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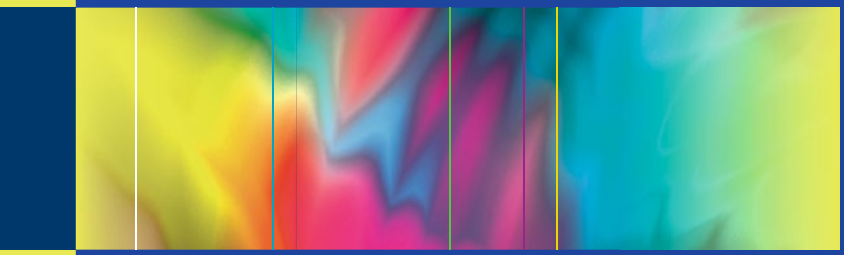

Quick Guide to Good Clinical Practice

How to Meet International Quality Standard in Clinical Research

Springer

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Cemal Cingi • Nuray Bayar Muluk

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We wish to dedicate this book to our lovely children 'Can Cemal Cingi', 'Alp Cingi' and 'Hakan Muluk' hoping them to be highly ethical and scientific all through their life.

Preface

Clinical trials are needed to develop new molecules or to set new treatment modalities as well as to improve present ones in medicine. On the other hand, we had the oath of Hippocrates, and we promised not to harm our patients. As clinicians, we need to do trials without any harm to anybody.

Good Clinical Practice (GCP) rules which cover international ethical and scientific quality standard for designing, conducting, recording and reporting trials came out to combine these two needs in order to standardise research protocols without any harm to patients or to healthy volunteers who will take part in clinical research plans.

The International Conference on Harmonization (ICH) provided GCP guidelines. Compliance with these standards and consistence with the principles that have their origin in the Declaration of Helsinki should be the aim of all clinical researchers.

In order to help the clinical researchers, we reviewed all related publications and rules and quoted the most important parts to set a practical guideline for clinicians. We hope this practical review will be a useful source and help all researchers.

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Chapter 1
Clinical Trials: Historical Aspects and Importance and New Drug Developments

1.1 Introduction

A clinical study is conducted for researches in human volunteers (also called participants) to achieve medical knowledge. Clinical studies can be done as clinical trials (interventional studies) or observational studies [1].

1.2 Clinical Trials

Clinical trials are performed for specific interventions according to the research plan. These trials are continued for 'medical products, such as drugs or devices; procedures; or changes to participants' behavior, such as dietary changes'. They compare medically the standard methods with placebo. Safety and efficacy are also investigated [1].

In an observational study, investigators can reach health data of the participants. Investigators may observe different groups of subjects [1].

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Who Conducts Clinical Studies?

Clinical studies are conducted by a principal investigator who is mainly a medical physician. A research team of 'physicians, nurses, social workers, and other health care professionals' are also worked for these studies [1].

Clinical studies can be sponsored, or funded, by 'pharmaceutical companies, academic medical centers, voluntary groups, and other organizations in addition to Federal agencies such as the National Institutes of Health, the U.S. Department of Defense, and the U.S. Department of Veterans Affairs'. Physicians and other individuals can also sponsor clinical research [1].

Clinical studies may be conducted in 'hospitals, universities, physicians' offices, and community clinics' [1]. The length of the study varies and participants should be given information for the study duration [1].

1.2.1 Why Are Clinical Studies Conducted?

- 'Evaluating one or more interventions (i.e., drugs, medical devices, approaches to surgery or radiation therapy) for treating a disease, syndrome, or condition'
- 'Finding ways to prevent the initial development or recurrence of a disease or condition including medicines, vaccines, or lifestyle changes, among other approaches'
- 'Evaluating one or more interventions aimed at identifying or diagnosing a particular disease or condition'
- 'Examining methods for identifying a condition or the risk factors for that condition'
- 'Exploring and measuring ways to improve the comfort and quality of life through supportive care for people with a chronic illness' [1]

1.2.2 Participating in Clinical Studies

There is a protocol of the research and it contains the information below:

- 'The reason for conducting the study'
- 'Who may participate in the study (the eligibility criteria)'
- 'The number of participants needed'
- 'The schedule of tests, procedures, or drugs and their dosages'
- 'The length of the study'
- 'The data related to the participants' [1]

For participation to the clinical studies, there are criteria called as eligibility.

Clinical studies have standards outlining who can participate, called eligibility criteria or inclusion criteria [1]. These are 'age, sex, the type and stage of a disease, previous treatment history, and other medical conditions' [1].

1.2.3 How Are Participants Protected?

An informed consent is signed by the participants. It gives information to the potential and enrolled participants. Signing this, the participants accept to enrol the study. It gives information for the risks and for potential benefits of the study [1].

Institutional review boards

Each clinical study and biological product or medical device must be 'reviewed, approved, and monitored by an institutional review board (IRB)'. An IRB is formed by 'physicians, researchers, and members of the community'. Its role is 'to ensure that the study is conducted ethically and that the rights and welfare of participants are preserved' [1].

Considerations for Participation

To participate the clinical study, medical knowledge should be given for 'the benefits and risks of therapeutic, preventative, or diagnostic products or interventions' [1].

Clinical trials are conducted for 'development and marketing of novel drugs, biological products, and medical devices' [1].

1.3 Historical Aspects of Clinical Trials

'The evolution of clinical research has a long and fascinating journey. The recorded history of clinical trials goes back to the biblical descriptions in 500 BC. It moves from dietary therapy – legumes and lemons – to drugs. After basic approach of clinical trial was described in 18th century, the efforts were made to refine the design and statistical aspects. These were followed by changes in regulatory and ethics milieu. This article highlights the major milestones in the evolution of clinical trials [2]'.

The first reference to a clinical trial can be found in the Bible. King Nebuchadnezzar II (605–562 BCE) ordered that a group of children be given meat and wine diet for three years. Another group of children were given pulses (e.g. beans, peas, lentils) and water. After 10 days, the king observed that 'pulses and water' group were fitter than 'meat and wine' group. The trial was stopped then.

Around the tenth century, the Persian scientist Ibn Sina (Avicenna) wrote 'Al-Quanun fi al-Tibb or the Canon of Medicine, a book that represented a comprehensive collection of all existing medical knowledge, incorporating Arabic medical lore and personal experience into the writings of Hippocrates, Galen, Dioscorides, and others'. He recommended that [3]:

- 'The drug must be pure'.
- 'The drug must be used on a "simple" disease'.

- 'The drug must be tested on at least 2 different types of disease'.
- 'The quality of the drug must correspond with the strength of the disease'.
- 'The timing of observations should be measured to rule out the effects of natural healing'.
- 'The drug must show consistency over several trials'.
- 'A drug should be tested in animals first, thereafter in humans, as the effects in animals and humans may not be the same'.

The Canon was 'the medical authority for centuries and set the standards for the practice of medicine in Europe, as well as the Middle East' [3].

1.3.1 562 BC–1537: Pre-James Lind Era

The world's first clinical trial is recorded in the 'Book of Daniel' in the Bible [4]. This experiment resembling 'a clinical trial was not conducted by a medical, but by King Nebuchadnezzar a resourceful military leader' [4]. During his rule in Babylon, Nebuchadnezzar's people ate only meat and drank only wine [4]. However, several young men of royal blood ate vegetables. The vegetarians were better nourished than the meat-eaters [4]. This was an open uncontrolled human experiment [2].

Avicenna (1025 AD) in his encyclopedic "Canon of Medicine" describes some interesting rules for the testing of drugs [5]. He suggests that "in the clinical trial a remedy should be used in its natural state in disease without complications". He also recommends that two cases of contrary types be studied and that study be made of the time of action and of the reproducibility of the effects [5]. These rules were related for contemporary approach in clinical trials. However, there seems to be no record of the application of these principles in practice.

"The first clinical trial of a novel therapy" was conducted accidentally by the famous surgeon Ambroise Pare in 1537 [4, 6]. In 1537 while serving with the Mareschal de Motegni, he was responsible for the treatment of the battlefield wounded soldiers. As the number of wounded was high and the supply of conventional treatment – oil – was not adequate to treat all the wounded, he resorted to unconventional treatments. He describes, "At length my oil lacked and I was constrained to apply in its place a digestive made of yolks of eggs, oil of roses and turpentine. That night I could not sleep at any ease, fearing that by lack of cauterization I would find the wounded upon which I had not used the said oil dead from the poison. I raised myself early to visit them, when beyond my hope I found those to whom I had applied the digestive medicament feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by arquebuses" [5]. 'However, it would take another 200 years before a planned controlled trial would be organized'.

1.3.2 1747: James Lind and Scurvy Trial

James Lind is considered the first physician to conduct a controlled clinical trial of the modern era [4–7]. As a surgeon working in a ship, Dr Lind (1716–94) was appalled by the high mortality of scurvy among the sailors. He planned a comparative trial of the most promising cure for scurvy [4–7]. His vivid description of the trial covers the essential elements of a controlled trial.

Lind's Treatise of 1953, which was written while he was a resident in Edinburgh and a fellow of the Royal College of Physicians, contains not only his well-known description of a

controlled trial showing which oranges and lemons were dramatically better than the other treatments for the disease but also a systematic review of previous literature on scurvy [8].

1.3.3 1800: Arrival of Placebo

The word of placebo was used in medical literature in the early 1800s [4]. Hooper's Medical Dictionary of 1811 defined it as 'an epithet given to any medicine more to please than benefit the patient'. However, in 1863, physician Austin Flint (USA) planned the first clinical study. He compared a dummy remedy with an active treatment in 13 patients with rheumatism. He applied herbal extract instead of an established remedy. In 1886, Flint described the study in his book *A Treatise on the Principles and Practice of Medicine*. 'This was given regularly, and became well-known in my wards as the placeboic remedy for rheumatism. The favorable progress of the cases was such as to secure for the remedy generally the entire confidence of the patients' [2].

1.3.4 1943: The First Double-Blind Controlled Trial (Patulin for Common Cold)

'The Medical Research Council (MRC) UK carried out a trial in 1943–4 to investigate patulin treatment for (an extract of Penicillium patulum) the common cold [6]. This was the first double-blind comparative trial with concurrent controls in the general population in recent times [9]. It was one of the last trial with non-randomized or quasi-randomized allocation of subjects [9]. The MRC Patulin Clinical Trials Committee (1943) was chaired by Sir Harold Himsworth and its statisticians were M Greenwood and W J Martin. This nationwide study included

over a thousand British office and factory workers suffering from colds. This was quite a challenging endeavor in the wartime'.

'The study was rigorously controlled by keeping the physician and the patient blinded to the treatment. The treatment allocation was done using an alternation procedure. A nurse allocated the treatment in strict rotation in a separate room. The nurse filled the record counterfoil separately and detached the code label for the appropriate bottle before asking the patient to visit the physician [9]. The statisticians considered this an effective random concurrent allocation. However, the outcome of the trial was disappointing as the analysis of trial data did not show any protective effect of patulin [9]'.

1.3.5 1946: The First Randomised Curative Trial (The Randomised Controlled Trial of Streptomycin)

The randomisation idea appeared in 1923. The first randomised control trial was conducted in pulmonary tuberculosis with streptomycin in 1946 (UK) [9, 10]. According to Dr Hill's randomisation scheme, alternation procedure of 'allocation concealment' was applied at the time patients were enrolled in the trial. In this trial, objective measures were used such as X-rays, and they were evaluated by experts who were blinded in the treatment of the patients [11].

'Sir Bradford Hill compelled his allocation ideas over several years with randomisation replacing alternation to better conceal the allocation schedule; however, he had only used them in disease prevention. Dr. Hill instituted randomization – a new statistical process which has been described in detail in the landmark BMJ paper of 1948 [10]'.

'Determination of whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case)

was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill. The details of the series were unknown to any of the investigators or to the coordinator and were contained in a set of sealed envelopes, each bearing on the outside only the name of the hospital and a number. After acceptance of a patient by the panel, and before admission to the streptomycin centre, the appropriate numbered envelope was opened at the central office; the card inside told if the patient was to be an S or a C case, and this information was, then, given to the medical officer of the centre. Patients were not told before admission that they were to receive special treatment. C patients did not know throughout their stay in hospital that they were control patients in a specific study; they were, indeed, treated as they would have been in the past, the sole difference being that they were admitted to the centre more rapidly than was normal. Usually, they were not in the same wards as S patients, whereas the same regime was maintained [2]'.

'Sir Bradford Hill was anxious that physicians would be unwilling to give up the doctrine of anecdotal experience. However, the trial quickly became a model of design and implementation and support Dr Hill's views and subsequent teaching, and resulted, after some years, in the present virtually universal use of randomised allocation in clinical trials [9]. The greatest influence of this trial lay in its methods affecting virtually every area of clinical medicine [11]. Over the years, as the discipline of controlled trials has grown in sophistication and influence, the streptomycin trial continues to be referred to as ground-breaking [11]'.

1.3.6 Evolution of Ethical and Regulatory Framework

'The ethical framework for human subject protection has its origins in the ancient Hippocratic Oath, which specified a prime

duty of a physician – to avoid harming the patient. However, this oath was not much respected in human experimentation and most advances in protection for human subjects have been a response to human abuses (e.g. World War II experiments)'.

'The first International Guidance on the ethics of medical research involving subjects – the Nuremberg Code was formulated in 1947. Although an informed consent for participation in research was described in 1900, the Nuremberg Code highlighted the essentiality of voluntariness of this consent [12]'.

'In 1948, Universal Declaration of Human Rights (adopted by the General Assembly of the United Nations) expressed concern about rights of human beings being subjected to involuntary maltreatment [12]. The brush with thalidomide tragedy helped the U.S. pass the 1962 Kefauver-Harris amendments, which strengthened federal oversight of drug testing and included a requirement for informed consent [13]'.

'In 1964 at Helsinki, the World Medical Association articulated general principles and specific guidelines on use of human subjects in medical research, known as the Declaration of Helsinki. The Declaration of Helsinki has been undergoing changes every few years, the last one being in 2008. However, the use of placebo and post-trial access continue to be debatable issues [2]'.

'In 1966, the International Covenant on Civil and Political Rights specifically stated, 'No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his consent to medical or scientific treatment' [12]. In 1966, Dr. Henry Beecher's study of abuses and the discovery of human exploitation of Tuskegee study in the 1970s reinforced the call for a tighter regulation of government funded human research [13]. The US National Research Act of 1974 and Belmont Report of 1979 were major efforts in shaping ethics of human experimentation. In 1996, International Conference on Harmonization published Good Clinical Practice, which has

become the universal standard for ethical conduct of clinical trials [2]'.

'In parallel to ethical guidelines, clinical trials began to become embodied in regulation as government authorities recognized a need for controlling medical therapies in the early 20th century. The FDA was founded in 1862 as a scientific institution and became a law enforcement organization after the US Congress passed the Food and Drugs Act in 1906. Afterwards, the legislation progressively demanded a greater accountability for marketing food and drugs and the need for testing drugs in clinical trials increased. The regulatory and ethical milieu will further continue to evolve as new scientific disciplines and technologies will become part of the drug development [2]'.

1.3.7 The Food and Drug Administration (FDA) in the USA

'In the 19th century, what little control over food and medications existed was the responsibility of the individual states and was inconsistent from state to state. The adulteration and misbranding of foods and drugs was commonplace, with snake oil salesmen increasing as the century progressed. Furthermore, many medicinal products were compounded in individual pharmacies, making oversight difficult. The first federal law which addressed the protection of the consumer with regard to therapeutic substances was the Vaccine Act of 1813, which established a national source for uncontaminated smallpox vaccine. However, the Vaccine Act was repealed after only 9 years due to a fatal accident and public scandal of a contaminated vaccine'.

'In 1862, the President Lincoln created the Division of Chemistry, the predecessor of the FDA, as part of the new Department of Agriculture. Starting in 1867, the Division of

Chemistry began investigating the corruption of agricultural commodities. Harvey Washington Wiley in his role as chief chemist expanded the investigative role of the Division of Chemistry in 1883. He was instrumental in the enactment of the Biologics Act of 1902 in response to the deaths of several children caused by contaminated smallpox vaccines and diphtheria antitoxins. This Act granted the federal government premarket approval for every biological drug and approval over the process and facility producing such drugs. He also compiled Foods and Food Adulterants, a 10-part study published from 1887 to 1902. In this study, he administered varying amounts of the questionable food additives which were in use to healthy volunteers to determine their affects on health. Based on these results and the filthy conditions described in Upton Sinclair's book, The Jungle, he unified a diverse group that included state chemists, food and drug inspectors, the General Federation of Women's Clubs, and national associations of physicians and pharmacists behind the Pure Food and Drugs Act (also known as the Wiley Act), which was signed into law by President Theodore Roosevelt on June 30, 1906'.

'The 1906 law recognized the privately produced US Pharmacopoeia (USP, originated in 1820) and the National Formulary as the official standards' for 'the strength, quality, and purity of drugs, and defined adulterated drugs as those that were listed in the USP', but failed USP specifications [3].

'In 1927, the Bureau of Chemistry was re-organized into the Food, Drug, and Insecticide Administration to oversee regulatory functions, and the Bureau of Chemistry and Soils to conduct non-regulatory research. In 1930, under an agricultural appropriation act, the name of the Food, Drug, and Insecticide Administration was shorted to the Food and Drug Administration (FDA)'.

The Durham-Humphrey Amendment of 1951 resolved 'the debate about what constituted a prescription medication and what could be considered over-the-counter'. The Food Additives Amendment of 1958 allowed the 'FDA to regulate dietary supplements'. In 1976, the Congress prohibited the FDA from

'controlling these products in response to pressure from supplement manufacturers'. Also in the same year, the Medical Device Amendments were passed, which divided devices into three categories [3]:

- 'Class I (eg, tongue depressors, gauze) are subject to reporting requirements and Good Manufacturing Practices'
- 'Class II (eg, blood pressure cuffs, sutures) are subject to the same controls as Class I plus product-specific performance standards developed by the FDA'
- 'Class III (eg, angioplasty catheters, artificial hearts) must pass an FDA approval process similar to novel drugs'.

All new devices are categorised as 'Class III, unless it can be shown to be substantially equivalent to a previously approved device' [3].

1.3.8 European Medicines Agency (EMEA)

'Although the EMEA was not established until 1995, numerous events paved the way for its creation. The European Union (EU) was first conceptualized in 1951, when six countries (Belgium, France, West Germany, Italy, Luxembourg, and the Netherlands) created the European Coal and Steel Community by pooling their resources into a common market. In 1957, the European Economic Community, the predecessor to the EU, expanded the common market beyond just coal and steel to all financial sectors of the member countries through the Rome Treaties. In 1973, the United Kingdom, Ireland, and Denmark joined the EU; Greece joined in 1981, Portugal and Spain in 1986, and Austria, Finland, and Sweden joined in 1995. In 2004, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, the Republic of Cyprus, the Slovak Republic, and Slovenia joined the EU, and, in 2007, Bulgaria and Romania joined for a total of 27 countries or member states. As in the

United States, disasters often prompted change in the EU. Thalidomide was introduced in Europe in 1957 to alleviate morning sickness in pregnant women. By 1960, thalidomide was available in more than 20 countries in Europe and Africa (it was never granted approval in the United States) [3]'.

'In 1965, the First European Directive, known as 65/65/EEC, was enacted by the Council of the European Economic Community and stated that no medicinal product could be placed on the market in a member state, unless the authorization was issued by the competent authority in that member state. Thus, pharmaceutical manufacturers had to seek an approval from each individual country before marketing was commenced in that country. The Second European Directive (75/319/EEC) in 1975 hoped to alleviate some of the multiplicity involved in seeking approval across Europe by introducing mutual recognition, so that authorization in one member country would allow marketing in other member countries without having to repeat the entire approval process. 75/319/EEC also established the Committee for Proprietary Medicinal Products (CPMP), which consisted of representatives of the member states to provide an opinion, if there was a dispute about any particular product in the various member states' [3].

1.3.9 Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

'In 1943, Japan passed the first Pharmaceutical Affairs Law, with revisions in 1948, 1960, and 1979. The Pharmaceutical Affairs Law, enacted by the Ministry of Health, Labor, and Welfare, regulated the quality, effectiveness, and safety of medical drugs and equipment'. In 2004, the 'Pharmaceuticals and Medical Devices Agency (PMDA)' was established as an 'independent, non-governmental agency separate from the Ministry of Health, Labor, and Welfare' [3].

1.4 Evolution of the Drugs

'The modern U.S. drug regulatory system has its roots in amendments to the 1938 FD&C Act that Congress passed a generation later, partly in response to the grim effects of thalidomide [14]. The 1938 act made major changes in the FDA's regulation of drugs. Manufacturers more commonly consulted with the agency before marketing a new product and the agency became increasingly involved in overseeing the design and conduct of clinical trials of experimental drugs [15]. Although the 1962 drug amendments purported simply to elaborate the new-drug approval system, they, indeed, transformed it [14]'.

Emergence of the New Drug System

- Expansion of jurisdiction: The premarket approval is required for 'novel drugs' [14].
- Oversight of clinical investigations: 'The act prohibits the interstate shipment of any novel drug for which the FDA has not approved an NDA' [14]. The FDA has supplemented this requirement with 'a mandate for review by a local institutional review board (IRB) and, to facilitate monitoring of compliance with both requirements', the agency has established detailed specifications for IRB operations and record keeping [14].

References

1. Learn About Clinical Studies. https://clinicaltrials.gov/ct2/about-studies/learn. Accessed online at 26 Oct 2015.
2. Bhatt A. Evolution of clinical research: a history before and beyond James Lind. Perspect Clin Res. 2010;1(1):6–10. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149409. Accessed online at 26 Oct 2015.
3. The Evolution of the clinical trials process – a brief history lesson. http://www.psoriasiscouncil.org/docs/chapter_01.pdf. Accessed online at 26 Oct 2015.

4. Collier R. Legumes, lemons and streptomycin: a short history of the clinical trial. CMAJ. 2009;180:23–4. [PMC free article] [PubMed].
5. Bull JP. MD Thesis: University of Cambridge; 1951. A study of the history and principles of clinical therapeutic trials.
6. Twyman RA. A brief history of clinical trials. The Human Genome. 2004. Sephttp://genome.wellcome.ac.uk/doc_WTD020948.html. Accessed 5 Oct 2009.
7. Dodgson SJ. The evolution of clinical trials. J Eur Med Writ Assoc. 2006;15:20–1.
8. Chalmers I, Milne I, Trohler U, Vandenbroucke J, Morabia A, Tait G, Dukan E. The James Lind Library editorial team. The James Lind Library: explaining and illustrating the evolution of fair tests of medical treatments. J R Coll Physicians Edinb. 2008;38:259–64.
9. Hart PD. A change in scientific approach: from alternation to randomised allocation in clinical trials in the 1940s. BMJ. 1999;319(7209):572–3.
10. MRC Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment of pulmonary tuberculosis. BMJ. 1948;2:769–83.
11. Yoshioka A. The randomized controlled trial of streptomycin. In: Emanuel EJ, Grady C, Crouch RA, Lie RK, Miller FG, Wendler D, editors. The Oxford textbook of clinical research ethics. Oxford: University Press Oxford; 2008. p. 46–60.
12. Indian Council of Medical Research Ethical Guidelines for Biomedical Research on Human Participants. 2006.
13. Sparks J. Timeline of laws related to the protection of human subjects Office of History National Institutes of Health. html. http://history.nih.gov/about/timelines_laws_human.html. Accessed 20 Sep 09.
14. Merrill RA. Regulation of drugs and devices: an evolution. Health Affairs13.3 (Summer 1994):47–69. http://search.proquest.com/docview/204490990?pq-origsite=summon. Accessed online at 26 Oct 2015.
15. Testimony of George Larrick, FDA Commissioner, at hearings on drug safety before a subcommittee of the House Committee on Government Operations, 88th Cong., 2d Sess. (1964), as quoted in P.B. Hutt and R.A. Merrill, Food and Drug Law: Cases and Materials, 2d ed. (Westbury, N.Y.: The Foundation Press, 1991), 522–523.

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

1. Handbook For Good Clinical Research Practice (GCP). Guidance for implementation. World Health Organization, 2002. http://apps.who.int/prequal/info_general/documents/GCP/gcp1.pdf. Accessed online at 13Oct 2015.

2. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH, April 1996.
3. Good clinical practice. Wikipedia https://en.wikipedia.org/wiki/Good_clinical_practice. Accessed online at 13 Oct 2015.
4. Verma K. Base of a research: good clinical practice in clinical trials. J Clin Trials. 2013;3:128. doi:10.4172/2167-0870.1000128.

Chapter 3
The Principles of GCP

3.1 The Principles of ICH GCP [1]

1. '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)'.
2. 'Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for individual trial subjects and society. A trial should be initiated and continued only if the anticipated benefits justify the risks'.
3. 'The rights, safety, and well being of trial subjects are the most important considerations and should prevail over the interests of science and society'.
4. 'The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial'.
5. 'Clinical trials should be scientifically sound, and described in a clear, detailed protocol'.

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6. ‘A trial should be conducted in compliance with a protocol that has received prior IRB/IEC approval/favourable opinion’.
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’.
8. ‘Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)’.
9. ‘Freely given informed consent should be obtained from every subject prior to clinical trial participation’.
10. ‘All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification’.
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)’.
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’.
13. ‘Systems with procedures that assure the quality of every aspect of the trial should be implemented’.

3.2 WHO Principles of GCP [2]

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. Three basic ethical principles of equal importance,

namely, respect for persons, beneficence, and justice, permeate all other GCP principles'.

Principle 2 'Research involving humans should be scientifically justified and described in a clear, detailed protocol'.

Principle 3 '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 '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 a 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 trial subjects'.

Principle 5 'Research involving humans should receive IEC/IRB approval/favourable opinion prior to initiation'.

Principle 6 'Research involving humans should be conducted in compliance with the approved protocol'.

Principle 7 '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 authorised representative should be obtained in accordance with applicable law'.

Principle 8 'Research involving humans should be continued only if the benefit-risk profile remains favourable'.

Principle 9 'Qualified and duly licensed medical personnel (i.e. physician(s) or, when appropriate, dentist(s)) should be

responsible for the medical care of trial subjects, and for any medical decision(s) made on their behalf'.

Principle 10 '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 'All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification'.

Principle 12 '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 'Investigational products should be manufactured, handled, and stored in accordance with applicable GMP and should be used in accordance with the approved protocol'.

Principle 14 'Systems with procedures that assure the quality of every aspect of a trial should be implemented'.

References

1. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH, April 1996.
2. Handbook for Good Clinical Research Practice (GCP). Guidance for implementation. World Health Organization, 2002. http://apps.who.int/prequal/info_general/documents/GCP/gcp1.pdf. Accessed online at 13 Oct 2015.

