Lesson 1: Clinical Trials Overview

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1. Introduction: What is a clinical trial?

- **Clinical Research video**
  - **https://vimeo.com/69337236**

Clinical research is an important part of the process of gaining better knowledge and understanding of human health and disease as well as the development of new and effective therapies for treating these diseases. Clinical trials represent an essential component of evidence based medical research.

Clinical trials are research studies involving people (healthy volunteers or patients) that test the safety and efficacy of a new treatment. A 'treatment' in this context could mean:

A medicine.

A medical device - such as a cardiac stent (used for narrow or weak blood vessels).

A surgical procedure.

A test for diagnosing an illness.

A clinical trial can also compare whether a new treatment is better than existing alternatives. No matter how promising a new treatment may appear during initial laboratory tests, clinical trials are necessary to prove and identify benefits and risks in humans. 'Better' in this context does not necessarily mean 'with a better efficacy' but may also signify 'fewer side effects (Adverse Drug Reactions, ADRs)' or 'better handling, less burden' and more. This is sometimes reflected in clinical trial designs which look for equivalence or non-inferiority to an existing treatment.

Clinical trials are designed by groups of doctors, scientists and other specialists. The trial design is usually based on a thorough analysis of existing research, and the recognition that certain questions about treatment, symptom control or side effects need to be answered. To draw up the best possible trial design, discussions involve medical staff, nurses, patients, statistical experts and support staff, as well as representatives from companies or funding agencies. The background, design and plan for the study are contained in a document known as the protocol.

2. How are clinical trials conducted?

To obtain approval for a clinical trial, the Clinical Trial Application (CTA) must be submitted to regulatory bodies called competent authorities. A Research Ethics Committee (REC) also reviews the protocol and gives a positive or negative opinion. This is to ascertain that the research respects the dignity, rights, safety and well-being of the people who are participating. In order to ensure compliance with ethical standards, the majority of clinical trial protocols are developed in line with the 'Declaration of Helsinki', a set of ethical standards for research involving human beings, human material or identifiable data, developed in 1964 by the World Medical Association (WMA) and revised several times.

Clinical trials on medicines are conducted in the United States and the European Union (EU) in compliance with regulations, directives and guidelines. The standard to which clinical trials are conducted is called Good Clinical Practice, as defined in a guideline by the International Conference on Harmonisation (ICH- GCP). This is an international quality standard and describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and ethics committees. GCPs cover aspects of monitoring, reporting and archiving of clinical trial data and incorporating supplements on the Essential Documents and on the Investigator's Brochure which had been agreed earlier through the ICH process.

3. Who conducts medicine clinical trials and why?

Clinical trials typically involve a number of different parties. It is helpful to understand who is leading the creation and the conduct of a trial and why they are doing it:

> A *sponsor* is the body (usually a company, university or hospital) that takes responsibility for organizing the trial and often funds the trial.
>
> An *investigator* (or investigators for multi-center trials) - the doctor(s) responsible for the performance of the trial.

Sometimes the sponsor will engage a contract research organization (CRO) to help with the logistics (organization) and the conduct of the trial.

Sponsors can be companies or government funded institutions/agencies. Both may perform trials in order to use the gathered data to support applications that will allow promotion and marketing of products for the approved indication(s).

They may also undertake studies in the best interests of the community to understand diseases. Occasionally they will collaborate with other partners to explore a particular problem, perhaps one that is not of commercial interest but is of interest to patients and the healthcare system.

Lesson 2A: Historical Overview

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1. Historical overview

Medicine, like other health and social sciences, is not an exact science. For example, ‘established treatments’ might not be suitable for some patients, might not work well for others and some patients simply cannot access them.

This means that research is important, because: established treatments need to be monitored and evaluated to find out when they are effective, i.e. when they work well.

We are always looking for new treatments.

Medicine is ‘experimental’, i.e. we learn as we go by using new ideas and techniques.

New diseases and conditions emerge and we need to find out how to treat them.

Research is critical in improving health. Over the past century, there has been great progress in scientific and medical research.

This includes the development of many new medicines, devices and techniques such as surgical, transplant and transfusion procedures. The field of health research has expanded tremendously in the past half century in terms of both:

Financial investment - more money is put into health research.

Diversity - more and more areas are considered and studied, including:

The factors that might affect health in defined populations (epidemiology), genes (genetics), humans and social behavior (anthropology and sociology), the factors that might affect access to health care (health systems research).

We have expanded our knowledge however gaps do remain. The knowledge and tools available are not always adequate to tackle existing health problems. There is a constant need to generate new information and develop improved and more effective ways of protecting and promoting health and reducing disease. Further advances in these areas require research involving human participants.

Research ethics aims to promote high standards of behavior in the conduct of research involving humans. It does this through an awareness of relevant values, principles and rules.

2. The evolution of research ethics

Research involving humans has been part of medicine for centuries. In the nineteenth century, the adoption of the experimental method in both science and medicine generated significant progress in research involving humans. However, when animal experimentation became current practice, some scientists, mainly physicians, began to question whether research on humans was needed. Various ethical debates arose within the scientific community regarding the appropriateness of such research.

By the beginning of the twentieth century, the idea of conducting research involving humans was becoming more acceptable as long as extensive studies were first conducted on animals. With the development of bacteriology (the study of bacteria) and the rise of pharmaceutical companies, the number of animals and humans used in research increased significantly.

Research in bacteriology at the end of the nineteenth century and the beginning of the twentieth century involved some ethically unacceptable practices. For example, infectious agents were injected in orphans, mentally disabled persons and prisoners without their consent or knowledge. Various other experiments were reported involving use of electric shocks on vulnerable individuals.

There had been some attempt to regulate human experimentation. For example:

> The Prussian Minister of Religious, Educational and Medical Affairs circulated a guideline on human experimentation in 1900. The German Reich Ministry of the Interior issued regulations on new therapy and human experimentation in 1931.

Yet, such guidelines were largely ignored. Although medical and scientific associations condemned the practices described above, they did not result in any professional, disciplinary or criminal charges. It is only following World War II and the Nuremberg trials that such charges were made.

3. Nuremberg Code

The Nuremberg trials in 1946 brought the issue of inhuman treatment of some individuals included in 'research' to the attention of the public. In one of the subsequent trials, twenty-three Nazi doctors and administrators were held responsible for the deaths of thousands of concentration camp prisoners who died during and after horrific experiments. The judges' verdict in 1947 included a section entitled 'Permissible Medical Experiments' which described ten principles to be followed in conducting research on humans. Known today as the 'Code of Nuremberg', it states as its first principle that 'the voluntary consent of the human participant is absolutely essential'.

4. The emergence of rules specific to research

More revelations about the inappropriate treatment of humans in research followed the Nuremberg trials and Code. This continued to raise the importance of research ethics and the need for some form of public oversight of research involving humans.

5. The first requirement for independent review

In 1953, the United States (US) established a federal funding requirement for institutional review by an independent committee of proposed research projects involving humans. This rule was limited to research conducted directly within the facilities of the National Institutes of Health (NIH) at Bethesda, Maryland, USA. Yet, the lay membership on these committees showed that biomedical research is an activity of public interest and the public has important views to share on its ethical aspects.

6. The development of international guidelines

The World Medical Association (WMA) published its first version of the Declaration of Helsinki in 1964, which has been revised several times since (last revision 2013). The first revision of the declaration in 1975 stated that protocols for clinical research should be sent to a ‘specially appointed committee for consideration, comment and guidance’. This was the first international statement on the concept of review of research where the review is independent from the researcher, the sponsor or any other influence. However, under the Declaration of Helsinki, the ultimate duty to ensure the protection of human participants remains with doctors.

7. Questionable research practices

During the latter half of the twentieth century, questionable research practices were reported in many different parts of the world. Some events were especially significant since they prompted regulatory activity and increased public scrutiny.

In 1966, Henry Beecher, an American doctor and researcher, described 22 cases of American researchers conducting ethically dubious research involving humans. He concluded that ‘it must be apparent that [participants] would not have been available if they had been truly aware of the uses that were made of them’ [Henry Beecher, Ethics and Clinical Research, 1966]. This was followed by other revelations of misconduct, most notably:

The Willowbrook case - the hepatitis virus was given to institutionalized mentally retarded children in an attempt to understand the natural history of the disease and to test the effect of a protein called ‘gamma globulin’ [US, Advisory Committee on Human Radiation Experiments, Report Chapter 3]

8. The emergence of formal requirements for ethics evaluation

Some events in research ethics are historically significant because they prompted concrete actions. In the Tuskegee syphilis study [US, Advisory Committee on Human Radiation Experiments, Report Chapter 3], researchers observed the effects of untreated syphilis in black men. Started in 1932, it was not until 1972 that revelations about the conduct of the study exposed the need for clearer guidance. A flurry of regulatory activity followed and a US federal statute (National Research Act, 1974) was adopted. This is still in force today. It formally requires research institutions to establish independent, local, multidisciplinary institutional review boards (IRBs). The purpose is to protect human research participants. These institutional review boards in the US have the same role as research ethics committees (RECs), as they are called in the EU and many other countries.

9. Publication of the Belmont Report

During the 1970s, a presidential commission was established in the US. Its aims were to identify ethical principles to guide research on humans and to develop guidelines for researchers and institutions. Its 1979 report, commonly called the Belmont Report, identified three basic principles of research involving humans:

Respect for persons - this requires respecting people’s autonomy (capacity to make informed, independent decisions) and protecting people with diminished autonomy (people who are less able to make informed, independent decisions on their own).

Beneficence - ‘doing good’, where the welfare of the research participant should be the goal of any clinical trial. In order to maintain this, harms should be minimized and benefits should be maximized.

Justice - Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of ‘fairness in distribution’ or ‘what is deserved’. An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. These three principles form the fundamental requirements for ethically acceptable research.

Over the years, the Belmont Report has become the basis of many documents that contain rules and guidelines to oversee ethical conduct in scientific research.

In the past few decades, a number of countries have developed legislation that regulates research involving humans. In many countries, clinical trials with investigational medicines or other products are tightly regulated through specific legislation.

The increase in rules and guidelines internationally has resulted in varying requirements that researchers and sponsors must meet. The International Conference on Harmonization (ICH) was initiated (April 1990) to develop a process to harmonize requirements, Within the clinical trial field the work aimed specifically for international multi-center clinical trials (i.e. trials held at more than one center or clinic). This resulted in the Good Clinical Practice (GCP) guideline.

The GCP guideline aims to:

1. Avoid the duplication of studies by making data generated in trials in one country admissible in other countries,
2. Speed up the medicine's development process. Despite regulatory and legislative provisions, recent history reminds us of the need for continued vigilance. The have been a number of cases where the basic principles of human research have not been followed. You can read about some of these examples in Further Reading (Optional).

10. Why research gets evaluated

There have been a number of examples of ethically questionable research. In some rare cases, significant violations resulted in criminal sanctions. These latter cases aside, many of the former unethical situations were rooted in the 'dual-role' of doctors who were also researchers.

In addition, it is generally accepted that participation in research may expose individuals to harm that they would not otherwise experience. This is one of the reasons why research involving humans requires review and approval by an independent REC according to accepted standards. This review serves to assess the ethical acceptability of research studies and helps researchers improve the quality of their projects.

The doctor's role [that can be extended to other healthcare providers] in the doctor-patient relationship is different from the researcher's role in the researcher-participant relationship, even if the doctor and the researcher are the same person. The doctor's primary responsibility is the health and well-being of the patient, whereas the researcher's primary responsibility is the generation of knowledge, which may or may not contribute to the research participant's health and well-being. Thus, there is a potential for conflict between the two roles. When this occurs, the doctor role must take precedence over the researcher.

Medical research is a well-funded enterprise, and study centers are sometimes offered considerable rewards for participating. These can include cash payments per research participant enrolled, equipment such as computers to transmit the research data, invitations to conferences to discuss the research findings, and co-authorship of publications on the results of the research.

This dual-role is relevant to all healthcare providers who have a relationship of trust with patients and who also conduct research. The potential conflicts between the two roles are minimized by the development and implementation of appropriate legislation and guidelines.

In the context of international collaborative research, there are often inequalities in resources between developed countries, which often sponsor research, and developing countries that host the research. This raises important ethical concerns, including the potential for exploitation. Given the need for research in developing countries, awareness of the risk of exploitation reinforces the need for robust evaluation of research by RECs

Lesson 2B: Values and Concepts of Ethics for Research Involving Humans

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1. Values and concepts of ethics for research involving humans

Ethics in research, like ethics in general, is based on values. Values are abstract concepts, like truth, dignity and fairness, which are widely considered to be of the greatest importance for human well-being. One of the most important statements of values is the 1948 United Nations (UN) Universal Declaration of Human Rights. The role of Research Ethics Committees (RECs) is to ensure that the human rights of participants in research are respected.

Values are often expressed as principles. For the purpose of this training material, the following is a list of principles of ethics that help to protect human rights and dignity and are discussed further in the document below and next lesson:

Justify the inclusion of humans in research by ensuring social value and scientific validity.

Bring about more good than harm.

Promote the interests of humans who participate in research before the interests of science and society.

Ensure voluntary participation - participants must be able to choose to take on the risks of research.

Distribute the risks and potential benefits of research fairly.

Show ongoing respect for persons.

Uphold transparency during the research process.

Because principles of ethics are, by their nature, fairly general, they need to be interpreted and applied to specific situations. One role of ethics is to show how general principles apply in specific situations. When the principles appear to conflict, it is the role of ethics and ethics review committees to identify and manage such conflicts.

There is a rich literature on ethics and its application to research. The analysis and discussion of principles of ethics in these philosophical texts can be useful to RECs faced with new or complex challenges when reviewing research protocols or applying regulations.

1.1. Social value

In light of the ethical principle of respect for persons, the justification for including individuals in a research project depends on the social value of the proposed research. Research will be considered as having value when the hypotheses or questions being researched have potential benefits. These benefits may relate to:

individuals or a particular population or sub-group, to society generally, in relation to an important topic or issue, or

to some combination of the above.

To have social value, a research project should be designed to solve a problem that is relevant to society concerns.

Case study: Malaria Trial

An anti-malarial medicine called atovaquone-proguanil was tested in a developing country. However, it was intended for use by travelers going to areas where malaria is common. Although the research burden was taken by the developing countries, the medicine turned out to be too expensive to be administered in those same countries. Conducting a research study to test new medicines that will not be affordable to the community that bears the burden of the research is an example of research that does not have social value in that community.

