Research-mid

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Ethics in medical research: part 1 introduction

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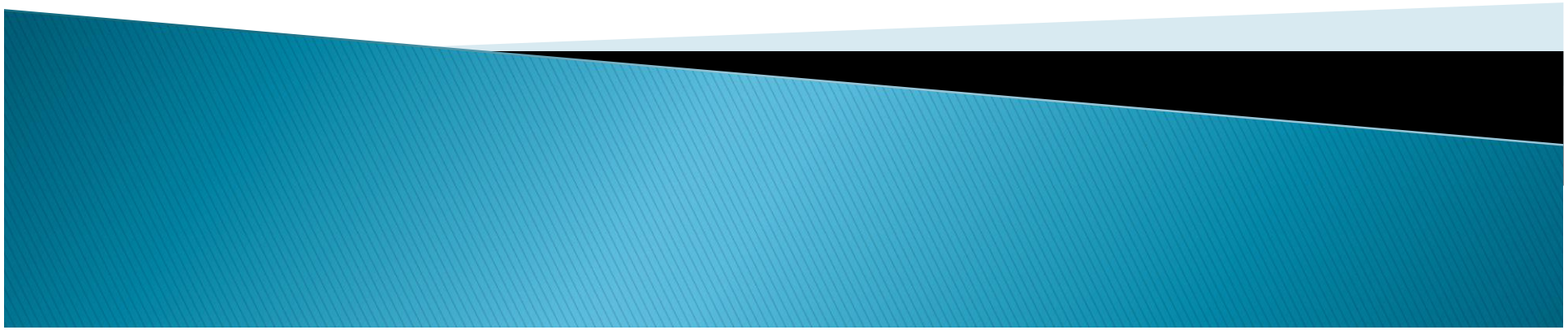
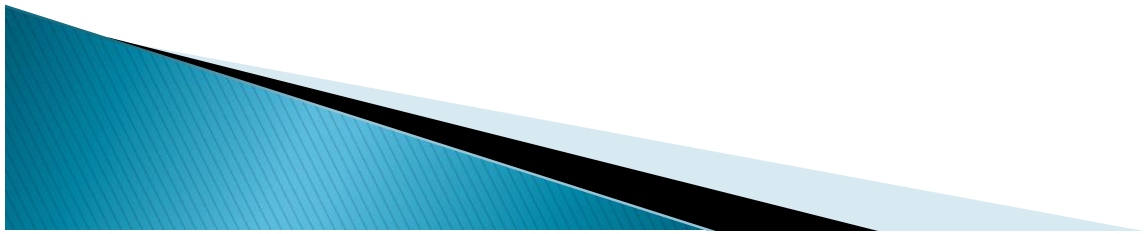


Research

- Research is the *systematic collection, analysis* and *interpretation of data* to answer a certain question or solve a problem



How to Minimize Risks to Research Participants:

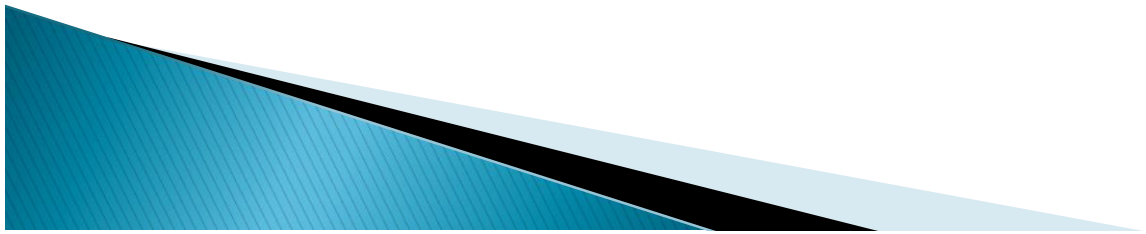
- Studies that require IRB approval:

a. Data from living individuals

b. Biological material from living individuals

c. Interaction or intervention with a living individual

d. Use of a non-approved, drug, device or biological

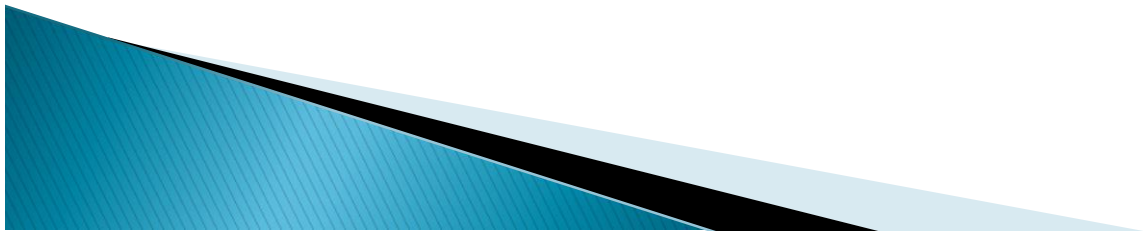


Clinical Trials Phases (0-IV)

- Each of these types of study requires the appropriate design to reach scientifically sound conclusions while protecting the participants and their identifiable human information.

