# Introduction to Clinical trials

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# Course goals

- To give an introduction to the concepts, principles, and methods used in clinical trials. Specifically
  - Define clinical trials
  - Discuss ethics of clinical trials
  - List statistcal issues of trial design
  - Review issues of cohort and endpoint definition
  - Describe the need for efficient management of data
  - Investigate monitoring of ongoing studies
  - Review analysis methods and reporting guidelines
- The mathematical detail will be de-emphasized but will be significant. The focus will be on examples.

# Audience

This course is directed towards students that want to understand the mechanics and implications of correct conceptualization, design and implementation of clinical trials. The required background includes

- Understanding of basic statistical concept such as
  - Hypothesis testing
  - Inference
  - Analysis of variance and regression
- Elements of experimental design

Some familiarity with clinical trials and more advanced concepts such as survival analysis is preferred.

# Definitions: What is an experiment?

An experiment is a series of observations made under controlled conditions.

This implies that studies where the intervention is applied for reasons out of the control (or even knowledge) of the investigator are not considered experimental studies.

A design of an experiment is the procedure that controls treatment administration and isolates the factors of interest.

# Definitions: What is a clinical trial?

Broadly speaking, a clinical trial is an experiment testing a medical intervention on human subjects.

Clinical trial design is the process by which the investigator

- Assigns treatment to the clinical trial participants
- Remove or minimize factors associated with
  - Outcome variability
  - Selection bias
  - Inconsistent application of treatment
  - Incomplete or biased ascertainment of the results

# What is and what is not a clinical trial

A clinical trial must fulfill, at a minimum, the following three characteristics:

- It must be an experiment carried out on *human subjects*.
  This eliminates all animal studies as being clinical trials even though they might be handled experimentally identically to clinical trials.
- It must be *prospectively* collecting data.
  This removes from consideration all retrospective studies
- It must be testing a *medical intervention*.
  This requirement excludes all "observational" or natural history epidemiological studies

# Common misconceptions

Common misconceptions about what a clinical trial is or is not are as follows:

- The existence of randomization does not ensure that a study is a clinical trial ...
- ... just as absence of randomization does not remove the possibility that an experiment is a clinical trial
- A study that does not have an internal control arm can still be a clinical trial (i.e., single-arm studies) although all studies are ultimately comparative (e.g., versus historical controls).

# Examples of clinical trials and other experimental studies

It is commonly accepted that the first clinical study was that of James Lind aboard the HMS Salisbury in 1,747 (Sutton, *J R Soc Med*, 2003). Lind chose twelve sailor suffering from scurvy (a vitamin-C deficiency) and offered two each the most popular scurvy interventions of the era:

- cider
- elixir of vitriol
- vinegar
- sea water
- oranges and lemons
- a "purgative mixture"

Sutton G.Putrid gums and 'Dead Men's Cloaths': James Lind aboard the Salisbury. *J R Soc Med*. 2003; **96**: 605608.

# Lind's study as a clinical trial

The two sailors receiving the oranges and lemons recovered sufficiently so that one of them was appointed as the nurse of the others. Nevertheless, the Royal Navy did not introduce citrus rations until 1795 (almost fifty years later).

**Question:** Is Lind's study a clinical trial?

# Lind's study as a clinical trial

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**Question:** Is Lind's study a clinical trial?

**Answer:** Lind's study is indeed a clinical trial (albeit not an optimally designed one) because:

- It is a prospective study
- It studies an intervention (actually six interventions)
- It applies these interventions on human subjects

Actually note that Lind had instinctively grasped the concept of response variation and administered each treatment to two subjects instead of one (this was quite extraordinary for his time when causation and determinism were the prevailing attitudes).

# Problems with Lind's study design

As advanced for its time as Lind's study might have been there were several design pitfalls that were inherent in his approach. We list some of them for expository purposes here and as a preview of several issues that will be addressed in this course.