1.2. Scientific validity or rigor

A project is scientifically valid if it has the potential to result in facts, reproducible observations or information in relation to the question under study. The phrase ‘scientific validity’ is used here to refer to the need for sound methodology and protocol design that is likely to lead to reliable conclusions. In qualitative research (i.e. research that looks at observations and descriptions rather than measurements and numbers), instead of scientific validity, research must have scientific rigor. In other words, it must use the appropriate research tools to meet the objectives of the study.

Research involving human participants that lacks scientific validity or rigor is inherently unethical. This is because it exposes participants to risks of harm or inconvenience without foreseeable benefit. This goes against the overarching principle of respect for persons and it is a waste of resources.

2. Bringing about more good than harm

In an ideal world, research might always 'do well' (i.e. beneficence) and 'not do harm' (i.e. non-maleficence). However, in today's world, a more realistic goal for research is to try to bring about more good than harm while avoiding unnecessary or disproportionate harm. Any harm caused by the research should be outweighed by the good that researchers hope to achieve. Thus, researchers should optimize the potential benefits of their research (e.g. health, safety, knowledge, satisfaction), and try to minimize the risks of unwanted effects associated with the research (e.g. reduced health, pain, exploitation, inconvenience, emotional burden).

Researchers have to take these principles into account when designing their projects in order to ensure that all risks have been minimized to the greatest extent possible and that remaining risks are justified in the context of the question being studied.

In conducting their review, RECs should pay particular attention to the well-being of research participants. However, they should also consider the potential benefits and risks for others, including those who may benefit from the results of the research.

The interests of persons who take part in trials as research participants should be of highest importance. It is central to ensuring respect for human dignity. This means that patients should not be entered into studies, no matter how important, if they are likely to suffer an unacceptable or unreasonable level of harm.

3. The interests of humans who participate in research must come before the interests of science and society

The interests of persons who take part in trials as research participants should be of highest importance. It is central to ensuring respect for human dignity. This means that patients should not be entered into studies, no matter how important, if they are likely to suffer an unacceptable or unreasonable level of harm.

4. Voluntary participation: choosing to take on the risks of research

Individuals are self-governing. This means that:

- Within limits set by society, people generally control or shape their own lives in significant and meaningful ways.
- They have personal goals, values and preferences.
- They can make and act on plans for themselves and their lives. This will take into account goals, values, preferences, the options before them and other matters

This self-governing ability is called 'autonomy'. It is often thought to be what sets humans apart from other beings. It is considered valuable and worth protecting. Autonomy is held in such high regard that it is considered part of the integrity of a person, that is, part of what makes a person complete or whole.

Historically, this principle is connected to the idea that all persons have intrinsic worth or value. This is independent of any special circumstances that might grant that person value. In other words, it doesn't matter who that person is or what they do, they still have value. Actively showing respect for the autonomy of others involves due appreciation of their abilities and opinions.

This includes their rights to: hold certain views make certain choices, and take certain actions based on personal values and beliefs.

In research involving human participants, researchers must conduct studies in a way that demonstrates respect for autonomy. This is particularly important when gaining a prospective participant's consent to take part - they must make sure that a participant is able to make their own choice about whether or not to participate in research. Consent is a process that may be achieved in different ways. However, for the consent to be valid or genuine, respect for autonomy is key (among other factors).

In some communities, the values of individuals are dependent on the values of the wider group (e.g. the family and/or community). Before a person can decide whether or not to give their individual consent to participate in research, they may need to consult, inform, or agree with members of their family (e.g. parents, head of household or spouse).

5. Fair distribution of the burden and potential benefits of research

In research ethics, justice refers specifically to the fair distribution of the burden and potential benefits of taking part in research. The meaning of a 'fair distribution' is often debated. Yet typically, researchers respect justice by ensuring that those who share in the burdens of research participation (e.g. by taking experimental medicine) also share in its potential benefits.

A more challenging aspect of justice is ensuring that research results will be accessible to both in general those who will benefit from them and more specifically those who took the research burden.

Planning to exclude groups of individuals from research (systematic exclusion) can also result in unfair distribution of benefits. A group might be excluded or suffer adverse drug reactions due to the lack of specific research on their shared characteristics, such as age, environment or nutrition. Exclusion of an affected group from a single research study might not be problematic on its own, but the exclusion of an affected group from an entire field or programme of research is certainly problematic. It is important to take a global view on systematic exclusion of certain groups and give serious thought to the '90/10 gap', as described below:

Quote from World Health Organization (WHO): 'The majority of biomedical research has been predominantly motivated by concern for the benefit of already privileged communities. This is reflected by the fact that the WHO estimates that 90% of the resources devoted to research and development on medical problems are applied to diseases causing less than 10% of the present global suffering. The establishment of international guidelines that assist in strengthening the capacity for the ethical review of biomedical research in all countries contributes to redressing this imbalance.'

[WHO Operational Guidelines for Ethics Committees, 2000]

6. Showing ongoing respect for persons

In research ethics, respect for humans should be present before a trial starts. This happens when projects are evaluated by RECs to ensure they meet the highest ethical standards and are worthy of participant consent. Continued respect for persons must also be shown during a trial and after it is completed. Some examples of this are:

Any new information that may be relevant to a participant's continued participation should be communicated to that person. They should be given the opportunity to reassess their consent.

Personal information about research participants must be kept confidential. It should not be shared with outside persons, i.e. people not involved in the trial.

The way in which research results are reported and published must be considered carefully to avoid stigmatizing groups and communities that participated in the research.

After the trial is completed, consideration should be given to whether participants in any placebo control group will receive the experimental medicine if it is proven to be effective and whether participants in the trial continue to receive the tested medicine once the trial is complete.

In developing countries, consideration should also be given to whether the wider community will be provided with access to the benefits arising from research. This is a contentious issue with no easy answer.

It is generally agreed that all of these concerns should be addressed before the research starts.

7. Upholding transparency during the research process

'Transparency' here means that an individual or group does not conceal information from others who have a legitimate interest in knowing that information.

Transparency is important in the research context because there are many interests (scientific, corporate, financial, personal, etc.) involved. Some of these interests may compete with each other. Without sufficient transparency, public trust in researchers and research generally may be hindered.

Striving to ensure a transparent research process is an ongoing task, as many factors may need to be addressed. For example, conflicts of interests are common among sponsors, governments, organizations hosting research, researchers and RECs. There are many types of conflicts of interests, some of which are more apparent than others, some manageable and others simply not. In dealing with such conflicts, researchers and RECs should adhere to the principle discussed above, that the interests of research participants should take priority over other types of interests.

One means of ensuring transparency in health research is to keep a registry of clinical trials. In the past, negative results from clinical trials may not have been reported. Starting in 2015, the EU Clinical Trials Register contains summaries of clinical trial results, both positive and negative. https://www.clinicaltrialsregister.eu

Lesson 2C: Overview of Normative Frameworks Applicable to Health Research Involving Humans and Introduction to Research Ethics Evaluation

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1. Overview of normative frameworks applicable to health research involving humans
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3. Institutional requirements

1. Overview of normative frameworks applicable to health research involving humans

The regulation of research involving humans has evolved over the past century. Within the last half century, it has taken the form of rules, guidelines and even state regulations. There is no single instrument that applies to all research involving humans worldwide. However, there are various instruments — some more and some less specific to research — that establish safeguards to oversee the conduct of research involving humans. This section will focus on instruments that are relevant to biomedical or health research.

1.1. International instruments

1.1.1 World Medical Association (WMA), Declaration of Helsinki

The WMA was founded in 1947. It showed concern over the state of medical ethics in general and took up the responsibility for setting ethical guidelines for the world's doctors. The WMA hoped that developing guidelines 'would help to impress on newly qualified doctors the fundamental ethics of medicine and would assist in raising the general standards of professional conduct.'

One of the early guidelines developed by the WMA is the Declaration of Helsinki, which provides recommendations to guide doctors from all over the world in biomedical research involving human participants. The original 1964 text of the Declaration of Helsinki has been revised several times over the years. It has had 'great impact on human experimentation and has served as a starter for establishing ethical committees in various countries to scrutinize research projects on human beings'.

It is referenced in many other international and national documents that address biomedical and other types of research. As such, the Declaration of Helsinki sets the core values that guide biomedical research.

1.1.2 World Health Organization (WHO)

The WHO is involved in many ways in supporting improved ethical standards and review processes for research with human participants. Guidance documents in this field have been developed directly by the WHO and cooperatively with other groups, particularly the Council for International Organizations of Medical Sciences (CIOMS).

Significant documents for researchers and RECs include:

> Operational Guidelines For Ethics Committees That Review Biomedical Research (2000).
>
> International Clinical Trials Registry Platform (ICTRP).

The WHO has also adopted Good Clinical Practice (GCP) guidelines that mirror the ICH-GCP discussed below.

1.1.3 Council for International Organizations of Medical Sciences (CIOMS)

The CIOMS is an international, non-governmental, non-profit organization. It was established jointly by the WHO and the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949. It represents the biomedical scientific community, for example Medical Research Councils.

The CIOMS has issued international guidelines, particularly used in low-resource countries, for the application of ethical principles in various key areas, including:

> International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002),
>
> International Ethical Guidelines for Epidemiological Studies (2009).

The CIOMS guidelines cross-reference the Declaration of Helsinki and add more specific guidance.

1.1.4 International Conference on Harmonization - Good Clinical Practice guidelines (ICH-GCP)

Clinical trials should be carried out according to the GCP guidelines developed by the ICH. Regulatory authorities in a number of countries require adherence to these guidelines. Thus, any country that adopts the ICH-GCP guideline technically follows the same standards when conducting clinical trials. The ICH-GCP is relevant for ethics since they refer to the principles of the Declaration of Helsinki and include guidance on various ethics-related processes and procedures. This includes ethics evaluation, investigator qualification, consent and confidentiality.

1.1.5 Other instruments

In addition to the texts described above, there are a number of other international instruments relevant to research involving humans that are broader in scope. For example, UNESCO has adopted several declarations, including:

- Universal Declaration on Bioethics and Human Rights.
- Universal Declaration on the Human Genome and Human Rights.

Such declarations provide guidance by establishing fundamental principles in their respective fields.

In the EU, the key standards are set by commission directive 2001/20/EC (the so called 'Clinical Trials Directive') which has been replaced in June 2014 by the new Clinical Trials Regulation 536/2014, effective in 2016.

1.2. National instruments

1.2.1 Regulations or guidelines specific to research involving humans

In most countries, there are regulations or guidelines that apply to any type of research involving humans. Typically, such regulations or guidelines will cover requirements for:

- Ethics review and positive opinion before the research starts
- Appropriate risk to potential benefit assessments
- Respect for autonomy - through consent and protection of confidentiality.

In addition, some countries also have regulations that apply to clinical trials for medicines and medical devices. In some countries, specific types of research (such as research involving human reproductive material) will receive additional regulatory oversight. In other countries, privacy legislation will apply to research using personally identifying information.

1.2.2 Broader regulations

In many countries, however, there are no research specific regulations or guidelines. This does not in any way mean that there is a gap in legal requirements. Indeed, broader based legal frameworks will provide guidance and minimal standards that must be met. Some examples are:

- In many countries with a civil code or a constitution, there will be broader provisions protecting individuals' physical integrity as well as requiring respect for autonomy.
- There may be provisions that require consent to treatment or regulations around privacy.
- Criminal law prohibitions could be invoked in the absence of other more specific provisions.

When researchers are also healthcare professionals (such as doctors, nurses, etc.) professional codes of conduct must be respected.

2. Broader regulations

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There may be provisions that require consent to treatment or regulations around privacy.

Criminal law prohibitions could be invoked in the absence of other more specific provisions.

When researchers are also healthcare professionals (such as doctors, nurses, etc.) professional codes of conduct must be respected.

3. Institutional requirements

Institutions where biomedical research is conducted (for example, hospitals, research institutions and universities) also bear responsibility for the ethical conduct of research involving humans. When researchers conduct their research abroad in other countries, their home institution maintains responsibility.

Governmental agencies that fund research, as well as many private and not-for-profit organizations, will often adopt research ethics guidelines that must be respected as a condition for funding. Well known examples, of such guidelines include:

> US National Institutes of Health (NIH): NIH Grants Policy Statement.
>
> UK Wellcome Trust: Research involving people living in developing countries: Position statement and guidance notes for applicants.
>
> EDCTP: EDCTP Guidelines on Ethics.

Lesson 3: Ethical Review Process by Ethics Committees and the Potential Role of Patients

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1. Authority, role and mandate of Research Ethics Committees (RECs)

Research Ethics Committees (RECs) are sometimes referred to as Institutional Review Boards (IRBs), Research Ethics Boards (REBs), Independent Ethics Committee (IEC) or simply Ethics Committee (EC). The legal status of RECs varies from country to country and they may be set up, and operate, according to different models. Most frequently, RECs will be set up by a government or an institutional authority (such as a hospital, research institution or university).

In some cases, RECs may be set up by private organizations. However, some countries do not allow 'private RECs' that are not publicly accountable in some way (such as through accreditation). There is, however, little hard data to suggest that the quality of ethics review conducted by private RECs differs from that of institutional or national RECs.

Despite legal and operational differences, the primary role of RECs remains the same:

> to ensure the well-being, safety and protection of persons who participate in all types of research involving humans.

Ensuring this protection involves collaboration between RECs and researchers to ensure that research meets the highest ethical standards.

RECs will typically accomplish this goal by the combination of the following activities:

- Ethics review and favorable opinion before the research starts.
- The continuing review of ongoing research.
- The active promotion of principles of ethics through education and training.

1.1. Independence of RECs and committee members

In order to properly perform their protective function, RECs must be independent from research sponsors, investigators and from any undue influence, such as political, institutional, professional or commercial.

REC independence is critical to ensuring that research participants' interests always come first and are not secondary to other interests such as scientific advancement or economic gain. REC independence is one of the four requirements for standardized ethical review. The others are constitution, competence and standard operating procedures - these are described later in this lesson.

Achieving REC independence is a challenge in many situations and is often a question of ensuring the following:

- Proper accountability (i.e. making sure the right people are responsible)
- Balanced membership (i.e. making sure the right mix of people are involved).

RECs' independence is promoted when they are made accountable as will be discussed below. In many countries, it is standard practice to exclude persons of authority within an institution or research center from being a member of the REC.