Ethical Design In Clinical Research

Although this may be morally obvious, it's also important practically because of the huge investments in money, effort, and personal risk and discomfort that the sponsor, investigators and the participants make.



Data Analysis

- An important part of research integrity is the analysis of data.
- It's critical to recognize the importance of appropriate statistical analysis.
- Statistical approaches should be developed as part of the study design.
- If possible, hypotheses should be well defined in advance.

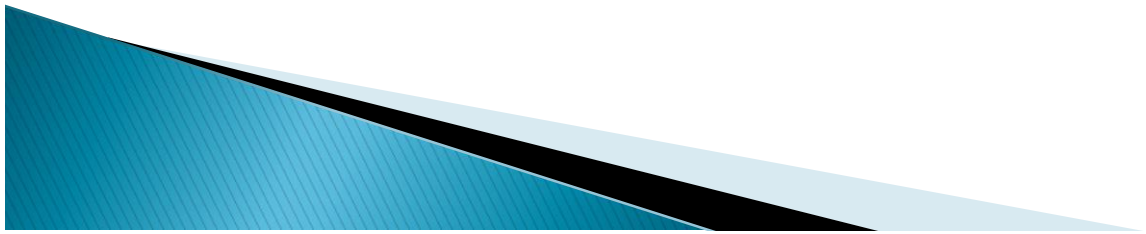
- Current statistical packages permit the mining of entire databases to identify statistically significant results that were not anticipated.
- No statistically significant different is an important result and must be published

Efficacy Versus Safety

- Efficacy: maximum response achievable from an applied or dosed agent
- In therapeutic studies, both efficacy of the interventions and their safety are generally studied simultaneously but the design may focus on one or the other.

Appropriate Risk to Benefit Ratio

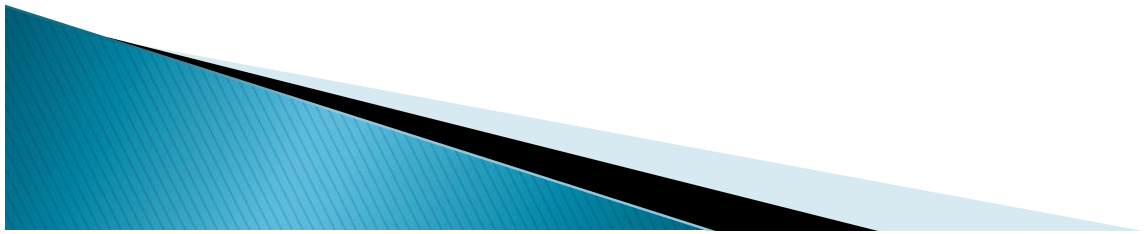
- Risk is defined as the probability of physical, psychological, social, or economic harm occurring as a result of participation in a research study.
- Both the probability and magnitude of possible harm in human research may vary from minimal to considerable.



Minimal Harm

- Minimal harm is defined as:

  "that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests".



Moderate and Maximal Risk

- Risk above this standard is more than minimal (moderate, maximal) and that imposes limitations on the conduct of the research and increases the requirements for monitoring.
- It also requires more stringent approval processes when studying children or otherwise vulnerable populations.
- Increased risk should be accompanied by the probability of appropriately increased benefits.

Benefits

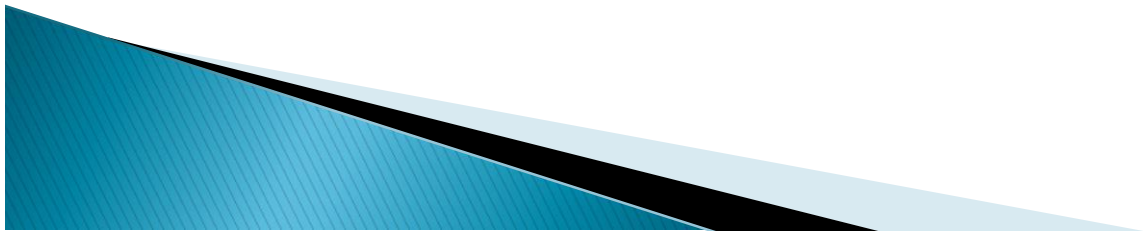
- Benefit applies to the potential of the research treatment to ameliorate a condition or treat a disease.
- This can apply to an individual participant or to a population.
- In research as in clinical medicine, results cannot be guaranteed but, as a consequence of prior work, a benefit may appear to be a reasonable expectation.
- Since this is research, an advantage for the treatment groups cannot be presupposed.
- Since the risks have not been fully evaluated, a statement of individual benefit should be made most cautiously if at all.
- The investigator should always distinguish between research and treatment and never lure the patient into participating in hopes of remission or cure.