- Lack of rigor in defining the cohort
  It is mentioned in the ship's log that there close to two dozen sailors suffering from scurvy. How were the twelve that ultimately received the treatments chosen?
- Small sample size
  Even with the inclusion of two sailors per treatment group, the sample size would be small for all but the most robust response

# Problems with Lind's study design (continued)

- Lack of randomization
  There was no way to ensure that the six groups (as small they might have been) were assigned the treatments in any random fashion.
- Not clearly defined endpoint
  It would appear that the study "endpoint" was for sailors to "improve" in some sense. This is of course totally vague and impossible to build a trial around it.

Nevertheless, Lind's was an exceedingly successful study!

# Clinical trials in the twentieth century

It is generally agreed that the first modern randomized clinical trial is that of the British Medical Research Council's (MRC) study of streptomycin for the treatment of pulmonary tuberculosis.

Medical Research Council. Streptomycin treatment of pulmonary tuberculosis: a Medical Research Council investigation. *BMJ* 1948; **2**: 769-82

# Design of the trial

The study had a treatment (streptomycin) and a control group. Both groups got the standard of care for the time, bed rest. The control group would be administered streptomycin if it were to be shown effective.

The treatment allocation was random and was stratified by gender. It was implemented through envelopes with the hospital name, the gender and containing a card with the character "S" for streptomycin and "C" for control (bed rest). The order of the envelopes was determined by random numbers.

Patients did not know that they were in a trial, which remained confidential throughout its 15 month duration.

# Design of the trial (continued)

Progress of patients was assessed by monthly X-rays that were reviewed by three experts that were blinded to the group allocation of the subject.

Bacteriological studies were reviewed by bacteriologists that were also blinded to treatment allocation.

# Study results: Response

The result of the study was that streptomycin was "helpful".

In the first analysis (six months into the study) there were 4 deaths out of 55 patients in the streptomycin arm and 15 among 52 patients allocated to bed rest alone (Fisher's exact test p=0.005).

However, over the subsequent 6 months, there were 9 additional deaths in the streptomycin arm and 9 more in the control group. Note that this analysis constitutes a second (preliminary) analysis of these results. This is something that would not likely be done today.

Tubercle bacilli could be cultured from the sputum of 47 of the 55 patients treated with streptomycin, compared with 50 of 52 patients in the control group (Fisher's exact test p=0.094).

# Study results: Response (continued)

Drug resistance to streptomycin was seen in most patients after four months of therapy, which prompted MRC to interrupt therapy after four months.

Development of resistance to streptomycin and, later, to para-aminosalycylic acid (PAS) led investigators to try these two drugs in combination, which significantly lowered the development of resistance (Daniels & Hill, *BMJ*, 1952).

Daniels M, Hill AB. Chemotherapy of pulmonary tuberculosis in young adults; an analysis of the combined results of three Medical Research Council Trials. *BMJ*1952; **1**:1162-68

# Study results: Safety

Toxic effects of streptomycin were observed in many patients in the MRC trial but were not considered severe enough to necessitate treatment discontinuation. These were

- Damage to the inner ear
- Nausea and vomiting, which led to a double-blind trial of an antihistamine drug (Bignall and Crofton 1949).

Bignall JR, Crofton J. Antihistamine drugs in the treatment of nausea and vomiting due to streptomycin. *BMJ* 1949; **1**:13–14.

# The legacy of the MRC trial

A great deal of the components of randomized clinical trials of today present in the 1948 MRC study (even though the ethical issues of lack of an informed consent would be unacceptable today!).

The definition of the control group as receiving the standard therapy of the time (bed rest) and of the treatment group receiving bed rest plus streptomycin eliminated a number of biases that could arise if alternative definitions of the cohorts had been used.

The mode of stratification and randomization and the care taken to maintain blindness of the central radiological and bacteriological review was excellent.

