licensed to do so, where required.[5,6] This means that the people who are needed to assist with the conducting of the study should be appropriately selected. The investigators should also have appropriate training or expertise to carry out the requirements of the specific study protocol. This is important to ensure the credibility of the research and to ensure the safety of the study subjects. From the authors' view, principle 10 differs from principle 9 as it refers to all persons involved in the research, whereas principle 9 refers to the person who is in charge of the research.

Principle 11

The eleventh principle states that all clinical trial information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.[5,6] This means that the research should have appropriate procedures for data handling and record keeping. This principle ensures the quality and integrity of the data obtained.

Principle 12

The twelfth principle states that the confidentiality of the records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements(s).[5,6] This means that the investigator must establish appropriate procedures for document control and data control in order to protect the privacy of the subjects. This principle also requires that the investigator inform the subjects concerned about the confidentiality of their records and about access to those records by monitors, auditors and the regulatory authorities.[11] The importance of this principle is that it ensures respect for the subjects' privacy and the confidentiality of the information obtained, and it also minimises the impact of the study on the subject's physical and mental integrity and on the personality of the subject. Thus it protects the life, health, privacy and dignity of the human subject.[15]

Principle 13

The thirteenth principle states that investigational products should be manufactured, handled and stored in accordance with applicable good manufacturing practice (GMP) and should be used in accordance with approved protocol.[5,6] This means that investigational products should be coded and labelled, should be properly handled and stored and should be used according to the approved study protocol. This principle is important to ensure that products are produced and controlled according to quality standards. For instance, it ensures the reliability of clinical trials by ensuring consistency between and within batches of investigational products. It also ensures consistency between the investigational product and the future commercial product, and therefore the relevance of the clinical trial to the efficacy and safety of the marketed product. This principle also protects the subjects of clinical trials from poor-quality products.

Principle 14

The fourteenth principle states that 'systems with procedures that assure the quality of every aspect of the trial should be implemented.[5,6] This means that the research should have procedures that control, assure and improve the quality of data and records. One of the ways this could be achieved is through developing and applying standard operating procedures that define responsibilities, specify records that need to be established and maintained, and specify methods and procedures to be used in carrying out study-related activities.[19] This principle is important because it ensures the quality and integrity of data, thus ensuring that the data obtained from the study is reliable enough for regulatory decision making.

The main purposes of the GCP are therefore to protect the rights and safety of participants involved in clinical trials and to ensure the quality and integrity of the data generated in clinical trials.

The other important aspects of the GCP guidelines are that they reduce country-to-country variations in research guidelines, decrease differences between regulatory authorities and streamline drug development and regulatory processes. The GCP guideline also provided pharmaceutical companies and investigators with a framework for conducting clinical trials in accordance with similar rules and regulations and conforming to high ethical and scientific standards. The GCP thus sets forth ethical principles in clinical research, ensures that treatment is offered to participants in an ethical manner, protects human subjects by requiring informed consent and ensures fairness in distribution.

Adverse events

The GCP also states that, if and when an adverse event or abnormality is identified, these events should be reported to the ethics committee and the sponsor of the research/clinical trial. In severe cases involving the death of a participant, the investigator is required to supply the sponsor and ethics committee with all the required information. The sponsor is

then responsible for ensuring that all records and details pertaining to the adverse event are kept in proper order and submitted to the authority in charge of the clinical trial or to the Medicinal Evaluation Task Force.[5,6]

Conclusion

As health care practitioners, physicians, scientists and researchers, we want only safe and effective treatments for our patients. Adhering to GCP is thus the best way to ensure this in a clinical trial and it is also in our patients' best interests. The conducting of clinical research in accordance with the principles of GCP helps to ensure that the participants in clinical research are not exposed to undue risk, and that data generated in the research are valid and accurate. Thus the GCP not only serves the interest of clinicians and those involved in the research process, but also protects the rights, safety and wellbeing of subjects and ensures that investigations are scientifically sound and advance public health goals.

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