Risk Versus Benefit Ratio

- A main role of IRBs is to determine the risk versus benefit ratio for clinical studies.
- They must make sure that the physical risk is not disproportionate to the benefits.
- When the physical risk is minimal they must determine that psychological and social risks such as stigma are not important.
- It is not ethical to conduct a study in which an individual or a group is labeled so as to be stigmatized or to be made less employable or insurable.

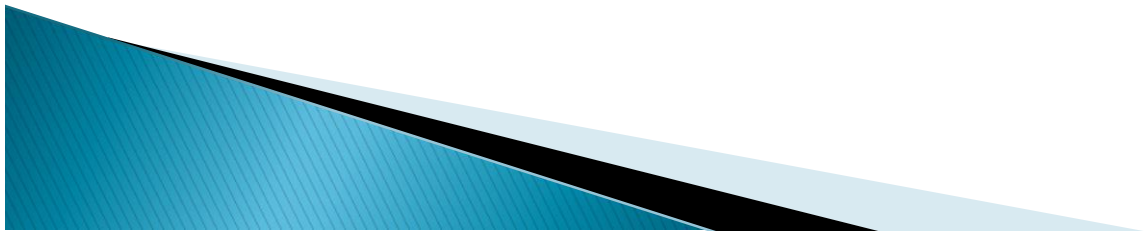
Controls

- Controls are research participants who receive an inactive treatment or stay on standard treatment
- In most trials they are selected by computer lottery from the group of eligible candidates with the condition under study.



Normal Controls

- Normal Controls are research participants who do not have the condition under study.
- Those taking current treatment according to updated clinical guidelines



Historical Controls

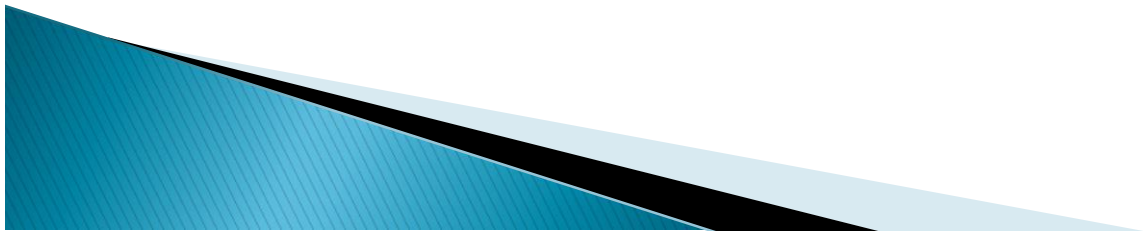
- Historical controls are subjects from prior studies or observational investigations whose data are compared with those of the current participants.
- Historical controls were used for years in clinical research and are still sometimes employed because they do not require additional data collection and risk.
- They often produce biases because the research population rarely duplicates the historical population.

Blinding

- Blinding refers to a process whereby the participant does not know whether he/she is receiving an active agent or a similar appearing inactive substance or mock procedure.
- Blinding is also used in research to refer to investigators who analyze components of a study without knowing the identity and treatment of the participant.

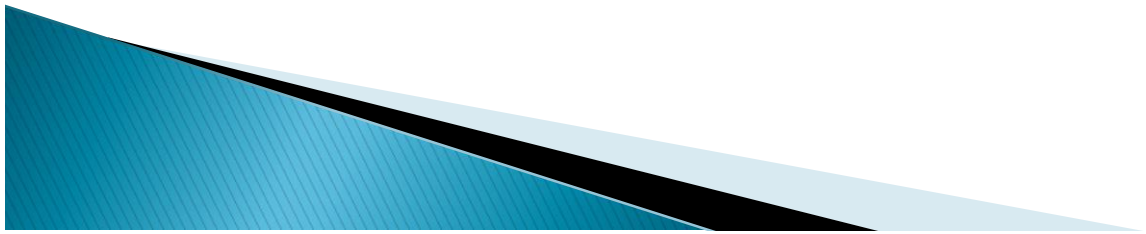
Double Blinding

- Double blinding is a process whereby neither the investigator nor the participant knows which agent the participant is receiving.
- Usually the research pharmacy holds the master list in case there are complications.
- Triple blinding: blind the statistician



Use of Placebos

- A placebo is an inactive version of a treatment identical in appearance to the real thing.