Chapter 4
The Drug Development Process and Evolution of Regulations

4.1 Introduction

Drug development is often a lengthy and expensive process. Extensive preclinical testing via in vitro and animal experimentation aims to select drugs most likely to work in humans. Under the current system, only about half of all drugs succeed in moving from phase 1 (dose finding) to phase 2 (safety and efficacy) [1]. For drugs that enter phase 2, less than one in three succeed; for those entering phase 3 (pivotal efficacy), that number decreases to less than one in two [1, 2]. Less than 20 % of drugs entering phase-1 testing successfully reach the end of the three-phase evaluation. The percentage can vary from one specialty area to another and can be less than 5–10 % for oncologic and neurologic diseases [3].

This process is not as radical as it may sound. More than four decades ago, Thomas Chalmers proposed that most scientific and ethical clinical trial designs should be based on the principle 'randomise the first patient' [4]. Chalmers provided compelling logic for why the first patient should be randomised and conducted a number of randomised trials in which he did randomise

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the first patient invited to participate in the study. However, almost half a century later, a large number of phase-1 and phase-2 trials are still nonrandomised. An evaluation of registered protocols first received by ClinicalTrials.gov between August 1, 2013, and August 15, 2013, showed that 53 of 105 phase-1 trials (50%) and 42 of 113 phase-2 trials (37%) were nonrandomised. These are likely to be underestimates, because nonregistration is likely to be far more common for nonrandomised studies than for randomised studies. Empirical studies show that almost all phase-1 studies in oncology are nonrandomised [5]. Across medicine, probably more than 80% of phase-1 studies and more than 50% of phase-2 studies are currently nonrandomised. This corresponds to many thousands of nonrandomised clinical trials conducted annually.

Once a specific dose (or dose range) has been selected for a new treatment, it makes little sense to collect uncontrolled observational data, instead of comparing this dose or doses against the best standard of care. The results of single-group, uncontrolled studies are always difficult to interpret. If the results are 'positive', it cannot be proven that they are not attributable to chance or a favourable sample of selected patients; if the results are unfavourable, the reverse arguments can be raised. Moreover, from an ethical perspective, in a randomised phase-1 or phase-2 trial, patients will have a 50% chance of being assigned to a better treatment, whereas in a single-group phase-1 or phase-2 trial, patients will be allocated to a treatment that (based on assumed eventual success rates) is far less than 50% likely to be the best currently available. The unethical dimension of nonrandomised clinical studies had already been recognised by Chalmers. In addition to being more ethical, adoption of randomised design throughout the drug development process would be likely to improve efficiency, i.e. it would enable faster development of new, successful treatments [6].

The proposed shift to randomised phase-1 and phase-2 trials could also help to identify more efficiently ineffective or

harmful treatments. This would be easier and more accurate to demonstrate in a randomised design than in an uncontrolled setting. Uncontrolled studies may lead to the abandonment of some potentially useful treatments or may fail to demonstrate the problems of many ineffective treatments and protract expensive clinical testing. For a development system with substantially high failure rates at all steps, not optimising study designs and their accuracy makes no sense [6].

4.2 Drug Development

Drug development can generally be divided into phases [7]. The first is the preclinical phase, which usually takes 3–4 years to complete. If successful, this phase is followed by an application to the US Food and Drug Administration (FDA) as an investigational new drug (IND). After an IND is approved, the next steps are clinical phases 1, 2 and 3, which require approximately 1, 2 and 3 years, respectively, for completion. Importantly, throughout this process, the FDA and the investigators leading the trials communicate with each other so that issues such as safety are monitored. The manufacturer then files a new drug application (NDA) with the FDA for approval. This application can either be approved or rejected, or the FDA might request further study before making a decision. Following acceptance, the FDA can also request that the manufacturer conducts additional postmarketing studies. Overall, this entire process, on average, takes between 8 and 12 years [8].

It is not surprising that, from conception to market, most compounds face an uphill battle to become an approved drug. For approximately every 5000–10,000 compounds that enter preclinical testing, only one is approved for marketing [9]. A 1993 report by the Congressional Office of Technology Assessment estimated the cost of developing a new drug to be

$359 million [10]. Newer figures place the cost at more than $500 million [11].

The first step, the preclinical phase, is to find a promising agent, which involves taking advantage of advances made in understanding a disease, pharmacology, computer science or chemistry. Breaking down a disease process into its components can provide clues for targeting drug development. For example, if an enzyme is determined to be a key component of a disease process, a researcher might seek ways to inhibit that enzyme. Advances in basic science might help by ascertaining the active enzyme site. Numerous compounds might be synthesised and tested before a promising agent emerges. Computer modelling often helps select what compounds might be the most promising [7].

The next step before attempting a clinical trial in humans is to test the drug in living animals, usually rodents. The FDA requires that certain animal tests be conducted before humans are exposed to a new molecular entity. The objectives of early in vivo testing are to demonstrate the safety of a proposed medication. For example, tests should prove that a compound does not cause chromosomal damage and is not toxic at the doses that would most likely be effective. The results of these tests are used to support the IND application that is filed with the FDA. The IND application includes chemical and manufacturing data; animal test results, including pharmacology and safety data; the rationale for testing a new compound in humans; strategies for protection of human volunteers; and a plan for clinical testing [8, 10]. If the FDA is satisfied with the documentation, the stage is set for phase-1 clinical trials.

Phase-1 studies focus on the safety and pharmacology of a compound [12]. During this stage, low doses of a compound are administered to a small group of healthy volunteers who are closely supervised. In cases of severe or life-threatening illnesses, volunteers with the disease may be used. Generally, 20–100 volunteers are enrolled in a phase-1 trial. These studies

usually start with very low doses, which are gradually increased. On average, about two thirds of phase-1 compounds will be found safe enough to progress to phase 2.

Phase-2 studies examine the effectiveness of a compound. To avoid unnecessarily exposing a human volunteer to a potentially harmful substance, studies are based on an analysis of the fewest volunteers needed to provide sufficient statistical power to determine efficacy. Typically, phase-2 studies involve 100–300 patients who suffer from the condition the new drug is intended to treat. During phase-2 studies, researchers seek to determine the effective dose, the method of delivery (e.g. oral or intravenous) and the dosing interval, as well as to reconfirm product safety [8, 12–14]. Patients in this stage are monitored carefully and assessed continuously. A substantial number of these drug trials are discontinued during phase-2 studies. Some drugs turn out to be ineffective, while others have safety problems or intolerable side effects.

Phase-3 trials are the final step before seeking FDA approval. During phase 3, researchers try to confirm previous findings in a larger population. These studies usually last from 2 to 10 years and involve thousands of patients across multiple sites. These studies are used to demonstrate safety and effectiveness further and to determine the best dosage. Despite the intense scrutiny a product receives before undergoing expensive and extensive phase-3 testing, approximately 10 % of medications fail in phase-3 trials [7].

If a drug survives the clinical trials, an NDA is submitted to the FDA. An NDA contains all the preclinical and clinical information obtained during the testing phase. The application contains information on the chemical makeup and manufacturing process, pharmacology and toxicity of the compound, human pharmacokinetics, results of the clinical trials and proposed labelling. An NDA can include experience with the medication from outside the USA as well as external studies related to the drug [7].

After receiving an NDA, the FDA completes an independent review and makes its recommendations. The Prescription Drug User Fee Act of 1992 (PDUFA) was designed to help shorten the review time. This act allowed the agency to collect user fees from pharmaceutical companies as financial support to enhance the review process. The 1992 act specifies that the FDA reviews a standard drug application within 12 months and a priority application within 6 months. Application for drugs similar to those already on the market is considered standard, whereas priority applications represent drugs offering important advances in addition to existing treatments. If the FDA staff feel during the review that there is a need for additional information or corrections, they will make a written request to the applicant. During the review process, it is not unusual for the FDA to interact with the applicant's staff [14].

Once the review is complete, the NDA might be approved or rejected. If the drug is not approved, the applicant is given the reasons why and what information could be provided to make the application acceptable. Sometimes, the FDA makes a tentative approval recommendation, requesting that a minor deficiency or labelling issue be corrected before final approval. Once a drug is approved, it can be marketed [7].

Some approvals contain conditions that must be met after initial marketing, such as conducting additional clinical studies. For example, the FDA might request a postmarketing, or phase-4 study, to examine the risks and benefits of the new drug in a different population or to conduct special monitoring in a high-risk population. Alternatively, a phase-4 study might be initiated by the sponsor to assess such issues as the longer-term effects of drug exposure, to optimise the dose for marketing, to evaluate the effects in paediatric patients or to examine the effectiveness of the drug for additional indications [13]. Postmarketing surveillance is important, because even the most well-designed phase-3 studies may not uncover every problem that could become apparent once a product is widely used.

Furthermore, the new product might be more widely used by groups who might not have been well studied in the clinical trials, such as elderly patients. A crucial element in this process is that physicians report any untoward complications. The FDA has set up a medical reporting programme called MedWatch to track serious AEs (1-800-FDA-1088). The manufacturer must report ADRs at quarterly intervals for the first 3 years after approval [11], including a special report for any serious and unexpected adverse reactions.

4.3 Recent Developments in Drug Approval

The Food and Drug Administration Modernization Act of 1997 (FDAMA) extended the use of user fees and focused on streamlining the drug approval process [12, 15]. In 1999, the 35 drugs approved by the FDA were reviewed in an average of 12.6 months, slightly more than the 12-month goal set by PDUFA [11]. This act also increased patient access to experimental drugs and facilitated an accelerated review of important new medications. The law ended the ban on disseminating information to providers about non-FDA-approved uses of medications. A manufacturer can now provide peer-reviewed journal articles about an off-label indication of a product if the company commits to filing a supplemental application to establish the use of the unapproved indication. As part of this process, the company must still conduct its own phase-4 study. As a condition for an accelerated approval, the FDA can require the sponsor to carry out postmarketing studies to confirm a clinical benefit and product safety. Critics contend the 1997 act compromises public safety by lowering the standard of approval [16]. Within a year after the law was passed, several drugs were removed from the market. Among these medications were mibefradil for hypertension, dexfenfluramine for morbid obesity, the antihistamine terfenadine and bromfenac sodium for

pain [17]. More recently, additional drugs including troglitazone were removed from the market. Although the increase in recalls might reflect the dramatic increase in drugs approved and launched [17], others argue that several safety questions were ignored [18, 19]. Another concern was that many withdrawn drugs were 'me-too drugs', which did not represent a noteworthy advance in therapy. Persons critical of the FDA believe changes in the approval process, such as allowing some new drugs to be approved based on only a single clinical trial, expanded use of accelerated approvals and the use of surrogate end points, have created a dangerous situation [19]. Proponents of the changes in the approval process argue that there is no evidence of increased risk from the legislative changes [20] and that these changes improve access to cancer patients and those with debilitating disease who were previously denied critical and life-saving medications.

4.4 Emergence of a New Drug System

While the basic elements of the FDA system of drug regulation had been established in 1962, many important details are products of later legislation or initiatives of the agency itself [21].

Expansion of Jurisdiction The premarket approval requirement was, from the outset, limited to 'new drugs'. A new drug was defined after 1962 as one that was not generally recognised by experts as safe and effective for its labelled uses. Although this definition embraced essentially all novel active prescription drug ingredients introduced after 1938, the act excluded several categories of drugs and left the status of others uncertain. The FDA's early implementation of these provisions was marked by a series of efforts to narrow the exceptions and to confirm the new drug status of products about which the statute left doubt.

It is a complicated story, but readers should be familiar with the results of the FDA's effort and appreciate its lessons [22].

Two concerns animated the FDA's efforts to bring all prescription drugs within its 'new drug' jurisdiction. First, the agency could see no logic in allowing 'me-too' copies to escape the limitations that applied to the pioneer product, even temporarily. Second, it was efficient to determine the limitations that ought to apply to a drug (and all copies) and implement these administratively by modifying the terms of its NDA. Then, any deviation would automatically render the product illegal [21].

One cannot overstate the significance of the shift in regulatory leverage that has resulted from Congress's adoption of premarket approval for prescription drugs and from the FDA's successful efforts to extend its coverage. From an environment in which drug makers could market any product that the government was unable to prove in court was, or bore claims that were, knowingly false, we have moved to a system in which no prescription drug may be marketed unless and until the FDA is convinced that it is safe and effective for the uses that the agency will allow on the label. Furthermore, the FDA takes the position that virtually any change in an approved new drug requires advance approval. Not only attempts to expand indications but also more modest changes in labelling, ingredients, the method or even the location of manufacture or packaging must first undergo FDA review [21].

Oversight of Clinical Investigations The act prohibits the interstate shipment of any new drug for which the FDA has not approved an NDA. Since 1938, however, the agency has been empowered to grant exemptions for investigational drugs [21]. From this authority have grown two types of regulatory requirements governing clinical studies.

One set of requirements is designed to assure the integrity of clinical trials. The core of these is the requirement that

investigators secure and document the informed consent of trial subjects. The FDA has supplemented this requirement with a mandate for review by a local IRB, and, to facilitate monitoring of compliance with both requirements, the agency has established detailed specifications for IRB operations and record-keeping. The second set of requirements is intended to increase the likelihood that clinical trials will produce acceptable evidence of a drug's safety and effectiveness. These requirements are set forth in regulations, in test guidelines for specific therapeutic classes and in FDA reviewer critiques of clinical protocols [21].

These diverse instructions constitute a growing body of FDA 'law' governing drug trials. While agency officials claim that these instructions embody what independent experts consider sound experimental design, many manufacturers and clinicians contend that FDA reviewers tend to demand more comprehensive studies than are needed to support sound judgements about effectiveness. The FDA assumes, of course, that any trial will follow the protocol and that the records submitted to the agency will truthfully reflect the observations of investigators; this assumption is not simply a matter of faith, as it is supported by an elaborate system for monitoring the veracity of drug sponsors and clinical investigators [21].

References

1. Paul SM, Mytelka DS, Dunwiddie CT, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010;9(3):203–14.
2. Djulbegovic B, Kumar A, Glasziou P, Miladinovic B, Chalmers I. Medical research: trial unpredictability yields predictable therapy gains. Nature. 2013;500(7463):395–6.
3. Bhattacharjee Y. Biomedicine. Pharma firms push for sharing of cancer trial data. Science. 2012;338(6103):29.

4. Chalmers TC. Randomization of the first patient. Med Clin North Am. 1975;59(4):1035–8.
5. Horstmann E, McCabe MS, Grochow L, et al. Risks and benefits of phase 1 oncology trials, 1991 through 2002. N Engl J Med. 2005;352(9):895–904.
6. Djulbegovic B, Hozo I, Ioannidis JPA. Improving the drug development process more not less randomized trials. JAMA. 2014;311(4):355–6.
7. Lipsky MS, Sharp LK. From idea to market: the drug approval process. J Am Board Fam Med. 2001;14(5). http://www.medscape.com/viewarticle/405869_3. Accessed online at 14 Oct 2015.
8. Heilman RD. Drug development history, "overview," and what are GCPs? Quality Assur. 1995;4:75–9.
9. Klees JE, Joines R. Occupational health issues in the pharmaceutical research and development process. Occup Med. 1997;12:5–27.
10. Stave GM, Joines R. An overview of the pharmaceutical industry. Occup Med. 1997;12:1–4.
11. Pharmaceutical Research and Manufacturers of America Publication. 21 Dec 2000. Available at http://www.phrma.org.
12. Cancer Trials: new drugs, new drug uses, and clinical trials. In: National Cancer Institute. Understanding trials. Posted 29 July 1999. Available at http://cancertrials.nci.nih.gov/understanding/indepth/fda/trials.html.
13. Leonard EM. Quality assurance and the drug development process: an FDA perspective. Quality Assur. 1994;3:178–86.
14. Walters PG. FDA's new drug evaluation process: a general overview. J Public Health Dent. 1992;52:333–7.
15. The FDA Modernization Act of 1997. (BG no 97–13.) FDA Backgrounder 21 November 1997. Available at http://www.fda.gov/opacom/backgrounders/modact.htm.
16. Marwick C. Concern expressed about FDA reform legislation. JAMA. 1997;278:459.
17. Kleinke JD, Gottlieb S. Is the FDA approving drugs too fast? Probably not-but drug recalls have sparked debate. BMJ. 1998;317:899.
18. Landow L. FDA approves drug even when experts on its advisory panels raise safety questions. BMJ. 1999;318:944.
19. Lurie P, Sasich LD. Safety of FDA-approved drugs. JAMA. 1999;282:2297.
20. Friedman MA, Woodcock J, Lumpkin MM, Shuren JE, Hass A, Thompson LJ. The safety of newly approved medicines: do recent market removals mean there is a problem? JAMA. 1999;281:1728–34.
21. Merrill RA. Regulation of drugs and devices: an evolution. Health Aff. 1994;13(3):47–69.
22. Hutt PB, Merrill RA. Food and drug law. Second edition, The Foundation Press, Inc: Westbury, New York. 1991;477–510.

Chapter 5
Planning Clinical Research

5.1 Introduction

To achieve their objectives, clinical trials should be designed, conducted and analysed according to sound scientific principles and should be reported appropriately. The essence of rational drug development is to ask important questions and answer them with appropriate studies. The primary objectives of any study should be clear and explicitly stated [1].

5.2 Methodology

5.2.1 Considerations for the Plan

5.2.1.1 Non-clinical Studies

Important considerations for determining the nature of non-clinical studies and their timing with respect to clinical trials include duration and total exposure proposed in individual

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patients, characteristics of the drug (e.g. long half-life, biotechnology products), disease or condition targeted for treatment, use in special populations (e.g. women of childbearing potential) and route of administration. The need for non-clinical information including toxicology, pharmacology and pharmacokinetics to support clinical trials is addressed in the ICH M3 and S6 documents [1].

Safety Studies

'For the first studies in humans, the dose that is administered should be determined by careful examination of the prerequisite non-clinical pharmacokinetic, pharmacological and toxicological evaluations (ICH M3). Early non-clinical studies should provide sufficient information to support selection of the initial human dose and safe duration of exposure, and to provide information about the physiological and toxicological effects of a new drug [1]'.

Pharmacological and Pharmacokinetic Studies

'The basis and direction of the clinical exploration and development rests on the nonclinical pharmacokinetic and pharmacology profiles, which include information such as the pharmacological basis of principal effects (mechanism of action); dose-response or concentration-response relationships and duration of action; study of the potential clinical routes of administration; systemic general pharmacology, including pharmacological effects on major organ systems and physiological responses; and studies of absorption, distribution, metabolism and excretion [1]'.

5.2.1.2 Quality of Investigational Medicinal Products

'Formulations used in clinical trials should be well characterised, including information on bioavailability wherever feasible. The formulation should be appropriate for the stage of drug develop-

ment. Ideally, the supply of a formulation will be adequate to allow testing in a series of studies that examine a range of doses. During drug development different formulations of a drug may be tested. Links between formulations, established by bioequivalence studies or other means, are important in interpreting clinical study results across the development program [1]'.

5.2.1.3 Phases of Clinical Development

'Clinical drug development is often described as consisting of four temporal phases (phases I–IV). It is important to recognise that the phase of development provides an inadequate basis for the classification of clinical trials because one type of trial may occur in several phases, and that the phase concept is a description, not a set of requirements. It is also important to realise that the temporal phases do not imply a fixed order of studies as for some drugs in a development plan the typical sequence will not be appropriate or necessary. For example, although human pharmacology studies are typically conducted during phase I, many such studies are conducted at each of the other three stages so they are sometimes labelled, nonetheless, as phase-I studies [1]'.

5.2.1.4 Special Considerations

'A number of special circumstances and populations require consideration on their own when they are part of the development plan [1]'.

Studies of Drug Metabolites

'Major active metabolite(s) should be identified and deserve detailed pharmacokinetic study. Timing of the metabolic assessment studies within the development plan depends on the characteristics of the individual drug [1]'.

Drug-Drug Interactions

'If a potential for drug-drug interaction is suggested by the metabolic profile, the results of non-clinical studies or information on similar drugs, studies on drug interaction during clinical development are highly recommended. For drugs that are frequently co-administered it is usually important that drug-drug interaction studies be performed in non-clinical and, if appropriate, in human studies. This is particularly true for drugs that are known to alter the absorption or metabolism of other drugs (ICH E7), or whose metabolism or excretion can be altered by the effects of other drugs [1]'.

Special Populations

'Some groups in the general population may require special study because they have unique risk/benefit considerations that need to be taken into account during drug development, or because they can be anticipated to need modification of the dose or schedule of a drug, as compared to general adult use. Pharmacokinetic studies in patients with renal and hepatic dysfunction are important to assess the impact of potentially altered drug metabolism or excretion. Other ICH documents address such issues for geriatric patients (ICH E7) and patients from different ethnic groups (ICH E5). The need for non-clinical safety studies to support human clinical trials in special populations is addressed in the ICH M3 document [1]'.

Investigations in Pregnant Women

'In general, pregnant women should be excluded from clinical trials when the drug is not intended for use in pregnancy. If a patient becomes pregnant during administration of the drug, treatment should generally be discontinued if this can be done safely. Follow-up evaluations of the pregnancy, foetus, and child

are very important. Similarly, for clinical trials that include pregnant women because the medicinal product is intended for use during pregnancy, follow-up of the pregnancy, foetus, and child is very important [1]'.

Investigations in Nursing Women

'Excretion of the drug or its metabolites into human milk should be examined when applicable. When nursing mothers are enrolled in clinical studies, their babies should be monitored for the effects of the drug [1]'.

Investigations in Children

'The extent of the studies needed depends on the current knowledge of the drug and the possibility of extrapolation from adults and children of other age groups. Some drugs may be used in children from the early stages of drug development (ICH M3)'.

'For a drug expected to be used in children, evaluation should be made in the appropriate age group. When clinical development is to include studies in children, it is usually appropriate to begin with older children before extending the trial to younger children and then infants [1]'.

5.2.2 Planning a Study

The main steps involved in planning a study are listed below [2]:

- Aim(s)
- Population
- Interventions
- Outcomes
- Data collection: measuring outcomes (when, by whom, how, to what level of accuracy)

- Confounding factors
- Inclusion and exclusion criteria
- Sampling strategy
- Study design
- Sample size
- Compliance
- Data storage and management
- Analysis

5.2.2.1 Aims

The first step in planning a study is to identify a clear, achievable and ethical aim. All studies need to have a purpose and aim to develop knowledge or understanding in a particular area [2].

5.2.2.2 Identifying the Population

This is the set of patients about whom we wish to make an inference. Identifying the population is not always straightforward. For example, will patients with DM (A5) include type 1, type 2, gestational, MODY, LADA, type 3, type 1.5, etc.? These different groups are likely to differ with regard to, for example, age, drug treatment and co-morbidities, and this heterogeneity would complicate an investigation [2].

5.2.2.3 Defining Interventions

An intervention is any action that is performed on the subject, or to his or her environment. This can include, for example, a drug treatment (including placebo), surgery, wearing a support device, counselling or a combination of two or more treatments [2].

5.2.2.4 Identifying the Outcome

Outcomes are endpoints or measures of the response to an intervention. The natural history of a disease such as DMD could be described by the different aids required (such as limb supports and a wheelchair), drug therapies and the time to these events. The occurrence, severity and time of onset of complications such as chest infection and osteoporosis would also be of interest [2].

5.2.2.5 Data Collection: Measuring Outcomes

There are several issues to consider when measuring an outcome. How will it be measured? When will it be measured and by whom? What is the level of accuracy and how valid and reliable is the measurement of the outcome? How will it be recorded and the data stored? Who will take responsibility for data management? These are particularly important matters when data are collected by more than one person and/or at more than one site.

Wherever possible, data should be measured and recorded as accurately as possible. It is tempting to group observations but this can be misleading and limiting. Suppose, for example, a researcher wishes to test his hypothesis that high heel height leads to back pain. Should he classify heels simply as 'high' and 'not high', as 'high', 'medium' and 'low' or as something else? Ideally, shoe heel height should be measured with a tape measure, at the back of the heel, and recorded in millimetres. Judgements such as high and low are subjective: someone who regularly wears flat shoes might regard 30 mm to be a high heel, whereas a stiletto-heel wearer might regard this as low [2].

5.2.2.6 Confounding Factors

Variables that are related to both the outcome of a study and the intervention can distort the effect of the intervention. These are known as confounding factors [3]. It is important to identify any such confounding factors during the planning phase and include them as independent variables [2].

5.2.2.7 Inclusion and Exclusion Criteria

As the names suggest, inclusion and exclusion criteria identify who will be included or excluded from the sample. Patients who could benefit from the intervention are described by the inclusion criteria. Those for whom the intervention is inappropriate or could be dangerous, or who have co-morbidities that could mask its effect, are identified by the exclusion criteria [2].

5.2.2.8 Sampling a Population

Sampling is a vital step in any research and governs any inferences that can be made. Often it is either not possible or not practical to select a random sample (e.g. if the population cannot be enumerated). In such cases, a clinician might choose to study a sample of patients in his/her clinic. Even if this sample itself is selected randomly, this does not constitute a truly random sample of the population; it is a random sample of a subset of the population that has not itself been chosen randomly. Such selections are referred to as convenience samples [2].

5.2.2.9 Types of Study Design

In a prospective study, subjects are selected from a population and analysed for a defined future outcome. In contrast, a ret-

rospective study is an analysis of existing data. A study is said to be experimental if the effect of an intervention is to be investigated (e.g. a drug treatment or exercise programme); otherwise it is an observational study. A study is described as cross-sectional if measurements are made at only one time point, while a longitudinal study analyses multiple time points. An analytical study is one in which the aim is to analyse the data gathered in order to make an inference about the effect of an intervention on an outcome variable. In a descriptive study, the data are summarised using descriptive statistics (e.g. measures of centre and spread frequencies) without consideration of the effects of one or more of the variables on the others.

One of the most widely known designs is the randomised controlled trial (RCT). A sample of subjects is selected from the population and allocated randomly to one of two or more groups (or arms) of the trial. One of the treatments is a control, which could be an existing treatment, a placebo or no treatment. Wherever possible, trials should be double blinded such that both the subjects and the researchers are unaware of the treatment allocations. However, although ideal, this may be impossible, for example, when one of the treatments is counselling, and the other is a drug therapy [2].

5.2.2.10 Identifying Risk Factors

Some of the most commonly reported studies involve identifying risk factors for disease. It would be unethical to deliberately subject individuals to something that could be harmful, although instances have been known. There are thus two primary ways of assessing risk factors for various diseases: prospective cohort and retrospective case-control studies. In a prospective cohort study, a group of healthy individuals is monitored until they develop the disease under investigation. These tend to be long, large and therefore expensive studies, but they provide the

most reliable results. Case-control studies involve comparing subjects with the disease (cases) with individuals who do not have the disease (controls) but who are otherwise similar (e.g. same gender, age, co-morbidities etc.). These are shorter studies and less expensive but less reliable than prospective cohort studies [2].