# The legacy of the MRC trial (continued)

The concept of central (and blinded) review, which is ubiquitous today, was also another area of excellent study implementation.

Perhaps most importantly, the attendant studies of resistance to streptomycin and the discovery of combination therapy to limit it were an monumental advancement in the area of infectious diseases well beyond TB!

# The thalidomide disaster and drug regulation

Thalidomide is a sedative, developed by German pharmaceutical company Grünenthal and sold from 1957 to 1961 mainly to pregnant women, as an antiemetic to combat morning sickness and as an aid to help them sleep.

Before its release, inadequate tests were performed to assess the drug's safety for the fetuses of women who had taken thalidomide during the first trimester of their pregnancies. From 1956 to 1962, approximately 10,000 children were born with severe malformities, including phocomelia and internal organ abnormalities, because their mothers had taken thalidomide during pregnancy.

# Frances Kelsey and the role of the resurgent FDA

Thalidomide was never widely used in the US due to the dogged resistance of an FDA reviewer, Dr. Frances Kelsey, who meticulously reviewed data on the drug. She particularly focused on rare cases of peripheral neuritis (numbing of the limbs) seen after prolonged use.

She knew, from malaria drug screening during WWII, that fetuses do not metabolize quinine and the effects of German measles on embryos were well known. This made her cautious about side effects that could affect the fetus even though they might not be observed in adults or children.

In 1962, in reaction to the tragedy, the United States Congress enacted laws requiring tests for safety during pregnancy before a drug can receive approval for sale in the U.S. Other countries enacted similar legislation.

Daemmrich A. A tale of two experts: Thalidomide and political engagement in the United States and West Germany. *Soc Hist Med* 2002 **15**: 137-158.

# Cancer chemotherapy in the United States

Great advances in clinical trials design and implementation were made as a response to the large trials required to investigate issues related to cancer therapy.

The origins of chemotherapy can be found in therapeutic application of chemical warfare agents (namely derivatives of mustard gases) for the treatment of lymphoma and the use of folate analogues (aminopterin and amethopterin - methotrexate) to treat acute lymphoblastic leukemia (ALL) (Goodman et al., *JAMA*, 1946).

Goodman LS, Wintrobe MM, Dameshek W, et al. Nitrogen mustard therapy. Use of methyl-bis(beta-chloroethyl)amine hydrochloride and tris(beta-chloroethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia, and certain allied and miscellaneous disorders. *J Am Med Assoc* 1946;**105**:475-476.

# 6-MP and the birth of the cancer cooperative groups

A great advance in cancer chemotherapy was the development of 6-mercaptopurine (6-MP) for the treatment of ALL. A randomized clinical trial was designed in 1954 that compared two regimens of 6-MP and methotrexate (Frei et al., *Blood*, 1958).

To identify enough patients for the study, two collaborative groups were eventually formed (the Children's Cancer Study Group and Cancer and Leukemia Group B) that are active today.

In addition, evidence that nitrogen mustards showed effect on adult solid tumors led to the formation of the Eastern Solid Tumor Group (which was renamed to the Eastern Cooperative Oncology Group - ECOG).

Frei EF, Holland JF, Schneiderman MA, et al. A comparative study of two regimens of combination chemotherapy in acute leukemia. *Blood* 1958;**13**:112648

# Combination chemotherapy

In 1965, Holland, Freireich, and Frei, the same team that studied 6-MP and methotrexate in the 50's, persevered through repeated failures and adapted to cancer chemotherapy the combination therapy for tuberculosis with combinations of drugs with a different mechanism of action.

By using different drugs concurrently, they hypothesized, it would be more difficult for tumor cells to develop resistance to the combination compared to each agent separately. Through their efforts, regimens like the POMP, a combination of methotrexate, vincristine 6-MP and prednisone and subsequent refinements thereof ultimately rendering ALL in children a largely curable disease.