Standard of Care:

- This term applies to the expected care in the medical community as a whole.
- Often, standard of care can be defined on the basis of practice guidelines, which are being developed by all medical specialties, element by element.
- The issue of standard of care becomes problematic when a study is to be performed in a developing country where it is impossible to provide medical care at anywhere near the level available in the developed world.
- The current expectation is that controls will be treated at the level of the Western standard of care, not the indigenous standard.

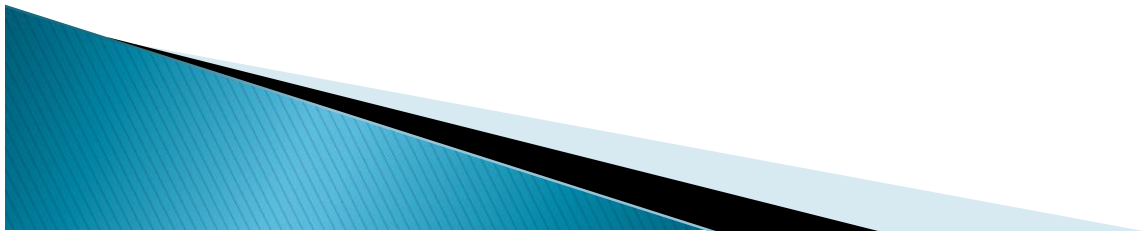
Protection of Research Participants Who and What?

Who should be involved?

- Individuals involved in the design and/or conduct of human subjects research.

What is the purpose?

- Preparation of investigators involved in the design and/or conduct of research involving human subjects to understand their obligations to protect the rights and welfare of subjects in research.



Autonomy

- Autonomy is understood to mean that becoming a research subject is a totally voluntary act.
- Individuals must be solicited without coercion or even implied coercion.
- Individuals must be fully informed and understand what they are signing up for.
- IRBs require that the prospective participants understand a long list of things before they can sign a consent document.

Autonomy

- If the study requires a vulnerable population to be studied, (children, cognitively impaired) then a surrogate who, presumably, has their best interests at heart (parent for child, relative for the patient with Alzheimer's disease) must sign for the participant.

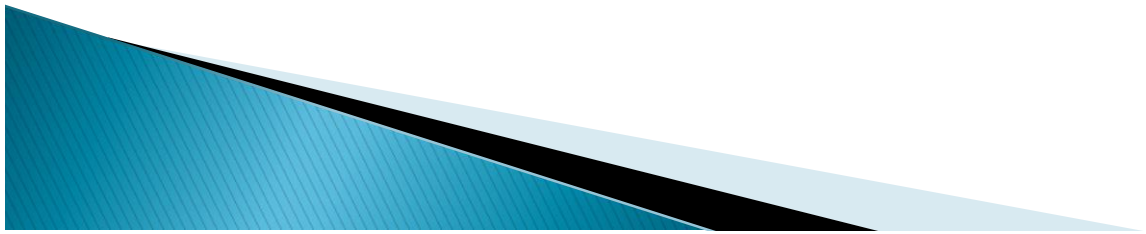
- Individuals under the age of 18 are given special protections; so many studies pertain to adults only.
- The rule of autonomy requires that individuals are able to provide informed consent.

Historical Events
The Nuremburg Code

- In the August 1947 the judges included a section called **Permissible Medical Experiments**.
- This section became known as the Nuremberg Code and was the first international code of research ethics.
- This set of directives established the basic principles that must be observed in order to satisfy moral, ethical, and legal concepts in the conduct of human subject research.

Coercion

"Influencing an individual decision about whether or not to do something by using explicit or implied threats (loss of good standing in job, poor grades, etc.)"



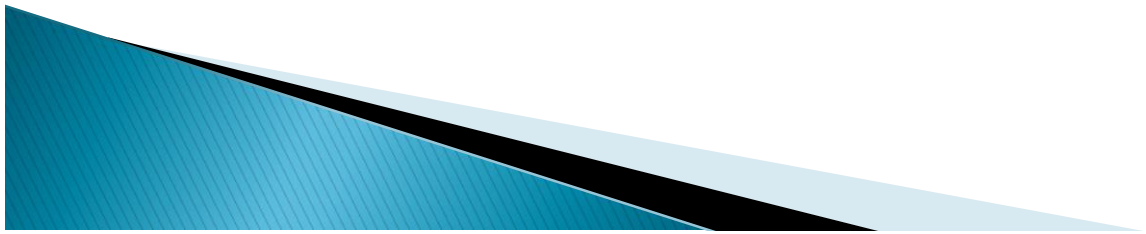
Undue Influence

"An offer of an excessive, unwarranted, inappropriate, or improper reward or other overture in order to obtain compliance" "excessive compensation"

- Undue inducements are troublesome because:
  - offers that are too attractive may blind prospective subjects to the risks or impair their ability to exercise proper judgment; and
  - they may prompt subjects to lie or conceal information that, if known, would disqualify them from enrolling — or continuing — as participants in a research project ".