5.2.2.11 Sample Size

Another question frequently asked is how many subjects are needed in a study. The sample size required for a study increases according to the variability of the data. Estimates of the likely variability of data can be obtained either from existing literature or by carrying out a pilot study that tests the feasibility of the main experiment and provides useful information about measures of centre and spread. Second, there is the effect size. This is a measure of the size and direction of the effect of a treatment (intervention). For continuous outcomes, this is usually expressed as a proportion of the standard deviation (SD) of the response: that is to say, it is calculated as (change in outcome with treatment, change in outcome with control) ÷ SD. This removes the effect of scale and allows comparisons to be made between different studies. When the outcome is binary (e.g. did the patient develop a hospital-acquired infection: Yes/No), one measure of effect size is the number of subjects who would need to be treated to prevent one outcome (e.g. the occurrence of one infection), and this is known as the 'number needed to treat'. Another measure of effect size in studies with binary outcomes is the odds ratio. This is the ratio of the odds of the outcome observed with one treatment divided by the odds observed with another, e.g. the odds of survival to 1 year with two regimes of chemotherapy in patients with pancreatic cancer. Provision should also be made for patients who drop out of the study [2].

5.2.2.12 Compliance

Compliance, or lack of it, is one of the hazards of clinical studies: patients do not always follow the instructions they are given. This is especially likely if the intervention is inconvenient or unpleasant. There are two approaches to the subsequent analysis of the data: per intention to treat (ITT) or per protocol (PP, sometimes referred to as modified ITT). In the former, data are analysed according to the stated intention (plan), and in the latter, patients who do not adhere to the protocol are omitted from the analysis [2].

5.2.2.13 Data Storage and Collection

Unless data are accurate, valid and reliable, the results of a medical research study will be unreliable. Security, including the protection of patient-identifiable data, is of critical importance when dealing with clinical information. Many institutions have a specialised unit that coordinates the collection, storage and management of research data, and this is the preferred option [2].

5.2.2.14 Analysis

Details of the analyses to be undertaken and the statistical tools to be used should be specified in the study plan [2].

References

1. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline. General considerations for clinical trials E8. Current Step 4 Version Dated 17 July 1997.

2. Cochrane LA, Puvaneswaralingam S. Clinical research for beginners – the importance of planning. Scottish Universities Med J. 2012;1(2):154–64.
3. Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin – converting – enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. N Engl J Med. 2001;344:1351–7.

Chapter 6
Preparation of Ethics Committee (IRB) Proposal

The ethics committee is responsible for reviewing a number of trial-related documents and giving their approval (or in some cases favourable opinion) before a study starts. Usually, the local IEC (or IRB in some countries) must be consulted [1].

6.1 ICH GCP Requirements for the Composition of the Ethics Committee (IRB)

- 'A reasonable number of members who collectively have the qualifications and experience to review and evaluate the science, medical aspects and ethics of the proposed trial'
- 'At least five members'
- 'At least one member whose primary interest is non-scientific (lay member)'
- 'At least one member who is independent of the trial site'

Only members who are independent of the investigator can vote or provide an opinion [1].

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At the time of writing, a new European Directive, if implemented, will control the constitution and working practices of ethics committees in Europe, similar to regulations in the USA. Until this time, investigators and sponsors have to deal with largely inefficient ethics committees, and the investigators should ensure that their local ethics committee fulfils the ICH GCP requirements [1].

6.2 What Documents Must Be Submitted to the Ethics Committee (IRB)?

Although there is currently a great diversity of documentation requested by ethics committees (IRBs), the ICH GCP guidelines are quite specific about the documents that need to be submitted. The investigator should make sure that final versions of the following documents are obtained from the sponsor and sent to the ethics committee (IRB) for review [1]:

- Trial protocol (and any amendments)
- Consent form and subject information sheets
- Subject recruitment procedures (e.g. advertisements)
- Investigator's brochure and any available safety information
- Information about payments and compensation available to subjects
- Investigator's current curriculum vitae
- Any other documents specifically requested by the ethics committee (IRB)

The investigator should never submit a draft document to the ethics committee (IRB) to speed up this rate-limiting step.

It is important to obtain a letter from the ethics committee (IRB) confirming that they have reviewed the above documents (adding the dates and versions seen) and have given their

approval or favourable opinion (or else reasons for disapproval). The letter should also give details about the date of the meeting and, if possible, a list of members who attended the meeting. This letter should be given to the trial monitor and a copy retained in the investigator's study file.

Many ethics committees (IRBs) fail to provide adequate documentation. To overcome this problem, it might be necessary to ask the sponsor to prepare a pro forma letter, which the ethics committee (IRB) can sign; this ensures that all necessary information has been included, and the appropriate GCP requirements have been fulfilled.

In some cases, the chairman of the ethics committee might inform the investigator that the study is acceptable and may be started. This is an unacceptable practice; ethics committee approval is valid only if a quorum of members has given approval, and their verdict has been received in writing [1].

6.3 Communication with an IRB/IEC

1. 'Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written ICFs, consent form updates, subject recruitment procedures (e.g. advertisements), and any other written information that is to be provided to subjects'.
2. 'As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the investigator's brochure. If the investigator's brochure is updated during the trial, the investigator/institution should supply a copy of the updated investigator's brochure to the IRB/IEC'.
3. 'During the trial the investigator/institution should provide to the IRB/IEC all documents subject to its review' [2, 3].

6.4 Compliance with Protocol

1. 'The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement'.
2. 'The investigator should not implement any deviation from, or changes to, the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change of monitor(s), change of telephone number(s))'.
3. 'The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol'.
4. 'The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it and, if appropriate, the proposed protocol amendment(s) should be submitted':

   (a) 'To the IRB/IEC for review and approval/favourable opinion'
   (b) 'To the sponsor for agreement and, if required'
   (c) 'To the regulatory authority(ies)' [2, 3]

References

1. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH, April 1996.
2. Hutchinson D. The Trial Investigator's GCP handbook: a practical guide to ICH requirements. Brookwood Medical Publications Ltd.; Surrey, UK, 1997.
3. ICH Harmonised Tripartite Guideline for good clinical practice. Second publication, Brookwood Medical Publications Ltd.; 1997.

Chapter 7
Preparation of Informed Consent

7.1 The Steps for Preparation of Informed Consent [1]

1. 'In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Before the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written ICF and any other written information that is to be provided to subjects'.
2. 'The written ICF and any other written information that is to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written ICF, and written information, should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to

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continue participation in the trial. The communication of this information should be documented'.

3. 'Neither the investigator nor the trial staff should coerce or unduly influence a subject to participate or to continue to participate in a trial'.
4. 'None of the oral and written information concerning the trial, including the written ICF, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence'.
5. 'The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information giving approval/favourable opinion by the IRB/IEC'.
6. 'The language used in the oral and written information about the trial, including the written ICF, should be as non-technical and as practical as possible, and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable'.
7. 'Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative'.
8. 'Prior to a subject's participation in a trial, the written ICF should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion'.

9. ‘If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written ICF and any other written information that is to be provided to subjects has been read and explained to the subject or the subject’s legally acceptable representative, and after the subject or the subject’s legally acceptable representative has orally consented to the subject’s participation in the trial, and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject’s legally acceptable representative, and that informed consent was freely given by the subject or the subject’s legally acceptable representative’.
10. ‘Both the informed consent discussion and the written ICF and any other written information that is to be provided to subjects should include explanations of the following’:

    (a) ‘That the trial involves research’.
    (b) ‘The purpose of the trial’.
    (c) ‘The trial treatment(s) and the probability for random assignment to each treatment’.
    (d) ‘The trial procedures to be followed, including all invasive procedures’.
    (e) ‘The subject’s responsibilities’.
    (f) ‘Those aspects of the trial that are experimental’.
    (g) ‘The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant’.
    (h) ‘The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this’.

(i) 'The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks'.
(j) 'The compensation and/or treatment available to the subject in the event of trial-related injury'.
(k) 'The anticipated prorated payment, if any, to the subject for participating in the trial'.
(l) 'The anticipated expenses, if any, provided to the subject for participating in the trial'.
(m) 'That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled'.
(n) 'That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that by signing a written ICF the subject or the subject's legally acceptable representative is authorising such access'.
(o) 'That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential'.
(p) 'That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial'.
(q) 'The person(s) to contact for further information regarding the trial and the rights of trial subjects, and who to contact in the event of trial-related injury'.

(r) 'The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated'.
(s) 'The expected duration of the subject's participation in the trial'.
(t) 'The approximate number of subjects involved in the trial'.

11. 'Before participation in a trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written ICF and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of signed and dated consent form updates and a copy of any amendments to the written information provided to subjects'.
12. 'When a clinical trial (therapeutic or nontherapeutic) includes subjects who can be enrolled in the trial only with the consent of the subject's legally acceptable representative (e.g. minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should assent, sign, and personally date the written informed consent'.
13. 'A nontherapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written ICF'.
14. 'Nontherapeutic trials may be conducted in subjects with the consent of a legally acceptable representative provided the following conditions are fulfilled':

(a) 'The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally'.

(b) 'The foreseeable risks to the subjects are low'.
(c) 'The negative impact on the subject's wellbeing is minimized and low'.
(d) 'The trial is not prohibited by law'.
(e) 'The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favourable opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed'.

15. 'In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When the prior consent of the subject is not possible, and the subject's legally acceptable representative is unavailable, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety, and well being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent, as appropriate, should be requested'.

7.2 Obtaining Informed Consent

Written informed consent has to be obtained from every subject who enters a trial, before any study-related procedures are undertaken.

Written informed consent should be obtained from each patient in accordance with regulatory requirements, GCP and the Declaration of Helsinki. Both the person taking consent and the patient should personally sign and date the consent form.

The investigator may screen age-sex registers or diagnostic indexes for suitable subjects without obtaining consent, but any screening involving the subject, even though it might be a routine procedure, will be considered to be study related if it is specified in the trial protocol.

A 20-point checklist for obtaining informed consent in accordance with ICH GCPs is shown in the checklist (Sect. 6.4). The subject should be given this information both verbally and in writing (subject information sheet). This list can be adapted as study relevant and used when obtaining the consent of study subjects. Use of the checklist is strongly recommended to ensure that all points are discussed with the subject.

The written information given to the subject should be in uncomplicated language, avoiding jargon and medical terminology. It should also be in the first language of the subject. It is often heard that the local ethics committee wishes the subject to receive only one sheet of paper. While this seems sensible in practice, it can be argued that informed consent has not been properly obtained if all the information listed in the checklist (Sect. 6.4) has not been presented [2].

7.3 Delegation of Consent Process

ICH GCPs allow the investigator to delegate the consent process to an appropriately qualified person, for example, a study nurse. However, to ensure that consent has been properly obtained, it is recommended that, if the study nurse has undertaken the consent

process, the investigator sees the subject shortly afterwards and ensures that the subject is fully informed. While it is commonly accepted that a nurse may be able to present the study to the subject at a more personable level, he/she might not be fully aware of the alternative treatments available to the subject or have a full understanding of the risks involved [2].

In studies involving children, it is necessary to obtain the consent of the parent or legal representative. Subjects who are mentally or physically incapable of giving informed consent (e.g. those with severe senile dementia or those who are unconscious) may enter trials by using a method of consent approved by the ethics committee (IRB) [2].

7.4 Checklist for Obtaining Informed Consent

- 'That the trial involves research'.
- 'The purpose of the trial'.
- 'The trial treatment(s) and the probability for random assignment to each treatment'.
- 'The trial procedures to be followed, including all invasive procedures'.
- 'The subject's responsibilities'.
- 'Those aspects of the trial that are experimental'.
- 'The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, foetus or nursing infant'.
- 'The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this'.
- 'The alternative procedure(s) or course(s) of treatment that may be available to the subject and their important potential benefits and risks'.

- 'The compensation and/or treatment available to the subject in the event of trial-related injury'.
- 'The anticipated pro-rated payment, if any, to the subject for participating in the trial'.
- 'That the subject's participation in the trial is voluntary and that the subject may refuse to participate or may withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled'.

'That the monitor(s), the auditor(s), the IRB/ethics committee, and the regulatory authority (ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written ICF, the subject or subject's legally acceptable representative is authorising such access'.

- 'That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential'.
- 'That the subject or subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial'.
- 'The person(s) to contact for further information regarding the trial and the rights of the trial subjects and who to contact in the event of trial-related injury'.
- 'The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated'.
- 'The expected duration of the subject's participation in the trial'.
- 'The approximate number of subjects involved in the trial'.

References

1. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH, April 1996.
2. Hutchinson D. The Trial Investigator's GCP handbook: a practical guide to ICH requirements. Brookwood Medical Publications Ltd.; Surrey, UK, 1997.

Chapter 8
Preparation of Findings Tables

Tables, figures and graphs help authors to present detailed results and complex relationships, patterns and trends clearly and concisely [1–4]; they also reduce the length of the manuscript and enhance readers' understanding of the study results. However, while well-presented tables and figures in research papers can efficiently capture and present information, poorly crafted tables and figures can confuse readers and impair the effectiveness of a paper [1].

8.1 Planning Your Paper: When to Use Tables and Figures

Producing effective tables and figures requires careful planning that begins at the manuscript-writing stage itself. Here's how to go about it:

- First, check out what your target journal has to say on the issue. Some journals limit the numbers of tables and figures and also have specific guidelines on the design aspects of these display items.

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- Next, decide whether to use tables, figures or texts to put across key information.
- After you have decided to use a display item, choose the display item that best fits your purpose, based on what you wish readers to focus on and what you want to present.

8.2 When to Choose Tables

- To show many and precise numerical values and other specific data in a small space [1]
- To compare and contrast data values or characteristics among related items [2] or items with several shared characteristics or variables [1]
- To show the presence or absence of specific characteristics [1]

8.3 Best Practices for Presentation of Tables and Figures

General guidelines [1]:

1. Ensure that display items are self-explanatory; some readers (and certainly reviewers and journal editors) turn their attention to the tables and figures before they read the entire text, so these display items should be self-contained.
2. Refer, but do not repeat; use the text to draw the reader's attention to the significance and key points of the table/figure, but do not repeat details.
4. Give clear, informative titles; table and figure titles should not be vague but should concisely describe the purpose or contents of the table/figure and should ideally draw the reader's attention to what you want him/her to notice (e.g. advantages and disadvantages of using sleep therapy with patients

suffering from schizophrenia). Also ensure that column headings, axis labels, figure labels, etc. are clearly and appropriately labelled.

5. Adhere to journal guidelines; check what your target journal has to say about issues like the numbers of tables and figures, the style of numbering, titles, image resolution, file formats, etc., and follow these instructions carefully.

Guidelines for tables [1]:

1. Combine repetitive tables; tables and figures that present repetitive information will impair communication rather than enhance it. Examine the titles of all your tables and figures and check whether they refer to the same or similar things; if they do, rethink the presentation and combine or delete the tables/graphs.
2. Divide the data; when presenting large amounts of information, divide the data into clear and appropriate categories and present them in columns titled accurately and descriptively.
3. Watch the extent of data in your tables; if the data you have to present are extensive and would make the tables too cluttered or long, consider making the tables a part of an appendix or supplemental material.
4. Declutter your table; ensure that there is sufficient spacing between columns and rows and that the layout does not make the table look too messy or crowded.

8.4 Completion of Record Forms in Research Facilities

The CRF is usually prepared by the sponsor of the study. When a subject is recruited to the study, they are allocated the next available study number, and this should be entered in the CRF

and against that subject's name on the study enrolment log. To preserve confidentiality, the subject's name should never be entered in the CRF or any other documentation that will be returned to the sponsor.

The investigator should ensure that the pages in the CRF are completed fully and legibly at every visit. The first instance and place where data are written down constitute source data, which have to be verifiable. Where possible, the results of assessments should be entered first into the subject file and then transcribed to the CRF. This ensures that data in the CRF can be verified during the process of source data verification when the monitor is required to check entries in the CRF against data in the subjects' files. For this reason, investigators should avoid the temptation to write the study data on sheets or scraps of paper or in notepads as this becomes the source data, and the regulatory authorities would expect this to be retained in addition to the CRFs.

There are strict rules for amending data in CRFs. It is important that only data collected by the investigator are analysed. If the sponsor was allowed to alter data in the CRF, this might lead to unreliable data being generated. An insistence that all changes in the CRF are signed and dated by the investigator (or approved coinvestigator) ensures that changes can be made only with the full knowledge and approval of the investigator.

This process might, at times, seem very tedious, but it is essential that the investigator takes all of the above steps; it is part of the study monitor's duties to look through the CRFs and ask the investigator to initial and date changes. When the reason for a change is not obvious, the investigator is required to write a reason in the CRF. One example might be if an entire page of the CRF is altered, which might happen if data were entered on the wrong page; the study monitor will point out to the investigator when it is necessary to give a reason [5].

References

1. Rodrigues V. Tips on effective use of tables and figures in research papers. http://www.editage.com/insights/tips-on-effective-use-of--tables-and-figures-in-research-papers. Accessed online at 15 Oct 2015.
2. Council of Science Editors. Journal style and format. In: Council of Science Editors, editor. Scientific style and format: the CSE manual for authors, editors, and publishers. 7th ed. Reston: Rockefeller University Press; 2006. p. 460.
3. American Psychological Association. APA editorial style. In: Publication manual of the American Psychological Association. 5th ed. Washington, DC: American Psychological Association; 2001. p. 147–201.
4. Durbin Jr CG. Effective use of tables and figures in abstracts, presentations, and papers. Respir Care. 2004;49(10):1233–7.
5. Hutchinson D. The Trial Investigator's GCP handbook: a practical guide to ICH requirements. Brookwood Medical Publications Ltd.; Surrey, UK, 1997.

Chapter 9
Setting the Ideal Statistical Methods

9.1 Introduction

The study design, sample size and statistical analysis must be able to properly evaluate the research hypothesis set forth by the clinical investigator. Otherwise, the consequences of a poorly developed statistical approach may result in a failure to obtain extramural funding and result in a flawed clinical study that cannot adequately test the desired hypotheses. Statisticians provide design advice and develop the statistical methods that best correspond to the research hypothesis [1].

9.2 Randomisation Plan

Random allocation of subjects to study groups is fundamental to the clinical trial design. Randomisation, which is a way to reduce bias, involves random allocation of the participants to the treatment groups. If investigators compare a new treatment

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against a standard treatment, the study subjects are allocated to one of these treatments by a random process. A general description of the randomisation approach may be introduced in the clinical method section of the proposal; for example, 'treatment assignment will be determined using stratified, blocked randomisation'. Specific randomisation details will need to be elaborated in the statistical method section, including how the allocation procedure will be implemented by, for example, computer programmes, a website, lists or sealed envelopes. If stratification is deemed necessary, include in the proposal a description of each stratification variable and the number of levels for each stratum, for instance, sex (male, female) or diabetes (type 1, type 2). However, keep the number of strata and stratum levels minimal [2].

9.3 Blinding

Knowledge of treatment assignment might influence how much of a dosage change is made to a study treatment or how an AE is assessed. Blinding or masking is another component of study design used to try to eliminate such bias [3]. In a double-blind randomised trial, neither the study subjects nor the clinical investigators know the treatment assignment. Describe the planned blinding scheme. For example, 'this is a double-blind randomised study to investigate the effect of propranolol versus no propranolol on the incidences of total mortality and of total mortality plus nonfatal myocardial infarction in 158 older patients with congestive heart failure [CHF] and prior myocardial infarction'. Specify who is to be blinded and the steps that will be taken to maintain the blinding. It is important that evaluators such as radiologists, pathologists or laboratory personnel who have no direct contact with the study subjects remain blinded to treatment assignments.

9.4 Sample Selection/Allocation Procedures

1. *Matching*: When confounding cannot be controlled by randomisation, individual cases are matched with individual controls who have similar confounding factors, such as age, to reduce the effect of the confounding factors on the association being investigated in analytical studies. This is most commonly seen in case-control studies.
2. *Restriction* (*specification*): Eligibility for entry into an analytical study is restricted to individuals within a certain range of values for a confounding factor, such as age, to reduce the effect of the confounding factor when it cannot be controlled by randomisation. Restriction limits the external validity (generalisability) to those with the same confounder values.
3. *Census*: A sample that includes every individual in a population or group (e.g. entire herd, all known cases). A census is not feasible when the group is large relative to the costs of obtaining information from individuals.
4. *Haphazard*, *convenience*, *volunteer*, *judgmental sampling*: Any sampling not involving a truly random mechanism. A hallmark of this form of sampling is that the probability that a given individual will be in the sample is unknown before sampling. The theoretical basis for statistical inference is lost and the result is inevitably biased in unknown ways. Despite their best intentions, humans cannot choose a sample in a random fashion without a formal randomising mechanism.
5. *Consecutive* (*quota*) *sampling*: Sampling individuals with a given characteristic as they are presented until enough with that characteristic are acquired. This method is possible for descriptive studies but unfortunately not much better than haphazard sampling for analytical observational studies.
6. *Random sampling*: Each individual in the group being sampled has a known probability of being included in the sample obtained from the group before the sampling occurs.

7. *Simple random sampling/allocation*: Sampling conducted such that each eligible individual in the population has the same chance of being selected or allocated to a group. This sampling procedure is the basis of the simpler statistical analysis procedures applied to sample data. Simple random sampling has the disadvantage of requiring a complete list of identified individuals making up the population (the list frame) before the sampling can be done.
8. *Stratified random sampling*: The group from which the sample is to be taken is first stratified on the basis of an important characteristic related to the problem at hand (e.g. age, parity, weight) into subgroups such that each individual in a subgroup has the same probability of being included in the sample, but the probabilities differ between the subgroups or strata. Stratified random sampling assures that the different categories of the characteristic that is the basis of the strata are sufficiently represented in the sample, but the resulting data must be analysed using more complicated statistical procedures (such as Mantel-Haenszel) in which the stratification is taken into account.
9. *Cluster sampling*: Staged sampling in which a random sample of natural groupings of individuals (houses, herds, kennels, households, stables) is selected and then all the individuals within the cluster are sampled. Cluster sampling requires special statistical methods for proper analysis of the data and is not advantageous if the individuals are highly correlated within a group (a strong herd effect).
10. *Systematic sampling*: From a random start in the first n individuals, sampling every nth subject/animal as they are presented at the sampling site (clinic, chute, etc.). Systematic sampling will not produce a random sample if a cyclical pattern is present in the important characteristics of the individuals as they are presented. Systematic sampling has the advantage of requiring only knowledge of the number of

subjects/animals in the population to establish n and that anyone presenting the subjects/animals is blind to the sequence so they cannot bias it [4].

9.5 Statistical Analysis Methodology

The statistical analysis methods for analysing study outcomes must be carefully detailed. Specifying these methods in advance is another way to minimise bias and maintain the integrity of the analysis. Any changes to the statistical methods must be justified and decided on before the blind is broken [5]. In the statistical analysis plan, not only must the statistical hypotheses to be tested be described and justified but which subjects and observations will be included or excluded in each analysis must also be detailed. The statistical analysis plan is driven by the research questions, the study design and the type of the outcome measurements. The analysis plan includes a detailed description of statistical testing for each of the variables in the specific aim(s). If several specific aims are proposed, an analysis plan should be written for each specific aim. Plan descriptive analyses for each group or planned subgroup. If subjects were randomly assigned to groups, there should be a description of subject characteristics that includes demographic information as well as baseline measurements or comorbid conditions. Specify anticipated data transformations that may be needed to meet analysis assumptions, and describe derived variables to be created such as area under the curve. Incorporate confidence intervals in the analysis plan for reporting treatment effects. Confidence limits are much more informative to the reader than are *P* values alone [6].

Statistical details and terminologies are not intended to be an obstacle for a young investigator. Instead, this is where a statistical expert can be a valuable resource to help the investigators use the

appropriate statistical methods and language that address the research hypotheses. Brief statistical analysis descriptions are written below.

9.5.1 Statistical Analysis Example for a Randomised Study

Statistical analysis. The full analysis set will include patients who have received at least one dose of medication or had one or more post randomisation, follow-up evaluations. Descriptive statistics will be computed for each treatment group; medians and percentiles will be reported for skewed continuous variables. For primary and secondary outcomes, descriptive statistics and 95 % confidence intervals will be used to summarise the differences between groups. The primary outcome of systolic blood pressure and other continuous variables will be assessed with a repeated-measures analysis using a mixed linear model approach. Because many of the inflammatory markers are positively skewed, interleukin 6 and C-reactive protein levels will be log transformed before analysis. The Wilcoxon rank sum test will be used to compare pill counts between groups. Hypothesis tests will be two sided using the 0.05 significance level. Bonferroni-type adjustments for multiple testing will be implemented to control type I errors. Statistical analysis will be performed using SAS software (SAS Institute, Cary, NC) [1].

9.5.2 Statistical Analysis Example for a Longitudinal Cohort Study

Descriptive/comparative statistics defines the biomarker levels in the different disease activity classes. We will compute and compare the mean/median and interquartile range of urine biomarker levels in different disease activity groups, after partitioning

patients in various ways: patients who attain any of the primary disease outcomes, i.e. World Health Organization class III or IV glomerulonephritis, patients with nephritic or nephrotic flares, or patients with end-stage renal disease. In addition, we will define the biomarker levels in patients with the following disease features: anaemia, leucopenia or thrombocytopenia. To compare multiple patient groups, analysis of variance (ANOVA) or the Kruskal-Wallis test will be used, depending on whether the biomarker values are normally distributed. Data transformations will be performed if necessary. If the omnibus ANOVA or Kruskal-Wallis test yields $P<0.05$, we will conduct pairwise group comparisons using either t tests or Wilcoxon rank sum tests with Bonferroni corrections. The generalised estimating equation approach will be used to evaluate whether urinary biomarkers vary significantly over time among different disease activity classes [1].

References

1. Adams-Huet B, Ahn C. Bridging clinical investigators and statisticians: writing the statistical methodology for a research proposal. J Investig Med. 2009;57(8):818–24. doi:10.2310/JIM.0b013e3181c2996c.
2. Pocock S. Clinical trials: a practical approach. New York: Wiley; 1983.
3. Day SJ, Altman DG. Statistics notes: blinding in clinical trials and other studies. BMJ. 2000;321:504.
4. Clinical Study Design and Methods Terminology. Clinical epidemiology & evidence-based medicine glossary. http://people.vetmed.wsu.edu/jmgay/courses/GlossClinStudy.htm. Accessed online at 16 Oct 2015.
5. International Conference on Harmonisation (ICH). Guidance for industry: E9 statistical principles for clinical trials. Rockville: Food and Drug Administration; 1998.
6. Altman D. Practical statistics for medical research. New York: Chapman & Hall/CRC; 1991.