A common example of a potential conflict of interest is when an international institution wishes to conduct a collaborative research project, e.g. with institutions in other countries. The foreign collaborating institution typically discusses the issue with the head of the local institution. It might be that the local institution will gain from participation in a trial sponsored by the foreign institution (e.g. a laboratory, equipment, employment). This could be a potential conflict of interest, i.e. if the head of the local institution was to sit on an ethics committee they would not appear to be objective. It is for this reason that many countries in such case do not allow heads of local institutions to sit on RECs.

REC members must also be in a position to conduct independent reviews of protocols. This means that they must be free from, or have declared and properly managed, any conflicts of interest.

If members have particular links with a given protocol, they should not participate in decisions concerning that protocol. Current practice requires them to declare the conflict of interest and they may be asked to leave the meeting room when that protocol is being discussed.

1.2. Composition and operational aspects

RECs are multi-disciplinary committees, drawing on the strengths of their members with varied backgrounds. The goal of a diversified membership is to ensure that RECs can collectively conduct a thorough and independent ethics evaluation of research projects.

Although specific requirements vary greatly, for a typical composition of REC membership is:

At least 5 members who collectively have the qualifications and experience required to ensure proper review of the ethical, scientific, medical and financial aspects of a trial.

At least one lay person, from a diverse educational (social sciences, law, etc.) and social background, as well as ensuring gender balance.

In many countries, it is further required that there be three non-scientific members: one legal, one ethicist and one representing the community.

REC members should be appointed for a fixed term by the recognized authority according to an established procedure. The REC may choose to invite outside experts who are not members to assist on particular aspects (often scientific) of a project.

1.3. Properly constituted RECs and standard operating procedures

The REC must be properly constituted and function according to applicable guidelines and regulations. It must also perform its functions according to its own written operating procedures.

Minimally, the following elements of any REC should be clearly established:

The authority which established the REC (Terms of Reference).

The REC's mandate, i.e. its function and duties (Standard Operating Procedures - SOP).

The REC composition, minimum 'quorum' requirements, i.e. the minimum number of people required to attend and vote in order to make a valid decision.

The procedure for appointing members.

Guidelines, and in some countries regulations, specify that REC operating procedures should cover at least the following aspects:

How meetings will be conducted, including scheduling and notifying members - this should also include the need to keep detailed minutes of meetings

How to submit an application to have a proposal reviewed, including the submission form

That the REC will make its decisions at announced meetings, a minimum number of people must be present in order for a decision to be made.

Process for ethics review, including:

initial review and continuing review of studies, expedited (rapid) review procedures, target time for notification of the decision to investigators (in the EU, timelines are mandated by 2001/20/EC).

A rule that no participant should be signed up before the REC has issued its written favorable opinion of the trial.

The investigator's duty to promptly report to the REC:

deviations from the protocol to remove immediate hazards to participants, changes that affect the initial balance of risks and benefits, serious and unexpected adverse drug reactions (ADRs), any new information that may have an impact on safety of participants or the conduct of the study.

RECs need to ensure their written procedures comply with their national, local or institutional legislation and requirements.

1.4. Ethical deliberation and decision-making

1.4.1 Ethical deliberation

For members of the REC, ethical deliberation refers to reflection (careful consideration) and discussion of research projects. This process should take into account the ethical principles and values of research ethics from relevant local and international guidelines. During the discussion, all members present should contribute and provide their expertise and perspectives. In order for each member of the committee to do this in a meaningful way, all documentation relevant to the review must be received and reviewed by all members before the discussion. Members must have enough time to communicate their points of view during the discussion. Sometimes different ethical norms and concepts appear relevant but lead to contradictory conclusions, in these cases a significant amount of reflection is required.

1.4.2 Reaching a decision

Reaching a decision is the second phase of decision-making.

In conducting their review, RECs usually evaluate aspects of the project:

Scientific validity.

Ethical and financial aspects.

Consent documentation.

Expected benefit vs burden/risk.

Any other documents to be provided to participants.

These are described in the following sections.

The REC has the authority to make the following decisions about research under their jurisdiction (authority) according to whether it meets ethical requirements:

Provide favorable opinion

Provide negative opinion

Request modifications

This applies to both proposed and ongoing research.

Consensus

Ideally, the REC deliberates and eventually comes to a collective opinion (or consensus) that all members find ethically satisfactory. Consensus reached by a REC is valid as long as it emerges out of deliberations that are honest, fair, and factually well-informed and follow standard operating procedures.

However, in reality it doesn't always work this way. Sometimes a decision is not 'thoroughly acceptable' to some members, but those members agree their concerns were heard and discussed, and they regard the process of deliberation and decision-making fair.

Making decisions by vote, as opposed to consensus, should be restricted to exceptional circumstances. This is because voting gives priority to the number of people who hold a certain opinion but does not take into account the reasoning behind the opinions held. A minimum quorum is required (and should be defined in the SOP) for voting in order to make a valid decision.

1.5. Dissenting and abstaining

If a minority of REC members consider a project or some aspect of a project unethical, the REC's operating procedures may state that an effort must be made to reach consensus. However, when a decision reached is not unanimously accepted by all members, the number of members dissenting and/or abstaining should be recorded in the minutes.

Dissenting members are those that do not agree with the majority decision.

Abstaining members are those that decide not to give their vote to either alternative.

Dissenting or abstaining members may also be offered the opportunity to join their opinion to the REC's decision in a minority report.

1.6. Due process

From a practical perspective, due process implies that:

- The REC will be impartial.
- It will make its decisions at announced meetings with a quorum.
- Only members who participate in deliberations will take part in decisions.
- Investigators/sponsors should have a fair opportunity to be heard (although not participate in the deliberation and decision).
- A decision (favorable or negative opinion) should be communicated in writing to the applicant and to the relevant authorities according to national requirements.

Appropriate archiving of records also promotes due process. The REC should ensure that it retains, and be ready to make available, relevant records of its decisions, procedures, etc., for the required time period.

1.7. Follow-up of ongoing research

RECs evaluate research projects initially as part of the decision process. They then re- evaluate ongoing research at regular intervals. With consideration of the researcher's suggestions, it is left to the discretion of the REC to determine the frequency of follow-up - or continuing review - of ongoing research. This would be based on the level of risk the project poses to human participants.

As part of the continuing review process, examples of events or instances that trigger the need for follow- up by the REC:

1. Any protocol amendment which is substantial and likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or the scientific value of the trial.
2. Serious and unexpected adverse events related to the conduct of the study or study product, and the response taken by investigators, sponsors, and regulatory agencies.
3. Any event or new information that may affect the benefit-risk ratio of the study.

1.7.1 The goal of continuing ethics review

The purpose of continuing ethics review is to find out if the research (including recruitment and informed consent process) is being conducted in compliance with the approved protocol. The review will also confirm that the potential benefits and burdens to research participants remain acceptable. If the burdens and/or potential benefits have changed, the participants should be informed of the change. They should then be asked to re-consent to the study, confirming their continued choice to participate in the research. They may also refuse to continue participation.

1.7.2 REC decisions during continuing review

If anything observed during follow-up is found to be unacceptable, the REC might:

Suspend or withdraw favorable ethical opinion of the research (until further information is provided and reviewed).

Request that new information, changes to the research, or changes to the balance of burdens and benefits be communicated to research participants to enable an informed choice or refusal to continue in the research.

Request modifications to the project or to the Informed Consent Form, which will require re-approval by the REC and a new informed choice or refusal from participants.

1.8. Accountability

Given their important role, RECs must be accountable for their work. This can be achieved in several ways.

First, RECs are immediately accountable to their constituting authority. This authority will require annual reports of activities. The constituting authority must also be committed to not overriding a negative REC opinion.

Second, RECs must demonstrate accountability towards researchers and the broader public. This can be achieved by promoting the transparency of its activities and decisions. For example:

- Guidelines for how to make an application should be freely accessible.
- REC members should evaluate research at officially announced meetings to allow researchers the opportunity to be heard.
- Opinions of RECs should be justified and well communicated.

Third, authorities or sponsors of clinical trials and research may inspect/audit a trial site. This may also include the REC that reviewed the research. In such cases, inspectors/auditors will look through minutes of meetings as well as records related to the research.

2. What research requires ethics evaluation?

Generally speaking, all research that involves humans must be evaluated by a REC. This must happen before the research begins or, more precisely, before any prospective participants are contacted for recruitment. This is often referred to as the 'ethics review requirement'.

The ethics review requirement also applies to research conducted with personal information found, for example, in medical files, or with human tissue and products such as genetic material.

Research with gametes (mature male or female sexual reproductive cells, i.e. sperm or egg), embryos and fetal tissue also requires prior ethics review in addition to a number of other requirements.

In some countries, certain types of research may be exempt from the ethics review requirement under certain conditions. Some examples of this are:

- When research 'involves only negligible risk' - i.e. there is no foreseeable risk of harm or discomfort to participants and any foreseeable risk involves no more than inconvenience to participants.
- When research 'involves the use of existing collections of data or records that contain only non- identifiable data about people, e.g. publicly accessible records, archives or publications'.

The REC will assess if research qualifies for one of these exemptions. A researcher cannot issue their own exemption for a study. An exemption must be issued by an REC.

Clinical trials are a good example of a type of research that has additional requirements. In Europe, sponsors of clinical trials for medicines must ask the National Competent Authority (NCA) for authorization to use an investigational medicine in a trial. Investigators are legally required to have both the NCA approval for use of an investigational medicine and REC favorable opinion before a trial can start.

It is particularly important to note that research that is not scientifically sound is not ethically acceptable. This is because it will expose participants to the burden and potential harms of research without having the possibility of yielding benefits to the participants and/or to society. Thus, the REC must ensure that appropriate scientific evaluation has occurred even if it does not conduct the scientific assessment itself. If research does not pass scientific evaluation, then it should be denied a favorable ethics opinion as well.

2.1. Particular cases

In some countries, research involving human reproductive material (stem cells, gametes, embryos) is forbidden. Where this is not the case, there will often be a requirement that national oversight committees review the research project in addition to the competent REC.

2.2. Levels of evaluation

It is generally accepted that RECs can adopt a proportionate approach to ethics evaluation. In other words, the greater the burden of research, the greater the scrutiny. In practice this means that RECs can use two approaches to ethics evaluation:

1. Evaluation by the full committee.
2. Evaluation by a sub-committee, which is also called 'expedited review'. If the operating procedures of a given REC allow, research that poses only minimal burden can have an expedited review. Minimal burden in this context is when the amount of harm expected in the research is less than that ordinarily encountered in daily life, or in routine medical, dental, or psychological exams. Research that poses greater burden deserves attention by the full REC to ensure proper safeguards are in place.

Full committee evaluation will involve all members' comments and discussion of all ethical issues arising from the proposed research. Deliberations will take place and members will aim to reach a consensus on the REC decision. This will take place in an ordinary REC meeting, scheduled according to the standard operating procedures.

RECs should establish standard operating procedures for expedited review of research proposals. These procedures should specify the following:

The nature of the applications, amendments and other considerations that will be eligible for expedited review.

The quorum requirements for expedited review.

The status of opinion - i.e. whether or not the opinion still needs to be confirmed by the full committee.

In some countries national regulations establish categories of research that pose no more than minimal burden that can receive expedited review.

3. Documents to be reviewed by RECs

The nature of research projects varies from one project to the next. Ethics evaluation practices also evolve over time. Hence, it is difficult to establish a definitive list of documents that the REC needs to conduct a full evaluation. Given the nature of ethics evaluation, the REC may ask to be provided with any document it considers important.

The REC must review:

- the protocol,
- the investigator's brochure,
- the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent as regards the specific restrictions laid down in Article 3, 2001/20/EC,
- provision for indemnity or compensation in the event of injury or death attributable to a clinical trial,
- any insurance or indemnity to cover the liability of the investigator and sponsor,
- the arrangements for the recruitment of participants.

For a full list of the review process and timings please refer to Article 6, Directive EC 2001/20/EC.

The ICH-GCP provides specific guidance on the content of protocols for clinical trials. To ensure it receives information on precise aspects of research it evaluates, the REC may want to request specific information in their submission forms. For example, a submission form may ask for:

- A summary of the protocol in non-technical language.
- A summary of potential benefits.
- A description of the ethical considerations.
- A description of the recruitment process and of the consent process.
- Actions that may be required by national law.

4. Disclosure to prospective participants

The following are some key elements that should be disclosed to prospective participants:

- The invitation to participate in the research.
- Research aims and methods.
- Identification of researchers and sponsors.
- Sources of funding.
- Any possible conflicts of interest, including institutions that the researcher is linked to.
- The anticipated benefits of the research.

Alternatives of the research intervention that are already available (if applicable).

Potential risks of the research.

The right to abstain (withhold) from participation in the study or to withdraw consent to participate at any time without reprisal.

Measures taken for the respect of the privacy of participants and for the confidentiality of records in which participants are identified.

Kind and amount of any compensation.

The address of who to contact at any time for more information.

Access to free treatment in case of injury from research procedures and compensation of resulting impairment, disability, and handicap.

Access to interventions identified as beneficial in the study or access to other appropriate care or benefits.

Lesson 4: The Fundamentals of Statistics

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8. Confidence interval

1. The purpose and fundamentals of statistics

Basics of hypothesis testing:

Null and alternative hypothesis

Sample size

Bias

Type I error

Type II error

Significance

Power

Confidence intervals

2. What is a hypothesis?

A hypothesis is a proposed assumption for a phenomenon that may or may not be true.

Hypothesis testing is the evaluation done by a researcher in order to either confirm or disprove a hypothesis. An existing hypothesis will be taken and tested to see its probability of being true or false.

2.1. Null and alternative hypothesis

Setting up and testing hypotheses is an essential part of statistical inference. In each problem considered, the question of interest is simplified into two competing claims or hypotheses, the null hypothesis (H0) and the alternative hypothesis (H 1).**The null hypothesis (H 0)** is formulated to capture our current understanding. The word 'null' can be thought of as 'no change'. A null hypothesis is typically the standard assumption and is defined as the prediction that there is no interaction between variables (a statement that proposes there is no relationship, for example, between a study medicine and a reduction in symptoms and that observations are the result of chance).

The alternative hypothesis (H_1) is formulated to capture what we want to show by doing the study. An alternative hypothesis in a clinical trial might be that the new medicine is better than the current treatment.