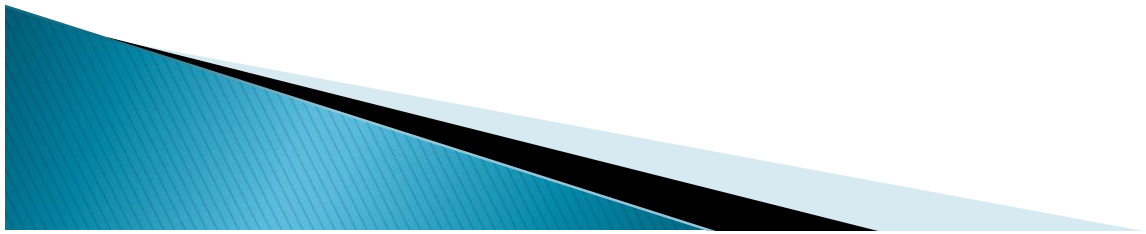
Undue Influence versus Compensation

- Some types of research involve a significant commitment from research participants in terms of time or effort, and investigators may wish to provide compensation .
- Institutions should consider establishing standards for fair and appropriate compensation .
- Compensation is meant to reimburse research participants for their time, research-related inconveniences and/or research-related discomforts
- Compensation **is not** a benefit of the research.



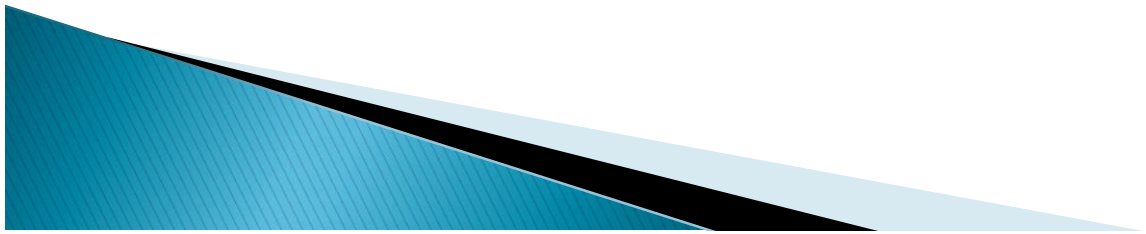
Voluntariness

- Individuals' decisions about participation in research should not be influenced by anyone involved in conducting the research: "...consent must be freely given or truly voluntary."



Comprehension

- Individuals must have the mental or decisional capacity to understand the information presented to them in order to make an informed decision about participation in research.



Participation of Pregnant Women in Research

- It is essential to prohibit:
  - Inducements of any kind to terminate a pregnancy.
  - Investigators from taking part in decisions about terminating a pregnancy.
  - Investigators from determining the viability of a neonate.

Children's Participation in Research

- Children may not have full capacity to make decisions in their own best interests; and therefore :
  - Children are considered a vulnerable population, and
  - Children are unable to provide "legally effective informed consent "

- Because children cannot provide informed consent, children provide assent* to participate in research, to the extent that they are able, and parents/guardians give permission for a child to participate in research .

* Assent: affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent."

Excluding Children From Research

- The NIH Policy and Guidelines on the Inclusion of Children in Research states that children must be included in all NIH-supported human subjects research unless "… there are scientific and ethical reasons not to include them ".

Obtaining Informed Consent From Prisoners

- Requirements specific to informed consent for prisoners are:
- Not to be under constraints as a result of their incarceration that could affect their ability to make a truly voluntary decision about whether or not to participate in research.
- Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole

2. Beneficence

Two general rules have been articulated as complementary expressions of beneficent actions:

- Do no harm.
- Maximize possible benefits and minimize possible harms.

The challenge inherent in applying the **Belmont principle of beneficence** is how to determine when potential benefits outweigh considerations of risks and vice versa.