Chapter 10
The Duties of a Clinical Research Coordinator

10.1 Introduction

Clinical trials are a team effort. It is essential that an investigator has colleagues who wish to assist with the trial. The 'principal investigator' is responsible for overseeing the trial and for the medical welfare of subjects who participate. A list of the usual responsibilities of the principal investigator is written below:

- Discuss, read and approve study protocol.
- Be familiar with all aspects of the trial and study drugs.
- Obtain ethics committee approval.
- Predict recruitment potential and identify suitable subjects.
- Undertake informed consent process (or supervise this, if delegated).
- Perform (or supervise) baseline and other trial-related assessments.
- Ensure that all other study personnel are kept fully informed at all times.
- Check that CRFs are being completed correctly.
- Sign off study documentation to confirm its validity.

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- Have regular meetings with trial monitor and other sponsor personnel.
- Take responsibility for the overall conduct of the study.
- Ensure that investigators' GCP responsibilities are fulfilled.

Coinvestigators might be needed to evaluate subjects at clinic visits. It should be kept in mind that the larger the number of assessors, the greater the variability; this means that the power of showing a difference between treatments is diminished.

Due to the large amount of administration and documentation generated during the course of a trial, it is recommended that a study administrator (e.g. a nurse coordinator or study site coordinator) is appointed to deal with these aspects [1].

10.2 Job Duties and Tasks of a Clinical Research Coordinator

1. Participate in the preparation and management of research budgets and monetary disbursements.
2. Inform patients or caregivers about study aspects and outcomes to be expected.
3. Code, evaluate or interpret collected study data.
4. Monitor study activities to ensure compliance with protocols and with all relevant local, federal and state regulatory and institutional polices.
5. Maintain required records of study activity including case report forms, drug dispensation records or regulatory forms.
6. Communicate with laboratories or investigators regarding laboratory findings.
7. Solicit industry-sponsored trials through contacts and professional organisations.
8. Order drugs or devices necessary for study completion.
9. Direct the requisition, collection, labelling, storage or shipment of specimens.

10. Arrange for research study sites and determine staff or equipment availability.
11. Review scientific literature, participate in continuing education activities or attend conferences and seminars to maintain current knowledge of clinical studies' affairs and issues.
12. Register protocol patients with appropriate statistical centres as required.
13. Prepare for, or participate in, quality assurance audits conducted by study sponsors, federal agencies or specially designated review groups.
14. Perform specific protocol procedures such as interviewing subjects, taking vital signs and performing electrocardiograms.
15. Interpret protocols and advise treating physicians on appropriate dosage modifications or treatment calculations based on patient characteristics.
16. Develop advertising and other informational materials to be used in subject recruitment.
17. Contact industry representatives to confirm the equipment and software specifications that are necessary for successful study completion.
18. Confer with healthcare professionals to determine the best recruitment practices for studies.
19. Organise space for study equipment and supplies.
20. Track enrolment status of subjects and document dropout information such as dropout causes and subject contact efforts.
21. Review proposed study protocols to evaluate factors such as sample collection processes, data management plans and potential subject risks.
22. Record adverse-event and side-effect data and confer with investigators regarding the reporting of events to oversight agencies.
23. Prepare study-related documentation such as protocol worksheets, procedural manuals, adverse-event reports, IRB documents and progress reports.

24. Participate in the development of study protocols including guidelines for administration or data collection procedures.
25. Oversee subject enrolment to ensure that informed consent is properly obtained and documented.
26. Maintain contact with sponsors to schedule and coordinate site visits or to answer questions about issues such as incomplete data.
27. Instruct research staff in scientific and procedural aspects of studies including standards of care, informed consent procedures or documentation procedures.
28. Identify protocol problems, inform investigators of problems or assist in problem-resolution efforts such as protocol revisions.
29. Dispense medical devices or drugs and calculate dosages and provide instructions as necessary.
30. Contact outside healthcare providers and communicate with subjects to obtain follow-up information.
31. Collaborate with investigators to prepare presentations or reports of clinical study procedures, results and conclusions.
32. Assess eligibility of potential subjects through methods such as screening interviews, reviews of medical records and discussions with physicians and nurses.
33. Schedule subjects for appointments, procedures or inpatient stays as required by study protocols [2].

10.3 Job Activities Associated with Being a Clinical Research Coordinator

1. *Getting information*: Observing, receiving and otherwise obtaining information from all relevant sources.
2. *Establishing and maintaining interpersonal relationships*: Developing constructive and cooperative working relationships with others and maintaining them over time.

3. *Making decisions and solving problems*: Analysing information and evaluating results to choose the best solution and solve problems.
4. *Organising*, *planning and prioritising work*: Developing specific goals and plans to prioritise, organise and accomplish your work.
5. *Updating and using relevant knowledge*: Keeping up to date technically and applying new knowledge to your job.
6. *Communicating with supervisors*, *peers or subordinates*: Providing information to supervisors, co-workers and subordinates by telephone, in written form, e-mail or in person.
7. *Documenting/recording information*: Entering, transcribing, recording, storing or maintaining information in written or electronic/magnetic form.
8. *Processing information*: Compiling, coding, categorising, calculating, tabulating, auditing or verifying information or data.
9. *Scheduling work and activities*: Scheduling events, programmes and activities, as well as the work of others.
10. *Interacting with computers*: Using computers and computer systems (including hardware and software) to programme, write software, set up functions, enter data or process information.
11. *Evaluating information to determine compliance with standards*: Using relevant information and individual judgment to determine whether events or processes comply with laws, regulations or standards.
12. *Identifying objects*, *actions and events*: Identifying information by categorising, estimating, recognising differences or similarities and detecting changes in circumstances or events.
13. *Communicating with persons outside the organisation*: Communicating with people outside the organisation, representing the organisation to customers, the public, government and other external sources. This information

can be exchanged in person, in writing or by telephone or e-mail.

14. *Training and teaching others*: Identifying the educational needs of others, developing formal educational or training programmes or classes and teaching or instructing others.
15. *Monitoring and controlling resources*: Monitoring and controlling resources and overseeing the spending of money.
16. *Coordinating the work and activities of others*: Getting members of a group to work together to accomplish tasks.
17. *Monitor processes*, *materials or surroundings*: Monitoring and reviewing information from materials, events or the environment, to detect or assess problems.
18. *Interpreting the meaning of information for others*: Translating or explaining what information means and how it can be used.
19. *Developing and building teams*: Encouraging and building mutual trust, respect and cooperation among team members.
20. *Guiding*, *directing and motivating subordinates*: Providing guidance and direction to subordinates, including setting performance standards and monitoring performance.
21. *Assisting and caring for others*: Providing personal assistance, medical attention, emotional support or other personal care to others such as co-workers, customers or patients.
22. *Resolving conflicts and negotiating with others*: Handling complaints, settling disputes and resolving grievances and conflicts or otherwise negotiating with others.
23. *Thinking creatively*: Developing, designing or creating new applications, ideas, relationships, systems or products including artistic contributions.
24. *Analysing data or information*: Identifying the underlying principles, reasons or facts of information by breaking down information or data into separate parts.

25. *Performing administrative activities*: Performing day-to-day administrative tasks such as maintaining information files and processing paperwork.
26. *Judging the qualities of things, services or people*: Assessing the value, importance or quality of things or people.
27. *Developing objectives and strategies*: Establishing long-range objectives and specifying the strategies and actions to achieve them.
28. *Estimating the quantifiable characteristics of products, events or information*: Estimating sizes, distances and quantities or determining the time, costs, resources or materials needed to perform a work activity.
29. *Provide consultation and advice to others*: Providing guidance and expert advice to management or other groups on technical-, system- or process-related topics [2].

10.4 Skills Needed for a Clinical Research Coordinator

1. *Reading comprehension*: Understanding written sentences and paragraphs in work-related documents.
2. *Active listening*: Giving full attention to what other people are saying, taking time to understand the points being made, asking questions as appropriate and not interrupting at inappropriate times.
3. *Writing*: Communicating effectively in writing as appropriate for the needs of the audience.
4. *Coordination*: Adjusting actions in relation to others' actions.
5. *Speaking*: Talking to others to convey information effectively.
6. *Critical thinking*: Using logic and reasoning to identify the strengths and weaknesses of alternative solutions, conclusions or approaches to problems.

7. *Monitoring*: Monitoring/assessing performance of yourself, other individuals or organisations to make improvements or take corrective action.
8. *Judgment and decision-making*: Considering the relative costs and benefits of potential actions to choose the most appropriate one.
9. *Time management*: Managing one's own time and the time of others.
10. *Management of personnel resources*: Motivating, developing and directing people as they work, identifying the best people for the job.
11. *Social perceptiveness*: Being aware of others' reactions and understanding why they react as they do.
12. *Complex problem-solving*: Identifying complex problems and reviewing related information to develop and evaluate options and implement solutions.
13. *Active learning*: Understanding the implications of new information for both current and future problem-solving and decision-making.
14. *Service orientation*: Actively looking for ways to help people.
15. *Persuasion*: Persuading others to change their minds or behaviour.
16. *Negotiation*: Bringing others together and trying to reconcile differences.
17. *Instructing*: Teaching others how to do something [2].

10.5 Abilities Needed to Be a Clinical Research Coordinator

1. *Written comprehension*: The ability to read and understand information and ideas presented in writing.
2. *Oral expression*: The ability to communicate information and ideas in speaking so others will understand.

3. *Oral comprehension*: The ability to listen to and understand information and ideas presented through spoken words and sentences.
4. *Written expression*: The ability to communicate information and ideas in writing so others will understand.
5. *Speech recognition*: The ability to identify and understand the speech of another person.
6. *Deductive reasoning*: The ability to apply general rules to specific problems to produce answers that make sense.
7. *Inductive reasoning*: The ability to combine pieces of information to form general rules or conclusions (includes finding a relationship among seemingly unrelated events).
8. *Problem sensitivity*: The ability to tell when something is wrong or is likely to go wrong. It does not involve solving the problem, only recognising there is a problem.
9. *Speech clarity*: The ability to speak clearly so others can understand you.
10. *Near vision*: The ability to see details at close range (within a few feet of the observer).
11. *Information ordering*: The ability to arrange things or actions in a certain order or pattern according to a specific rule or set of rules (e.g. patterns of numbers, letters, words, pictures, mathematical operations).
12. *Category flexibility*: The ability to generate or use different sets of rules for combining or grouping things in different ways.
13. *Selective attention*: The ability to concentrate on a task over a period of time without being distracted.
14. *Fluency of ideas*: The ability to come up with a number of ideas about a topic (the number of ideas is important, not their quality, correctness or creativity).
15. *Originality*: The ability to come up with unusual or clever ideas about a given topic or situation or to develop creative ways to solve a problem [2].

10.6 Knowledge, Experience and Education Required to Be a Clinical Research Coordinator

1. *Medicine and dentistry*: Knowledge of the information and techniques needed to diagnose and treat human injuries, diseases and deformities. This includes symptoms, treatment alternatives, drug properties and interactions and preventive healthcare measures.
2. *English language*: Knowledge of the structure and content of the English language including the meaning and spelling of words, rules of composition and grammar.
3. *Administration and management*: Knowledge of the business and management principles involved in strategic planning, resource allocation, human resources modelling, leadership techniques, production methods and coordination of people and resources.

References

1. Hutchinson D. The Trial Investigator's GCP handbook: a practical guide to ICH requirements. Brookwood Medical Publications Ltd.; Surrey, UK, 1997.
2. Clinical Research Coordinator. http://job-descriptions.careerplanner.com/Clinical-Research-Coordinator.cfm. Accessed online at 14 Oct 2015.

Chapter 11
The Duties of Clinical Researchers

A clinical investigator involved in a clinical trial is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan and the applicable regulations; for protecting the rights, safety and welfare of subjects under the investigator's care; and for the control of drugs under investigation. The clinical investigator must also meet the requirements set out by the FDA, European Medicines Agency (EMA) or other regulatory bodies. The qualifications must be outlined in a current resume and readily available for auditors [1].

Clinical investigators face challenges during the conduct of clinical trials that are distinctly different from those encountered during the routine practice of medicine. Many of these challenges stem from regulatory requirements, the Guidelines for Good Clinical Practice (GCP) and the rigorous nature of clinical trials. When conducting a clinical trial, it is important that clinical investigators successfully meet all research expectations [2]. A clinical investigator's primary responsibility is to conduct research that contributes to generalisable knowledge while protecting the rights and welfare of human participants [3].

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11.1 Conducting Ethical Research

It is important to conduct research in an ethical manner. Investigators must be diligent throughout all stages while conducting a clinical trial, which include the steps of designing the protocol and deciding which trials to conduct, as well as during the performance of the study and after the conclusion of the study. Although there are multiple regulatory safeguards designed to ensure the ethical conduct of research, it is ultimately the investigator's responsibility to ensure that the research is fair and equitable to study participants. When the investigator is also the sponsor of the study, then responsibilities also include protocol design [3].

The majority of investigators respect the importance of conducting ethical research, but even the most cognisant investigators may encounter unexpected challenges. For example, an ethical dilemma can arise when the control arm of a trial does not correlate with the standard treatment typically prescribed by the physician. Issues like this need to be discussed during trial design and considered as part of the decision to implement new trials at the site. Clinical investigators need to review the protocol in detail and understand the primary end point of every study they oversee. This practice prevents inadvertent issues arising that can affect patient safety and/or the scientific integrity of the study. For example, if a study is designed to provide adjuvant treatment to patients, but the investigator is slow to identify the first signs of relapse, then the quality of the science suffers and can, potentially, affect approval of the agent by the FDA. Understanding the research protocol and investigator's brochure [4] helps to prevent potential issues [3].

11.2 Informed Consent Process

Informed consent is a process that extends beyond a patient simply signing a consent form. Clinical research requires that individuals be fully informed about the study they are being offered.

Throughout the informedconsent process, potential research participants should be given the opportunity to learn about the research study and have all their questions answered.

According to the Belmont Report [3], individuals must be given the opportunity to make informed choices with regard to how they will be treated and what interventions they will participate in. Potential participants should be informed about the risks, anticipated benefits and any alternative treatment options they have, including hospice care. An appropriate informed consent process needs to be conducted by a qualified individual who understands the clinical trial protocol and has knowledge about the potential benefits and adverse effects of the therapeutic agent under investigation [3].

If the investigation is a randomised, controlled clinical trial, research staff must alert potential participants to the concept of randomisation. The potential participant must also be informed about the treatment that will be given to individuals who are randomly assigned to the control arm of the trial. They should be told that neither they nor their provider can control which arm of the trial they are randomised to. Patient-oriented educational materials about clinical trials are available, free of charge, on ASCO's patient education website,www.cancer.net [5].

11.3 Statement of Investigator

In the USA, when conducting clinical research with an investigational agent, such as a drug or a biologic, an investigator must comply with all applicable FDA rules and regulations. An investigator must also complete the Statement of Investigator (FDA Form 1572) before participating in an FDA-regulated investigation [6]. FDA Form 1572 is a legally binding document designed to inform clinical investigators of their research obligations and secure the investigators' commitment to follow pertinent FDA regulations. By signing this form, the investigator confirms that they will abide by all FDA regulations [3].

11.4 Reporting Adverse Events

It is required to document all AEs that occur during the course of a clinical investigation. Keeping a log of AEs is a helpful organisational tool, and such logs should be reviewed during regularly scheduled research team meetings. It is important that a principal investigator be aware of AEs because an event may trigger the need for a dose adjustment. Serious or unanticipated events should be addressed immediately and may require meeting outside regularly scheduled team meetings [3].

11.5 Maintaining Accurate Records

The importance of maintaining accurate records when conducting clinical research cannot be overstated. It is important that all collected data match the information found in source documents, such as a pathology report or the patient's medical record. In addition, issues such as protocol deviations must be well documented. A situation that occurs today may not be reviewed or questioned until months or years in the future. It is almost impossible to recall particular study conduct events during an audit unless they have been well documented [3].

As with many investigator responsibilities, an investigator is permitted to delegate tasks associated with data collection and documentation to a qualified individual. However, it is important that the investigator knows that this individual will appropriately conduct the delegated tasks. One way to ensure clear communication between an investigator and staff is to use a delegation log, which is a signed record of which study tasks have been assigned to which individual. It is important that the investigator be available to the staff to answer questions and make decisions [3].

11.6 Steps to Becoming a Clinical Trial Investigator

Being involved in clinical trials enables physicians to learn, become exposed to new medical therapies and provide additional options or alternative treatments for their patients. The following steps are an overview of the process for professionals interested in conducting clinical trials [7]:

1. *Learn about regulations.* Before becoming involved in clinical research, physicians should have a thorough understanding of the various regulations related to the field. That will help them to ensure that their study sites are in, and remain in, compliance. In the USA, physicians conducting clinical trials should be familiar with parts *50*, *54*, *56* and *312* of the Code of Federal Regulations (CFR) Title 21. These regulations define what is required by the US FDA. Other countries have their own requirements.

   Those who want to conduct trials should know about GCP, which refers to the principles and processes investigators are expected to follow. Compliance with GCP ensures that the rights, well-being and confidentiality of study subjects are protected. It also assures the collection of reliable data for submissions to regulatory agencies.
2. *Establish the needed infrastructure.* Many physicians plan to integrate clinical research space into their existing practices. To accommodate the conduct of clinical trials, they have to think about drug storage, archive space and equipment, as well as providing workspace for clinical research associates.

   Also, the practice will need a clinical research coordinator, who will handle the management and documentation of the trial.
3. *Search for clinical trials.* Many physicians browse helpful websites, such as CenterWatch.com and ClinicalTrials.gov,

while others contact drug companies whose products they prescribe. A physician can also submit his or her contact information into an online database of potential investigators. Many contract research organisations (CROs), including PPD (define acronym, or, better, replace with full term as this acronym does not appear again), recruit clinical trial investigators this way.

4. *Complete needed forms.* Once a physician has been identified as a potential investigator, he or she is required to complete several forms. These forms are required documentation needed to register the physician as a clinical trial investigator and to track and evaluate the ethical and procedural conduct of trials.

   Required documents for an IND trial in the USA include a confidential disclosure agreement; Form FDA 1572; a protocol, amendment and signature page; an investigational drug brochure; curriculum vitae for the principal investigator and sub-investigators; an IRB/IEC approval letter and roster; laboratory certifications and normal ranges; and the principal investigator's financial disclosure statement.
5. *Prepare for a pre-study visit.* As part of the qualification process for a newly awarded study, each potential study site will be visited by a CRA to evaluate the investigator's experience, expertise and interest, as well as his or her staff, facility and potential patient population available for the trial. This visit is called a pre-study site visit. There are also several other items the CRA might want to discuss during the visit, including whether the physician is engaged in competing studies at the same time.
6. *Receive IRB approval.* An IRB or an IEC is a group designated to protect the rights, safety and well-being of patients involved in a clinical trial. They do that by reviewing all aspects of the trial and approving its startup. An IRB or IEC must give approval before any clinical trial can begin and then keep close tabs on the progress of the research.

7. *Sign the contract.* Before the clinical trial starts, the investigator and the sponsor or a CRO needs to sign a contract. This usually lists the investigator's responsibilities, including the number of subjects he or she is expected to enrol, timelines for enrolment and the regulatory requirements. It also includes the sponsor's responsibilities.
8. *Get Ready for a site initiation visit.* A CRA will conduct a site initiation visit after the IRB or IEC has given its approval, and the contract and all essential documents have been completed. The purpose of this visit is to ensure that everything is in place for the investigator to begin enrolling patients.
9. *Enrol first patients.* An investigator or his or her staff is normally responsible for recruiting patients, scheduling their visits, retaining them and making sure they are compliant with the protocol throughout the trial.
10. *Take advantage of the opportunity.* A clinical investigator's role is crucial in the development and advancement of drugs, therapies and medical devices. However, investigators also gain multiple advantages, including the opportunity to learn new skills and explore new challenges.

References

1. Clinical investigator. Wikipedia. https://en.wikipedia.org/wiki/Clinical_investigator. Accessed online at 15 Oct 2015.
2. Baer AR, Devine S, Beardmore CD, Catalano R. Clinical investigator responsibilities. J Oncol Pract. 2011;7(2):124–8.
3. International Conference on Harmonisation, Good Clinical Practice (ICH GCP). 1.34 Investigator. http://ichgcp.net/?page_id=377.
4. International Conference on Harmonization, Good Clinical Practice (ICH GCP). 1.36 investigator's brochure. http://ichgcp.net/?page_id=381.

5. Cancer.Net.Clinical Trials. www.cancer.net/clinicaltrials.
6. US Food and Drug Administration. Statement of investigator (Title 21, Code of Federal Regulations Part 312). http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf.
7. Steps to Become a Clinical Trial Investigator. http://www.ppdi.com/Participate-In-Clinical-Trials/Become-an-Investigator/Process. Accessed online at 15 Oct 2015.

Chapter 12
The Phases of Clinical Studies

12.1 Introduction

The phases of clinical research are the steps of scientists' experiments during a health intervention in an attempt to find enough evidence for a process that would be useful as a medical treatment. In the case of a pharmaceutical study, the phases start with drug design and drug discovery, go on to animal testing, then start by testing in only a few human subjects and expand to test in many more study participants if the trial seems safe and useful [1].

Clinical trials involving new drugs are commonly classified into four phases. Clinical trials of drugs may not fit into a single phase. For example, some may blend from phase I to phase II or from phase II to phase III. Therefore, it may be easier to think of early-phase studies and late-phase studies [2]. The drug development process will normally proceed through all four phases over many years. If the drug successfully passes through phases I, II and III, it will usually be approved by the national regulatory authority for use in the general population. Phase-IV studies are 'post-approval' [1].

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12.2 Preclinical Studies

Before pharmaceutical companies start clinical trials on a drug, they conduct extensive preclinical studies. These involve in vitro (test tube or cell culture) and in vivo (animal) experiments using wide-ranging doses of the study drug to obtain preliminary efficacy, toxicity and pharmacokinetic information. Such tests assist pharmaceutical companies to decide whether a drug candidate has scientific merit for further development as an investigational new drug [1].

12.3 Phase 0

Phase-0 trials are the first clinical trials among people. They aim to learn how a drug is processed in the body and how it affects the body. In these trials, a very small dose of a drug is given to about 10–15 people [3].

'Phase 0 trials are also known as human micro dosing studies and are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as expected from preclinical studies. Distinctive features of phase-0 trials include the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (what the body does to the drugs)' [4].

A phase-0 study gives no data on safety or efficacy being, by definition, a dose too low to cause any therapeutic effect. Drug development companies carry out phase-0 studies to rank drug candidates to take forwards into further development on the basis of which has the best pharmacokinetic parameters in humans. They enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data [1].

12.4 Phase I

Phase-I trials aim to find the best dose of a new drug with the fewest side effects. The drug will be tested in a small group of 15–30 patients. Doctors start by giving very low doses of the drug to a few patients. Higher doses are given to other patients until side effects become too severe or the desired effect is seen. The drug may help patients, but phase-I trials are to test a drug's safety. If a drug is found to be safe enough, it can be tested in a phase-II clinical trial [3].

Initial Safety Trials on a New Medicine 'An attempt is made to establish the dose range tolerated by volunteers for single and multiple doses. Phase-I trials are sometimes conducted in severely ill patients (e.g. in the field of cancer) or in less ill patients when pharmacokinetic issues are addressed (e.g. metabolism of a new antiepileptic medicine in stable epileptic patients whose microsomal liver enzymes have been induced by other antiepileptic medicines). Pharmacokinetic trials are usually considered phase-I trials regardless of when they are conducted during a medicine's development' [5, 6].

Phase-I trials are the first stage of testing in human subjects. Normally, a small group of 20–100 healthy volunteers will be recruited. This phase is designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics and pharmacodynamics of a drug. These trials are often conducted in a clinical trial clinic, where the subject can be observed by full-time staff. These clinical trial clinics are often run by contract research organisations (CROs), who conduct these studies on behalf of pharmaceutical companies or other research investigators. The subject who receives the drug is usually observed until several half-lives of the drug have passed. Phase-I trials also normally include dose ranging, also called dose-escalation studies, so that the best and safest dose can be found and to discover the point at which a compound is too poisonous to administer [7].

Phase Ia (Single Ascending Dose) In single ascending dose studies, small groups of subjects are given a single dose of the drug, while they are observed and tested for a period to confirm safety [1, 8] Typically, a small number of participants, usually three, are entered sequentially at a particular dose [2]. If they do not exhibit any adverse side effects, and the pharmacokinetic data are roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. If unacceptable toxicity is observed in any of the three participants, an additional number of participants, usually three, are treated at the same dose [1, 2].

Phase Ib (Multiple Ascending Dose) Multiple ascending dose studies investigate the pharmacokinetics and pharmacodynamics of multiple doses of a drug, looking at safety and tolerability. In these studies, a group of patients receives multiple low doses of the drug, while samples (of blood and other fluids) are collected at various time points and analysed to acquire information on how the drug is processed within the body. The dose is subsequently escalated for further groups, up to a predetermined level [1, 8].

12.5 Phase II

Phase-II trials further assess safety as well as whether a drug works. The drug is often tested among patients with a specific type of cancer. Phase-II trials are performed in larger groups of patients compared to phase-I trials. Often, new combinations of drugs are tested. Patients are closely watched to see if the drug works. However, the new drug is rarely compared to the current (standard-of-care) drug that is used. If a drug is found to work, it can be tested in a phase-III clinical trial [3].

Once a dose or range of doses has been determined, the next goal is to evaluate whether the drug has any biological activity or effect [2]. Phase-II trials are performed on larger groups

(100–300) and are designed to assess how well the drug works, as well as to continue phase-I safety assessments in a larger group of volunteers and patients. Genetic testing is common, particularly when there is evidence of variation in metabolic rates [2]. When the development process for a new drug fails, this usually occurs during phase-II trials, when the drug is discovered not to work as planned or to have toxic effects [1].

'Phase-II studies are sometimes divided into phase IIA and phase IIB' [1].

- 'Phase IIA is specifically designed to assess dosing requirements (how much drug should be given)'.
- 'Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose(s))'.

Some trials combine phase I and phase II and test both efficacy and toxicity [1].

Phase IIa 'Pilot clinical trials to evaluate efficacy (and safety) in selected populations of patients with the disease or condition to be treated, diagnosed, or prevented. Objectives may focus on dose–response, type of patient, frequency of dosing, or numerous other characteristics of safety and efficacy' [5, 6].