These two hypotheses should be stated in such a way that they become mutually exclusive. That is, if one is true, the other must be false.

When performing a hypothesis test, we evaluate if the hypothesis (alternative hypothesis) is more probable than the existing hypothesis (null hypothesis).

When applying hypothesis testing, we assume that the null hypothesis is true until it can be shown with a certain probability that the alternative hypothesis instead is likely to be true and the null hypothesis can be rejected.

Hypothesis testing could be compared to the procedures adopted in a courthouse:

The null hypothesis covers our current understanding or knowledge, i.e. the accused is innocent, which we need to trust unless we have sufficient evidence otherwise.

The statement we want to prove with our experiment, i.e. the accused is guilty (the alternative hypothesis).

Then the lawyers present their case showing evidence in support of the alternative hypothesis. The accused remains innocent (H 0) until there is sufficient evidence to prove guilt (H 1) – only then can the null hypothesis be rejected.

2.2. What is hypothesis testing?

Hypothesis tests typically examine a random sample from the population for which statements formulated in the hypothesis should be applicable (valid). The selected samples can range in how representative of the population they are. This is why hypothesis testing on samples can never verify (or disprove) a hypothesis with certainty (i.e. probability = 1) only say that it has a certain probability to be true or false.

Hypothesis tests are used in determining what outcomes of a study would lead to a rejection of the null hypothesis or acceptance of the alternative hypothesis. In other words, the outcome of a hypothesis test is to either 'reject the null hypothesis in favor of the alternative hypothesis' or to conclude that there is 'not enough evidence to reject the null hypothesis'.

Distinguishing between the null hypothesis and the alternative hypothesis is done with the help of two conceptual types of errors (type I and type II).

3. Type I and Type II errors

An experiment testing a hypothesis has two possible outcomes: either H0 is rejected or it is not. Unfortunately, as this is based on a sample and not the entire population, we could be wrong about the true treatment effect. Just by chance, it is possible that this sample reflects a relationship which is not present in the population – this is when type I and type II errors can happen.

All statistical hypothesis tests have a probability of making type I and type II errors. For example, blood tests for a disease will erroneously detect the disease in some proportion of people who don't have it (false positive) and will fail to detect the disease in some proportion of people who do have it (false negative).

Type I - when you falsely assume that you can reject the null hypothesis and that the alternative hypothesis is true. This is also called a false positive result. A type I error (or error of the first kind) is the incorrect rejection of a true null hypothesis. Usually a type I error leads one to conclude that a supposed effect or relationship exists when in fact it doesn't. Examples of type I errors include a test that shows a patient to have a disease when in fact the patient does not have the disease, or an experiment indicating that a medical treatment should cure a disease when in fact it does not.

Type I errors cannot be completely avoided, but investigators should decide on an acceptable level of risk of making type I errors when designing clinical trials. A number of statistical methods can be used to control the type I error rate.

Type II - when you falsely assume you can reject the alternative hypothesis and that the null hypothesis is true. This is also called a false negative result. A type II error (or error of the second kind) is the failure to reject a false null hypothesis. This leads to the conclusion that an effect or relationship doesn't exist when it really does. Examples of type II errors would be a blood test failing to detect the disease it was designed to detect, in a patient who really has the disease; or a clinical trial of a medical treatment concluding that the treatment does not work when in fact it does.

	Null Hypothesis is true	**Null hypothesis is false**
Reject the null hypothesis	**Type I error** False positive	Correct Outcome True positive
Fail to reject the null hypothesis	Correct outcome True negative	**Type II error** False negative

In this process of distinguishing between the two hypotheses, specific parametric limits (e.g. how much type I error will be permitted) must also be established. A test's probability of making a type I error is denoted by α (alpha). A test's probability of making a type II error is denoted by β (beta), this number is related to the power or sensitivity of the hypothesis test, denoted by $1 - \beta$. These error rates are traded off against each other: for any given sample set, the effort to reduce one type of error generally results in increasing the other type of error. For a given test, the only way to reduce both error rates is to increase the sample size, and this may not always be feasible.

4. Sample size

In order to have confidence that the trial results are representative, it is critically important to have a 'sufficient' number of randomly-selected participants in each trial group.

Sample size is the total number of participants included in a trial.

An estimate of the required sample size is needed and must be specified in the study protocol before recruitment starts. It is also necessary to control the probability with which a real effect can be identified as statistically significant.

Too few participants or observations will mean that real effects might not be detected, or they will be detected but at a level that is statistically insignificant (a type II error, which is directly proportional to sample size). It is just as true that it is unacceptable for a medicine to be tested on too many patients. Thus, studies with either too few or too many patients are both methodologically and ethically unjustified. Bear in mind that it is only possible to detect rare side effects in a large sample size and sufficient exposure time, this makes the challenging of estimating sample size complex.

In practice, the sample size used in a study is determined based on:

1) Magnitude of the expected effect.
2) Variability in the variables being analyzed.
3) Desired probability that the null hypothesis can correctly be rejected when it is false.

5. Sampling error

In statistics, sampling error may occur when the characteristics of a population are estimated from a subset, or sample, of that population. Since the sample does not include all members of the population, statistics on the sample will differ from parameters under evaluation for the entire population. For example, if one measures the blood pressure of a hundred individuals from a population of one million, the average value for blood pressure won't be the same as the average value of all one million people.

Since sampling is typically done to determine the characteristics of a population, the difference between the sample and population values is considered a sampling error. The severity of the sampling error can be reduced by increasing the size of the study sample.

6. Power of a statistical test

A term often used in clinical research is 'statistical power'. The power of a statistical test is the probability that it will correctly lead to the rejection of a null hypothesis (H0) when it is false– i.e. the ability of the test to detect an effect, if the effect actually exists. Statistical power is inversely related to beta or the probability of making a type II error. In short, power = 1 – β.

In some cases, we may not be able to reject the null hypothesis, not because it's true, but because we do not have sufficient evidence against it. This might be because the experiment is not sufficiently large to reject H0. As such, the power of a test can be described as the probability of not making a type II error (not rejecting the null hypotheses when in fact it false).

Statistical power is affected chiefly by the size of the effect and the size of the sample used to detect it. Bigger effects are easier to detect than smaller effects, while large samples offer greater test sensitivity than small samples

7. Significance level

In everyday language significant means important, but when used in statistics, 'significant' means a result has a high probability of being true (not due to chance) and it does not mean (necessarily) that it is highly important. A research finding may be true without being important.

The significance level (or α level) is a threshold that determines whether a study result can be considered statistically significant after performing the planned statistical tests. It is most often set to 5% (or 0.05), although other levels may be used depending on the study. It is the probability of rejecting the null hypothesis when it is true (the probability to commit a type I error). For example, a significance level of 0.05 indicates a 5% risk of concluding that a difference exists when there is no actual difference.

p-value

The probability value (p-value) is the likelihood of obtaining an effect at least as large as the one that was observed, assuming that the null hypothesis is true; in other words, the likelihood of the observed effect being caused by some variable other than the one being studied or by chance.

The p-value helps to quantify the proof against the null hypothesis:

> a large p-value suggests that the observed effect is very likely if the null hypothesis is true.
>
> a small p-value (equal to or less than the significance level) suggests that the observed evidence is not very likely if the null hypothesis is true – i.e. either a very unusual event has happened or the null hypothesis is incorrect.

The p-value is compared with a pre-defined cut-off for the test (significance level). If it is smaller than this value, the estimated effect is considered to be significant. Often a p-value of 0.05 or 0.01 (written '$p \leq 0.05$' or '$p \leq 0.01$') are chosen as cut-offs.

This is more easily illustrated by an example:

We have a medicine 'A' which decreases blood pressure. We therefore set our null hypothesis as being: 'Medicine A will NOT decrease blood pressure'. We also decide that the significance level should be 0.05. We run a study using medicine A and observe an average decrease in blood pressure of 20%. Was this due to chance? (null hypothesis true) Or due to the effect of medicine A?`(null hypothesis false). Now we calculate the p-value (the probability) that this result occurred if the null hypothesis was true (the results occurred by chance). The p-value was calculated to be 0.03. Since the p-value (0.03) is less than the significance level we set (0.05) we are able to reject the null hypothesis and conclude that that the measured decrease in blood pressure is likely to be due to the effects of medicine A, rather than being due to chance.

The p-value is compared with a pre-defined cut-off for the test (significance level). If it is smaller than this value, the estimated effect is considered to be significant. Often a p-value of 0.05 or 0.01 (written '$p < 0.05$' or '$p< 0.01$') are chosen as cut-offs. These are called the 'significance levels' of the experiment.

8. Confidence interval

The 'confidence interval' is used to express the degree of uncertainty associated with a sample statistic. The confidence level is used to describe uncertainty in the interval estimate.

It is a calculated range of values that is likely to include the population parameter we look for. The likelihood (probability) that the confidence interval will contain the population parameter is called the confidence level. Traditionally confidence levels are set at 95% or 99%. This means that we are 95% (or 99%) sure that the measured effect lies within the true range.

For instance, instead of estimating the mean (average) age of a population is 15 years, we say that the mean age is between 13 and 17. This confidence interval contains the single value we are estimating and gives a wider net to be right.

Lesson 5: Principles of Sample Size Calculation

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1. Introduction

In a clinical trial, the objective is to get information about the effect of a treatment in a certain patient population who are likely to benefit from that treatment. However, the researchers cannot administer this treatment to the entire population. It would not be realistic for ethical and financial reasons. Therefore, the clinical trial will be conducted only on a selected sample from the population of patients. This population sample should be representative of the whole population in order to allow the generalizations of the clinical trial findings.

2. Why sample size is important

Sample size calculation is the act of determining the appropriate number of participants to include in a clinical trial. The size of the sample should be adequate allowing statistical analyses to show relevant treatment effects and to generate conclusive results. The larger the number of participants in a trial, the more reliable the conclusions will be. However, larger studies require more resources (both in terms of finances and patient commitment) and may increase the risk for participants to be exposed to inefficient or even unsafe treatment. It is therefore important to optimize the sample size. Moreover, calculating the sample size in the design stage of the study is increasingly becoming a requirement when seeking ethical committee approval for a research project.

The wide range of formulas that can be used for specific situations and study designs makes it difficult for most investigators to decide which method to use. The calculation of the sample size is troubled by a large amount of imprecision, because investigators rarely have good estimates of the parameters necessary for the calculation. Unfortunately, the required sample size is very sensitive to the choice of these parameters and small differences in selected parameters can lead to large differences in the sample size.

2.1. Components of sample size calculations

In order to calculate the sample size, one must have some idea of the results expected in a study. In general, the greater the variability in the outcome variable (e.g. blood pressure) across study population, the larger the sample size required to assess whether an observed effect is a true effect. On the other hand, the more effective (or harmful!) a tested treatment is, the smaller the sample size needed to detect this positive or negative effect. Calculating the sample size for a trial requires five basic components.

Summary of the components for sample size calculations - Component Definition

1. Alpha (α) (Type I error): The probability of falsely rejecting the null hypothesis (H) and detecting a statistically significant difference when the groups in reality are not different, i.e. the chance of a false-positive result.
2. Beta (β) (Type II error): The probability of falsely accepting H and not detecting a statistically significant difference when a specified difference between the groups exists in reality, i.e. the chance of a false-negative result.
3. Power (1-β): The probability of correctly rejecting H and detecting a statistically significant difference when a specified difference between the groups in reality exists.
4. Minimal clinically relevant difference: The minimal difference between the groups that the investigator considers biologically plausible and clinically relevant.
5. Variance: The variability of the outcome measure, expressed as the Standard Deviation (SD) in case of a continuous outcome.

Abbreviations:

H - null hypothesis; the null hypothesis states that compared groups are not different from each other.

SD - standard deviation.

3. Sample versus population

The key to understanding sample size calculation is to understand the underlying concepts of statistical inference, i.e. using the information from a (random) sample to draw conclusions (inferences) about the population from which the sample was taken.

Analyzing the information in a sample will lead to an (observed) estimate for the treatment effect. This should help to predict the true treatment effect in the broader patient population. Every time a sample is taken, by the mere definition of a sample (at least a random one), a different estimate will be obtained. If you looked at several samples together, they will provide a clear picture of the true treatment effect and the variability (i.e. the spread of data, the measure of how far the numbers in a data set are away from the mean or median) underlying the estimation. However, in practice, only one sample is taken, i.e. the trial is run once. So, from the observed effects in samples, what can be determined about the true but unknown treatment effect in the population? This is where statistical inference comes in, more specifically through the concept of hypothesis testing.

4. Sample size calculation

Sample size calculation is an essential part of the design of a clinical trial. The size of the study should be adequate in order to generate conclusive results. Calculating the appropriate sample size requires feedback on various aspects of the trials, such as the study design, the tested hypotheses, the targeted study power and the type I and II errors.

5. What drives a sample size calculation?

There are 5 key drivers in sample size calculations.

5.1. The design of the clinical trial

A trial with only one or several experimental treatments arms in a Phase II setting will require a different approach from a randomized comparative Phase III trial. Furthermore, the sample size needed for a study depends on the assumption of the size of the difference between the two treatments being studied. In a study where a large difference between the treatments is assumed, the difference should be observable in a smaller sample, whereas a larger sample size is needed to detect a small difference between two treatments. The situation becomes more complex when more than two treatment groups are planned since there is no longer one single clear alternative hypothesis. A test strategy must be defined upfront and adequate measures applied to maintain the overall type I error.

5.2. The choice of the primary endpoint(s)

Endpoints in clinical research are the outcomes measured during the study that are used to assess the efficacy of the treatment. They can be of different types:

1. Binary vs. continuous: binary indicates whether an event has occurred (occurrence or relief of symptoms), while continuous represents a specific measure or count (e.g., blood pressure).

2. Landmark: its goal is to have a fixed time (time-to-event) after the initiation of the treatment, where analysis of survival can be conducted.

The type of endpoint (continuous, binary or time-to-event) can have a major impact on the size of a trial. Moreover, the sample size will have to be increased in case of multiple endpoints. The significance level may have to be adapted for limiting the overall type I error rate.

5.3. The research hypotheses

The magnitude of the targeted treatment effect specified in H is a crucial parameter. The required sample size will decrease as the expected effect relative to the comparator increases. A common defect in clinical trials is that too few patients are entered in the trial to have a high probability of detecting a difference.