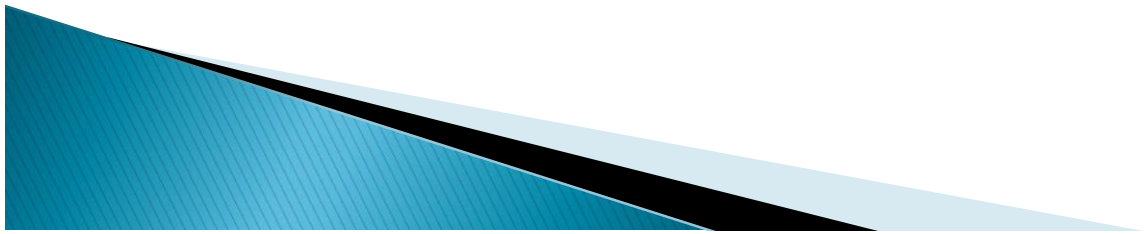
Privacy and Confidentiality

Investigators are responsible for

- Protecting privacy of individuals.
- Confidentiality of data .

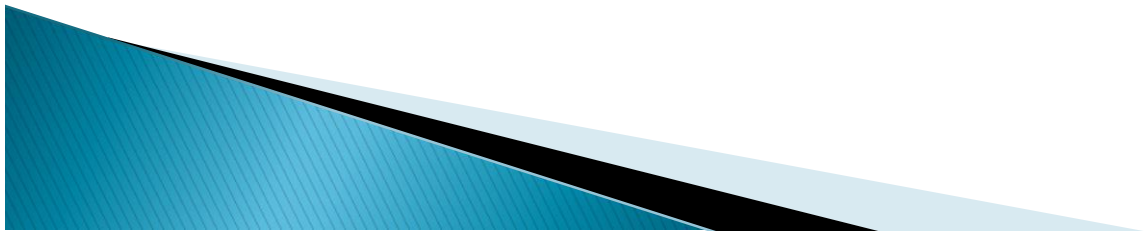
  - *Privacy* means being “free from unsanctioned intrusion”.

  - *Confidentiality* means holding secret all information relating to an individual, unless the individual gives consent permitting disclosure.



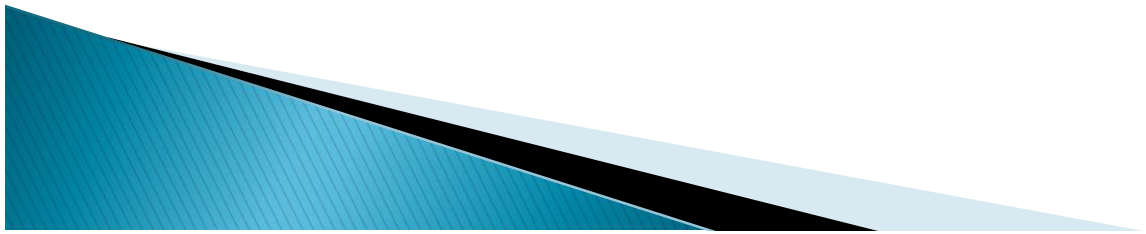
Institutional Review Boards(IRB)

- IRBs determine:
  - “the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice ”



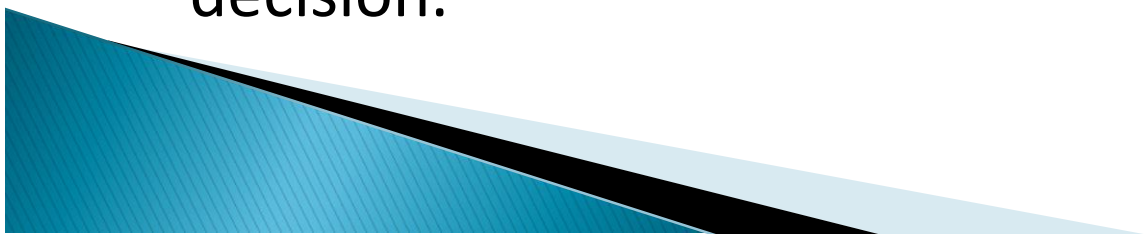
Equity vs. Equality in Human Subjects Research

- The meanings of “equity” and “equality” are similar, but not the same.
  - To treat“ **equitably** ”means to treat fairly;
  - To treat“ **equally** ”means to treat in exactly the same way.



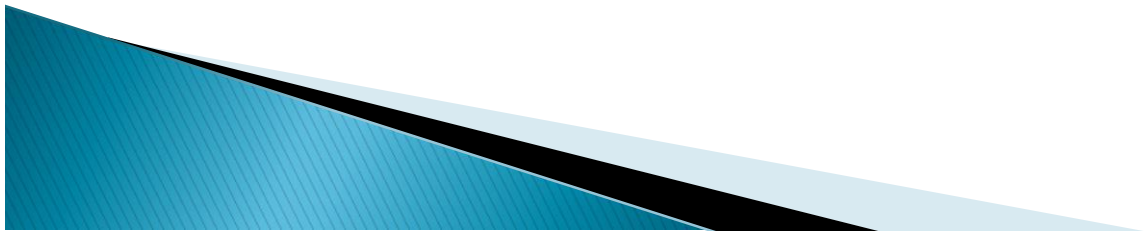
1947 The Nuremberg Code

The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision.