Phase IIb 'Well-controlled trials to evaluate efficacy (and safety) in patients with the disease or condition to be treated, diagnosed, or prevented. These clinical trials usually represent the most rigorous demonstration of a medicine's efficacy. Sometimes referred to as pivotal trials' [5, 6].

12.6 Phase III

This phase is designed to assess the effectiveness of a new intervention and, thereby, its value in clinical practice [1, 2]. 'Phase-III studies are randomised controlled multicenter trials on large patient

groups (300–3000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective a drug is, in comparison with the current "gold standard" treatment. Because of their size and comparatively long duration, phase-III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions'. Phase-III trials of chronic conditions or diseases often have a short follow-up period for evaluation, relative to the period of time the intervention might be used in practice [2]. This is sometimes called the 'premarketing phase' because it actually measures consumer response to the drug [1].

Phase-III trials compare a new drug to the standard-of-care drug. These trials assess the side effects of each drug and which drug works better. Phase-III trials enrol 100 or more patients.

Often, these trials are randomised. This means that patients are put into a treatment group, called trial arms, by chance. Randomisation is needed to make sure that the people in all trial arms are alike. This lets scientists know that the results of the clinical trial are due to the treatment and not to differences between the groups. A computer programme is often used to randomly assign people to the trial arms [3].

There can be more than two treatment groups in phase-III trials. The control group gets the standard-of-care treatment. The other groups get a new treatment. Neither a patient nor the patient's doctor can choose the group. The patient will also not know which group he/she is in until the trial is over.

Every patient in a phase-III study is watched closely. The study will be stopped early if the side effects of the new drug are too severe or if one group has much better results. Phase-III clinical trials are often needed before the FDA will approve the use of a new drug for the general public [3].

Phase IIIa Trials conducted after the efficacy of a medicine is demonstrated, but prior to regulatory submission of an NDA or other dossiers. These clinical trials are conducted in patient

populations for whom the medicine is eventually intended. Phase-IIIa clinical trials generate additional data on both safety and efficacy in relatively large numbers of patients in both controlled and uncontrolled trials. Clinical trials are also conducted in special groups of patients (e.g. renal failure patients) or under special conditions dictated by the nature of the medicine and the disease. These trials often provide much of the information needed for the package insert and labelling of the medicine [5, 6].

Phase IIIb Clinical trials conducted after regulatory submission of an NDA or other dossier, but prior to the medicine's approval and launch. These trials may supplement earlier trials, may complete earlier trials or may be directed towards new types of trials (e.g. quality of life, marketing) or phase-IV evaluations. This is the period between submission and approval of a regulatory dossier for marketing authorisation [3, 5].

12.7 Phase IV

'A phase-IV trial is also known as a postmarketing surveillance trial. Phase-IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold (e.g. after approval under the FDA Accelerated Approval Program). Phase-IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer period than was possible during the phase-I to phase-III clinical trials' [1].

Phase-IV trials test new drugs approved by the FDA. The drug is tested in several hundreds or thousands of patients. This allows for better research on short-lived and long-lasting side effects and safety. For instance, some rare side effects may be found only in large groups of people. Doctors can also learn more about how well the drug works and whether it is helpful when used with other treatments [3].

Studies or Trials Conducted After a Medicine is Marketed to Provide Additional Details About the Medicine's Efficacy or Safety Profile Different formulations, dosages, durations of treatment, medicine interactions and other medicine comparisons may be evaluated. New age groups, races and other types of patients can be studied. Detection and definition of previously unknown or inadequately quantified adverse reactions and related risk factors are an important aspect of many phase-IV studies. If a marketed medicine is to be evaluated for another (i.e. new) indication, then those clinical trials are considered phase-II clinical trials. The term postmarketing surveillance is frequently used to describe those clinical studies in phase IV (i.e. the period following marketing) that are primarily observational or non-experimental in nature, to distinguish them from well-controlled phase-IV clinical trials or marketing studies [5, 6].

12.8 Summary of Clinical Trial Phases

Preclinical

Primary goal: Testing of a drug in non-human subjects, to gather efficacy, toxicity and pharmacokinetic information

Dose: Unrestricted

Patient monitor: A graduate-level researcher (Ph.D.)

Typical number of participants: Not applicable (in vitro and in vivo only) [1]

Phase 0
Primary goal: Pharmacodynamics and pharmacokinetics, particularly oral bioavailability and half-life of the drug
Dose: Very small, subtherapeutic
Patient monitor: Clinical researcher
Typical number of participants: Ten people
Notes: Often skipped for phase I [1]

Phase I
Primary goal: Testing of drug on healthy volunteers for dose ranging
Dose: Often subtherapeutic, but with ascending doses
Patient monitor: Clinical researcher
Typical number of participants: 20–100 people
Notes: Determines whether a drug is safe to check for efficacy [1]

Phase II
Primary goal: Testing of a drug on patients to assess efficacy and safety
Dose: Therapeutic dose
Patient monitor: Clinical researcher
Typical number of participants: 100–300 people
Notes: Determines whether a drug can have any efficacy; at this point, the drug is not presumed to have any therapeutic effect whatsoever [1].

Phase III
Primary goal: Testing of a drug on patients to assess efficacy, effectiveness and safety
Dose: Therapeutic dose

Patient monitor: Clinical researcher and personal physician

Typical number of participants: 1000–2000 people

Notes: Determines a drug's therapeutic effect; at this point, the drug is presumed to have some effect [1]

Phase VI

Primary goal: Postmarketing surveillance – watching drug use among the public

Dose: Therapeutic dose

Patient monitor: Personal physician

Typical number of participants: Anyone seeking treatment from their physician

Notes: To watch drug's long-term effects [1]

References

1. Phases of clinical research. Wikipedia. https://en.wikipedia.org/wiki/Phases_of_clinical_research. Accessed online at 15 Oct 2015.
2. DeMets D, Friedman L, Furberg C. Fundamentals of clinical trials. 4th ed. New York: Springer; 2010. ISBN 978-1-4419-1585-6.
3. Phases of clinical trials. http://www.nccn.org/patients/resources/clinical_trials/phases.aspx. Accessed online at 15 Oct 2015.
4. No authors listed. Phase 0 trials: a platform for drug development? Lancet. 2009;374(9685):176.
5. Spilker B. Guide to clinical trials. New York: Raven Press; 1984. p. XXii–Xxiii.
6. Phases of clinical trials. http://www.virginia.edu/vpr/irb/HSR_docs/CLINICAL_TRIALS_Phases.pdf. Accessed online at 15 Oct 2015.
7. Shamoo AE. The myth of equipoise in phase 1 clinical trials. Medscape J Med. 2008;10(11):254.
8. Norfleet E, Gad SC. Phase I clinical trials. In: Gad SC, editor. Clinical trials handbook. Hoboken: Wiley; 2009. p. 247. ISBN 978-0-470-46635-3.

Chapter 13
Safety in Clinical Trials

13.1 Introduction

The responsibility for the safety of the subjects in a clinical trial is shared between the sponsor, the local site investigators (if different from the sponsor), the various IRBs that supervise the study and (in some cases, if the study involves a marketable drug or device) the regulatory agency for the country where the drug or device will be sold [1].

For safety reasons, many clinical trials of drugs are designed to exclude women of childbearing age, pregnant women and/or women who become pregnant during the study. In some cases, the male partners of these women are also excluded or required to take birth control measures [1].

"Clinical trials provide the evidentiary basis for regulatory approvals of safe and effective medicines. With long development cycles and ever-increasing costs in conducting clinical trials, both the pharmaceutical industry and regulators are making efforts to be more proactive in safety evaluations. Early safety signal detection not only leads to better patient protection but also has the potential to save development costs" [2].

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'Safety evaluation is a central component at all stages of the drug development lifecycle. Prior to the marketing authorisation of a drug, rigorous safety monitoring and evaluations from preclinical to all stages of clinical trials are required. Pharmaceutical sponsors need to characterize the safety profile of the product adequately to obtain regulatory approval and marketing authorisation. The approved product label contains essential information about the product's benefits and risks. Continued vigilance regarding safety is critical as more data and experience are gathered from a broader patient population once the product is on the market' [3–5].

13.2 Safety Monitoring

13.2.1 Sponsor

'Clinical trial sponsors, usually pharmaceutical companies, are responsible for developing the clinical trial protocol. The protocol describes every aspect of the research, including the rationale for the experiment, objectives, trial population with detailed inclusion and exclusion criteria, administration of the investigational therapies, trial procedures, data collection standards, endpoints and sample size. The protocol also details the safety reporting procedures, specifically the requirements for expedited reporting of serious AEs. The informed consent form (ICF) is used to disclose current information about the investigational drug and about the procedures, risks and benefits for subjects who participate in the clinical trial. Informed consent is a vital part of the research process' [2].

13.2.2 Subjects

'Subjects are patients or healthy volunteers who agree to participate in a clinical trial and have signed the ICF. Along with other

information, the ICF provides important safety information so that subjects can make an informed decision on whether to participate in the trial. The informed consent must be given freely, without coercion, and must be based on a clear understanding of what participation involves. By giving consent, subjects permit the investigators to collect health information and body measurements as per the protocol. While subjects are encouraged to follow the protocol to trial completion, they can withdraw at any time. They do not need to give a reason for withdrawing consent. In a phase-1 clinical trial, when the drug is first used in humans, healthy volunteers are compensated for their time and willingness to be exposed to unknown risks. Later-phase trials are mostly conducted in patients with the disease of interest, and payments to these subjects for participation are contentious. The main concern is that the payment could be coercive or serve as undue inducement leading to impaired judgment in relation to trial participation' [6].

13.2.3 Investigators

'Investigators are qualified individuals who are trained and experienced in providing medical care to subjects enrolled in the trial. Investigators identify potential subjects and educate them about trial participation to ensure that they can make an informed decision. While the trial is ongoing, investigators are expected to adhere to the protocol treatment plan in delivering care. They observe, evaluate, manage and document all effects of treatment, including the reporting of AEs. Investigators are ultimately accountable and responsible for the conduct of the clinical trial and for the safety of the subjects under their care' [2]

13.2.4 Institutional Review Board/Ethics Committee

'The IRB, also known as the ethics committee, is charged with protecting the rights and welfare of human subjects recruited to

participate in research protocols conducted under the auspices of the institution to which the IRB is affiliated' [2]

13.2.5 Data and Safety Monitoring Board

'The data and safety monitoring board (DSMB), also called a DMC, is an expert committee, independent of the sponsor, chartered for one or more clinical trials. The mandate of the DSMB is to review, on a regular basis, the accumulating data from the clinical trial to ensure the continuing safety of current participants and those yet to be enrolled. The DSMB may review efficacy data at pre-defined interim points to assess whether there is overwhelming evidence of efficacy or a lack thereof, such that the clinical equipoise at the beginning of the trial is no longer justified. The DSMB has the additional responsibility of advising the sponsor regarding the continuing validity and scientific merit of the trial. Not all clinical trials require a formal DSMB. DSMBs are most common in double blind randomised phase-3 trials. Members of the DSMB typically include clinical trial experts, including physicians with the appropriate specialty, at least one biostatistician and possibly a person(s) from other disciplines, such as biomedical ethics, basic science/pharmacology or law' [2].

The DSMB is an independent group of doctors, medical ethicists, statisticians and other health professionals who monitor a clinical trial for safety and scientific relevance throughout the study period. For example, if a new treatment is causing many patients to drop out of the study because of severe side effects, the DSMB may recommend stopping the study. Alternatively, sometimes a new treatment works so well that it is unethical to continue to give it to one group of patients and not the other. In this case, the DSMB may recommend stopping the standard treatment and offering the new treatment to all participants in the study. A DSMB is especially useful for large clinical trials

that are taking place in many locations because they review all of the data accumulated from all clinical trial sites [2]. A DSMB is separate from an IRB. The IRB usually looks at the clinical trial before it starts. The DSMB reviews the study after it starts and makes recommendations to the IRB about stopping or continuing the study [7].

13.2.6 Regulatory Authorities

'In the US, before the initiation of a first-in-human clinical trial, pharmaceutical sponsors must submit an IND application to the FDA as required by law. The FDA reviews the IND (typically within 30 calendar days) for safety to ensure that research subjects will not be subjected to unreasonable risk. In 2010, the FDA issued guidance to sponsors and investigators on safety reporting requirements for human drug and biological products that are being investigated under an IND and for drugs that are the subjects of bioavailability (BA) and bioequivalence (BE) studies, which are exempt from the IND requirements [8]. The guidance provided the agency's expectations for timely review, evaluation and submission of relevant and useful safety information and implemented internationally harmonised definitions and reporting standards. The EMA is the European Union's FDA equivalent. The agency has several scientific committees that carry out the evaluation of applications from pharmaceutical companies. In other parts of the world, regulatory authorities will have similar mandates, but may operate under different local laws and regulations' [2].

13.2.7 Medical Community and Patients

'Clinical trials generate data that contribute to the body of knowledge about the treatment and the disease in question that

benefit the broader medical community and, ultimately, patients. Safety information relating to one product may be informative to other practitioners using a similar class of agents. In 1997, the US Congress passed the Food and Drug Modernization Act (FDAMA), requiring clinical trial registration' [2].

References

1. Clinical trial. Wikipedia. https://en.wikipedia.org/wiki/Clinical_trial. Accessed online at 15 Oct 2015.
2. Yao Bi Zhu L, Jiang Q, Xia HA. Safety monitoring in clinical trials. Pharmaceutics. 2013;5:94–106.
3. United States Food and Drug Administration. Guidance for industry, premarketing risk assessment, 2005. Available online: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126958.pdf. Accessed 9 Oct 2012.
4. Food and Drug Administration (FDA). Guidance for industry, development and use of risk minimization action plans, 2005. Available online: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126830.pdf. Accessed 9 Oct 2012.
5. Food and Drug Administration (FDA). Guidance for industry, good pharmacovigilance practices and pharmacoepidemiologic assessment, 2005. Available online: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf. Accessed 9 Oct 2012.
6. Grady C. Payment of clinical research subjects. J Clin Invest. 2005;115:1681–7.
7. Patient Safety and Informed Consent. http://www.cancer.net/navigating-cancer-care/how-cancer-treated/clinical-trials/patient-safety-and-informed-consent. Accessed online at 15 Oct 2015.
8. Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for industry and investigators: safety reporting requirements for INDs and BA/BE studies, 2010. Available online: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf. Accessed 9 Oct 2012.

Chapter 14
Setting the Size

14.1 Sample Size

The most important question that a researcher should ask when planning a study is: 'How large a sample do I need?' If the sample size is too small, even a well-conducted study may fail to answer its research question or to detect important effects or associations or may estimate those effects or associations too imprecisely. Similarly, if the sample size is too large, the study will be more difficult and costly, and the size may even lead to a loss in accuracy. Hence, optimum sample size is an essential component of any research. Careful consideration of sample size and power analysis during the planning and design stages of clinical research are crucial [1].

Statistical power is the probability that an empirical test will detect a relationship when a relationship exists. In other words, statistical power explains the generalisability of the study results and its inferential power to explain population variability. Sample size is directly related to power; all else being equal, the bigger a sample, the higher the statistical power. If the statistical

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power is low, this does not necessarily mean that an undetected relationship exists but does indicate that the research is unlikely to find such links if they exist [2].

With the study design and the makeup of the study sample determined, the sample size estimates can be obtained. Fundamental to estimating sample size are the concepts of statistical hypothesis testing, type-I error, type-II error and power. In planning clinical research, it is necessary to determine the number of subjects required to ensure that the study achieves sufficient statistical power to detect the hypothesised effect. If the reader is not familiar with the concept of statistical hypothesis testing, introductory biostatistics texts and many websites cover this topic. Briefly, in trials to demonstrate improved efficacy of a new treatment over placebo/standard treatments, the null hypothesis is that there is no difference between treatments, and the alternative hypothesis is that there is a treatment difference. The research hypothesis usually corresponds to the alternative hypothesis, which represents a minimal meaningful difference in clinical outcomes. Statistically, either we reject the null hypothesis in favour of the alternative hypothesis or we fail to reject the null hypothesis.

Typically, the sample size is computed to provide a fixed level of power under a specified alternative hypothesis. Power is an important consideration for several reasons. Low power can cause a true difference in clinical outcomes between study groups to go undetected. However, too much power may yield statistically significant results that are not meaningfully different to clinicians. The probability of a type-I error (>) of 0.05 (two sided) and powers of 0.80 and 0.90 has been widely used for sample size estimation in clinical trials. The sample size estimate will also allow estimation of the total cost of the proposed study [3].

A clinical trial that is conducted without attention to sample size or power information carries the risk of either failing to detect clinically meaningful differences (type-II error) because

not enough subjects have taken part or of taking an unnecessarily excessive number of samples for a study. Both cases fail to adhere to the ethical guidelines of the American Statistical Association, which recommend avoiding the use of an excessive or inadequate number of research subjects by making informed recommendations for study size [3].

14.2 What Information Is Needed to Calculate Power and Sample Size?

The components that most sample size programmes require for input include:

- Choose type-I error.
- Choose power.
- Choose clinical outcome variable and effect size (differences between means, proportions, survival times and regression parameters).
- Variation estimate.
- Allocation ratio [4].

14.3 Clinical Outcome Measures

Clearly describe the clinical outcomes that will be analysed by the statistician. The variable type and distribution of the primary outcome measurement must be defined before sample size and power calculations can proceed. The sample size estimates are mainly needed for the primary outcome. However, providing power estimates for secondary outcomes is often helpful to reviewers [4].

14.4 Effect Size

As an example, suppose a parallel group study is being designed to compare systolic blood pressure between two treatments, and the investigators want to be able to detect a mean difference of 10 mmHg between groups. This 10-mmHg difference is referred to as the effect size, detectable difference or minimal expected difference [4].

14.5 How Is the Effect Size Determined?

An effect size is chosen that is based on clinical knowledge of the primary endpoint. A sample size that B worked with in a published paper is no guarantee of success in a different setting. The selected effect size is unique to the study intervention and the specific type of participants in the study sample and, perhaps, constitutes an aspect of the outcome measurement that is unique to the clinic or laboratory [5].

The investigator and statistician examine the literature, the investigator's own past research or a combination of the above to determine a study effect size. To investigate a difference in mean blood pressure between two treatments, the effect size options might be 2, 6, 10 or 20 mmHg. Which of these differences do you need to have the ability to detect? This is a clinical question, not a statistical question. Effect size is a measure of the magnitude of the treatment effect and represents a clinically or biologically important difference. Choosing a 20-mmHg effect size yields a smaller sample size than a 10-mmHg effect size because it is easier to statistically detect the larger difference. However, an effect size of 10 mmHg, or a smaller magnitude, may be a more realistic treatment effect and less likely to result in a flawed or wasted study [4].

14.6 Variation Estimates for Sample Size Calculations

In addition to effect size, we may need to estimate how much the outcome varies from person to person. For a continuous outcome, the hypothesised difference in systolic blood pressure, for example, is an effect size of 10 mmHg, and a study with a blood pressure SD of 22 mmHg will have lower power than a study where the SD is 14 mmHg. For a continuous outcome such as blood pressure, a measure of the variation is another part of the formula needed to compute the sample size. An estimate of variation can be derived from a literature search or from the investigator's preliminary data. Obtaining this information can be a challenge for both the clinical investigator and the statistician [4].

Consider sample size scenarios for detecting differences in blood pressure when comparing two treatments based on a *t* test. An SD of 14 mmHg is chosen to estimate the variation. Sample sizes are calculated for powers of 0.80 and 0.90 at the two-sided 0.05 significance level. Notice that the smaller effect sizes require a larger sample size and that the sample size increases as the power increases from 0.80 to 0.90. Determining a reasonable and affordable sample size estimate is a team effort. There are practical issues such as budgets or recruitment limitations that may come into play. Too large a sample size could preclude the ability to conduct the research. The research team will assess scenarios with varying detectable differences and power. Typically, a scenario can be worked out that is both clinically and statistically viable. The elements of sample size calculations presented here pertain to relatively simple designs. Cluster samples or family data need special statistical adjustments. For a longitudinal or repeated measures design, the correlation between the repeated measurements is incorporated into the sample size calculations [6, 7].

The power of a study tells us how confidently we can exclude an association between two parameters. For example, regarding the previous research question of the association between NCC and epilepsy, a negative result might lead one to conclude that there is no association between NCC and epilepsy. However, the study might not have been sufficiently powered to exclude any possible association, or the sample size might have been too small to reveal an association [1].

The sample sizes seen in the two meningitis studies mentioned earlier (?) are calculated numbers. Using estimates of prevalence of meningitis in their respective communities, along with variables such as the size of the expected effect (expected rate difference between treated and untreated groups) and level of significance, the investigators in both studies would have calculated their sample numbers ahead of enrolling patients. Sample sizes are calculated based on the magnitude of effect that the researcher would like to see in his treatment population (compared with placebo). It is important to note that variables such as prevalence, expected confidence level and expected treatment effect need to be predetermined to calculate sample size. As an example, Scarborough et al. [8] stated that, 'On the basis of a background mortality of 56 % and an ability to detect a 20 % or greater difference in mortality, the initial sample size of 660 patients was modified to 420 patients to detect a 30 % difference after publication of the results of a European trial that showed a relative risk of death of 0.59 for corticosteroid treatment'. Determining existing prevalence and effect size can be difficult in areas of research where such numbers are not readily available in the literature. Ensuring adequate sample size has an impact on the final results of a trial, particularly negative trials. An improperly powered negative trial could fail to detect an existing association simply because not enough patients were enrolled. In other words, the result of the sample analysis would have failed to reject the null hypothesis (that there is no difference between the new treatment and the alternative treatment),

when in fact it should have been rejected, which is referred to as type-II error. This statistical error arises because of inadequate power to explain population variability. Careful consideration of sample size and power analysis is one of the prerequisites of medical research [1].

References

1. Suresh K, Thomas SV, Suresh G. Design, data analysis and sampling techniques for clinical research. Ann Indian Acad Neurol. 2011;14(4):287–90. doi:10.4103/0972-2327.91951.
2. Tamela FD, Ketchen Jr JD. Organizational configuration and performance: the role of statistical power in extant research. Strateg Manage J. 1999;20:385–95.
3. American Statistical Association. Ethical guidelines for statistical practice: executive summary. Amstat News. April 1999:12Y15.
4. Adams-Huet B, Ahn C. Bridging clinical investigators and statisticians: writing the statistical methodology for a research proposal. J Investig Med. 2009;57(8):818. doi:10.231/JIM.0b013e3181c2996c.
5. Lenth RV. Some practical guidelines for effective sample size determination. Am Stat. 2001;55:187Y193.
6. Ahn C, Jung SH. Effect of dropouts on sample size estimates for test on trends across repeated measurements. J Biopharm Stat. 2005;15:33Y41.
7. Ahn C. Sample size requirement for clinical trials with repeated binary outcomes. Drug Inf J. 2008;42:107Y113.
8. Scarborough M, Gordon S, Whitty C, French N, Njale Y, Chitani A. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. N Engl J Med. 2007;357:2441–50.

Chapter 15
Setting the Ideal Method

15.1 Introduction

Designing a clinical study involves narrowing a topic of interest into a single focused research question, with particular attention paid to the methods used to answer the research question from a cost, viability and overall effectiveness standpoint. Once we have a fairly well-defined research question, we need to consider the best strategy to address these questions. Further considerations in clinical research, such as the clinical setting, study design, selection criteria, data collection and analysis, are influenced by the disease characteristics, prevalence, time availability, expertise, research grants and several other factors [1].

15.2 Setting

One of the first steps in a clinical study is choosing an appropriate setting in which to conduct the study (i.e. hospital, population based). Some diseases, such as migraine, may have a

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different profile when evaluated in the population than when evaluated in a hospital. On the other hand, acute diseases such as meningitis would have a similar profile in the hospital and in the community. The observations in a study may or may not be generalisable, depending on how closely the sample represents the population at large [1].

Both De Gans et al. [2] and Scarborough et al. [3] looked at the effect of adjunctive dexamethasone in bacterial meningitis. Both studies are good examples of using a hospital setting. Because the studies involved acute conditions, they utilised the fact that sicker patients will seek hospital care, to concentrate their ability to find patients with meningitis. By the same logic, it would be inappropriate to study less acute conditions in such a fashion as it would bias the study towards sicker patients.

If the sample were to be restricted to a particular age group, sex, socioeconomic background or stage of the disease, the results would be applicable to that particular group only. Hence, it is important to decide how a sample is selected. After choosing an appropriate setting, attention must be turned to the inclusion and exclusion criteria. These are often locale specific. If we compare the exclusion criteria for the two meningitis studies mentioned above, we see that in the study by de Gans [2], patients with shunts, prior neurosurgery and active tuberculosis were specifically excluded; in the Scarborough study, however, such considerations did not apply, as the locale was considerably different (sub-Saharan Africa vs. Europe) [1].

15.3 Validity (Precision) and Reliability (Consistency)

Clinical research generally requires making use of an existing test or instrument. These instruments and investigations have usually been well validated in the past, although the populations in which

such validations were conducted may be different. Many such questionnaires and patient self-rating scales (MMSE or QOLIE, for instance) were developed in another part of the world. Therefore, to use these tests in clinical studies locally, they require validation. Socio-demographic characteristics and language differences often influence such tests considerably. For example, consider a scale that uses the ability to drive a motor car as a 'quality of life' measure. Does this measure have the same relevance in India, where only a small minority of people drive their own vehicles, as it does in the USA? Hence, it is very important to ensure that the instruments that we use have good validity [1].

Validity is the degree to which the investigative goals are measured accurately. The degree to which the research truly measures what it intended to measure [4] determines the fundamentals of medical research. Another measurement issue is reliability. Reliability refers to the extent to which the research measure is a consistent and dependable indicator of medical investigation. In measurement, reliability is an estimate of the degree to which a scale measures a construct consistently when it is used under the same conditions with the same or different subjects. Reliability (consistency) describes the extent to which a measuring technique consistently provides the same results if the measurement is repeated. The validity (accuracy) of a measuring instrument is high if it measures exactly what it is supposed to measure. Thus, the validity and reliability together determine the accuracy of the measurement, which is essential to make a valid statistical inference from medical research [1].

15.4 Types of Study Design

There are many different types of study, and each has merits in particular situations [5]. In a prospective study, subjects are selected from a population and analysed for a defined future

outcome. In contrast, a retrospective study is an analysis of existing data. A study is said to be experimental if the effect of an intervention (e.g. a drug treatment or exercise programme) is investigated; otherwise, it is an observational study. A study is described as cross sectional if measurements are made at only one time point, while a longitudinal study analyses multiple time points. An analytical study is one in which the aim is to analyse the data gathered to make an inference about the effect of an intervention on an outcome variable. In a descriptive study, the data are summarised using descriptive statistics (e.g. measures of centre and spread, frequencies) without consideration of the effects of one or more of the variables on the others [6].