5.4. Type I and type II error rate

In general, the smaller the error rates and/or the larger the study power desired the larger the required sample size. The acceptable type I and II error rates should be defined in order to reflect the consequences of making the particular type of error.

5.5. Resources

Patient availability and financial constraints may limit the sample size of a clinical trial.

Lesson 6: The Concept of Blinding in Clinical Trials

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1. Blinding of the trial
2. Why do we blind?
3. What are the potential sources of bias in a trial and who can and should be blinded?
4. Types of blinding
5. Unblinded
6. Single blind
7. Double blind
8. Triple blind
9. Unblinding the trial
10. Ways patient experts can contribute

1. Blinding of the trial

Blinding is a procedure in which one or more parties in a trial are kept unaware of which treatment arms participants have been assigned to, i.e. which treatment was received.

Blinding is an important aspect of any trial. How a trial was blinded should be accurately recorded in order to allow readers to interpret the results of a study. If blinding is ever broken during a trial on individual participants, it needs to be justified and explained.

2. Why do we blind?

Blinding is used to prevent conscious or unconscious bias in the design of a clinical trial and how it is carried out. This is important because bias can affect recruitment and allocation, care, attitudes, assessments, etc.

It is used to ensure the objectivity of participants, study staff, clinicians, data collectors, outcome adjudicators and data analysts.

The Concept of Blinding in Clinical Trials https://edu.eupati.eu/mod/book/tool/print/index.php?id=1574 3. What are the potential sources of bias in a trial and who can and should be blinded?

The relevance of blinding in a randomized clinical trial will vary according to circumstances.

The trial participant Blinding participants to the treatment they have received is particularly important when the response criteria are subjective, such as alleviation of pain, but less important for objective criteria, such as disease progression (e.g. cancer). If participants are not blinded, knowledge of group assignment may affect their behavior in the trial and their responses to subjective outcome measures. For example, a participant who is aware that he is not receiving active treatment may be less likely to comply with the trial protocol. Those aware that they are receiving or not receiving therapy are more likely to provide biased assessments of the effectiveness of the intervention — most likely in opposite directions — than blinded participants.

Clinical staff administering treatment Similarly, medical staff and clinicians caring for patients should be blinded to treatment allocation to minimize possible bias in patient management and in assessing disease status. Blinded clinicians are much less likely to transfer their attitudes to participants or to provide differential treatment to the active and control (placebo) groups than are unblinded clinicians.

The doctor assessing treatment Blinding of data collectors and outcome adjudicators (sometimes the same individuals) is crucial to ensure unbiased ascertainment of outcomes. For example, in a randomized controlled trial in patients, neither active treatment regimen (tested medication vs. comparator) was superior to placebo when assessed by blinded specialists, but there was an apparent benefit of treatment with the test medication, when unblinded specialists performed the assessments.

The team interpreting results Bias may also be introduced during the statistical analysis of the trial through the selective use and reporting of statistical tests. This may be a subconscious process spurred by investigators eager to see a positive result, but the consequences are profound. The best method to avoid this potential bias is blinding of the data analyst until the entire analysis has been completed.

4. Types of blinding

- Unblinded or open label: All are aware of the treatment(s)
- Single blind or single-masked : The participants are blinded but no one else is
- Double blind or double-masked: The participants and clinicians / data collectors are blinded
- Triple blind: The participants, clinicians / data collectors and outcome adjudicators / data analysts are blinded

5. Unblinded

An open-label trial is one in which no blinding is used and all parties are aware of the allocation of participants to treatment groups.

Open-label trials may be used:

For surgical procedures*.

When changes in lifestyle are required.

When endpoints are objective and cannot be interpreted in different ways.

For studies in life-threatening situations.

In post-marketing surveillance.

When ethical considerations do not permit blinding.

When no control group can be used.

*It should be noted that surgical procedures can be blinded but are extremely difficult to blind. This is very hard especially if participants can be compared.

6. Single blind

A trial in which one party, the investigator or, usually, the participants, is unaware of what medicine the participant is receiving. Also called single-masked studies they provide some control when double blinding is impossible or not appropriate.

Single-blind trials are used where the experimenters either must know the full facts (for example, when comparing sham to real surgery) and so the experimenters cannot themselves be blind, or where the experimenters will not introduce further bias and so need not be blind. However, there is a risk that subjects are influenced by interaction with the researchers – known as the experimenter's bias.

7. Double blind

A clinical trial design in which neither the participants nor investigators know which participants are receiving the experimental medicine and which are receiving a placebo (or comparator therapy). Double- blind trials are thought to produce objective results, since the expectations of the investigator and the participant do not affect the outcome. Also called double-masked trial.

Considered best-controlled trial design.

Decreased chance of preconceived notions or physical cues (e.g. the placebo effect, observer bias, experimenter's bias) to distort the results.

The key that identifies the participants and which group they belonged to is kept by a third party and is not revealed to the researchers until the study is over.

Should be used whenever possible.

In trials in studies comparing two active compounds (test medicine and comparator) and when the two treatments cannot be made identical, double dummy is a technique for retaining the blind. Supplies are prepared for Treatment A (active and indistinguishable placebo) and for Treatment B (active and indistinguishable placebo). Participants then take two sets of treatment; either A (active) and B (placebo), or A (placebo) and B (active).

For example, if we want to compare two medicines, one presented as green tablets and one as pink capsules, we could also supply green placebo tablets and pink placebo capsules so that both groups of patients would take one green tablet and one pink capsule.

8. Triple blind

A triple blind trial means that participants, clinicians, data collectors, outcome adjudicators and data analysts do not have access to details of group assignment. This ensures that bias for or against the tested treatment is very unlikely to occur.

Medicine may still be labelled as A or B during analysis.

Analyst is blinded to which treatment is which.

Helps to avoid bias in the analyzed results.

9. Unblinding the trial

Unblinding is the process by which the allocation code is broken so that the appropriate persons e.g. investigator, clinical staff, participants, and/or the trial statistician become aware of the intervention for a participant in a trial.

Unblinding must be undertaken by a pre-determined process to ensure that participants are not unblinded unnecessarily and the study results are not compromised. Equally, unblinding should occur in a responsive manner when it is clinically indicated.

Unblinding is required:

> To make clinical treatment decisions or when an unexpected serious adverse event occurs and the intervention must be made known. This is called emergency unblinding (to protect the participant). Unblinding should only occur for that participant and not the entire study.
>
> During an unmasked analysis in accordance with the study analysis plan (e.g. a planned interim analysis).
>
> At the request of the Data Safety Monitoring Board.
>
> At the conclusion of the study to determine the effect of the intervention.

It may be done by:

1. Contacting the holder of the blinding information (e.g. sponsor, CRO, etc.) to find out details of what treatment a participant received.
2. Contacting an automated service.

10. Ways patient experts can contribute

An example of how patients can be involved can be discovered in the IPERGAY trial that can be found on the European AIDS Treatment Group website: http://www.aidsmap.com/Second-European-PrEP-study- closes-placebo-arm-early-due-to-high-effectiveness/page/2917367/

Lesson 7: Critical Review of Trial Results

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1. What are clinical trials results?

2. What is a clinical study report?

3. Why access to clinical trial results is important?

4. Critical reading

5. How to perform critical reading

1. What are clinical trials results?

The results of a clinical study or trial are all the data and statistical analyses generated during that clinical trial. Trial results include the following elements:

Description of trial population: the number of participants per treatment arm who started, completed, or dropped out of the trial.

Baseline data: data collected at the beginning of a clinical trial. These data include demographics such as age and gender, patient characteristics such as height, weight, performance status, blood pressure, etc., and trial-specific measures such as disease characteristics, previous treatment, etc.

Measures capturing the effect of the treatment on participants. For example, medicine activity in a Phase II trial, patient survival and/or quality of life in Phase III trials.

Adverse events experienced by the trial participants related or not to the tested treatment e.g. pain, nausea and other side effects.

2. What is a clinical study report?

The clinical study report (CSR) is the formal document describing the results of a clinical trial. It therefore represents a fundamental building block in the argument for use of the treatment in humans.

The results of all clinical trials conducted in humans must be recorded in a clinical study report.

The E3 Guideline defines the type of report to be used for most clinical trials conducted in three major geographic regions (Europe, Japan, and the United States).

This report usually runs to several hundred pages. Clinical study reports are prepared by the trial sponsor and forwarded to regulatory authorities.

Access to such reports or even summary data will be possible in the future via the EU database. (www.clinicaltrialsregister.eu).

3. Why access to clinical trial results is important?

The concept of evidence-based medicine (EBM) was created in the early 1980s as clinical practice became more data-driven and literature based. EBM is now an essential part of what is taught at medical school. Information on treatment efficacy and safety is important for making informed treatment decisions by the patients and their physicians.

It is important not to limit the search for evidence about a treatment to a single publication. When comparing results coming from different sources, it is important to keep in mind the different levels of evidence. The hierarchy of evidence relates to the strength of the trial design and not necessarily to the clinical significance. Randomized, controlled, blinded trials provide the best scientific evidence of benefit and risk but sometimes are not available. Meta-analysis can be flawed because of publication bias.

In general, the hierarchy of trials for obtaining evidence is:

a.) Adequately powered,randomised controlled trial, or meta-analysis of randomized trials showing statistically consistent results.

b) Randomized trials inadequately powered, possibly biased, or showing statistically inconsistent results.

c) Non-randomized trials with concurrent controls.

d) Non-randomized trials with historical controls (i.e. typical single arm Phase II trial).

e) Expert committee review, case reports, retrospective trials.

Patients can learn about clinical trial results from their doctor and also by accessing the published information directly. Access to clinical trial results for researchers is paramount for improving the efficiency in research by reducing the duplication or replication of research efforts.

4. Critical reading

It is estimated that every year, some 20,000 biomedical journals publish around six million articles supplemented by about 17,000 biomedical books. It is necessary for the reader to be able to critically interpret trial results and also evaluate the quality of the design of the clinical trials published in the scientific literature or elsewhere.

The three most common sources of errors in publication are:

1. The risk of misuse and misinterpretation of statistical tests and their outcomes, due to the confusion about the meaning of the numbers (estimates) and the interpretation of hypothesis tests (p-values, power).

2. Data dredging (data mining) or testing large numbers of hypotheses in a single data set in the search for a positive effect. When numerous hypotheses are tested, it is virtually certain that some will falsely appear statistically significant. This is because almost every data set with any degree of randomness is likely to contain some coincidental correlations. If they are not cautious, a researcher using data mining techniques can be

easily misled by these apparently significant results.

3. Bias. In research, bias occurs when systematic error is introduced into data sampling or hypothesis testing by selecting or encouraging one outcome or answer over others. Of note, bias is not always introduced intentionally, for example calibration error, or unknown confounding variables. Bias may affect the results of a clinical trial by deviating the effect of interest from its true value: estimates of association can be systematically larger or smaller than the true association. In extreme cases, bias can cause a perceived association which is directly opposite to the true association. Bias may also take the form of systematic favoritism in the way results are reported or in the way they are interpreted in the discussion and conclusion on clinical trial results.

5. How to perform critical reading

The reader must take into account relevant information from the best available sources. The reader should search the literature to identify relevant articles by using the available tools, e.g. PubMed. The reader could also consider texts published by reputable organizations aiming to inform patients and lay people. However, the reader will have to critically appraise any publication for its quality and usefulness.

The reader should address the following questions:

Critical reading checklist

Is the trial relevant to the reader's needs for information?

Are the objectives and the hypotheses clear?

1. Can the results of the trial be generalized to the broader population? The reader needs to consider to whom the results of the trial can be applied. The characteristics of the recruited population sample need to be described.
2. Are all treatments used in the trial clearly detailed, would the experimental treatment be relevant to the reader's question?
3. What are the patients' likely benefits and harms from the treatment?
4. Does a conflict of interest exist? Consider whether the authenticity and the objectivity of the research can be relied upon.

Is the trial methodology appropriate to assess the stated hypothesis?

1. Is the control treatment a fair comparator that corresponds to current practice? Placebo, available therapy or best supportive care, historical control group?
2. The trial population should be clearly defined, as well as whether the whole population or a sub- set has been studied and whether there is any possible selection bias. Consider the relevance of any patients who have dropped out of the trial, the reasons for dropping out and the relevance for the results and conclusions of the research.
3. Was the control group well matched? Are the exclusion criteria valid?
4. Are the trial endpoints well defined and meaningful?

5. Is it clear how the trial was powered for the primary endpoint?
6. Was the trial long enough for the outcome measure to occur and for capturing enough events?

Are the results convincing?

1. The results should be clearly and objectively presented in sufficient detail. For example, results should be broken down. What about the statistics used - are they appropriate? Are there any alternative explanations for the results?
2. Identify the rate of loss to follow-up and how non-responders have been dealt with. For example, have they have been considered as treatment failures or included separately in the analysis?

3. Check for any bias. Consider the possibility of any confounding variables. For example, age, social class, smoking, disease duration, co-morbidity. Assess whether the researchers controlled or reduced this risk.

Is the discussion section convincing?

1. The discussion should include all the results of the trial and not just those that have supported the initial hypothesis.

2. Have the initial objectives been met, and has the research question been answered?

3. Have the authors taken into account possible bias and acknowledged the possible limitations of the trial?

4. Check whether any incorrect generalizations have been made by inappropriately applying the trial results to a different type of population.

5. Check whether the discussion fits with existing knowledge and opinion (always look for other publications on the same topic).

Is the demonstrated effect clinically significant?

Critically assess if claimed effects are clinically relevant, i.e. do they have a significant effect on the health of a patient? For instance, a statistically significant effect may be of such low magnitude that it is not clinically relevant for the patient. Of note, the larger the size of the trial, the smaller the magnitude of the effect that can be detected. As such, a statistically significant but non-clinically relevant effect could be the result of an over-sized or over-powered clinical trial.

On the other hand, the absence of evidence doesn't mean evidence of absence of any effect. Indeed, when a statistically significant difference isn't found between the trial arms, it does not mean that the compared treatments are equivalent. The statistical test measures the strength of evidence against the null hypothesis of no difference, not the evidence for it. Even if the efficacy of treatments truly differs, a statistical test may be non-significant due to chance (type II error), or because of an insufficient amount of available information (small trial size, lack of power).

Are the conclusions valid?

The conclusions provided by the author should be supported by the available data. Check that the conclusions relate to the stated aims and objectives of the trial.