# Combination chemotherapy (continued)

This approach was extended to the lymphomas in the late 1960s when a nitrogen mustard, vincristine, procarbazine and prednisone known as the MOPP regimen was shown that it could cure patients with Hodgkin's and non-Hodgkin's lymphomaa. Currently, nearly all successful cancer chemotherapy regimens use this paradigm of multiple drugs given simultaneously.

The success of these approaches paved the way for our understanding of combination therapy in other diseases, most notably HIV.

# Evolution of statistical issues in clinical trials

The evolution of statistical analysis and design issues during those early trials is chronicled by Gehan (*Clin Can Res*, 1997). He identified four main areas as having been developed in these studies:

- A quantitative approach to clinical trial design and analysis
- The randomized controlled trial (RCT)
- The non-randomized controlled trial
- The use of regression models in clinical studies

But perhaps more importantly, cancer cooperative groups brought forth an appreciation for competent management and analysis of data produced by these studies.

Gehan EA. The scientific basis of clinical trials: Statistical aspects. *Clin Can Res* 1997; **3**:2587–2590

# AIDS Clinical trials

The advent of AIDS had a huge impact on the design and analysis of clinical trials compared to previously defined standards. Given the recent nature of this disease, the affected population, and an overwhelming and, to say the least, "creative" patient advocacy, led to an overhaul of the deliberate and conservative approach of previous clinical trials.

# Issues arising in AIDS clinical trials

As listed in the article by Ellenberg and others (*JASA*, 1992) AIDS, as a disease, is different from cancer in that clinical trials in HIV are not categorized by organ but by clinical stage and purpose (e.g., early stage antiretroviral studies versus late stages prophylaxis trials, studies of treatment for opportunistic infection versus oncology protocols). Other areas that saw great advances due to HIV research are:

- Surrogate marker research
- A resurgence of factorial designs in clinical trials
- Designing studies allowing for patient co-enrollment
- Analysis in the presence of treatment modification
- Analysis of longitudinal endpoints

Ellengberg SS, Finkelstein DM, Schoenfeld DA. Statistical issues arising in AIDS clinical trials. *JASA* 1992; **87**:562–569

# The parallel track and expanded access

The major however contribution of HIV/AIDS in clinical trial design has been the inclusion of patient advocates in all levels of decision-making and trial design and the expanded access to investigational drugs that have minimal safety data.

In response to the concerns of activists, the FDA initiated several reforms to shorten the approval process. Chief among them was the replacement of clinical endpoints with surrogate markers or intermediate endpoints that did not take as long to observe. A record number of drugs were approved as a result based, not on survival or time to AIDS as it was the case up to that point, but on surrogate endpoints such as CD4 increases and viral suppression.

# The politicization of the FDA

Since 1962, the FDA was vested with the authority of approving all drugs sold in the US. There has always been criticism for the slow speed, cost and delay of bringing promising drugs to market. No one has articulated a more extreme position against the FDA than nobel laureate economist Milton Friedman (e.g., interview for the program Uncommon Knowledge, February 10, 1999).

Others have resisted efforts to accelerate approval of unproven medical therapies and can be seen as supporting a stronger and more deliberate drug approval process (Society of Clinical Trials Board of Directors, *Clinical Trials*, 2006).

Society of Clinical Trials Board of Directors. The Society for Clinical Trials opposes US legislation to permit marketing of unproven medical therapies for seriously ill patients. *Clinical Trials*, 2006; **3**:154–157

# Coming full circle: Vioxx

Rofecoxib (Vioxx) is a popular anti-inflammatory drug. Its popularity is linked to the favorable gastrointestinal toxicity profile (compared to, say, aspirin or other anti-inflammatory medications).

In 2004, Vioxx was pulled from drug store shelves after it was associated with increased risk of cardiovascular disease and strokes, but not before over a million patients in the US alone had taken the medication and up to 140,000 of excess serious coronary heart disease may have been associated with Vioxx use (Graham et al., *Lancet*, 2005).