1964 Declaration of Helsinki (Finland)

"*In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject*."

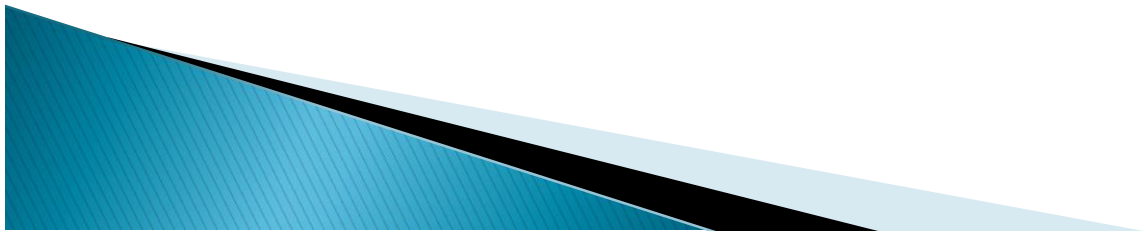


The six key principles:

1. Research should be designed, reviewed and undertaken to ensure integrity, quality and transparency.

2. Research staff and participants must normally be informed fully about the purpose, methods and intended possible uses of the research, what their participation in the research entails and what risks, if any, are involved. Some variation is allowed in very specific research contexts.

3. The confidentiality of information supplied by research participants and the anonymity of respondents must be respected.



The six key principles:

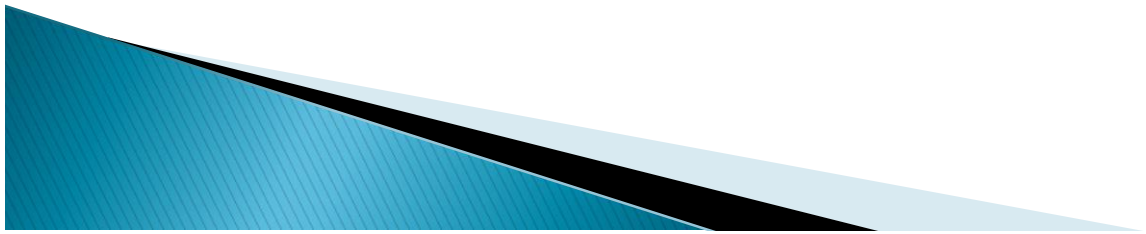
4. Research participants must take part voluntarily, free from any coercion.

5. Harm to research participants must be avoided in all instances.

6. The independence of research must be clear, and any conflicts of interest or partiality must be explicit.

BPS Code of Human Research Ethics
By the British Psychological Society

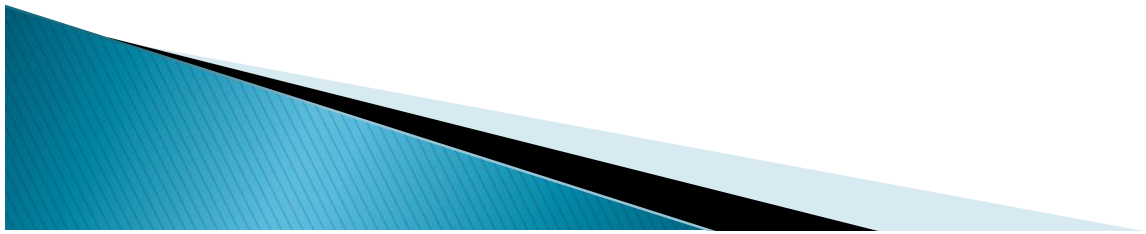
- Respect for the Autonomy and Dignity of Persons
- Scientific Value
- Social Responsibility
- Maximising Benefit and Minimising Harm



BPS Code of Human Research Ethics

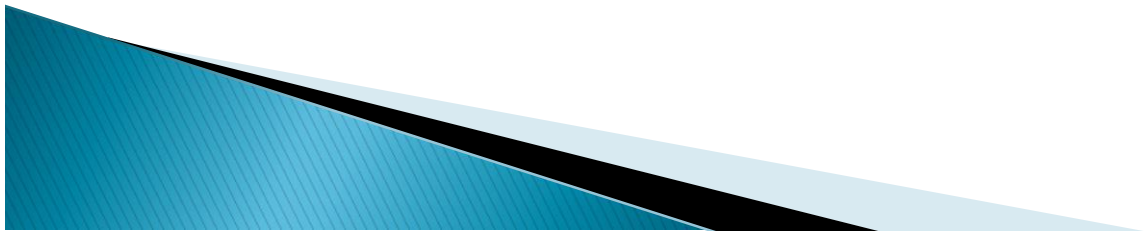
- Social Responsibility

The discipline of psychology, both as a science and a profession, exists within the context of human society. Accordingly, a shared collective duty for the welfare of human and non-human beings, both within the societies in which psychology researchers live and work, and beyond them, must be acknowledged by those conducting the research.