For all of the above questions it is of importance that the reader be sufficiently knowledgeable and equipped to critically appraise and review the data to avoid drawing erroneous conclusions. Knowledge of the (basics of the) R&D process and methodology (including statistics) as well as of legislative requirements is of paramount importance.

Lesson 11: Principles of New Trial Designs

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    2.1. Adaptive designs in rare diseases
3. Possible approaches in adaptive design
    3.1. Example 1: Group sequential design
    3.2. Example 2: Multi-arm, multi-stage design (MAMS)
    3.3. Example 3: Seamless Phase II/Phase III design
    3.4. Example 4: Response-adaptive randomization
4. Patient Involvement
5. Further Reading

1. Introduction

In the traditional paradigm of clinical trial design, each new treatment must go through a strict development process. After successful Phase I trials, a Phase II trial is needed to show sufficient efficacy and safety. When this has been demonstrated, the medicine goes into Phase III trials, where it is compared with a standard treatment (control). Doing this for each treatment separately requires a long period of time, a large number of patients, and substantial financial resources. Additionally, in the traditional approach, modifications are not allowed during the course of the trial.

One new approach to clinical trial design is an adaptive clinical trial design. Adaptive clinical trials include a pre-planned opportunity for modification of one or more specified aspects of the trial. This is usually based on the analysis of interim data from participants during the trial.

There are many reasons to use adaptive designs (or adaptive pathways) in clinical trials. In an environment subject to economic challenges, adaptive designs appear to be appealing for pharmaceutical industry, academic institutions, clinicians, and patients.

2. Adaptive designs

Adaptive designs are relatively flexible clinical trial designs, allowing for modifications during the course of the trial in order to streamline and optimize the process. Analyses of the accumulating study data are performed at pre-planned time points within the trial (interim analysis), can be performed in a fully blinded or unblinded manner, and can occur with or without formal statistical hypothesis testing. Adaptive designs allow for real-time learning during the course of a trial; they are relatively flexible as they allow for modifications during the course of the trial, in order to streamline and optimize the process. It is important that the process is modified only in such a way that the validity and integrity of the trial are not affected.

Adaptive designs can pose operational challenges because of their complexity, and the process of adapting a trial can introduce bias. This bias can be either statistical or operational – for example, if an adaptation suggests that the results of a trial point in a certain direction.

The adaptive design may improve trial efficiency for the sponsor and the participants in the trial. However, if it is not properly conducted, there is a high risk that such a trial can generate clinical results that are difficult to interpret or translate into daily practice.

2.1. Adaptive designs in rare diseases

Clinical trials for rare diseases are typically small out of necessity. Planning a small clinical trial, particularly for a rare disease, can present several challenges. Small trials exhibit more variability than larger trials, which implies that standard designs may lead to trials adequate only for large effects.

The specific requirements of rare disease trials make adaptive designs particularly appealing. Classical trials for rare disease are typically powered for large effects. The power of a statistical test is the ability of the test to detect an effect, if the effect actually exists. In statistical terms, it is the probability that it will correctly lead to the rejection of a null hypothesis.

In some cases, we may not be able to reject the null hypothesis, not because it is true, but because we do not have sufficient evidence against it. This might be because the experiment is not large enough to reject the null hypothesis. As such, the power of a test can be described as the probability of not making a Type II error (not rejecting the null hypothesis when in fact it is false).

Adaptive designs provide an appealing alternative because:

> They shorten the development process without compromising validity or efficacy. Ineffective treatments can be identified earlier on. They permit a more efficient use of resources.

However, it is important to recognize what an adaptive design can or cannot do in the case of rare diseases. Most importantly, adaptive designs cannot make a medicine more effective. They can, however, identify ineffective treatments earlier. Such early identification can minimize the resources allocated to the study of an ineffective treatment and will allow the redistribution of resources to more promising treatments.

3. Sections 3-5 moved to “Extra Reading”

Lesson 14: Contribution of Patient

Organizations to Advertisement, Recruitment, Informed Consent and Protection of Study Participants in Clinical Trials

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1. Who contributes to the running of a clinical trial?
2. How are clinical trial participants protected?
3. How are patients informed about a trial?
    3.1. Information used to recruit participants for clinical trials
4. Patients can get information from their healthcare professionals
    4.1. The next steps
    4.2. What is informed consent?
5. GCP checklist for informed consent
6. Protection for vulnerable populations
    6.1. Other things to consider when dealing with vulnerable populations
7. Informed consent in studies with participation of minors
8. Patient involvement in the informed consent process
9. Patient involvement in clinical development
10. Types of activities where the public can get involved

1. Who contributes to the running of a clinical trial?

Clinical trials are run with contributions from many different organizations such as:

Research institutes.

Patient organizations.

Pharmaceutical companies.

Governments.

Universities.

There are many important details when setting up and running a clinical trial, such as:

The trial designs.

Scientific and ethical review procedures.

Deciding which participants should be included in the trial.

Finding and recruiting the appropriate participants.

Guarantee full protection of participants taking part in the clinical trial.

And more...

To provide input into all these different aspects, different stakeholders need to be involved throughout the entire clinical trial process as sponsors, investigators, regulators or participants.

2. How are clinical trial participants protected?

During the design and before a clinical trial can start, there are several elements that ensure the protection of participants:

Scientific review:

A Clinical Trial Application for the investigational medicinal product (IMP), has to be submitted to the national competent authority of the member state in which the sponsor plans to conduct the clinical trial. They review the documents to ensure the clinical trial is scientifically sound, and the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial participant.

They also:

Assess whether the methods to collect data are appropriate.

Determine whether the most suitable participants are planned to be included.

Review if the people running the trial are suitably qualified.

- Some review processes also ask for input from patients on the proposed trial design.

Institutional review – Ethics review:

A Research Ethics Committee (REC) is there to safeguard the rights, safety, and well-being of all participants in a clinical trial. Its positive opinion is required before a clinical trial can start.

The REC specifically evaluates:

(a) the relevance of the clinical trial and the trial design;

(b) whether the evaluation of the anticipated benefits and risks is satisfactory and whether the conclusions are justified;

(c) the protocol;

(d) the suitability of the investigator and supporting staff;

(e) the investigator's brochure;

(f) the quality of the facilities;

(g) the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent;

(h) provision for indemnity or compensation in the event of injury or death attributable to a clinical trial;

(i) any insurance or indemnity to cover the liability of the investigator and sponsor;

(j) the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial participants and the relevant aspects of any agreement between the sponsor and the site;

(k) the arrangements for the recruitment of participants:

* Special attention is paid to trials that may include vulnerable participants,
* the REC also assures that there is no coercion or undue influence on the trial participants, and
* conducts reviews of each ongoing trial at intervals appropriate to the degree of risk to human participants.

Clinical trial guidelines pertaining to the approval of a clinical trial:

The Clinical Trials Directive and Regulation harmonizes the rules in the EU for the approval of a clinical trial conducted in a member state. As regards NCAs, the details are set out in the Commission Detailed guidance on the request to the competent authorities for authorization of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) http://ec.europa.eu/health/files/eudralex/vol-10/2010_c82_01/2010_c82_01_en.pdf

With regards to Ethics Committees: Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (http://ec.europa.eu/health/files/eudralex/vol-10/12_ec_guideline_20060216_en.pdf)

These guidance:

Provide public assurance that the rights, safety and well-being of trial participants are protected.

Establishes principle for the written informed consent documentation:

the documentation needs to be written in a non-technical language and should be understandable to the patient or the patient's representative.

3. How are patients informed about a trial?

Doctors in clinics or hospitals.

Pharmacies.

- Advertisement.
- Social media.
- Recruitment agencies.
- Pharmaceutical company website.
- Clinical trial website.
- Clinical trial registries (e.g. EUCTR, clinicaltrials.gov).
- Patient organizations.

The methods used to advertise clinical trials are controlled by legislation.

Advertising is used by pharmaceutical companies and research organizations to recruit for clinical trials and employ a range of techniques to advertise their trials. In recent years there has been a move away from traditional print-based methods, such as posters in doctors' offices, towards the use of digital tools. These new tools range from dedicated clinical trial recruitment websites, EUCTR (EU clinical trials register), to social media sites.

Trial organizers will also seek potential participants via information provided through many sources such as patient organizations, pharmacies and clinical trial registries.

3.1. Information used to recruit participants for clinical trials

Regardless of the route used to reach out to potential participants, all advertisements for trial participants should be included in the CTA (as part of the protocol) to be reviewed by the REC.

The format used to recruit participants in the advertisements can be diverse; however, the advertisements should always:

- Include the contact details for the organization running the clinical trial.
- State the disease studied and purpose of the trial.
- Give the criteria to determine when a patient can take part in the trial.
- Mention the time needed for completing the trial.

On the other hand, advertisements must not:

- Promise a good outcome or a cure for the disease the patient has.
- Be coercive, especially when a trial is trying to recruit vulnerable patients, such as those with learning difficulties.
- State that the medicine being tested is safe or that it works.

In the UK the 'OK to ask' campaign is run by the National Institute for Health Research and is aimed at promoting the fact that it's good to ask about clinical research. (deleted link that is no longer active)

4. Patients can get information from their healthcare professionals

Healthcare professionals may recommend clinical research as a treatment option for their patients. However, a patient may also ask their healthcare professional about clinical research, and whether it might be right for them. Sometimes clinical trials are the only way to provide therapy to patients in serious need. This is still practiced in HIV/AIDS. Early access programs may be too slow or cumbersome, but a trial can save several lives.

In the UK the 'OK to ask' campaign is run by the National Institute for Health Research and is aimed at promoting the fact that it's good to ask about clinical research.

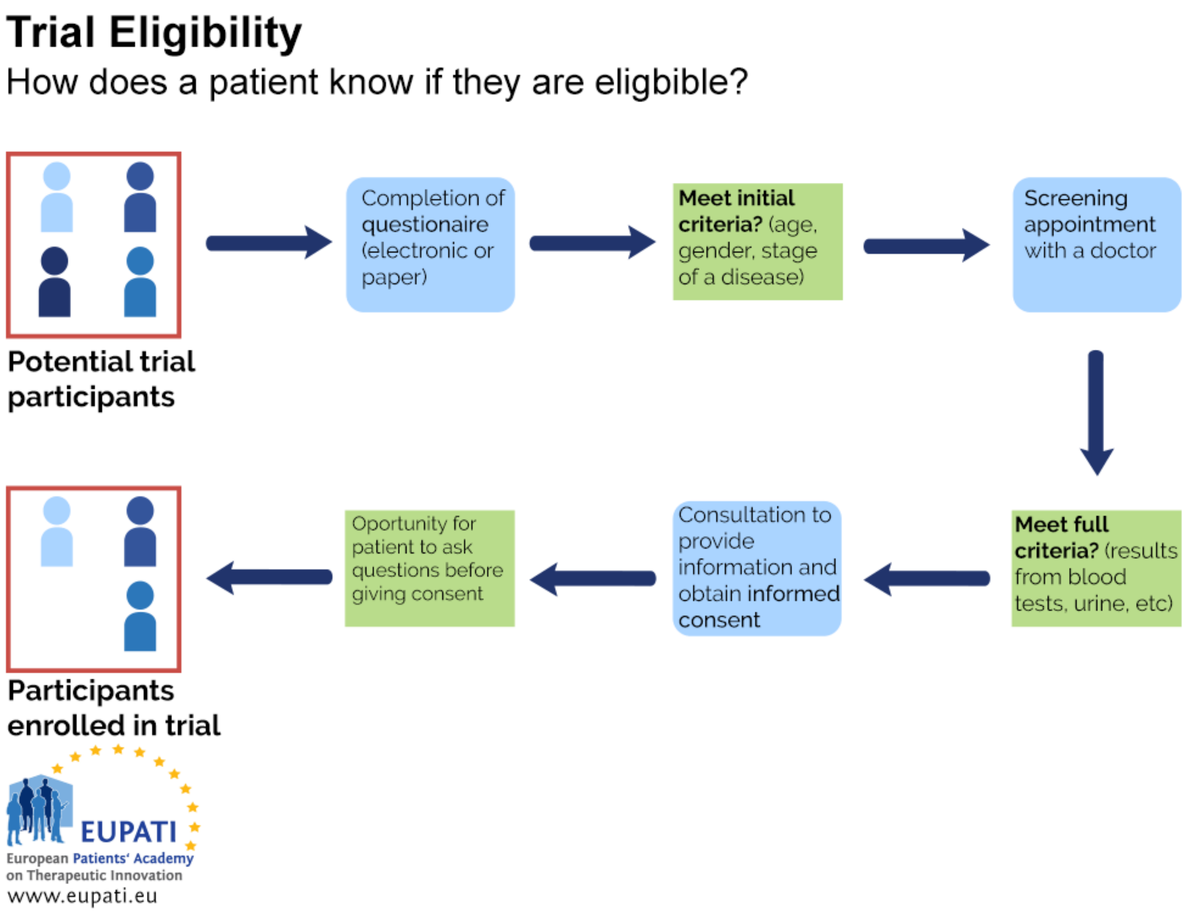
4.1. The next steps

When a patient has decided that they would like to enroll in a trial, there are several essential steps that need to be followed before they can 'sign up':

Enrolment - is the process of signing up or recruiting participants into a clinical trial.

Eligibility - the number of participants enrolled in a study varies greatly depending on the phase of the trial and the trial design. It must be found out whether a participant will meet the requirements outlined in the protocol (inclusion/exclusion criteria) to join the trial.

Informed consent - the participant can then sign the written informed consent after going through the process with a suitably qualified person, usually a member of the research team.



Prior to formal enrolment into a clinical trial, patients who are interested in participating will go through a screening process. Details of a person's medical condition will determine whether they can enter a clinical trial, usually based on information such as age, gender, the type and stage of a disease and previous treatment history (inclusion/exclusion criteria). Potential participants are usually asked to complete an initial questionnaire to determine whether they are eligible.

Those who meet the initial requirements are then invited for further screening, usually with a doctor or other healthcare professional directly involved in the trial.

Once the screening determines that the patient meets the inclusion criteria, the patient has a consultation where more and detailed information about the trial is provided, questions can be asked and an informed consent is signed (or refused).

4.2. What is informed consent?

There are several procedural safeguards built into the clinical trial process that continue throughout the study to protect the participant.