Graham DJ, Campen D, Hui R, Spence M, Cheetham C, Levy G, Shoor S, Ray WA. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet*, 2005; **365**:475–481

# A new swing of the pendulum

As it became apparent during the subsequent litigation, Merck had known about increased cardiovascular toxicity at least as early as 2001 (Psaty & Kronmal, *JAMA*, 2008) prompting an outcry to strengthen procedures for drug safety and approval.

Psaty BM, Kronmal RA. Reporting Mortality Findings in Trials of Rofecoxib for Alzheimer Disease or Cognitive Impairment. *JAMA*, 2008; **299**:1813–1817. For legal documents cited in the article please see http://www.biostat.washington.edu/research/Rofecoxib.

# Ethics of clinical trials

# Why clinical trials are ethical

The following presentation is focused in five areas:

- Duality in the obligation of physicians
- historically derived principles of ethics
- contemporary principles
- concerns about randomization and the use of placebos
- professional conduct

# Equipoise versus uncertainty

In order for patients to be ethically placed in a clinical trial two principles must be at work:

- Equipoise
- Uncertainty

# Equipoise

*Equipoise* is a collective state of uncertainty about the superiority of one versus the other treatment given in a clinical trial. This means that the majority of experts in the field are uncertain about the superiority of one treatment versus another.

Note that individual practitioners may have strong beliefs about the superiority of one treatment but this is not contradictory to having a state of equipoise in the field.

# Uncertainty

*Uncertainty* is the state where an individual practitioner is not certain about the superiority of one treatment versus another.

Note that this may be a minority view (i.e., the field is convinced about the superiority of the treatment). If a practitioner is not in a state of uncertainty about the treatments involved in the trial, Peto and Baigent (1998) contend that they should not include any of their patients in this trial.

A "critical mass" of uncertain experts leads to a state of equipoise.

# The duality of physicians' duties

Physicians and other individuals involved with caring for patients face a dual set of duties:

One is to protect the individual patient under their care.

The other is to gain knowledge from individual patients that will benefit the community (even if it does not necessarily benefit the individual patient).


APRIL 23, 2002
Powell's Mission Impossible
TIME
HOW MEDICAL TESTING HAS TURNED MILLIONS OF US INTO...
HUMAN GUINEA PIGS

## The artificial distinction between clinical practice and research

An area causing difficulties with ethics (and related to the duality described above) is the often artificial distinction between what constitutes "clinical practice" (activities to benefit individual patient) and what constitutes "research" (gaining knowledge for the common good).

The distinction is often artificial because few things physicians do to treat individual patients do not generate knowledge for the common good and actions that benefit the community also benefit individual patients.

# Examples of the conflicting roles of physicians
## Teaching and training

The duty of physicians to teach and train new physicians holds risks for the patients because of inexperienced practitioners as well as because teaching institutions may perform more tests than necessary in order to train their students.

# Examples of the conflicting roles of physicians
## Vaccination

With respect to vaccination, the most *practical* strategy for all individual patients would be to be vaccinated. However, the most *safe* strategy for an individual patient is to have everyone else be vaccinated.

Since patients' behavior cannot be guaranteed, the physician has to prescribe vaccination to his or her patients and accept the risks of an unsafe vaccine.

# Examples of the conflicting roles of physicians Triage

Triaging happens when not all patients can receive care at the same time so the physician has to make a decision that places the interests of one patient above those of another.

This may happen, for example, in an emergency room (where the most serious injuries are treated first), the battlefield or can be a system of *rationing* care in resource constrained settings (e.g., provide anti-HIV medications to those with most advanced disease) but can also appear in situations such as for-profit medicine or as costs of care increase rapidly.

# Examples of the conflicting roles of physicians Abortion

In this case the duties of physicians are confusing and controversial not the least because it is not clear from all perspectives to whom (i.e., the mother or the fetus) is the "patient" and thus should enjoy the duties of the physician.