One of the most widely known designs is the RCT. A sample of subjects is selected from the population and allocated randomly to one of two or more groups (or arms) of the trial. One of the treatments is a control, which could be an existing treatment, a placebo or no treatment. Wherever possible, trials should be double blinded such that both the subjects and the researchers are unaware of the treatment allocations. However, although ideal, this may be impossible, for example, when one of the treatments is counselling and the other is a drug therapy [6].

A parallel group design is an RCT in which subjects are allocated randomly to either the treatment or the control group. By allocating subjects completely randomly, the expectation is that any known or unknown factors that could affect the outcome – other than the treatment(s) – will be equally distributed between each arm of the trial. However, this does not necessarily prove to be the case, and one way of dealing with this is to use a matched design [8] in which the subjects in each arm are matched for the factors known to affect the response to the treatment (e.g. age, BMI) [6].

Further efficiency can be achieved by using a within-subjects design, in which individuals are allocated to both arms of the

trial (simultaneously or consecutively). As a result, the intersubject variability is eliminated because each subject acts as his/her own control. Interventions that can be applied simultaneously include topical treatments applied to each leg. If treatments are consecutive (e.g. the comparison of two drugs to relieve chronic pain), care should be taken to avoid a carry-over effect between treatments by allowing a washout period. In addition, the order in which treatments are applied should be randomised to avoid any order effects [6].

Cross-sectional studies provide information about a population of interest at a particular moment in time. Examples include surveys to estimate the prevalence of a disease and studies to investigate the reliability of a measuring instrument [6].

15.5 Identifying Risk Factors

There are two primary ways of assessing risk factors for various diseases: prospective cohort and retrospective case-control studies. In a prospective cohort study, a group of healthy individuals is monitored until they develop the disease under investigation. These studies tend to be long, large and, therefore, expensive but provide the most reliable results. Case-control studies involve comparing subjects with the disease (cases) with individuals who do not have the disease (controls) but who are, otherwise, similar (e.g. same gender, age, co-morbidities, etc.). These are shorter studies and less expensive but less reliable than prospective cohort studies. Despite its shortcomings, this type of design has generated some important findings, most notably the association between tobacco smoking and lung cancer, found by Professor Richard Doll and his team [7].

15.6 Compliance

Compliance, or a lack of it, is one of the hazards of clinical studies: patients do not always follow the instructions they are given. This is especially likely if the intervention is inconvenient or unpleasant. There are two approaches to the subsequent analysis of the data: per ITT or PP, sometimes referred to as modified ITT. In the former, data are analysed according to what the plan and intention stated, and, in the latter, patients who do not adhere to the protocol are omitted from the analysis. For example, suppose there are two arms of a trial in which Group 1 follows a low-fat diet and walk for 20 min each day and Group 2 follows a low-fat diet plan. If a patient in Group 1 follows the diet but does not exercise, then in the ITT analysis the patient would be included in Group 1, whereas the PP analysis would exclude him/her from the analysis. There are some repercussions that can arise with PP analyses [8], and many statisticians prefer the ITT option [9].

15.7 Data Storage and Collection

Unless data are accurate, valid and reliable, the results of a medical research study will be unreliable. Security, including the protection of patient-identifiable data, is of critical importance when dealing with clinical information. Many institutions have a specialised unit that coordinates the collection, storage and management of research data, and this is the preferred option [6].

15.8 Analysis

Details of the analyses to be undertaken and the statistical tools to be used should be specified in the study plan. This will be the subject of a subsequent article [6].

References

1. Suresh K, Thomas SV, Suresh G. Design, data analysis and sampling techniques for clinical research. Ann Indian Acad Neurol. 2011;14(4):287–90. doi:10.4103/0972-2327.91951.
2. De Gans J, de Beek VD. Dexamethasone in adults with bacterial meningitis. N Engl J Med. 2002;324:1549–56.
3. Scarborough M, Gordon S, Whitty C, French N, Njale Y, Chitani A. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. N Engl J Med. 2007;357:2441–50.
4. Golafshani N. Understanding reliability and validity in qualitative research. Qual Rep. 2003;8:597–607.
5. Fleiss JL. The design and analysis of clinical experiments. New York: John Wiley & Sons; 1986.
6. Cochrane LA, Puvaneswaralingam S. Clinical research for beginners – the importance of planning. Scottish Univ Med J. 2012;1(2):154–64.
7. Doll R, Hill AB. Smoking and carcinoma of the lung. BMJ. 1950;2(4682):739–48.
8. Abraha I, Montedori A, Romagnoli C. Modified intention to treat: frequency, definition and implication for clinical trials [abstract]. Sao Paulo: XV Cochrane Colloquium; 2007. p. 86–7.
9. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. BMJ. 1999;319:670–4.

Chapter 16
Ethics of Clinical Research

16.1 Introduction

Ethics, an essential dimension of human research, is considered both a discipline and practice. For clinical research, ethically justified criteria for the design, conduct and review of a clinical investigation can be identified by obligations to both the researcher and human subjects. Informed consent, confidentiality, privacy, privileged communication and respect and responsibility are key elements of ethics in research [1].

The ethical conduct of a clinical trial does not end with the formulation of the study design and a signature on an ICF. Protecting the rights, interests and safety of research subjects must continue throughout the study duration. Subject safety monitoring is the responsibility of several groups, including RECs or IRBs, investigators and their research staffs, sponsors and DMCs, also called DSMBs, especially in the USA. Reports during the last few years of the deaths of research subjects and deficiencies in the monitoring of clinical trials have raised serious concerns regarding the systems and processes by which subject safety is currently monitored [2–5].

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16.2 Research Ethics' Declarations

There are treaties and declarations for the fundamental principles of ethical conduct in biomedical research: the Nuremberg Code [6], the Declaration of Helsinki [7], the EU Convention on Human Rights and Biomedicine [8], the Convention on Human Rights and Biomedicine (the Oviedo Convention) [9], various guidelines promulgated by the Council for International Organizations of Medical Sciences [10] and a number of treaties and conventions [11–14]. Principles have been enunciated specifically to protect human subjects from harm and to demonstrate respect for their autonomy. The two comprehensive and pioneering documents about research ethical issues are considered to be the Nuremberg Code and the Declaration of Helsinki.

16.2.1 Nuremberg Code (1947)

In the twentieth century, the judgement of the trial of Nazi doctors at Nuremberg is the commonly recognised starting event for modern research ethics. It contained ten paragraphs, referred to as the Nuremberg Code [6]:

No. 1: Voluntary consent is to be based on sufficient knowledge of the nature, duration, purpose, methods, inconveniences, hazards, and effects of the research.
No. 2: Research is expected to yield fruitful results for the good of society not procurable by other methods.
No. 3: Research is to be based on animal research and prior knowledge.
No. 4: All unnecessary physical or mental suffering and injury are to be avoided.
No. 5: No experiment is to be conducted in which death or disabling injury will occur (except where physicians are also subjects).

No. 6: Degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved.
No. 7: Preparation and facilities are provided to protect subjects against even the remote possibility of injury, disability, or death.
No. 8: The research is to be conducted by scientifically qualified persons and requires the highest degree of skills and care.
No. 9: Subjects are free to bring an experiment to an end if they have reached the physical or mental state where continuance seems impossible.
No. 10: Researchers are to be prepared to terminate the experiment if they have cause to believe, according to their good faith, skill, and judgment, that continuation is likely to result in injury, disability, or death to a subject.

16.2.2 Declaration of Helsinki

In 1964, the Declaration of Helsinki, published by the World Medical Association, introduced an authoritative attestation of the need for prior review of any kind of human research [7]. Although the Declaration emphasised the scientific standards that should govern scholarly research, it allowed more freedom to physicians to omit the application of consent procedures in special circumstances [15]. This shortcoming of the Declaration indicated that the rights and safety of research participants still lay with the individual investigator. Today, the Declaration of Helsinki is considered a document of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

16.3 Research Ethics Committees (RECs) or Institutional Review Boards (IRBs)

RECs or IRBs [5, 16] aim to safeguard the welfare, dignity and safety of participants, ensure that ethically approved research is conducted in line with the approved protocol and promote public confidence in the conduct of human research. RECs play key roles in promoting ethical practices in biomedical research and in identifying solutions to ensure that the interests of researchers and society do not take precedence over the rights of the participants [16].

The IRB has numerous protection responsibilities that include initial and continuing review of the study protocol and related documents, review of the documentation of informed consent (though it is particularly difficult for IRBs to adequately monitor the informed consent process, even with unannounced 'spot checks') and review of reports of unanticipated problems and of AEs [5].

16.4 Data Safety Monitoring Boards (DSMBs)

The establishment of DSMBs was based on the recognition in the 1960s that independent means of interim monitoring of accumulating data were essential to determine ongoing subject safety in a trial. Essentially, individuals closely involved in trial design and conduct might not be fully objective in reviewing interim data for emerging concerns of harm to trial subjects. To provide the necessary monitoring, DSMBs usually consist of individuals with pertinent expertise in the disease under study, as well as statisticians, ethicists and sometimes community representatives [5].

DSMBs have been used increasingly due to the increasing number of industry-sponsored trials with mortality or major

morbidity endpoints, heightened awareness in the scientific community of problems in analysis that might lead to bias or inaccurate results and the previously mentioned concerns that IRBs are unable to properly monitor subject safety in multicenter trials [5].

The focus of DSMBs is on the total safety experience in a trial. The members of the DSMB therefore review aggregate data at predefined intervals and consider differences in the rates of clinical endpoints to determine whether clear benefits or harm might be occurring. They also review individual reports of AEs and consider the frequency, severity and types of AEs and serious adverse events (SAEs). A decision to stop a trial is made when, using preplanned statistical analyses, significant differences in either benefits or harm are observed among the study arms or when there have been an excessive number of AEs in one of the study groups [5].

16.5 Good Clinical Practice

'The cornerstone of sponsor and investigator responsibilities is the concept of good clinical practice, which is detailed in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline #6 [17]. GCP standards were developed to provide guidance to investigators that would result in common approaches to clinical trials performed in multiple countries. GCP forms a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials, thereby providing assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. GCP has several objectives concerning the protection of trial subjects, quality of data, and transparency of trial conduct [17]'.

16.6 Important Topics for Research Ethics

16.6.1 Informed Consent

Informed consent refers to an ethical and legal doctrine based on the understanding that all interventions (diagnostic, therapeutic, preventive or related to scientific studies) in the medical field should be performed only after a participant has been informed about the purpose, nature, consequences and risks of the intervention and has freely consented to it [18]. The primary focus of consent should be on informing and protecting research subjects, through disclosure and discussion of relevant information, as well as by meaningful efforts to promote participants' understanding, and by ensuring that decisions to participate, or to continue participating, are always made voluntarily. Informed consent is the ethical cornerstone of RCTs, where volunteers are given the option to participate in a trial that includes randomisation or to remain outside the trial and receive traditional medical treatment. Mandatory conditions for an informed consent include provision of detailed information to a subject, adequate understanding of the information provided and expression of consent to, and/or authorisation for, the intervention [19].

The researcher's primary moral responsibility is to design a clinical trial that will answer a research question without exposing human subjects to undue risks in the process [20]. When fully informed subjects give their consent, they acknowledge their role as research participants and take responsibility for their designated roles. Assuming that the research question is significant, the trial is well structured and the risks to the individual patient are justified, the tension between collective ethics and individual ethics is obviated when individual subjects give their informed consent. This holds true if the primary intent of the investigator is to compare two treatments, not to provide better overall care to the subject [21].

16.6.2 Patient Information Sheet

Once informed consent has been obtained, the research subject is given a patient information sheet, detailing the following aspects of the study: (1) title of the research project, (2) invitation to participate in the research, (3) purpose and significance of research, (4) time commitments, (5) termination of participation and indication of voluntary contribution, (6) risks involved, (7) costs and compensation and (8) anonymity and confidentiality [1].

16.6.3 Confidentiality

Confidentiality means the non-disclosure of certain information except to another authorised person. The concept of confidentiality applies insofar as the information a person reveals to a professional is private and has limits on how and when it can be disclosed to a third party [22]. Various dimensions of confidentiality described in the literature include human rights, confidentiality in relation to young persons, domestic violence, true anonymisation of data, validity of consent for disclosure, cancer and genetic registers, fertility, involuntary disclosure and safeguards [23]. There is no breach of confidentiality if the following recordings, for any purpose, are used, as long as they are effectively anonymised [24]:

(a) Conventional X-rays
(b) Images taken from pathology slides
(c) Laparoscopic images of the inside of the abdominal cavity
(d) Images of internal organs and ultrasound images

16.6.4 Privacy

Privacy is the quality of being secluded from the presence or view of others. Privacy in research refers to the right of an individual to

make decisions concerning how much information about their physical status, health, social network and thoughts and feelings will be shared with investigators [25]. To protect the privacy rights of family members, researchers must be careful in determining whether family members should be considered as research participants.

16.6.5 Privileged Communication

Privileged communication includes conversations within the context of a protected relationship, such as that between the doctor and patient, therapist and client, attorney and client, husband and wife or priest and penitent; under the common law, such privilege involves a number of rules excluding evidence that would be adverse to a fundamental principle or relationship if it were disclosed [26]. Such communications are secure, are reliable and meant to be kept among the directly involved parties.

16.6.6 Respect and Responsibility

Respect in research refers to respect for people and respect for truth. People have the right to dignity and privacy (informed consent and confidentiality). Respect for truth implies probity and respect for the intellectual rights of others. All possible efforts should be directed to avoid plagiarism and making false conclusions by over- or underemphasising the results [27]. Responsibility for a human subject involves voluntary informed consent, avoiding deception, rewards and incentives, privacy and disclosure. Additionally, researchers are responsible for maintaining the reputation of educational research by adhering to the highest standards of quality research. When publishing the research, investigators should disclose any competing or financial interests [1].

16.7 Ethics for the Paediatric Population

The word 'child' is not limited to the age range of 2 to 11 years, as defined in ICH E11. Further subsets of the paediatric population, as defined in ICH E 11, are preterm newborn infants, term newborn infants (birth to 27 days), infants from 1 to 23 months and adolescents from the age of 12 up to, but not including, 18 years. By emancipation or when the child reaches adulthood during the time in which he or she is participating in the trial, an adolescent may become legally competent to make decisions and to give informed consent [28, 29]. It should be noted that these age groups correlate poorly with maturation, especially from the developmental point of view, and trials may be performed across age groups, with consequences for the ethical aspects of their conduct [28].

16.7.1 Informed Consent from a Legal Representative

As a child (minor) is unable to provide legally binding consent, informed consent must be sought from the parents/legal representative on the child's behalf. Article 4(a) of the Clinical Trials Directive requires that the specific and written informed consent of a parent/legal representative must be sought prior to enrolling a child in a trial. Information should be given by an experienced investigator, or his adequately trained delegate, to each parent, or the legal representative, regarding the purpose of the trial and its nature, the potential benefits and risks and the names of the investigators responsible for conducting the trial, with background professional information (such as education, work experience) and direct contact details (telephone and e-mail) for further information regarding the trial. The parent/legal representative should be given sufficient time and necessary information to consider the

benefits and risks of involving the child in the clinical trial. When providing such information, it is important to take into consideration the fear and uncertainty of parents, especially when they are inexperienced with respect to the child's condition. However, the parents/legal representative might need more in the way of detailed and explicit information and, hence, more time to reflect on the implications of consenting, especially since they bear the full responsibility for the child, unlike adult trials where the subject takes the responsibility for himself/herself [28].

References

1. Gurayaa SM. Ethics in medical research. J Microscopy Ultrastruct. 2014;2:121–6.
2. Walters L. The oversight of human gene transfer research. Kennedy Inst Ethics J. 2000;10:171–4.
3. Steinbrook R. Improving protection for research subjects. N Engl J Med. 2002;346:1425–30.
4. Steinbrook R. Protecting research subjects: the crisis at Johns Hopkins. N Engl J Med. 2002;346:716–20.
5. Silverman H. Ethical issues during the conduct of clinical trials. Proc Am Thorac Soc. 2007;4(2):180–4.
6. Encyclopedia of Bioethics. In: Post SG, Reich WT (Eds.). 3rd Edition, Section IV. New York: Macmillan, 2004.
7. Saif M. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Med Assoc. 2000;284:3043–5.
8. Nys H, Stultiëns L, Borry P, Goffin T, Dierickx K. Patient rights in EU Member States after the ratification of the Convention on Human Rights and Biomedicine. Health Policy. 2007;83(2):223–35.
9. Nys H. Towards an international treaty on human rights and biomedicine-some reflections inspired by UNESCO's Universal Declaration on Bioethics and Human Rights. Hein Online; 2006.
10. Bhutta ZA. Ethics in international health research: a perspective from the developing world. Bull World Health Org. 2002;80(2):114–20.

11. Alexander D, Dommel FW. The convention on Human Rights and Biomedicine of the Council of Europe. Kennedy Inst Ethics J. 1997;7(3):259–76.
12. Simon-Lorda P, Tamayo-Velázquez MI, Barrio-Cantalejo I. Advance directives in Spain. Perspectives from a medical bioethicist approach. Bioethics. 2008;22(6):346–54.
13. Mowbray AR. Cases and materials on the European Convention on Human Rights. Oxford: Oxford University Press; 2007.
14. Leuprecht P. Innovations in the European system of human rights protection: is enlargement compatible with reinforcement. Transnatl Law Contemp Prob. 1998;8:313.
15. Garrafa V, Solbakk JH, Vidal S, Lorenzo C. Between the needy and the greedy: the quest for a just and fair ethics of clinical research. J Med Ethics. 2010;36(8):500–4.
16. Martín-Arribas MC, Rodríguez-Lozano I, Arias-Díaz J. Ethical review of research protocols: experience of a research ethics committee. Rev Esp Cardiol English Edn. 2012;65(6):525–9.
17. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). E6(R1). Good clinical practice: consolidated guideline. Available at: www.ich.org. Also published in Fed Reg. 1997;62:25691–25709E7.
18. Glickman SW, McHutchison JG, Peterson ED, Cairns CB, Harring-ton RA, Califf RM, et al. Ethical and scientific implications of the globalization of clinical research. N Engl J Med. 2009;360(8):816–23.
19. Agre P, Campbell FA, Goldman BD, Boccia ML, Kass N, McCullough LB, et al. Improving informed consent: the medium is not the message. IRB: Ethics Hum Res. 2003;25(5):S9–11.
20. Pullman D, Wang X. Adaptive designs, informed consent, and the ethics of research. Control Clin Trials. 2001;22(3):203–10.
21. Lilford RJ, Jackson J. Equipoise and the ethics of randomization. J R Soc Med. 1995;88(10):552.
22. Mielke HW. Research ethics in pediatric environmental health: lessons from lead. Neurotoxicol Teratol. 2002;24(4):467–9.
23. Woodward Z, Argent VP. Patient confidentiality. Curr Obstet Gynaecol. 2005;15(3):211–4.
24. Mandl KD, Szolovits P, Kohane IS, Markwell D, MacDonald R. Public standards and patients' control: how to keep electronic medical records accessible but private. Medical information: access and privacy. Doctrines for developing electronic medical records. Desirable characteristics of electronic medical records. Challenges and limitations for electronic medical records. Conclusions commentary: open approaches

to electronic patient records. Commentary: a patient's viewpoint. BMJ. 2001;322(7281):283–7.
25. Fisher CB. Privacy and ethics in pediatric environmental health research—part I: genetic and prenatal testing. Environ Health Perspect. 2006;114(10):1617.
26. Miller RA, Schaffner KF, Meisel A. Ethical and legal issues related to the use of computer programs in clinical medicine. Ann Intern Med. 1985;102(4):529–36.
27. Tauber AI. Patient autonomy and the ethics of responsibility. Cambridge: The MIT Press; 2005.
28. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. 2008. ftp://ftp.cordis.europa.eu/pub/fp7/docs/ethical-considerations-paediatrics_en.pdf. Accessed online at 16 Oct 16 2015.
29. Clinical investigation of medicinal products in the paediatric population. ICH E11. CPMP/ICH/2711/99. http://www.emea.europa.eu/pdfs/human/ich/271199EN.pdf.

Chapter 17
Recruitment and Enrolment

17.1 Introduction

Achieving clinical trial research participant enrolment is clearly essential to conducting a successful trial. Adequate enrolment provides a basis for projected participant retention, resulting in evaluative patient data. Without sufficient patient retention from the time of study initiation to closeout, the number of remaining participants may prove to be too small a pool from which to derive conclusive proof or disproof of the goal of the clinical trial sponsor. Obtaining final evaluative data is dependent on successful patient retention. Patients cannot be retained without an initial pool of enrolled volunteers. This initial pool of screened, then enrolled, participants depends on designing a successful patient recruitment strategy. 'A major focus in all clinical trials is on the recruitment of subjects. Where and how to do this depends on the demographics of the target population and the condition under investigation'. [1, 2].

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17.2 Patient Recruitment

The goal of patient recruitment is to raise awareness of clinical trial opportunities and to encourage enrolment. Services are contracted by pharmaceutical companies, biotechnology companies, medical device companies, CROs or a medical research site. Services include [3]:

Study feasibility: Evaluating whether the study may be performed in a given country and how effective it will be in enrolling patients [3].

Population research: Discovering the motivational drivers of target patient populations is commonly gathered through focus groups and may involve caregivers and physicians [3].

Site selection: Choosing the optimal recruiting sites for study participation may play a role in the type of patients recruited. For example, in breast cancer survivors, evidence indicates that recruiting via letters or at the oncologist's office results in the recruitment of similar patients [4].

Site assessment: Investigating the operational, management, technical and clinical experience capabilities of participating sites helps in deciding what support they will need to successfully recruit patients for the study, improving forecasting and return on investment [3].

Recruitment materials: Patient-directed communications designed to attract study referrals and raise enrolment, which may include brochures, posters, letters and flyers [3].

Media support: Whether directed to patients and/or caregivers, advertising can raise study awareness and drive patient referral volume. Some patient recruitment providers possess in-house capabilities for developing, producing and editing all content, while others rely on

third-party vendors. Some popular media for patient recruitment advertising are television, radio, newspaper, the Web (e.g. banner ads and word links), outdoor notices (e.g. bus stops) and social media [5, 6] (e.g. Twitter messages and YouTube videos) [3].

Media management: To exact the greatest value from media advertising, media buying services ensure placement in patient-rich geographic areas along with current market buying discounts and opportunities [3].

Site training materials: Specially designed instructional tools that assist site staff in introducing the study to patients, explaining study procedures to patients and performing informed consent procedures with patients [3].

Study website: Serving as an online hub for study information and sometimes prescreening, the study website usually describes the study, provides disease-related resources and allows patients to indicate their interest in study participation [3].

Patient referral follow-up: When a site may be short of staff or overwhelmed by a spike in patient referrals, a PRO (define acronym or, better, replace with full term as this acronym does not appear again) may offer administrative support by scheduling site appointments and following up with patients who may present enrolment challenges (e.g. a patient who has recently moved and needs a closer site location) [3].

Translations: Providing cultural and regulatory-compliant translation of recruitment materials into various languages in accordance with country-specific requirements [3].

Community outreach: To expand study awareness, outreach efforts may include participation at local health fairs or networking among community service groups, patient support groups and other neighbourhood

organisations and institutions (e.g. churches and barbershops).

Physician outreach: When study recruitment depends in large part on physician referrals, outreach measures can include forums where doctors, specialists and healthcare providers gather to view a presentation on the study and how their patient pool may be eligible for participation. It may also include direct mail programmes where collateral is sent to physicians with the aim of increasing referral volume [3].

Site support: From resolving pre-trial operational issues to tailored support (e.g. referral processing, subject status updates and protocol clarifications), site support ensures study challenges are immediately addressed [3].

Monitoring and reporting: To assess the effects of patient recruitment activities on enrolment, ongoing monitoring is performed. Assessing study metrics allows the sponsor to adjust recruitment efforts as needed to ensure maximum return on investment [3].

17.3 Patient Enrolment

'Risk' is one of the most important words in the clinical research lexicon. Patient risk is carefully managed and monitored by IRBs and the FDA. But what about risks to clinical trial viability?

Patient enrolment is one of the biggest stumbling blocks in the path of a clinical trial. According to the statistics, most trials do stumble; 80 % are delayed by at least 1 month due to enrolment, and 72 % of trials are delayed by more than 1 month [1]. These delays can filter through the entire drug development pipeline, causing a cascade of missed deadlines.

So how should the enrolment risk be managed? In the clinic, powerful decision-making tools such as the risk-benefit ratio,

treatment benchmarks and monitoring procedures are used to guide patient care. The same approaches can be adapted to prevent and mitigate clinical trial enrolment problems [5].

17.3.1 The Patient Population

The broad boundaries of every patient population are set by the ethical guidelines laid out in the Declaration of Helsinki. The patient population is further restricted by enrolment criteria in a clinical trial protocol. Every inclusion and exclusion criterion affects enrolment; that may sound obvious. But how much does a certain inclusion and exclusion requirement affect enrolment? The answer to that question is far from obvious [5].

17.3.2 Enrolment Planning

Enrolment planning is a necessity for every study, every time. Organisers should consider the following [6]:

Determine your site's feasibility: Should you even take this study? Every protocol has its challenges, but some are more difficult than others. If your first instinct is one of doubt, then it may be best to pass on the opportunity entirely. Overestimating your site's capabilities and not being able to deliver on it are likely to hurt you more in the end.

It's not always about advertising: Many sites turn to advertising first, without mapping out a plan. Keep in mind that advertising is only one tactic that can be employed when trying to reach your enrolment goals.

Pick the 'lowest-hanging fruit': Reach out to the best qualified and easiest-to-contact potential participants first. You may find great success here, thus minimising your need to do anything else.

Exhaust low-cost options first: Community outreach, networking and physician referrals are a few examples of low- or

no-cost recruitment options, which your site should first explore.

Work 'inside out': Simply put, work your database! Phone calls, e-mails, postcards, Facebook posts and Twitter tweets should all be parts of your plan of attack for helping to fill your study [6].

17.3.3 Take the Time to Research and Understand the Potential Participant

Who is the ideal participant? It is best to narrow this down from the inclusion criteria on the protocol. Find out where the peak prevalence/incidence rates are, and let that help guide your decisions [6].

What is going to motivate the patient to participate? There has to be a motivational factor driving someone to consider participation. Is it because they are seeking new treatment? Or perhaps they do not have health insurance and the medical exams provided at no cost are a benefit for the subject.