Informed consent is one of the ways that participants are protected during enrolment into a clinical trial and continues throughout the trial. During this process, potential participants learn the purpose and the potential burdens, risks and benefits of a trial before deciding whether or not they wish to participate.

Informed consent explains the trial to potential participants in understandable language including:

- Purpose.
- Procedures.
- Risks and potential benefits. Participant rights including the right to:
  - Make an independent decision about participating.
  - Leave the study at any time without jeopardizing future treatment.

Sponsors are encouraged to have patient organizations read the informed consent documentation for content and language prior to submitting the CTA.

5. GCP checklist for informed consent

Both the informed consent discussion and the written informed consent form, and any other written information to be provided to patients, should include explanations according to the Guideline for Good Clinical Practice)

The guideline should include explanations of the following:

- The trial involves research.
- Purpose of the trial.
- Trial treatments and probability for random assignment to each treatment.
- Procedures (including invasive) to be followed in the trial.
- Participant's responsibilities.
- What aspects are experimental.
- Reasonably foreseeable risks or inconveniences to the participant.
- Whether there are expected benefits for the participant or there is no intended clinical benefit.
- Alternative treatments, and their important potential benefits and risks.
- Compensation or treatment available in the event of trial-related injury.
- Anticipated payment, if any, for the participating patient.
- Anticipated expenses, if any, for the participating patient.

Additionally, participants must be informed of:

- The participation in the trial is voluntary and the person may refuse to participate or withdraw from the trial at any time, without penalty or loss of benefits to which the person is otherwise entitled.

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

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

The participant or the participant's legal representative will be informed when information relevant to the participant's willingness to continue participation in the trial becomes available.

Contact details to obtain further information regarding the participant's rights, and whom to contact in the event of trial-related injury.

Foreseeable circumstances or reasons for which the participation in the trial may be terminated.

The expected duration of the participation in the trial and the approximate number of participants involved.

6. Protection for vulnerable populations

REC's should safeguard the rights, safety, and well-being of all participants in a clinical trial, thus, they pay special attention to trials that may include vulnerable populations or participants.

According to the Committee for Medicinal Products for Human Use (CHMP), Guideline for Good Clinical Practice, vulnerable populations are defined as:

'Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of a retaliatory response associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate'.

Some examples of vulnerable participants are:

Anyone who could be pressured into taking part in the trial by a superior:

- Healthcare staff.
- Members of the armed forces.
- Prisoners.

Anyone who is particularly vulnerable to coercion:

- Patients with incurable or rare diseases.

- People in nursing homes or the elderly.

- Patients in emergency situations.

- Pregnant women.

- Ethnic minority groups.

- People with special needs or who are incapable of giving consent.

- Refugees or those from developing countries.

- Children.

6.1. Other things to consider when dealing with vulnerable Populations

- Researchers should sensitively explore the individual's abilities and the nature of their special needs. Information about the trial may need to be presented to individuals in a different format. Individuals need to be given plenty of time to think about the trial and ask any questions that they have.
- Children and their parents/legal guardians should be involved in the informed consent process in proportion to the ability of the child to weigh the benefits and risks of the trial. This is known as assent.
- Special care must be taken to make sure elderly people do not feel pressured or coerced into taking part in a trial. Prisoners should not be used as participants in a trial unless the trial is specifically looking at topics directly related to prisons or prisoners. Care must be taken to avoid healthcare staff feeling pressured to take part in a trial. Assumptions should also not be made about their knowledge of the trial and healthcare staff must be provided with the same detailed information about the trial as other participants Special care must be taken not to overly emphasize the benefits of taking part in a trial in patients who have a rare disease or incurable disease for which there may be few treatment options.

Care must be taken to avoid unintentional coercion to individuals in developing countries by offering them incentives such as free health care in order to take part in the trial. Local regulations must be taken into account.

7. Informed consent in studies with participation of minors

In studies requiring participation of minors, two types of informed consent can be used:

- Signed informed consent from the parent or legal guardians or legally acceptable representatives (LAR).
- Signed informed consent from the minor.

The language of these two documents should be different and appropriate to the level of understanding of the person signing.

Sample text for parent/legal guardian

Malaria is one of the most common and dangerous diseases in this region. The vaccine that is currently being used is not as good as we would like it to be but there is a new vaccine which may work better. The purpose of this research is to test the new vaccine to see if it protects young children better than the current vaccine.

Example text for minors (12–16 years)

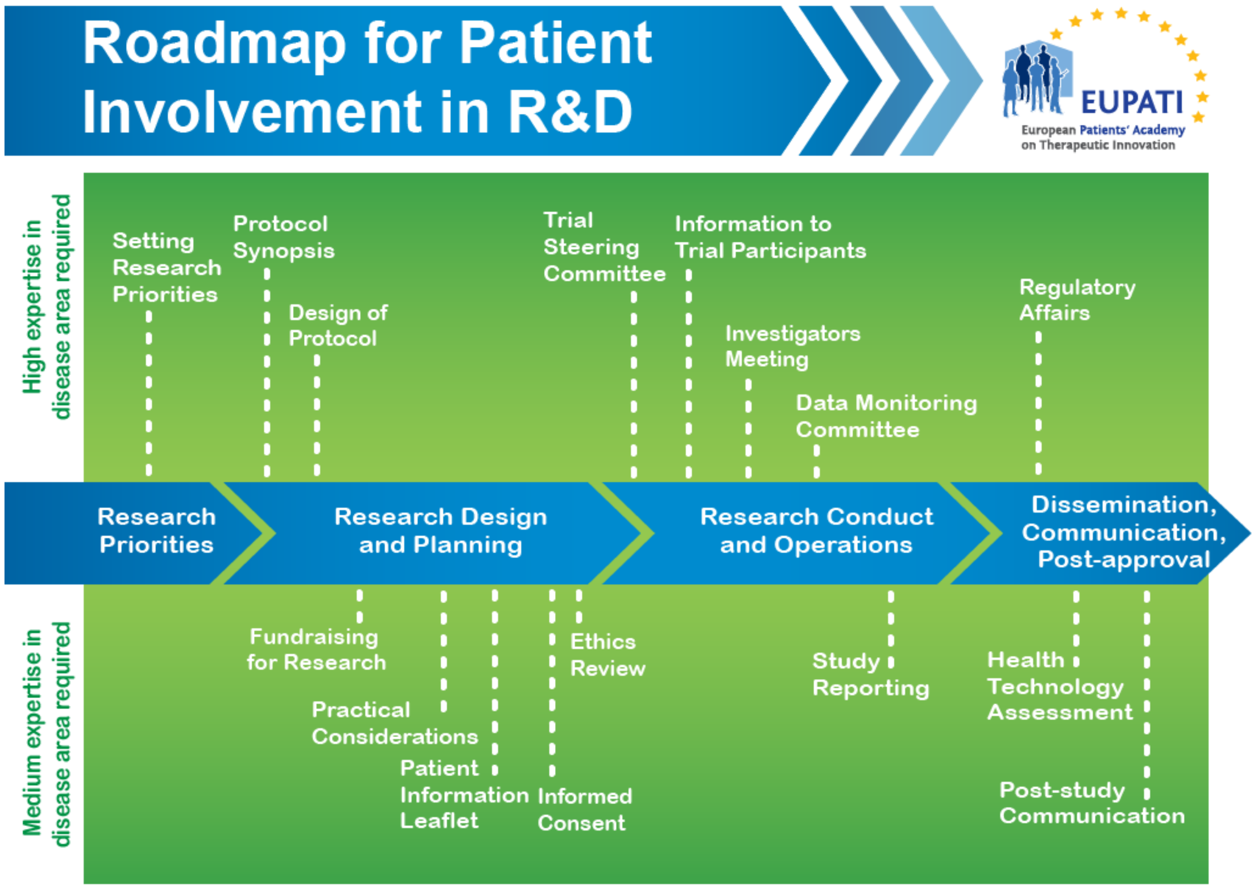
We want to find better ways to prevent malaria before it makes children sick. We have a new vaccine to prevent malaria which we are hoping might be better than the one that is currently being used. In order to find out if it is better we have to test it.

8. Patient involvement in the informed consent process

Patient representatives can work with the trial organizers to design the informed consent. They can help ensure that the informed consent documentation:

- Is written entirely in understandable and non-technical or scientific language.
- Does not contain persuasive language.
- Explains that participation in the study is entirely voluntary.
- Provides fair perspectives on the possible disadvantages and risks of participation.
- Outlines any direct benefits for the individual and any other beneficial outcomes of the study, including furthering our understanding of the research topic.

9. Patient involvement in clinical development



10. Types of activities where the public can get involved

Contributing to patient information leaflets to help recruit and inform people by telling them what they need to know in language they will understand.

Joining an ethics committee whose job it is to make sure that research carried out respects the dignity, rights, safety and well-being of the people who take part.

Being part of an advisory group to a research project which helps to develop, support and advise the project.

Helping to design a questionnaire, thinking through approaches to gaining good quality information from people in a research study.

Working with others to help communicate research findings to members of the public.

Examples of public involvement in clinical trials:

1. Patients and carers contributed significantly to the protocol for a large UK-based multicenter NIHR Health Technology Assessment- funded study (MUSTARDD-PD) researching the management of people with mild dementia associated with Parkinson's disease. People provided constructive ideas around how to raise the subject of dementia

with this target population and suggested alternative wordings to make all the study practicalities much clearer.

2. The PURPOSE (Pressure Ulcer Programme of Research) team at the Leeds Clinical Trials Research Unit found the pressure ulcer community to be a seldom heard group due to the lack of an existing service user/carer group and the complex health needs of many people in the community. Therefore, a small network of service users, carers and family members with some personal experience of preventing or living with pressure ulcers was formed.

A flexible 'asset based' approach to involvement was used to take on various roles depending on skills, needs and the level of commitment the members felt able to give. Preparation workshops supported this process by enabling network members to reflect upon their experience and expertise. Research opportunities are sent out to the network as they arise. They also offer opportunities for people to contribute from home, allowing input from people with work/carer commitments or mobility issues.

1. The Wales Cancer Trials Unit (WCTU) is strongly committed to public involvement focused on professional working partnerships with the patients. To identify volunteers who are able to contribute effectively and confidently at technically complex meetings, a formal recruitment process was established. Trials staff are involved with the selection and training of new volunteers and the mentoring of existing ones.

A support volunteer's role includes:

- Recruiting research partners to trials.
- Supporting both research partners and trial managers.
- Reviewing current support systems.
- Identifying development opportunities for research partners.
- Ensuring links with the Involving People network.

Lesson 16: Participants’ Rights and Obligations and the Role Patient Organizations can play

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1. Introduction

This topic deals with the rights and obligations of research participants, in the framework of clinical research. The role of patient organizations before and during the trial, and more precisely during the enrolment and retention phases, will also be discussed. The difficulty to recruit and retain participants is one of the major problems that clinical research faces.

2. Participant’s rights

Participants have rights and they are protected under law when participating in clinical trials. The European Commission Directive and Regulation establish that ’Human dignity and right to the integrity of the person are recognized in the Charter of Fundamental Rights of the European Union’. The Charter requires that any intervention in the field of biology and medicine cannot be performed without the free and informed consent of the person concerned.

The informed consent process is one of the key aspects of protecting research participants. It is designed to respect the autonomy of individuals and to protect their freedom of choice. It is imperative that the decision to volunteer for a study is individual and free from undue influences that might persuade a person to consent to greater than reasonable risk.

Prior to study enrolment, the participant has a right to fair information in order to be able to understand all the possible benefits and risks and burdens involved with participating in the clinical trial, the purpose and the overall plan for the trial: the methods used, the location and time required. The participant (patient or healthy volunteer) has the right to know everything that is going to happen in a study. As participating in a clinical trial may imply the imposition of unknown risks (a new medicine with unknown side-effects) and burdens (extra tests and procedures) in comparison to the standard of care, a full disclosure and understanding of all the implications of research participation is essential. This right is accompanied by the possibility to ask any questions and express all concerns about the participation in the study.

In practice, the informed consent is a process where a member of the research team explains, in clear and understandable language, all the aspects of the trial(s), and where the potential participant receives information both verbally and in writing. The potential participant has the right to refuse to take part in research and, if a decision to take part is made, the participant can decline participation or withdraw from the clinical trial at any time and for any reason without prejudice or loss of future treatment.

During the trial, the participants have both rights and protections to make sure their privacy and the confidentiality of their data are maintained. The informed consent process does not end once the form is signed. If new benefits, risks, or side effects are discovered during a study, the researchers must inform the study participants. There are also post-trial obligations for the sponsor regarding the appropriate follow-up with study participants. For example, study participants have the right to claim continued access to beneficial treatment at the end of clinical trials (expanded access/compassionate use).

3. Participant’s obligations

What are the obligations of a participant whether they are a patient or healthy volunteer, when agreeing to take part in research? Before answering this question, it should be clear on which grounds participants have obligations.

Participant obligations are not like professional obligations. The supporters of the view that patients have obligations ground their claim in the common good and common need. For example, according to Evans, a list of ten duties could be enumerated; like for example: ’the duty to uphold his own health, the duty to protect the health of others, the duty of truthfulness, the duty of compliance, the duty to seek and access healthcare responsibly, the duty to participate in research, the duty of recovery or maintenance etc...’ [1]. This range of positive obligations is relevant for the case of the research participant:

a) Participant's adherence: Patient adherence can be an issue in clinical research. It can apply to several different facets of clinical trials, like adherence to trial procedures, study visit compliance, adherence to medications and reporting of adverse events. The impact of a poor medication adherence by research participants may have detrimental effects on a trial, calling into question the scientific validity of the results.

b) Participant's health: It is a generally accepted obligation to maintain one’s own health. Whilst enrolled in a trial, participants should take special care to further minimize risks to their health.

c) Truthfulness: By informing doctors of symptoms, research participants are asked to report any adverse events in order to protect themselves and others. Study participants should also inform doctors of any other important factor that can impact the study results (such as the use of other medicines or substances that could interact with the investigational product). In general, any action which could undermine the integrity of the trial, should be avoided.

There is no doubt that the notion of participant's obligations or responsibilities is debatable; and especially when participants take risks during research. There is a temptation to counter this with discussion regarding the duties of the sponsor against a system of duties for the participants. Responsible behavior of the research participant should be promoted.

One reason is that the concept of generalization of clinical trial results for the entire population of patients implies that patient behaviors inside and outside of a trial should be as identical as possible. It is in the interest of patient organizations to make sure that the actual diversity of the patient population is reflected in clinical trials.