Situations where the life of the mother is threatened by the proliferation of the fetus or cases of en-utero surgery to relieve congenital problems are examples of conflicts that may arise for the physician.

# Examples of the conflicting roles of physicians
## Organ donation

Donating one's organs or tissues is never risk free or of benefit to the donor. Even when a donor is kept alive through artificial means there is no medical benefit *for that individual patient* to be derived by donating his or her organs.

Nevertheless, physicians assist and perform organ transplantations all the time, understanding that such altruistic behavior illustrates their dual and conflicting roles.

# Examples of the conflicting roles of physicians Quarantine, reporting and contact tracing

Another issue demonstrating the often conflicting multiple roles of physicians is when they are required to quarantine, report a patient's condition or trace their contacts. There are many issues surrounding these activities that place a patient's and the community's interests at odds with the physician in the middle.

Personal freedom of movement and patient confidentiality are only some of the issues involved. This is one of the reasons that the public has been against requiring tracking HIV cases. Contrast this to the Severe Acute Respiratory Syndrome (SARS) epidemic where restrictions and isolation were placed on people with SARS or the controversy surrounding Andrew Speaker, a patient with extremely drug resistant (XDR) tuberculosis (TB) (http://www.cdc.gov/tb/publications/factsheets/general/TravelInfo.pdf).

# Historically derived principles of ethics

There is a small number of historical landmarks that led to the current understanding. The first one is the *Nuremberg code* that was derived as a reaction to the medical atrocities of Nazi medical doctors during the second World War (in fact 4 out of the 7 people executed at Nuremberg were physicians).

In 1964, the World Medical Association produced the Declaration of Helsinki. This has been updated five times, most recently in 2000. The current version is the 2004 version (that includes one clarification in 2002 and one more in 2004).

Later, in 1993, the Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO), issued the International ethical guidelines for biomedical research involving human subjects.

# Historically derived principles of ethics
# The Nuremberg Code

The Nuremberg code principles are:

- Study participants must give voluntary consent
- There is no reasonable alternative to conducting the experiment
- The results must have basis in biological knowledge and animal experimentation
- Procedures should avoid unnecessary suffering
- There is no expectation for death or disability
- The risk is consistent with the humanitarian importance of the study
- Subjects must be protected from injury
- The study must be conducted by qualified scientists
- The subject can stop participation at will
- The investigator must stop the experiment if injury is likely

# Historically derived principles of ethics
# Contributions of the Nuremberg Code

The Nuremberg Code is a ground breaking document. Its main contribution is the concept of informed consent. All subsequent guidelines included some form of language regarding informed consent, apprising the study subjects of the risks and benefits of the experimental treatment.

Protecting subjects from undue harm and injury was another contribution of the Nuremberg Code.

# Historically derived principles of ethics
# The Helsinki declaration

In 1964, the World Medical Association (WMA) issued the Declaration of Helsinki specifically to guide clinical research.

The Declaration of Helsinki included two crucial statements:

- Concern for the interests of the subject must always prevail over the interests of science and society.
- In any medical study, every patient–including those of a control group, if any–should be assured of the best proven diagnostic and therapeutic method.

These are critical guidelines that have far reaching implications in human research.

# Historically derived principles of ethics
# The International ethical guidelines for biomedical research involving human subjects

These guidelines, first published in 1993 and revised in 2000, address ethical issues in research involving developed and developing countries, especially when the host country does not have guidelines of its own.

