Chapter 2
The Definition of GCP

2.1 Introduction

Clinical research is necessary to establish the safety and effectiveness of health and medical products and practices. Much of what is known today about the safety and efficacy of specific products and treatments has come from randomised, controlled clinical trials that are designed to answer important scientific and healthcare questions. Randomised controlled trials form the foundation for 'evidence-based medicine', but such research can be relied upon only if it is conducted according to principles and standards collectively referred to as 'good clinical research practice' (GCP) [1].

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible [2].

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GCP is an international quality standard that is provided by the International Conference on Harmonisation (ICH), an international body that defines standards, which governments can transpose into regulations for clinical trials involving human subjects. GCP follows the ICH GCP guidelines [3]. GCP enforces tight guidelines on ethical aspects of a clinical study. High standards are required in terms of comprehensive documentation of the clinical protocol, record keeping, training and facilities, including computers and software. Quality assurance and inspections ensure that these standards are achieved. GCP aims to ensure that studies are scientifically authentic and that the clinical properties of investigational products are properly documented. Ongoing research shows that whether conducting research involving a new drug, a behavioural intervention or an interview or survey, GCP provides investigators and their study teams with the tools to protect human subjects and to collect quality data [3, 4].

The objective of this ICH GCP guidance was to provide a unified standard for the European Union (EU), Japan and the USA, to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions [2].

The guidance was developed considering the current GCPs of the European Union, Japan and the USA, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO) [2].

2.2 Definitions

1. *Adverse drug reaction (ADR)*: 'During pre-approval clinical experience with a new medicinal product or new uses, all noxious and unintended responses to a medicinal product related to any dose should be considered ADRs, particularly as the therapeutic dose may not have been established. The

phrase 'responses to a medicinal product' means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. An ADR relating to marketed medicinal products is: a response to a drug that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function' [2].

2. *Adverse event (AE)*: 'An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, which may or may not be related to the medicinal (investigational) product'.
3. *Amendment (to the protocol)*: This is similar to the 'protocol amendment', which may be explained as 'A written description of a change to, or formal clarification of, a protocol'.
4. *Applicable regulatory requirement(s)*: 'Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products of the jurisdiction where a trial is conducted'.
5. *Approval (in relation to institutional review boards (IRBs))*: 'The affirmative decision of an IRB that a clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, GCP, and the applicable regulatory requirements'.
6. *Audit*: 'A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analysed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s)'.

7. *Audit certificate*: 'A declaration of confirmation by the auditor that an audit has taken place'.
8. *Audit report*: 'A written evaluation by the sponsor's auditor of the results of the audit'.
9. *Audit trail*: 'Documentation that allows reconstruction of the course of events'.
10. *Blinding/masking*: 'A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single blinding usually refers to the subject(s) being unaware, and double blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s)'.
11. *Case report form (CRF)*: 'A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject'.
12. *Clinical trial/study*: 'Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study the absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous'.
13. *Clinical trial/study report*: 'A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report'.
14. *Comparator (product)*: 'An investigational or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial'.

15. *Compliance (in relation to trials)*: 'Adherence to all the trial-related requirements, GCP requirements, and applicable regulatory requirements'.
16. *Confidentiality*: 'Prevention of disclosure, to other than non-clinical individuals, of a sponsor's proprietary information or of a subject's identity'.
17. *Contract*: 'A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract'.
18. *Coordinating committee*: 'A committee that a sponsor may organize to coordinate the conduct of a multicenter trial'.
19. *Coordinating investigator*: 'An investigator assigned responsibility for the coordination of investigators at different centres participating in a multicenter trial'.
20. *Contract research organisation (CRO)*: 'A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions'.
21. *Direct access*: 'Permission to examine, analyse, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g. domestic and foreign regulatory authorities, sponsors, monitors, and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information'.
22. *Documentation*: 'All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records; and scans, X-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken'.