4. Role of patient organizations

Patient organizations can play a significant role in raising awareness about clinical trials and therefore help the recruitment and retention of patients in clinical trials, due to their close relationship with patients. Clinical trial sponsors have started to partner with patient associations to benefit from their knowledge on diseases and their networks. Nowadays, the roles of patient organizations in the clinical research enterprise are numerous. We will focus on their role, once the study has been designed, very often with the input from patient organizations, and approved.

4.1. Informed consent and protocol review

In an increasing number of trials and disease areas, the involvement of patient organizations in protocol reviews has become common practice. The fields of HIV/AIDS or chronic myelogenous leukemia are good examples of how community advisory boards can provide meaningful input into trial design from the aspect of the patient community.

Expert patients and advisory boards also usually look at draft informed consent documents to determine their fairness and clarity for the patient or trial participant and can also intervene in different study design issues. Patient representatives can also contribute to making sure that the correct or most-in-need communities are approached by the investigators, especially in situations when trials are also used as means to provide access to life-saving medication.

4.2. Dissemination, promotion and comprehension

Patient organizations can contribute to the dissemination of information on clinical trials and help patients to understand study aims and designs. Patient organizations involved in research activities can help to select trials for their community and inform about studies on their websites and on social networks. They can also serve as a referral source to clinical trial sites.

As patient organizations produce educational materials for different topics related to diseases and treatments, they have experience in explaining in lay terms the features of a clinical trial in order to meet the needs of patients. They may be able to mobilize resources to focus on study goal comprehension, understanding the patients' perception of benefits and risks, and take time to assess with the patients their reasons for either accepting or refusing to take part in research.

The benefit of working with patient organizations can also be illustrated in the particular case of research in small populations, such as in rare diseases. Patient organizations have developed skills to produce effective communication in order to involve vulnerable or special populations. For example, adapting material according to specific literacy levels will engage populations more effectively. In conclusion, patient organizations may influence (positively or negatively) the recruitment of patients into clinical trials by using their networks, partnering in the creation of recruitment materials, and engagement in publicity campaigns. Through their communication channels, interactions with the media, patient organizations can also play a crucial role in disseminating to patients the results of previous studies and keeping the momentum to engage patients to participate in trials.

4.3. Study adherence and retention

Although investigators make every effort to ensure adherence in clinical trials, participants with suspicions of being under a placebo arm, for example, may not be compliant with their medications. Patient organizations may provide the study participants with support to improve adherence to medications.

In collaboration with the research team, the patient organization could help finding solutions to provide continuing supervision of the regimen. It can be noticed that communication during the trial helps to retain trial participants and promote adherence to treatment.

Dissemination of trial results is critical to engage patients in the community. When patients are kept informed of the study progress and achievements, during and after their participation in a clinical trial, positive feelings associated with trial participation are produced, and participants are kept interested in pursuing their contribution to the study. Valuing participation is indeed a key parameter of participant retention and adherence; an equal responsibility for all stakeholders.

The role of other patients involved in online social networks should not be underestimated. Patient-to- patient support, regarding study comprehension and adherence, is becoming a reality for some groups of patients connected through social networks.

4.4. Individual support and protection

Patient organizations have a role of support and protection to their constituents. Patients frequently need independent advice regarding their participation or discontinuation of participation in a clinical trial.

5. References

1. Evans HM: Do patients have duties? Journal of medical ethics 33(12), 689-694 (2007).

Lesson 20: Basics of quality Management in Clinical Trials

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1. Why Quality Management?

You have already learned enough about clinical trials to know that it generally takes a lot of resources to set one up. No matter whether it is a large international trial conducted at several centers, or just a small trial with few patients at a single center, clinical trials are always expensive. They cost a lot of money, e.g. for medicine, laboratory tests, databases, extra personnel, etc. But they are also expensive in terms of the time that they take:

- The researchers involved often need to spend a lot of time on both scientific and administrative tasks.
- The sponsor spends time monitoring the trial.

Another important point is that a clinical trial uses the time and energy of the patients who are willing to participate without even knowing if the experiment will lead to a useful treatment.

It is easy to understand how important it is to prevent anything unforeseen happening that would put the safety participants and the result of the trial at risk.

What could actually go wrong when conducting a clinical trial?

1.1. What could actually go wrong when conducting a clinical trial?

- Wrong medication given to patient.
- Measurements taken at the wrong time.
- Participant did not show up for appointment.
- Participant included in the trial even though they were not eligible.

- Adverse reaction not reported.
- No back-up of data entered into the computer.
- Wrong statistical analysis is being used to calculate the result of the trial.

When thinking about this question one realizes that many things could go wrong in the course of a clinical trial. These were some examples, but many more can be found.

It also becomes evident that most of the mistakes that can occur during a clinical trial can be avoided simply by proper planning and regular control of the trial procedures. This is what is understood as 'quality management'.

Quality management is described in the Guideline for Good Clinical Practice (ICH-GCP guideline). It is the responsibility of the 'sponsor' i.e. the person, institution, organization or company that takes responsibility for initiation, management and/or financing of the clinical trial. If the trial is large, the sponsor may not be able to oversee all activities and might even lack the necessary qualifications for ensuring the proper quality of all steps of the trial. In such circumstances, the sponsor is obliged to hire qualified people to help ensure that the trial is planned, conducted and analyzed correctly.

Quality management activities can be divided into two sub-groups – those done before starting the trial (quality assurance or QA) and those done after the trial has been initiated (quality control or QC). Examples of these activities are described below.

Quality assurance (QA) can be described as the activities done in order to avoid any mistakes happening, whereas quality control (QC) might be described as the activities done in order to identify and to correct mistakes that have occurred. Both are regarded as equally important and it should always be carefully considered how to incorporate both QA and QC activities in each individual trial. They are necessary to ensure the validity of the trial.

The following parts of this lesson describe the QA and QC activities as defined in the GCP-guideline.

2. Standard Operating Procedures (SOPs)

Standard operating procedures (SOPs) are defined in the GCP-guideline as: 'Detailed, written instructions to achieve uniformity of the performance of a specific function'. It is not a requirement to have SOPs when performing clinical trials, since one may also have detailed, written instructions in the trial protocol. However, most organizations and hospital departments working with many trials usually have SOPs that describe the critical procedures of a trial. Often the SOPs are more general and can be used for many trials. For example:

- An SOP can describe the procedures used when informing patients about a new trial.
- If measurement of blood pressure is the most important parameter in a certain trial, a specific SOP can be developed describing exactly how this must be done and by whom, as there are multiple methods available to measure blood pressure.

SOPs are characterized as being 'controlled documents'. This is to ensure that old and new versions of the instructions are not mixed, and that one always has access to all pages and attachments of the SOP in force. It is also important to be able to document the version of an instruction that has been followed in a clinical trial in case of an inspection from the health authority years after the trial has been completed.

SOPs are always assigned a version number and it is stated from what date they should be used. Whenever a new version is made, all old versions must be replaced. It is however important that old versions are archived. The purpose of this is to ensure transparency if procedures are changed during the course of a clinical trial. There must be a named person who has the task of managing SOP replacements and archiving. In fact, one must also have a separate SOP that describes the procedures for writing, approving, distributing, replacing and archiving SOPs. This is normally the first SOP written!

It is the responsibility of the sponsor of the trial to establish a system of SOPs, if necessary. If an SOP system has been established, all personnel involved in a trial should be trained in the relevant SOPs. This training must of course be completed before undertaking any trial related duties and must be documented as well.

3. Audits

Even though SOPs are an important part of quality management activities, they cannot stand alone. Imagine you are writing an SOP and you have misunderstood the procedure! You might be very skilled in producing good descriptions of the work to be performed, but if you have misunderstood the process, your instructions might lead to a situation where the procedure is repeatedly performed incorrectly.

So how can we avoid this situation? One possibility is to invite independent experts to supervise the organization and operational procedures of the clinical trial. This will provide an impartial view on how the trials are or should be performed. This supervision is called ‘audit’ and the independent experts are called ‘auditors’. It is the responsibility of the sponsor to ensure that audits are performed on a regular basis.

According to the GCP-guideline an ‘independent’ auditor means that the sponsor and the auditor should not be working within the same organizational unit. A sponsor may hire an external auditor, but many pharmaceutical companies often employ their own auditors. In this case, the auditors work in a completely separate department.

In practice an audit may be performed in two different ways:

- The auditor uses one trial as an example and evaluates all the procedures that have been used in that trial.
- The auditor looks at one specific procedure. For example, they might look at the procedure for ‘reporting of adverse reactions’ and then evaluate a number of trials where this has been performed.

Auditors normally work systematically with both types of audits. A thorough audit of a trial normally takes several days as the auditors have to examine all activities and documents of the trial. The audit will evaluate trial conduct and compliance with what has been described in:

- The relevant SOPs.
- The protocol of the trial.
- GCP-guideline.
- Applicable regulatory requirements.

Definition of an audit in the GCP-guideline:

'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, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).'

An audit may be initiated for two reasons: either as a part of a routine supervision or in response to a special concern that has been raised about a certain trial. The latter type of audit is called 'for cause audit' and may be a useful tool for a trial sponsor if they have a concern about malpractice in a trial.

The most important part of the audit is often what takes place afterwards. Each deviation from the intended trial conduct is described. These are called 'findings' and are always graded in two to three categories expressing how serious they are. These findings are described in an audit report. If a deviation can compromise the trial result or the patients' safety or rights, the sponsor must describe concretely how the situation will be handled. It is equally important that the sponsor implements so called 'corrective actions' to ensure that the deviation will not happen again. When the audit is completed the auditor will issue an audit certificate which confirms that the audit has taken place.

4. Monitoring

Unlike audits, monitoring is part of the routine control of the trial process and is always carried out for all trials. It is a QC activity and as such is not intended to oversee systems but simply to control that a trial is being performed according to how it has been planned, described and approved.

Definition of monitoring in the GCP-guideline:

'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, standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).'

Monitoring is carried out by a monitor, who must be trained in the trial protocol and GCP-guideline. They must not be taking part in conducting the study. According to the GCP-guideline monitoring should normally be performed before, during and after the trial. This is normally practiced as follows.

Monitoring before the trial: Initiation visit (one visit at each center)

Purpose:

- To check and document that everything is ready for trial initiation at a center before the first patient is enrolled.

Examples of activities:

* Is the trial approved by relevant authorities?

* Are all personnel adequately trained?

* Is the trial medicine on site and properly labelled and stored?

* Is relevant rescuing equipment in place in order to guarantee patient safety?

* Have necessary agreements with other departments been made? Are the forms for data recording ready to use?

4.2. Monitoring during the trial: Monitoring visits (often many visits at each center)

Monitoring during the trial: Monitoring visits (often many visits at each center)

Purpose:

To check and document that the trial is being conducted as planned.

Examples of activities:

* Have all patients signed the Informed Consent Form?

* Have all patients been registered on an ID-list and allocated a unique trial number?

* If a blinded trial, has the blinding of trial medicine been compromised?

* Have all patients received the correct trial medicine?

*Have all data been correctly entered into the trial database?

* Have possible adverse reactions been registered and reported according to the procedures?

* Have any problems registered at previous monitoring visits been resolved?

4.3. Monitoring after the trial: Close-out visit (one visit at each center)

Monitoring after the trial: Close-out visit (one visit at each center)

Purpose:

To verify and document that the trial has been closed properly at each center.

Examples of activities:

Have necessary reports been submitted to the authorities? Is all trial medicine accounted for? Have all questions regarding the data registration been solved? Have all lists and reports been signed as necessary? Have possible adverse reactions in participants been resolved or minimized? Has trial participation been appropriately noted in the personal medical records of participating patients? Are there any procedures in place for archiving of trial data?

One of the duties of a monitor is to write a monitoring report after each visit. This report describes what has been checked, and what follow-up needs to be done and by whom. The report is always sent to the sponsor of the trial who has the overall responsibility of the trial. A copy of the report will be sent to the investigator who is responsible for trial conduct at the center.

An important part of monitoring a trial is to check whether all trial data have been registered correctly in the trial database. This is done by comparing the data entries in the database with the documents where the trial data was originally recorded (the source data).

5. Inspections

Inspections are another check of all trial related activities, but they are conducted by the regulatory authority(ties) and are as such not part of the quality management which is planned by the sponsor. However, if an inspection is performed, it will ensure and typically increase the quality of a trial by flagging short-comings and requiring corrective actions.

Definition of inspections in the GCP-guideline: *'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. They may be located at the site of the trial, at the sponsor's and/or contract research organizations (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).'*

As with audits, inspections may also be performed on a 'for-cause' basis if, for instance, the clinical trial is part of the documentation for a new medicine. They may also be performed simply by chance as a part of a routine control. Following an inspection of a trial the sponsor will receive an inspection report stating all the details that have been examined and the 'findings' that have been made by the inspectors. The findings will be graded into 'minor', 'major' and 'critical'. 'Critical' findings are those that actually have put participant safety, participant rights or the trial result at a considerable risk. The inspection report will outline what requirements the inspectors have made for the trial. In the worst case, an inspector may suspend or even terminate a trial.

Lesson 21: Options for data collection and patient-reported outcomes (PROs)

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5. Patient reported outcomes (PROs, ePROs)

5. Patient reported outcomes (PROs, ePROs)

The term PRO (patient reported outcome) is used for all data that is directly provided by patients. This includes all types of questionnaires and diaries either in paper or electronic form. If an electronic hand- held system such as a tablet or text messaging (SMS) are used, it is called ePRO. Typically, this electronic data is either in a daily diary form in the patient’s hands, or questionnaires administered during site visits.

In our rapidly developing electronic world the technical tools that can be utilized to receive this data in an efficient, patient-friendly manner are constantly evolving.

Advantages of ePRO:

- Higher quality of data:
  - Automated edit checks ensure PRO data is often 100% clean – no need for extensive data cleaning.
  - Alarms and context-sensitive eDiary design achieves higher adherence to protocol.
- Immediate intervention possible when problems or deviations occur.
- Allows clinicians to concentrate on treating their patients - and spend less time on data entry.

Disadvantages of ePRO:

- Greater technical effort and therefore more expensive than paper.
- Not all patients are familiar with modern technology.
- Like every electronic instrument there can be failures and break-downs.
- More time required for the site staff to explain the use of the system to the patient.
- Access to the internet needs to be available.