# Historically derived principles of ethics
# The CIOMS guidelines

The CIOMS guidelines are as follows:

- Ethical justification and scientific validity of biomedical research involving human beings
- Ethical review committees
- Ethical review of externally sponsored research
- Individual informed consent
- Obtaining informed consent: Essential information for prospective research subjects
- Obtaining informed consent: Obligations of sponsors and investigators
- Inducement to participate
- Benefits and risks of study participation
- Special limitations on risk when research involves individuals who are not capable of giving informed consent
- Research in populations and communities with limited resources

# Historically derived principles of ethics
# The CIOMS guidelines (continued)

- Choice of control in clinical trials
- Equitable distribution of burdens and benefits in the selection of groups of subjects in research
- Research involving vulnerable persons
- Research involving children
- Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent
- Women as research subjects
- Pregnant women as research participants
- Safeguarding confidentiality
- Right of injured subjects to treatment and compensation
- Strengthening capacity for ethical and scientific review and biomedical research
- Ethical obligation of external sponsors to provide health-care services

# Implications of the CIOMS guidelines on international clinical research

Guideline 10 created principals for research involving subjects in "populations and communities with limited resources." Researchers are required to ensure, among other things, that persons in underdeveloped communities will not be involved in research that could be carried out reasonably well in developed communities, and that the research is "responsive to the health needs and the priorities of the population or community in which it is to be carried out . . ."

# General ethical principles

The following are major ethical principles emanating from the previously described guidelines that govern all human research:

- Respect for persons (autonomy)
- Beneficence and nonmaleficence
- Justice

# General ethical principles
# Respect for persons (autonomy)

This principle involves the ability of patients to decide what should happen to them during their illness. This principle also includes protections for persons with limited autonomy that ensures that they will be protected from harm or abuse.

# General ethical principles
## Beneficence

Beneficence reflects the right of the patient to derive benefit and minimize harm. This principle also implies that the risks should be concomitant to the anticipated benefit to be derived by the research.

Indirect implications of the beneficence principle is that the research design be sound and that the investigators are competent to both conduct the trial and safeguard the welfare of the research subjects (this is sometimes considered as a related principal of nonmaleficence - do no harm).

# General ethical principles
## Justice

The principle of justice refers to the fair distribution of the burdens and the benefits of research.

*Injurstice* occurs when the burdens of research are disproportionately applied to particular segments of the population.

A related issue, "vulnerability", refers to being incapable to protect one's interests because of lack of capability to give informed consent, lack of means of accessing health care, or belonging to minority or subordinate parts of a group.

# Contemporary principles

- Collaborative partnership
  This implies that the research involve the community it takes place in
- Scientific value
  Useful knowledge will be derived from the results of the study
- Scientific validity A poorly or improperly designed study is, by definition, unethical
- Fair subject selection
  Risk must be distributed fairly, and exploitation of vulnerable populations must be avoided. Voluntary selection is a foundation of this principle
- Favorable risk-benefit
  Subjects at undue risk or otherwise vulnerable must be excluded from research

# Contemporary principles
# Independent review

Proposed and ongoing research must be reviewed by independent institutions (e.g., IRB, DSMB, FDA, etc.) IRB approve human research studies that meet specific prerequisites:

- The risks to study participants are minimized
- The risks are reasonable in relation to the anticipated benefits
- The selection of participants is equitable
- Informed consent is obtained and is appropriately documented for each participant
- There are adequate provisions for monitoring data collected to ensure the safety of the study participants
- the privacy of the participants and confidentiality of the data are protected

# Contemporary principles
# Informed consent

Informed consent is the process of transmitting to the patient culturally relevant information about risks and benefits about participating in research. The elements of informed consent are as follows:

- Information provided to the patient
- Comprehension of this information by the patient
- Assessment of the voluntary nature of the consent

# Informed consent in cases of emergency situations

Obtaining informed consent in emergency situation may be difficult or impossible. The following are requirements when research can be undertaken without informed consent:

- An independent physician and an IRB agree that the research addresses a life-threatening situation
- The patient is in a life-threatening situation
- Conventional treatments are unproven or unsatisfactory
- The research is necessary to determine the safety and efficacy of the treatment and cannot be carried out otherwise.
- Informed consent cannot feasibly be obtained from the patient or legal representative
- The risks and benefits of the exp. procedure are reasonable compared with those of the underlying medical condition of the patient and standard treatments
- Additional protections are in place such as consultations with the community, advance public disclosure of the study design and risks, public disclosure of the study results, and FDA review of the study protocol.