23. *Essential documents*: 'Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced'.
24. *Good clinical practice (GCP)*: 'A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected'.
25. *Independent data monitoring committee (IDMC) (data and safety monitoring board, monitoring committee, data monitoring committee)*: 'An IDMC that may be established by 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'.
26. *Impartial witness*: '1A person who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the ICF and any other written information supplied to the subject'.
27. *Independent ethics committee (IEC)*: 'An independent body (a review board or a committee, institutional, regional, national, or supranational body), constituted of medical/scientific professionals and nonmedical/non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing a favourable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting the informed consent of the trial subjects'.

28. *Informed consent*: 'A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF'.
29. *Inspection*: 'The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or CRO's facilities, or at other establishments deemed appropriate by the regulatory authority(ies)'.
30. *Institution (medical)*: 'Any public or private entity or agency or medical or dental facility where clinical trials are conducted'.
31. *Institutional review board (IRB)*: 'An independent body constituted of medical, scientific, and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting the informed consent of the trial subjects'.
32. *Interim clinical trial/study report*: 'A report of intermediate results and their evaluation based on analyses performed during the course of a trial'.
33. *Investigational product*: 'A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way that differs from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use'.

34. *Investigator*: 'A person responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Sub investigator'.
35. *Investigator/institution*: An expression meaning 'the investigator and/or institution, where required by the applicable regulatory requirements'.
36. *Investigator's brochure*: 'A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects'.
37. *Legally acceptable representative*: 'An individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in a clinical trial'.
38. *Monitoring*: 'The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s)'.
39. *Monitoring report*: 'A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs'.
40. *Multicentre trial*: 'A clinical trial conducted according to a single protocol but at more than one site and, therefore, carried out by more than one investigator'.
41. *Non-clinical study*: 'Biomedical studies not performed on human subjects'.
42. *Opinion (in relation to independent ethics committee)*: 'The judgment and/or the advice provided by an IEC'.
43. *Original medical record*: It is related to source documents.
44. *Protocol*: 'A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be

provided in other protocol-referenced documents. Throughout the ICH GCP guidance, the term protocol refers to protocol and protocol amendments'.

45. *Protocol amendment*: 'A written description of a change(s) to or formal clarification of a protocol'.
46. *Quality assurance (QA)*: 'All planned and systematic actions that are established to ensure that a trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s)'.
47. *Quality control (QC)*: 'The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for the quality of trial-related activities have been fulfilled'.
48. *Randomisation*: 'The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments to reduce bias'.
49. *Regulatory authorities*: 'Bodies having the power to regulate. In the ICH GCP guidance, the expression "regulatory authorities" includes the authorities who review submitted clinical data and those who conduct inspections. These bodies are sometimes referred to as competent authorities'.
50. *Serious adverse event (SAE) or serious adverse drug reaction (serious ADR)*: 'Any untoward medical occurrence that at any dose:

    - Results in death,
    - Is life-threatening,
    - Requires inpatient hospitalization or prolongation of existing hospitalization,
    - Results in persistent or significant disability/incapacity, or
    - Is a congenital anomaly/birth defect'.

51. *Source data*: 'All information in original records and certified copies of original records of clinical findings, observations,

or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)'.

52. *Source documents*: 'Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)'.
53. *Sponsor*: 'An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial'.
54. *Sponsor-investigator*: 'An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g. it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator'.
55. *Standard operating procedures (SOPs)*: 'Detailed, written instructions to achieve uniformity of the performance of a specific function'.
56. *Sub-investigator*: 'Any individual member of a clinical trial team designated and supervised by an investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g. associates, residents, research fellows). See also Investigator'.
57. *Subject/trial subject*: 'An individual who participates in a clinical trial, either as a recipient of an investigational product(s) or as a control'.

58. *Subject identification code*: 'A unique identifier assigned by an investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports AEs and/or other trial-related data'.
59. *Trial site*: 'The location(s) where trial-related activities are conducted'.
60. *Unexpected adverse drug reaction*: 'An adverse reaction, the nature or severity of which is inconsistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)'.
61. *Vulnerable subjects*: 'Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in a case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent'.
62. *Well-being (of the trial subjects)*: 'The physical and mental integrity of the subjects participating in a clinical trial'.

References

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