Who is the ideal target? While most times this is the potential subject himself/herself, there are many studies that require the attendance of a caregiver or family member; an example would be a moderate-to-severe Alzheimer's study. For studies like this, it is important to keep both audiences in mind as you develop your plan and any messaging [6].

17.3.4 Engage with Sponsors

What do sponsors and CROs want to see with respect to enrolment planning?

A written plan, specific to your site: Just the act of putting an actual plan on paper will go a long way in the eyes of a sponsor or CRO. This demonstrates accountability and a willingness to succeed.

'Smart' planning: As mentioned previously, exhausting low- or no-cost options, in addition to working 'inside out', will be viewed positively. Planning right from the start, even at feasibility, is your best approach.

Allocation of budget for each tactic: Site recruitment budgets are often incredibly lean. Sponsors and CROs will appreciate you assigning estimated costs to each recruitment tactic.

Justification for recommendations and costs: Along with costs for each endeavour, it will help to explain why you are making your recommendations. Perhaps you are recommending television; your position will be supported if you mention that television is the most widely used media vehicle in your market in relation to your target audience.

Metrics, funnel or yield: In the simplest terms, 'What will this deliver?' Constructing a funnel with an estimated return on a sponsor's or CRO's investment will demonstrate stewardship over the budget they have provided to you [6].

References

1. Frank G. Current challenges in clinical trial patient recruitment and enrollment. SoCRA Source. 2004;2(February):30–8.
2. De Looze F. Clinical trials in general practice: recruitment models. Presented at the international clinical trials symposium. 1999.
3. Patient recruitment. Wikipedia. https://en.wikipedia.org/wiki/Patient_recruitment. Accessed online at 19 Oct 2015.
4. Zhou ES, Dunsiger SI, Pinto BM. Proactive versus reactive recruitment to a physical activity intervention for breast cancer survivors: does it matter? Clin Trials. 2013;10(4):587–92.
5. Abelson MB, Welch D, McLaughlin J. Patient enrollment: risks to clinical trial viability. http://www.retinalphysician.com/articleviewer.aspx?articleID=100315. Accessed online at 19 Oct 2015.
6. Patient Recruitment and Retention in Clinical Trials. 10 strategies for success. Forte Research Systems, Inc. Madison, 2013. www.forteresearch.com. Accessed online at 19 Oct 2015.

Chapter 18
Why We Need Clinical Consent and Other Documentation

18.1 Introduction

The essential documents for clinical trials are the following [1]:

- Investigator's brochure
- Clinical study protocol
- Subject information and informed consent form
- Clinical study reports
- Case report form (CRF)

18.2 Investigator's Brochure (IB)

The IB contains preclinical and clinical information related to an investigational drug. The information should be presented in a concise, simple, objective, balanced form. The IB includes a title page, which provides the sponsor's name, the identity of the investigational product (products), an edition number and date and the number and date of the edition it supersedes as well. The

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sponsor may wish to include a confidentiality statement setting out the IB as a confidential document. A standard IB usually includes the following sections [1]:

- List of abbreviations
- Contents
- 'Summary – a brief description of the significant physical, chemical and pharmaceutical properties of the investigational product, and also pharmacological, toxicological, pharmacokinetic, metabolic and therapeutic information that is relevant to the appropriate stage of the clinical trial'.
- 'The introduction provides the chemical name (and generic and trade names, if approved) of the investigational product, all active components, pharmacological class, the rationale for performing further research with the investigational product and anticipated indications for its use. This section should provide the general approach to be followed in evaluating the investigational product'.
- 'Physical, chemical and pharmaceutical properties and formulation of the medicinal product'.
- Non-clinical studies: this section provides the data from animal studies regarding the non-clinical pharmacological, pharmacokinetic, metabolic and toxicological characteristics of the investigational drug.
- Clinical studies: this section provides information on pharmacokinetics, biotransformation, safety and efficacy in humans, as well as data on postmarketing experience if the product under investigation has already been approved for use for other indications.
- Conclusions and guidance for the investigator
- References (the references should be provided at the end of each section)

The IB should be reviewed at least annually and revised as necessary in compliance with standard procedures established by the drug development company [1].

18.2.1 Introduction

'The IB is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the information to facilitate understanding of the rationale for, and compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and nonpromotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by individuals from disciplines generating the described data [2]'.

'This guidance delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e. a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance

with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with GCP, relevant new information may be so important that it should be communicated to the investigators, and possibly to the IRBs/IECs and/or regulatory authorities before it is included in a revised IB [2]'.

'Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator- sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guidance [2]'.

18.2.2 General Considerations

The IB should include:

18.2.2.1 Title Page

'This should provide the sponsor's name, the identity of each of the investigators and others involved in the trial, details of the investigational product (i.e. research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is

also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided [2]'.

18.2.2.2 Confidentiality Statement

'The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC [2]'.

18.2.2.3 Contents of the Investigator's Brochure

'The IB should contain the following sections, each with literature references where appropriate':

Summary

'A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product'.

Introduction

'A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product(s)'s pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement

should provide the general approach to be followed in evaluating the investigational product [2]'.

Physical, Chemical and Pharmaceutical Properties and Formulation

'A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties'.

'To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given'.

'Any structural similarities to other known compounds should be mentioned [2]'.

Non-clinical Studies

Introduction

'The results of all relevant non-clinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and possible unfavourable and unintended effects in humans [2]'.

'The information provided may include the following, as appropriate, if known/available: species tested; number and sex of animals in each group; unit dose (e.g. milligram/kilogram (mg/kg)); dose interval; route of administration; duration of dosing; information on systemic distribution; duration of post-exposure follow-up; and results. Results may include the following aspects: nature and frequency of pharmacological or toxic effects; severity or intensity of pharmacological or toxic

effects; time to onset of effects; reversibility of effects; duration of effects; and dose response. Tabular format/listings should be used whenever possible to enhance the clarity of the presentation [2]'.

'The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e. the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis [2]'.

(a) *Non-clinical pharmacology*
'A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g. special studies to assess pharmacological actions other than the intended therapeutic effect(s)) [2]'.

(b) *Pharmacokinetics and product metabolism in animals*
'A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species [2]'.

(c) *Toxicology*
'A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate':

'Single dose; Repeated dose; Carcinogenicity; Special studies (e.g. irritancy and sensitization); Reproductive toxicity; Genotoxicity (mutagenicity) [2]'.

Effects in Humans

Introduction

'A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results from any use of the investigational product(s) other than in clinical trials, such as from experience during marketing'.

(a) *Pharmacokinetics and product metabolism in humans*
'A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available':

'Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination)'.

'Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form'.

'Population subgroups (e.g. gender, age, and impaired organ function)'.

'Interactions (e.g. product-product interactions and effects of food)'.

'Other pharmacokinetic data (e.g. results of population studies performed within clinical trial(s)) [2]'.

(b) *Safety and efficacy*
'A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials has been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of ADRs for all the clinical trials (including those for all the studied indications) are useful. Important differences in ADR patterns/incidences across indications or subgroups should be discussed'.

'The IB should provide a description of the possible risks and ADRs to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s)'.

(c) *Marketing experience*
'The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g. formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration [2]'.

Summary of Data and Guidance for the Investigator

'This section should provide an overall discussion of the nonclinical and clinical data, and should summarize the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can

be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate ADRs or other problems in clinical trials. The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and ADRs, based on previous human experience, and on the pharmacology of the investigational product [2]'.

18.3 Clinical Study Protocol

After the objectives and design of a clinical study have been determined, these issues should be documented in the study protocol. This is a document containing instructions for all the parties involved in the clinical trial that establishes specific objectives for each participant and provides guidelines for their performance. The study protocol should ensure adequate performance of the clinical trials and collection and analysis of data that are further submitted to the regulatory authorities for review and consideration [1]. The following sections should be included in the study protocol [1]:

- Introduction (brief description of the problem and treatment regimen(s))
- Objectives and purposes of the study

- Study duration
- Number of subjects

- Informed consent
- Opinion of the ethics committee
- Subject selection criteria:

  – Inclusion criteria
  – Exclusion criteria

- Methodology:

  – Study plan
  – Study schedule
  – Study visits
  – Study assessments/procedures
  – Definition of efficacy endpoints
  – Treatment cycles

- Safety reporting:

  – Adverse events (AEs)
  – Serious adverse events (SAEs)
  – Abnormal laboratory test values
  – Abnormal values of other safety parameters
  – Withdrawal from the study

- Clinical laboratory parameters
- Other safety parameters
- Concomitant medications
- Data analysis
- Appendixes

The following appendixes may be included in the study protocol: patient information sheet/written information and/or ICF. Instruction sheet (e.g. for study subjects or study site staff).

Terms (both medical and law terms) that may be difficult for study subjects to understand should be avoided in the production of the abovementioned documents containing patient

information. If special terms are used in the documents, they should be clarified or explained [1].

18.3.1 Protocol Amendment

A protocol amendment describes major changes to the initial study protocol. A protocol amendment must be again approved by the ethics committee [1].

18.4 Informed Consent

Informed consent is one of the most important elements of the system that ensures the ethics of medical experiments and protection of the rights of the study subjects. Informed consent is the process by which a subject voluntarily confirms his/her willingness to participate in a clinical trial, after having been informed of all aspects of the study. Informed consent should be documented by means of a written, signed and dated ICF.

Potential subjects should be informed of the objectives and methods of the study, the drug product and treatment regimen, the available alternative treatments, potential risks and benefits, and possible complications and discomforts that may arise from participation in the study.

Based on information that he/she has received and understood, the potential subject must freely give consent to participate in a study. The informed consent should not be obtained through inducement or coercion. The subject should be aware that he/she may withdraw from the study at any time and that this will not affect his/her future medical care in any way [1].

18.4.1 The Main Principles of Informed Consent

The subject should be informed of the following [1]:

- The purposes of the trial
- The methods of the trial
- The study drug(s) and treatment regimens
- Available alternative treatment(s)
- The potential risks and benefits and possible discomforts

The subject should understand [1]:

- That informed consent should be given freely
- That consent should not be obtained through inducement or coercion
- That he/she may withdraw from the study at any time
- That withdrawal from the study will not affect his/her future medical care

18.5 Study Progress Reports

The investigator should provide written reports on study progress to the ethics committee. These may be the interim report on the interim results of the study and their assessment based on the analysis conducted in the course of the study, or the final report, a full, comprehensive description of the study including descriptions of the investigational materials and study design, as well as the presentation and assessment of the results of a statistical analysis. Additionally, the investigator should prepare written reports on all major changes that might affect study performance and/or increase risk to study subjects. These are the following: AE report or ADR report, patient entry form (patient entry card/patient notification form) and patient withdrawal

form, protocol deviation/violation report, study termination report, etc.

Reporting on study progress is the responsibility of not only the investigator but also the study monitor, who should provide written reports on each study monitoring visit (monitor report). The expert report is prepared for the regulatory authorities by an expert in the appropriate field (company officer or independent person) and covers different aspects of drug development [1].

18.6 Case Record Form (CRF)

The CRF is a paper or electronic document designed to record all the information for an individual study subject required by the study protocol.

The case record form is used for several purposes [1]:

- To ensure data collection in accordance with the study protocol
- To ensure fulfilling of the regulatory authorities' requirements for data collection
- To facilitate effective, comprehensive data processing and analysis, and results reporting, and to promote safety data sharing between the study team and other departments of the institution

The data collected at the study site during the course of a study should be comprehensive and provide true and fair information on what happened to each study subject. The study will reliably answer questions concerning the efficacy and safety of the investigational drug only if the above criteria are met.

All CRFs should include the following data:

- Study title and number
- Investigator's name
- Study subject/patient ID (number and initials)

- Inclusion/exclusion criteria
- Demographic data
- Detailed description of dosage regimens of investigational drug
- Concomitant treatment
- AEs (side effects and intercurrent diseases)
- Conclusion on subject's health
- Investigator's signature and date

Additionally, CRFs should include special pages to record the following information [1]:

- Past medical history
- Results of physical examination
- Primary and secondary diagnoses
- Relevant previous treatment
- Baseline characteristics, results of interim assessments, evaluation of efficacy endpoints, laboratory tests, description of study procedures, etc.

All CRFs should be legible and suitable for duplication and possible additional sharing.

References

1. Essential Documents for Clinical Trials. Medtran. http://www.medtran.ru/eng/trials/trialdocumentation.htm. Accessed online at 19 Oct 2015.
2. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH, Apr 1996.

Chapter 19
Monitoring the Trial

19.1 Purpose

'The purposes of trial monitoring are to verify that':

(a) 'The rights and well being of human subjects are protected'.

(b) 'The reported trial data are accurate, complete, and verifiable from source documents'.

(c) 'The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s) [1–3]'.

19.2 Selection and Qualifications of Monitors

(a) 'Monitors should be appointed by the sponsor'.

(b) 'Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented'.

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(c) 'Monitors should be thoroughly familiar with the investigational product(s), the protocol, written ICF and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s) [1–3]'.

19.3 Extent and Nature of Monitoring

'The sponsor should ensure that trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general, there is a need for on-site monitoring before, during, and after the trial; however, in exceptional circumstances, the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance, can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified [1–3]'.

19.4 Monitor's Responsibilities

'The monitor(s), in accordance with the sponsor's requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site':

1. 'Acting as the main line of communication between the sponsor and the investigator'.

2. 'Verifying that the investigator has adequate qualifications and resources (and that these remain adequate throughout the trial period, and that the staff and facilities, including laboratories and equipment, are adequate to safely and properly conduct the trial and that they remain adequate throughout the trial period)'.
3. 'Verifying, for the investigational product(s)':
   (a) 'That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial'.
   (b) 'That the investigational product(s) is supplied only to subjects who are eligible to receive it and at the protocol-specified dose(s)'.
   (c) 'That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s)'.
   (d) 'That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately'.
   (e) 'That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor's authorised procedures'.
4. 'Verifying that the investigator follows the approved protocol and all approved amendment(s), if any'.
5. 'Verifying that written informed consent was obtained before each subject's participation in the trial'.
6. 'Ensuring that the investigator receives the current IB, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s)'.
7. 'Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial'.

8. ‘Verifying that the investigator and the investigator’s trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorised individuals’.
9. ‘Verifying that the investigator is enrolling only eligible subjects’.
10. ‘Reporting the subject recruitment rate’.
11. ‘Verifying that source data/documents and other trial records are accurate, complete, kept up-to-date, and maintained’.
12. ‘Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial’.
13. ‘Checking the accuracy and completeness of CRF entries, source data/documents, and other trial-related records against each other. The monitor, specifically, should verify that’:

    (a) ‘The data required by the protocol are reported accurately on CRFs and are consistent with the source data/documents’.
    (b) ‘Any dose and/or therapy modifications are well documented for each of the trial subjects’.
    (c) ‘Adverse events, concomitant medications, and intercurrent illnesses are reported in accordance with the protocol on the CRFs’.
    (d) ‘Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs’.
    (e) ‘All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs’.

14. ‘Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appro-

priate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorised to initial CRF changes for the investigator. This authorisation should be documented'.

15. 'Determining whether all AEs are appropriately reported within the time periods required by GCP, the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s)'.
16. 'Determining whether the investigator is maintaining the essential documents'
17. 'Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations [1–3]'.

19.5 Monitoring Procedures

'The monitor(s) should follow the sponsor's established written SOPs as well as the procedures that are specified by the sponsor for monitoring a specific trial [1–3]'.

19.6 Monitoring Report

(a) 'The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication'.
(b) 'Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted'.
(c) 'Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the sig-

nificant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance'.

(d) 'The review and follow-up of the monitoring report by the sponsor should be documented by the sponsor's designated representative [1–3]'.

References

1. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH, Apr 1996.
2. Hutchinson D. The trial investigator's GCP handbook: a practical guide to ICH requirements. Brookwood Medical Publications Ltd. Surrey, UK, 1997.
3. Committee: ICHS: ICH Harmonised Tripartite Guideline for Good Clinical Practice. Second publication, Brookwood Medical Publications Ltd.; Richmond, Surrey, UK, 1997.

Chapter 20
Inspection

20.1 Introduction

The IND regulations went into effect in 1963. Ever since, the US FDA has conducted clinical site inspections under what is known as the bioresearch monitoring programme. The agency now conducts several hundred inspections of clinical investigators annually to obtain compliance with the regulations and to ensure that data submitted to the FDA are substantiated by appropriate records.

An FDA inspection is not an indictment and generally does not mean that the investigator's work is suspect. It is simply a quality assurance process that is used to verify clinical data and regulatory compliance. That said, it can still be an unnerving experience, particularly if you are not prepared. Hopefully, the information presented here, much of it taken directly from information provided by the FDA, will help you and your staff better understand the process and how to 'survive' it [1].

Regulatory inspections are an important and essential part of clinical research; they are required to evaluate the integrity of the data submitted to health authorities, the presence of

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infrastructure to conduct clinical research, measures implemented to protect patient's interest and safety, the adequacy of site/sponsor quality systems and verification of compliance with the principles of ICH-GCP as well as with local regulations [2].

Inspections generally occur after submission of data for marketing approval of an investigational drug; however, inspections may happen at any time during the performance of a trial, as in the FDA's Early Intervention Program [2].

All health authorities, such as the US FDA, EMA and others to whom data have been submitted from Indian site(s), may conduct inspections at the respective study sites [2].

20.2 The Types of Inspections

The most common type of inspection is classified by the FDA as a 'routine' inspection and is generally triggered by an NDA submission. Routine inspections account for over 80 % of the inspections performed by the FDA each year. Generally, the clinical investigators who enrol the most patients in the NDA's pivotal trials are the most likely candidates for a routine inspection.

'For-cause' inspections are much more infrequent and generally arise only when the agency receives reports of, or otherwise becomes aware of, suspicious behaviour by a clinical investigator. What might prompt the FDA to conduct a 'for-cause' inspection? Here are a few things that certainly raise the odds of being selected for an audit:

- Conducting a large volume of clinical trials
- Conducting clinical studies outside one's field of specialisation
- Reporting significantly better efficacy, fewer adverse effects or different laboratory results than other investigators studying the same drug

- Having apparent access in too many patients with a specific disease state for the locale or practice setting
- Complaints from a patient or sponsor of an alleged violation of the regulations, protocol or human rights [1]

Before the inspection, assemble the following documents in a private area, removing any materials related to any other study [1]:

- Protocol.
- IB and IND safety reports.
- Form FDA 1572 with accompanying CVs.
- IRB correspondence, including approval documentation and final report to IRB and sponsor.
- IRB-approved ICF.
- IRB-approved advertising.
- Study-related correspondence, excluding investigator agreement and financial information.
- Monitor sign-in log.
- Laboratory certification documents.
- Drug accountability records.
- Each subject's signed informed consent.
- Also, assess the support areas (pharmacy, laboratory) to be sure they are properly prepared; the FDA may tour the facility.
- Finally, be prepared to answer the following questions:
- Where was the study done?
- What special equipment was used?
- Who assisted in performing the study?
- What were each person's specific duties?
- Describe the sponsor's monitoring procedures and your interaction with the monitor.
- How did you account for the drug received, dispensed to/returned from subjects? Were all drugs returned to the sponsor?

The following items are routinely examined [1]:

- Adequacy of communication with the IRB, including the initial submission document, AE reporting and progress reports
- Completeness of accountability documentation for the receipt, storage, administration and return of test articles (drug, device, etc.)
- Compliance with the study protocol and documentation that each deviation/amendment received IRB and sponsor approval
- Appropriateness of the informed consent process (Did the patient properly consent? Was the correct IRB-approved version used?)
- Prompt and complete reporting of AEs to the IRB and sponsor
- Compliance with the record retention requirements and that the investigator had immediate access to the study records during the trial
- Adequate monitoring of the site and communication with the sponsor

The inspector's next step is to audit the data. He will compare the data that were submitted to the agency with the medical charts and source documents supporting the data. This would include medical charts, laboratory reports, the drug accountability logs, pharmacy records and similar study documents. This review will not be limited to the data collected during the trial. The inspector will review data from both before and after the subject's participation. This is to ensure the subject had the medical condition under treatment and that excluded medications were not given to the subject during the study period. Generally, only a subset of the data will be reviewed, but this could be expanded if the inspector finds problems with the initial sample. When the inspector has completed the audit, she/he will meet with the investigator to discuss the findings.

After her/his visit, the FDA inspector will write an establishment inspection report and submit it to FDA headquarters. It is

not routinely sent to the investigator or sponsor. After the report has been evaluated, the investigator will receive a letter. There are three possible scenarios for this letter.

The letter may simply acknowledge that the inspection has been completed and no significant deficiencies have been found. Only 20 % of inspections result in this type of letter. The letter may list deficiencies noted during the investigation but indicate that no specific response is necessary. However, the investigator should take voluntary steps to correct and improve this situation as these areas will be the focus of the next investigation. About 70 % of inspections result in this type of letter [1]. The third type of letter, comprising the last 10 %, describes serious negative findings identified by the inspector. In this case, the investigator's status and the data collected during the trial are in serious jeopardy. An immediate detailed response is required to explain how these discrepancies will be addressed. This would be an ideal time to get help from the sponsor; the pharmaceutical company has a lot at stake here as well! Failure to adequately respond can result in the investigator being disqualified from conducting other studies, rejection of the study data and perhaps the entire marketing application and even potential criminal proceedings. Investigators referred for criminal prosecution are generally clinical investigators who have knowingly or willingly submitted false information to a research sponsor [1].

Within 4–6 months, the establishment inspection report is available upon request to the investigator, the sponsor and the general public (including other potential sponsors) via the Freedom of Information Act. Sponsors and CROs routinely obtain this information when evaluating potential research sites. If a site has a discrepancy noted by the FDA inspector, it will not necessarily cause it to be passed over for future studies, but those responsible will certainly need to show the potential sponsor that the discrepancy has been addressed and procedures to prevent future recurrences have been implemented [1].

20.3 Pre-inspection Activities

Health authorities generally contact sponsors to arrange for site inspections and confirmation of dates. Subsequently, there may be direct communication between health authorities and sites. Inspectors may request pre-inspection documents such as the curriculum vitae of (sub)investigators, SAEs and also documentation of sponsor oversight, such as monitoring reports. It should be noted that site data (as submitted in a marketing approval package) would generally have been thoroughly reviewed by assessors, inspectors and other subject matter experts before inspection. Therefore, inspectors may come prepared with specific queries about safety and efficacy data, GCP compliance issues and/or other points [2].

The sponsor role is to coordinate between inspectors and site personnel and ensure that all documents are present/made available during inspection, all internal subject matter experts have been informed to be available for any queries/document requests, site personnel are available, appointments have been made for facility tour/queries with all departments involved in study (e.g. laboratories, pharmacy, radiology, archival, etc.) and logistics have been taken care of. Usually sites need to sign a statement to confirm that access to patient files will be granted [2].

20.4 Inspection Process

Generally, inspections are conducted by either one or two inspectors and may last for 1 week depending on the study [2]. All site personnel who had a significant role in the conduct of the trial should be present during the inspection – principal investigator (PI), sub-investigators (SIs), study coordinator (SC), radiologists, lab personnel and pharmacists [2]. Sponsor

representatives may be present at the site to facilitate the process; however, it should be clearly understood by all personnel that site inspection and site personnel should be at the forefront. Undue interference by sponsors may not be taken well by the inspectors [2].

The inspection starts with an opening meeting at which introductions are made, and the purpose of the inspection is discussed. The PI/representative makes a general presentation about the site and study and addresses initial questions from inspectors. It is an appropriate time to discuss the inspection schedule, availability of site personnel, logistic arrangements, etc. to ensure the smooth performance of the inspection, with minimum interference in routine site schedules. If there have been important deviations from GCP, it might be wise to be frank with the inspectors and explain why they occurred and how measures were taken to prevent them from happening again [2].

The inspection generally involves a facility tour to evaluate site infrastructure as well as the site's (written) standard operation procedures and processes for their adequacy to conduct clinical trials. It may include laboratories (if study-related laboratory tests were done locally) and a review of laboratory equipment, process, calibrations, quality control methods, accreditation documents and training and handling of study-specific laboratory queries; radiology/other equipment used in the study, their calibration and maintenance schedule; archival storage area for documents and its security, pest controls, humidity and fire controls; investigational drug storage accessibility, security, storage conditions, temperature records, thermometer calibrations, stock checks, labelling and accountability logs; and outpatient department and clinical trial facility [2].

The inspection focus is on the investigator's role in the study, the delegation of duties (with documentation), qualification of site staff and ethical issues including the consent process and ethics committee review [2].

The data review generally includes subject history, informed consent, subject eligibility, investigational drug administration, compliance, safety reporting, compliance with study procedures and other study-specific issues. There is frequent interaction between inspectors and site personnel to clarify points and issues and to provide supporting documents [2].

The inspection also involves team member interviews – PI, SI, SC and laboratory personnel, among others. The sponsor/monitor may also be interviewed to evaluate their supervision, protocol knowledge and adequacy to identify and resolve issues [2].

The inspectors may also focus on insurance coverage for subjects and a disaster plan in case of an emergency like fire or flood, among other related matters [2].

At the end, there is an exit meeting where findings are shared with site and sponsor personnel. Only if the investigator agrees, the sponsor may attend the closeout meeting. This also provides an opportunity for site personnel to clarify any points concerning the findings or to provide a better context for some of the points raised [2].

20.5 Communication of Results

The FDA may issue a list of findings referred to as FD483, which is handed over to the principal investigator at the end of the inspection. A detailed inspection report is issued to the site, and inspection results are entered into the FDA database. The findings are classified into the following: no action indicated, no objectionable conditions or practices were found during the inspection; voluntary action indicated, objectionable conditions were found but the problems do not justify further regulatory

action and any corrective action is left to the investigator to take voluntarily; and official action indicated, objectionable conditions were found and regulatory and/or administrative sanctions by the FDA are indicated [2].

While not all FDA inspections require a written response, in general practice, the site/sponsor will review the findings, analyse the root cause and submit an effective CAPA plan to the FDA within 15 days [2].

The reporting inspector on behalf of the EMA also issues a report of the main findings to the company inspected. The findings are classified into critical, major and minor. The site and sponsor have to provide response/remedial actions within 15 days [2].

Some national health authorities may give a 30-day timeline for a response [2].

20.6 Common Findings

Protocol noncompliance, inadequate/inaccurate records, inadequate drug accountability, informed consent issues and adverse event reporting were some of the most common findings observed during recent FDA inspections. The warning letter clearly demonstrates that GCP violations are unacceptable; in the event they occur, immediate and effective action is expected. The principal investigator is responsible for the site's compliance to GCP norms and will be held accountable for noncompliance; lack of or delayed action plans to resolve and prevent the issues may result in further actions by the FDA. In addition, the sponsor may be criticised for not having identified the issues and not taking action, such as holding further patient enrolment until the issues were resolved or had improved [2].