# Aspects of the Informed Consent reviewed by the IRB

The IRB focus intensely on the Informed Consent document. The following components must be present in the Informed Consent Document

- It must be indicated that the study involves research
- Describes foreseeable risks and discomfort
- Describes potential benefits and alternatives
- Describes the extent to which privacy data will be maintained
- Informs the participant about treatment of injuries incurred
- Provides contact information about whom to contact with questions
- A crucial aspect of the document is to clearly inform to the patients that participation is voluntary and no loss in benefits will result from not entering or discontinuing the study.

# Contemporary principles
# Respect for subjects

This principle is related to the way that subjects are approached and treated as part of the research study. Aspects of the respect for the subjects are:

- Privacy
- Allowing discontinuation of participation without penalty
- New information generated by the study must be made available to the participants
- The interests of the participants should be continuously monitored throughout the study

# Contemporary principles
# The right for privacy

Patient right to privacy has a long tradition. It has been strengthened more recently with the institution of the Health Insurance Portability and Accountability Act (HIPAA), whose main focus is to guarantee the security of and privacy of health information.

Maintaining privacy requires patient consent, restricting collection of personal information to only the absolutely necessary items, taking precautions to ensure the physical security or private patient records (e.g., storing them in locked cabinets, providing internet and general computer security.

# Ethical justification of clinical research methods
## Randomization

The ethical justification of randomization emanates from two ethics tenets: *equipoise*, which allows allocation of all treatments under comparison to patients, and because randomization produces a sound design (another ethical requirement) by minimizing bias in the allocation of treatment.

Randomization must be continuously assessed during the performance of the study and stopped if evidence arises that makes randomization unethical.

# Ethical justification of clinical research methods
## Treatment preference

Investigators that have a treatment preference should not be allowed to participate in the study. This may violate the principle of autonomy because an investigator may exert undue influence on the participants to accept the treatment.

The same is the case for patients that have a specific preference. They should not be enrolled in the study even if this preference is for an ancillary treatment not part of the study (because it would make them more likely to drop out of the study).

# Ethical justification of clinical research methods Monitoring

Convincing evidence arising during the conduct of the study, which makes continuation of the study unethical should be included in the design and conduct of the study.

Interim analyses and safety monitoring of the study are required oversights (the former particularly in comparative studies) and Monitoring Committees must included as part of routine monitoring of the studies.

# Ethical justification of clinical research methods
## Placebo controls

The power of suggestion must be considered when evaluating a treatment, but withholding treatment may not be ethical. The choice of the appropriate control depends on the belief of the physicians in the assessed treatment and the availability of alternatives.

It is not appropriate to replace effective therapy with a placebo, even with "informed consent".

Placebo-controlled trials may be justified when the standard therapy is weakly effective and toxic so withholding it may be acceptable.

# Professional statistical ethics

Statisticians must maintain integrity in their professional work.
Specifically:

- Objectively present their findings
- Avoid deceptive statements
- Disclose conflicts of interest

# Professional statistical ethics
## Openness

Statistical work must be open to external assessment of quality and approprietness. Specifically:

- Delineate the limits of the investigation and the inferences derived from it
- Emphasize that statistical analysis may be an essential component of the study just like all other essential aspects of the investigation
- Document data sources, inaccuracies in the data, steps taken to address them and procedures used and assumptions for their use
- Make data available for analyses to other qualified parties with appropriate safeguards to maintain privacy
- Recognize that selection of a specific statistical procedure is a matter of judgement and another statistician may select an alternative procedure
- Direct criticisms of the statistics to the study methods and not the persons conducting it