References

1. Surviving an FDA inspection of your clinical trial site. Emissary guiding clinical development. http://emissary.com/16-clinical-research-articles/focus-on-clinical-investigators-a-coordinators/42-fda-inspection. Accessed online at 20 Oct 2015.
2. Marwah R, Van de Voorde K, Parchman J. Good clinical practice regulatory inspections: lessons for Indian investigator sites. Perspect Clin Res. 2010;1(4):151–5. doi:10.4103/2229-3485.71776.

Chapter 21
Ethics: Institutional Review Board/Independent Ethics Committee (IRB/IEC)

21.1 Responsibilities

1. 'An IRB/IEC should safeguard the rights, safety, and well being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects'.
2. 'The IRB/IEC should obtain the following documents':

   'Trial protocol(s)/amendment(s), written ICF(s) and consent form updates that the investigator proposes to use in the trial, subject recruitment procedures (e.g. advertisements), written information to be provided to subjects, IB, available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may require to fulfil its responsibilities. The IRB/IEC should review a proposed clinical trial within a reasonable time and document their views in writing, clearly identifying the trial, the documents reviewed, and the dates for the following':

   - 'Approval/favourable opinion'
   - 'Modifications required prior to its approval/favourable opinion'

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- 'Disapproval/negative opinion'
- 'Termination/suspension of any prior approval/favourable opinion'

3. 'The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests'.
4. 'The IRB/IEC should conduct a continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year'.
5. 'The IRB/IEC may request more information. In the judgment of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety, and/or well being of the subjects'.
6. 'When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative, the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately address relevant ethical concerns and meet applicable regulatory requirements for such trials'.
7. 'Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible, the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately address relevant ethical concerns and meet applicable regulatory requirements for such trials (i.e. in emergency situations)'.
8. 'The IRB/IEC should review both the amount and method of payment to subjects to ensure that neither presents problems of coercion or of undue influence on the trial subjects. Payments to a subject should be pro-rated and not wholly contingent on completion of the trial by the subject'.
9. 'The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written ICF and any other written information to be provided to subjects. The way in which payment will be pro-rated should be specified [1–3]'.

21.2 Composition, Functions and Operations

1. 'The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include':

   (a) 'At least five members'
   (b) 'At least one member whose primary area of interest is in a non-scientific area'
   (c) 'At least one member who is independent of the institution/trial site'

   'Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter. A list of IRB/IEC members and their qualifications should be maintained'.
2. 'The IRB/IEC should perform its functions according to written operating procedures, maintain written records of its activities and minutes of its meetings, and comply with the GCP and applicable regulatory requirement(s)'.
3. 'An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present'.
4. 'Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise'.
5. 'The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC'.
6. 'An IRB/IEC may invite non-members with expertise in special areas for assistance [1–3]'.

21.3 Procedures

'The IRB/IEC should establish, document in writing, and follow its procedures, which should include':

1. 'Determining its composition (names and qualifications of the members) and the authority under which it is established'
2. 'Scheduling, notifying its members of, and conducting, its meetings'
3. 'Conducting initial and continuing review of trials'
4. 'Determining the frequency of a continuing review, as appropriate'
5. 'Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC'
6. 'Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial'
7. 'Specifying that no deviations from, or changes to, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change of monitor(s), telephone number(s))'
8. 'Specifying that the investigator should promptly report to the IRB/IEC':

    (a) 'Deviations from, or changes to, the protocol to eliminate immediate hazards to the trial subjects'
    (b) 'Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial'
    (c) 'All ADRs that are both serious and unexpected'
    (d) 'New information that may affect adversely the safety of the subjects or the conduct of the trial'

9. ‘Ensuring that the IRB/IEC promptly notifies in writing the investigator/institution concerning’:

   (a) ‘Its trial-related decisions/opinions’
   (b) ‘The reasons for its decisions/opinions’
   (c) ‘Procedures for appeal of its decisions/opinions [1–3]’

21.4 Records

‘The IRB/IEC should retain all relevant records (e.g. written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies)’.

‘The IRB/IEC may be asked by investigators, sponsors, or regulatory authorities to provide copies of its written procedures and membership lists [1–3]’.

References

1. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH, Apr 1996.
2. Hutchinson D. The trial investigator’s GCP handbook: a practical guide to ICH requirements. Brookwood Medical Publications Ltd. Surrey, UK, 1997.
3. Committee: ICHS: ICH Harmonised Tripartite Guideline for Good Clinical Practice. Second publication, Brookwood Medical Publications Ltd.; Richmond, Surrey, UK, 1997.

Chapter 22
Responsibilities of the Investigator

22.1 Investigator's Qualifications and Agreements

1. 'The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through an up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies)'.
2. 'The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current IB, in the product information, and in other information sources provided by the sponsor'.
3. 'The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements'.
4. 'The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies)'.

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5. 'The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties' [1–3].

22.2 Adequate Resources

1. 'The investigator should be able to demonstrate (e.g. based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period'.
2. 'The investigator should have sufficient time to conduct and complete the trial properly within the agreed trial period'.
3. 'The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely'.
4. 'The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions [1–3]'.

22.3 Medical Care of Trial Subjects

1. 'A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions'.
2. 'During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to the subject for any AEs, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical

care is needed for intercurrent illness(es) of which the investigator becomes aware'.
3. 'It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed'.
4. 'Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights [1–3]'.

22.4 Communication with IRB/IEC

1. 'Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, a written ICF, consent form updates, subject recruitment procedures (e.g. advertisements), and any other written information that is to be provided to subjects'.
2. 'As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the IB. If the IB is updated during the trial, the investigator/institution should supply a copy of the updated IB to the IRB/IEC'.
3. 'During the trial the investigator/institution should provide to the IRB/IEC all documents subject to its review [1–3]'.

22.5 Compliance with Protocol

1. 'The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and that which was

given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement'.

2. 'The investigator should not implement any deviation from, or changes to, the protocol without the agreement of the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change of monitor(s), change of telephone number(s))'.
3. 'The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol'.
4. 'The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted':

   (a) 'To the IRB/IEC for review and approval/favourable opinion'
   (b) 'To the sponsor for agreement and, if required'
   (c) 'To the regulatory authority(ies) [1–3]'

22.6 Investigational Product(s)

1. 'Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution'.
2. 'Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to

an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution'.

3. 'The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor'.
4. 'The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s)'.
5. 'The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol'.
6. 'The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly [1–3]'.

22.7 Randomisation Procedures and Unblinding

'The investigator should follow the trial's randomisation procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g. accidental unblinding, unblinding due to a serious AE) of the investigational product(s) [1–3]'.

22.8 Informed Consent of Trial Subjects

1. 'In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Before the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written ICF and any other written information that is to be provided to subjects'.
2. 'The written ICF and any other written information that is to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written ICF, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented'.
3. 'Neither the investigator nor the trial staff should coerce or unduly influence a subject to participate or to continue to participate in a trial'.
4. 'None of the oral and written information concerning the trial, including the written ICF, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence'.
5. 'The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable

representative, of all pertinent aspects of the trial including the written information given approval/favourable opinion by the IRB/IEC'.

6. 'The language used in the oral and written information about the trial, including the written ICF, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable'.
7. 'Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative'.
8. 'Prior to a subject's participation in the trial, the written ICF should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed-consent discussion'.
9. 'If a subject is unable to read, or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed-consent discussion. After the written informed-consent form and any other written information that is to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed-consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's

legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative'.

10. 'Both the informed-consent discussion and the written informed-consent form and any other written information to be provided to subjects should include explanations of the following':

    (a) 'That the trial involves research'.
    (b) 'The purpose of the trial'.
    (c) 'The trial treatment(s) and the probability for random assignment to each treatment'.
    (d) 'The trial procedures to be followed, including all invasive procedures'.
    (e) 'The subject's responsibilities'.
    (f) 'Those aspects of the trial that are experimental'.
    (g) 'The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant'.
    (h) 'The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this'.
    (i) 'The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks'.
    (j) 'The compensation and/or treatment available to the subject in the event of trial-related injury'.
    (k) 'The anticipated pro-rated payment, if any, to the subject for participating in the trial.
    (l) The anticipated expenses, if any, to the subject for participating in the trial'.
    (m) 'That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled'.

(n) 'That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written ICF, the subject or the subject's legally acceptable representative is authorising such access'.

(o) 'That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential'.

(p) 'That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial'.

(q) 'The person(s) to contact for further information regarding the trial and the rights of trial subjects, and who to contact in the event of trial-related injury'.

(r) 'The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated'.

(s) 'The expected duration of the subject's participation in the trial'.

(t) 'The approximate number of subjects involved in the trial'.

11. 'Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed-consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's

legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects'.

12. 'When a clinical trial (therapeutic or nontherapeutic) includes subjects who can be enrolled in the trial only with the consent of the subject's legally acceptable representative (e.g. minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should assent, sign and personally date the written informed consent'.
13. 'A non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written informed-consent form'.
14. 'Non-therapeutic trials may be conducted in subjects with the consent of a legally acceptable representative provided the following conditions are fulfilled':

    (a) 'The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally'.
    (b) 'The foreseeable risks to the subjects are low'.
    (c) 'The negative impact on the subject's well being is minimized and low'.
    (d) 'The trial is not prohibited by law'.
    (e) 'The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favourable opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed'.

15. ‘In emergency situations, when prior consent of the subject is not possible, the consent of the subject’s legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject’s legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety, and well being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject’s legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested [1–3]’.

22.9 Records and Reports

1. ‘The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in CRFs and in all required reports’.
2. ‘Data reported on CRFs, which are derived from source documents, should be consistent with the source documents or any discrepancies should be explained’.
3. ‘Any change or correction to a CRF should be dated, initialled, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections. Sponsors should provide guidance to investigators and/or the investigators’ designated representatives on making such corrections. Sponsors should have written procedures to ensure that changes or corrections in CRFs made by sponsor’s designated representatives are documented, necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections’.

4. 'The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents'.
5. 'Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained'.
6. 'The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution'.
7. 'Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records [1–3]'.

22.10 Progress Reports

1. 'Where required by the applicable regulatory requirements, the investigator should submit written summaries of the trial's status to the institution. The investigator/institution should submit written summaries of the status of the trial to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC'.
2. 'The investigator should promptly provide written reports to the sponsor, the IRB/IEC, and, where required by the

applicable regulatory requirements, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects [1–3]'.

22.11 Safety Reporting

1. 'All SAEs should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g. IB) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious ADRs to the regulatory authority(ies) and the IRB/IEC'.
2. 'Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the periods specified by the sponsor in the protocol'.
3. 'For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g. autopsy reports and terminal medical reports) [1–3]'.

22.12 Premature Termination or Suspension of a Trial

'If a trial is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the

subjects and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition':

1. 'If the investigator terminates or suspends a trial without the prior agreement of the sponsor, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension'.
2. 'If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC with a detailed written explanation of the termination or suspension'.
3. 'If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see Sects. 3.1.2 and 3.3.9), the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension [1–3]'.

22.13 Final Report(s) by Investigator/Institution

'Upon completion of the trial, the investigator should, where required by the applicable regulatory requirements, inform the institution, and the investigator/institution should provide the sponsor with all required reports, the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any report(s) they require of the investigator/institution [1–3]'.

References

1. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH, April 1996.
2. Hutchinson D. The Trial Investigator's GCP handbook: a practical guide to ICH requirements. Brookwood Medical Publications Ltd.; Surrey, UK, 1997.
3. Committee: ICHS: ICH Harmonised Tripartite Guideline for Good Clinical Practice. Second publication, Brookwood Medical Publications Ltd.; Richmond, Surrey, UK, 1997.

Chapter 23
Responsibilities of the Sponsor

23.1 Quality Assurance and Quality Control

1. 'The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s)'.
2. 'The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities'.
3. 'Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly'.
4. 'Agreements, made by the sponsor with the investigator/institution and/or with any other parties involved with the clinical trial should be in writing, as part of the protocol or in a separate agreement [1–3]'.

C. Cingi, N. Bayar Muluk, *Quick Guide to Good Clinical Practice*,
DOI 10.1007/978-3-319-44344-7_23,

23.2 Contract Research Organisation (CRO)

1. 'A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control'.
2. 'Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing'.
3. 'Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor'.
4. 'All references to a sponsor in this guidance also apply to a CRO to the extent that a CRO has assumed the trial-related duties and functions of a sponsor [1–3]'.

23.3 Medical Expertise

'The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial-related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose [1–3]'.

23.4 Trial Design

1. 'The sponsor should utilize qualified individuals (e.g. bio-statisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analysing and preparing interim and final clinical trial/study reports'.

2. ‘For further guidance see: Clinical Trial Protocol and Protocol Amendment(s), the ICH Guidance for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol, and conduct [1–3]’.

23.5 Trial Management, Data Handling, Record-Keeping and Independent Data Monitoring Committee

1. ‘The sponsor should utilise appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports’.
2. ‘The sponsor may consider establishing an independent DMC (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings’.
3. ‘When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should’:
   (a) ‘Ensure and document that the electronic data processing system(s) conforms to the sponsor’s established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation)’.
   (b) ‘Maintain SOPs for using these systems’.
   (c) ‘Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail)’.

(d) ‘Maintain a security system that prevents unauthorised access to the data’.
(e) ‘Maintain a list of the individuals who are authorised to make data changes’
(f) ‘Maintain adequate backup of the data’.
(g) ‘Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing)’.

4. ‘If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data’.
5. ‘The sponsor should use an unambiguous subject identification code that allows identification of all the data reported for each subject’.
6. ‘The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial’.
7. ‘The sponsor should retain all sponsor-specific essential documents in conformity with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s)’.
8. ‘If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformity with the applicable regulatory requirement(s)’.
9. ‘If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the appropriate regulatory authorities’.
10. ‘Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s)’.

11. ‘The sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor’.
12. ‘The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial-related records are no longer needed [1–3]’.

23.6 Investigator Selection

1. ‘The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources to properly conduct the trial for which the investigator is selected. If a coordinating committee and/or coordinating investigator(s) are to be utilised in multicenter trials, their organisation and/or selection are the sponsor’s responsibility’.
2. ‘Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date IB, and should provide sufficient time for the investigator/institution to review the protocol and the information provided’.
3. ‘The sponsor should obtain the investigator’s/institution’s agreement’:

(a) 'To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC';
(b) 'To comply with procedures for data recording/reporting: and'
(c) 'To permit monitoring, auditing, and inspection'
(d) 'To retain the essential documents that should be in the investigator/institution files until the sponsor informs the investigator/institution these documents are no longer needed. The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement [1–3]'.

23.7 Allocation of Duties and Functions

'Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions [1–3]'.

23.8 Compensation to Subjects and Investigators

1. 'If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence'.
2. 'The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s)'.

3. ‘When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s) [1–3]’.

23.9 Financing

‘The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution [1–3]’.

23.10 Notification/Submission to Regulatory Authority(ies)

‘Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)), should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol [1–3]’.

23.11 Confirmation of Review by IRB/IEC

1. ‘The sponsor should obtain from the investigator/institution’:
   (a) ‘The name and address of the investigator’s/institution’s IRB/IEC’
   (b) ‘A statement obtained from the IRB/IEC that it is organised and operates in accordance with GCP and the applicable laws and regulations’

(c) 'Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written ICF(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested'

2. 'If the IRB/IEC conditions its approval/favourable opinion upon change(s) in relation to any aspect of the trial, such as modification(s) of the protocol, written ICF and any other written information that is to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favourable opinion was given by the IRB/IEC'.
3. 'The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC re-approvals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of approval/favourable opinion [1–3]'.

23.12 Information on Investigational Product(s)

1. 'When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied'.
2. 'The sponsor should update the IB as significant new information becomes available [1–3]'.

23.13 Manufacturing, Packaging, Labelling and Coding Investigational Product(s)

1. 'The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterised as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s)'.
2. 'The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations'.
3. 'The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage'.
4. 'In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding'.
5. 'If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials [1–3]'.

23.14 Supplying and Handling Investigational Product(s)

1. 'The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s)'.
2. 'The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favourable opinion from IRB/IEC and regulatory authority(ies))'.
3. 'The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) during the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorised by the sponsor and in compliance with the applicable regulatory requirement(s))'.
4. 'The sponsor should':

   (a) 'Ensure timely delivery of investigational product(s) to the investigator(s)'.
   (b) 'Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s)'.
   (c) 'Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim)'.
   (d) 'Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition'.

5. ‘The sponsor should’:
   (a) ‘Take steps to ensure that the investigational product(s) are stable over the period of use’.
   (b) ‘Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period [1–3]’.

23.15 Record Access

1. ‘The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection’.
2. ‘The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection [1–3]’.

23.16 Safety Information

1. ‘The sponsor is responsible for the ongoing safety evaluation of the investigational product(s)’.
2. ‘The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies)

of findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial [1–3]'.

23.17 Adverse Drug Reaction Reporting

1. 'The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all ADRs that are both serious and unexpected'.
2. 'Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting'.
3. 'The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s) [1–3]'.

23.18 Monitoring

23.18.1 Purpose

'The purposes of trial monitoring are to verify that':

(a) 'The rights and well being of human subjects are protected'.
(b) 'The reported trial data are accurate, complete, and verifiable from source documents'.
(c) 'The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s) [1–3]'.

23.18.2 Selection and Qualifications of Monitors

(a) 'Monitors should be appointed by the sponsor'.
(b) 'Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented'.
(c) 'Monitors should be thoroughly familiar with the investigational product(s), the protocol, written ICF and any other written information that is to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s) [1–3]'.

23.18.3 Extent and Nature of Monitoring

'The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance, can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified [1–3]'.

23.18.4 Monitor's Responsibilities

'The monitor(s), in accordance with the sponsor's requirements, should ensure that the trial is conducted and documented

properly by carrying out the following activities when relevant and necessary to the trial and the trial site':

(a) 'Acting as the main line of communication between the sponsor and the investigator'.
(b) 'Verifying that the investigator has adequate qualifications and resources (and these remain adequate throughout the trial period), and that the staff and facilities, including laboratories and equipment, are adequate to safely and properly conduct the trial (and that these remain adequate throughout the trial period)'.
(c) 'Verifying, for the investigational product(s)':

    (i) 'That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial'
    (ii) 'That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s)'
    (iii) 'That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s)'
    (iv) 'That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately'
    (v) 'That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor's authorised procedures'

(d) 'Verifying that the investigator follows the approved protocol and all approved amendment(s), if any'.
(e) 'Verifying that written informed consent was obtained before each subject's participation in the trial'.
(f) 'Ensuring that the investigator receives the current IB, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s)'.

(g) 'Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial'.
(h) 'Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorised individuals'.
(i) 'Verifying that the investigator is enrolling only eligible subjects'.
(j) 'Reporting the subject recruitment rate'.
(k) 'Verifying that source data/documents and other trial records are accurate, complete, kept up-to-date, and maintained'.
(l) 'Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial'.
(m) 'Checking the accuracy and completeness of the CRF entries, source data/documents, and other trial-related records against each other'.

'The monitor specifically should verify that':

(i) 'The data required by the protocol are reported accurately on the CRFs and are consistent with the source data/documents'.
(ii) 'Any dose and/or therapy modifications are well documented for each of the trial subjects'.
(iii) 'Adverse events, concomitant medications, and intercurrent illnesses are reported in accordance with the protocol on the CRFs'.
(iv) 'Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs'.
(v) 'All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs'.

(n) 'Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorised to initial CRF changes for the investigator. This authorisation should be documented'.
(o) 'Determining whether all AEs are appropriately reported within the time periods required by GCP, and the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s)'.
(p) 'Determining whether the investigator is maintaining the essential documents'.
(q) 'Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations [1–3]'.

23.18.5 Monitoring Procedures

'The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial [1–3]'.

23.18.6 Monitoring Report

(a) 'The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication'.
(b) 'Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted'.

(c) ‘Reports should include a summary of what the monitor reviewed and the monitor’s statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance’.
(d) ‘The review and follow-up of the monitoring report by the sponsor should be documented by the sponsor’s designated representative [1–3]’.

23.19 Audit

‘If or when sponsors perform audits, as part of implementing quality assurance, they should consider [1–3]’.

23.19.1 Purpose

‘The purpose of a sponsor’s audit, which is independent of, and separate from, routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements’.

23.19.2 Selection and Qualifications of Auditors

(a) ‘The sponsor should appoint individuals who are independent of the clinical trial/data collection system(s) to conduct audits’.
(b) ‘The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor’s qualifications should be documented [1–3]’.

23.19.3 Auditing Procedures

(a) 'The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports'.
(b) 'The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s)'.
(c) 'The observations and findings of the auditor(s) should be documented'.
(d) 'To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case-by-case basis, when evidence of serious GCP noncompliance exists, or in the course of legal proceedings'.
(e) 'Where required by applicable law or regulation, the sponsor should provide an audit certificate [1–3]'.

23.20 Noncompliance

1. 'Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by any member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance'.
2. 'If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's

participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should promptly notify the regulatory authority(ies) [1–3]'.

23.21 Premature Termination or Suspension of a Trial

'If a trial is terminated prematurely or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s) [1–3]'.

23.22 Clinical Trial/Study Reports

'Regardless of whether a trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial/study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial/study reports in marketing applications meet the standards of the ICH Guidance for Structure and Content of Clinical Study Reports. (The ICH Guidance for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.) [1–3]'.

23.23 Multicentre Trials

For multicentre trials, the sponsor should ensure that:

1. 'All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given an approval/favourable opinion by the IRB/IEC'.
2. 'The CRFs are designed to collect the required data at all multicenter trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to collect the additional data'.
3. 'The responsibilities of the coordinating investigator(s) and the other participating investigators are documented before the start of the trial'.
4. 'All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs'.
5. 'Communication between investigators is facilitated [1–3]'.

References

1. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH, April 1996.
2. Hutchinson D. The Trial Investigator's GCP handbook: a practical guide to ICH requirements. Brookwood Medical Publications Ltd.; Surrey, UK, 1997.
3. Committee: ICHS: ICH Harmonised Tripartite Guideline for Good Clinical Practice. Second publication, Brookwood Medical Publications Ltd.; Richmond, Surrey, UK, 1997.

Chapter 24
Clinical Trial Protocols

'The contents of a trial protocol should generally include the following topics. However, site-specific information may be provided on a separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol-referenced documents, such as an IB'.

24.1 General Information

1. 'Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s)'.
2. 'Name and address of the sponsor and monitor (if other than the sponsor)'.
3. 'Name and title of the person(s) authorised to sign the protocol and the protocol amendment(s) for the sponsor'.

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see http://www.textcheck.com/certificate/6YXd9a.

C. Cingi, N. Bayar Muluk, *Quick Guide to Good Clinical Practice*,
DOI 10.1007/978-3-319-44344-7_24,

4. 'Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial'.
5. 'Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s)'.
6. 'Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable) who is responsible for all trial-site-related medical (or dental) decisions (if other than investigator)'.
7. 'Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial [1–3]'.

24.2 Background Information

1. 'Name and description of the investigational product(s)'
2. 'A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial'
3. 'Summary of the known and potential risks and benefits, if any, to human subjects'
4. 'Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s)'
5. 'A statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s)'
6. 'Description of the population to be studied'
7. 'References to literature and data that are relevant to the trial, and that provide background for the trial [1–3]'

24.3 Trial Objectives and Purpose

'A detailed description of the objectives and the purpose of the trial [1–3]'.

24.4 Trial Design

'The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include':

1. 'A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial'
2. 'A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages'
3. 'A description of the measures taken to minimise/avoid bias, including (for example)':

   (a) 'Randomisation'
   (b) 'Blinding'

4. 'A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s)'
5. 'The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any'
6. 'A description of the 'stopping rules' or 'discontinuation criteria' for individual subjects, parts of trial, and entire trial'
7. 'Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any'
8. 'Maintenance of trial treatment randomisation codes and procedures for breaking codes'
9. 'The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data [1–3]'

24.5 Selection and Withdrawal of Subjects

1. 'Subject inclusion criteria'.
2. 'Subject exclusion criteria'.
3. 'Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying':
   (a) 'When and how to withdraw subjects from the trial/investigational product treatment'
   (b) 'The type and timing of the data to be collected for withdrawn subjects'
   (c) 'Whether and how subjects are to be replaced'
   (d) 'The follow-up for subjects withdrawn from investigational product treatment/trial treatment [1–3]'

24.6 Treatment of Subjects

1. 'The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial'
2. 'Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial'
3. 'Procedures for monitoring subject compliance [1–3]'

24.7 Assessment of Efficacy

1. 'Specification of the efficacy parameters'
2. 'Methods and timing for assessing, recording, and analysing efficacy parameters [1–3]'

24.8 Assessment of Safety

1. 'Specification of safety parameters'
2. 'The methods and timing for assessing, recording, and analysing safety parameters'
3. 'Procedures for eliciting reports of, and for recording and reporting, AEs and intercurrent illnesses'
4. 'The type and duration of the follow-up of subjects after AEs [1–3]'

24.9 Statistics

1. 'A description of the statistical methods to be employed, including timing of any planned interim analysis(ses)'.
2. 'The number of subjects planned to be enrolled. In multicenter trials, the number of enrolled subjects projected for each trial site should be specified. Reasons for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification'.
3. 'The level of significance to be used'.
4. 'Criteria for the termination of the trial'.
5. 'Procedure for accounting for missing, unused, and spurious data'.
6. 'Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate)'.
7. 'The selection of subjects to be included in the analyses (e.g. all randomised subjects, all dosed subjects, all eligible subjects, subjects suitable for evaluation) [1–3]'.

24.10 Direct Access to Source Data/Documents

'The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents [1–3]'.

24.11 Quality Control and Quality Assurance

Quality Control and Quality Assurance should be performed [1–3]

24.12 Ethics

Description of ethical considerations relating to the trial [1–3]

24.13 Data Handling and Record-Keeping

Data Handling and Record-Keeping should be performed and maintained [1–3]

24.14 Financing and Insurance

'Financing and insurance if not addressed in a separate agreement [1–3]'

24.15 Publication Policy

'Publication policy, if not addressed in a separate agreement [1–3]'

24.16 Supplements

'Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guidance for Structure and Content of Clinical Study Reports [1–3]'.

References

1. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH, April 1996.
2. Hutchinson D. The Trial Investigator's GCP handbook: a practical guide to ICH requirements. Brookwood Medical Publications Ltd.; Surrey, UK, 1997.
3. Committee: ICHS: ICH Harmonised Tripartite Guideline for Good Clinical Practice. Second publication, Brookwood Medical Publications Ltd.; Richmond, Surrey, UK, 1997.