Institutional Review Board (IRB)

- Also known as an *Independent Ethics Committee (IEC)* or *Ethical Review Board (ERB)* is a committee that has been formally designated to approve, monitor, and review biomedical and behavioral research involving humans with the aim to protect the rights and welfare of the research subjects .

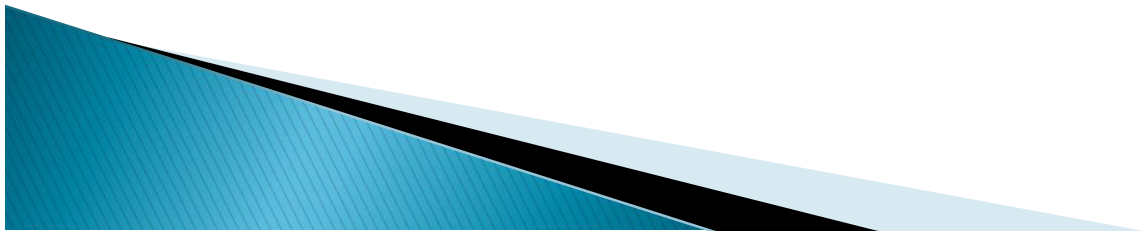


Structure of Ethics Committees

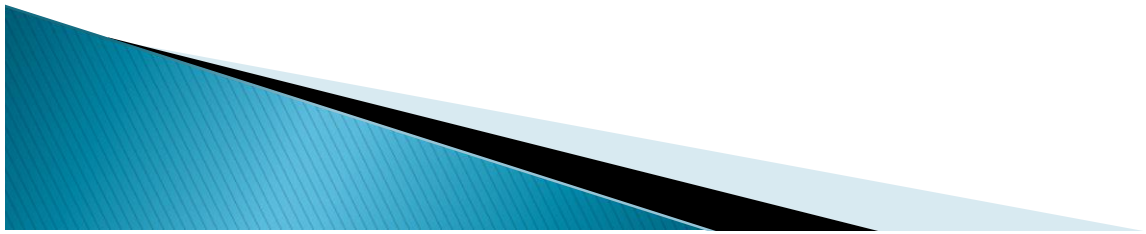
1. Chair: Preferably from outside the Institution
2. Member secretary: from the same organization or institute
3. 1-2 Clinicians from various specialties
4. 1-2 Basic medical Scientists
5. One legal expert or retired judge
6. One social scientist or representative of voluntary agency
7. One philosopher/ethicist
8. One lay person
9. According to the application, subject experts could be invited to offer views

- The IRB must have at least five members.
- The members must have enough experience, expertise, and diversity
- If the IRB works with studies that include vulnerable populations, the IRB should have members who are familiar with these groups.

- The IRB should include both men and women.
- The members of the IRB must not be all of the same profession.
- The IRB must include at least one scientist and at least one non-scientist. These terms are not defined in the regulations.

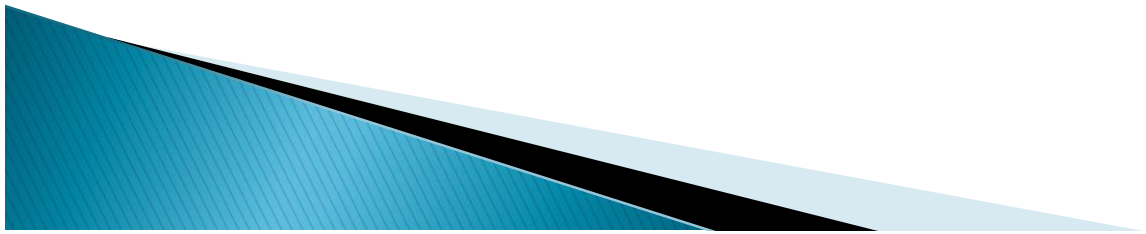


- The IRB must include at least one person who is not affiliated with the institution or in the immediate family of a person affiliated with the institution. These are commonly called "Community Members".
- IRB members may not vote on their own projects.
- The IRB may include consultants in their discussions to meet requirements for expertise or diversity, but only actual IRB members may vote.



Responsibilities of IRB

- Risks to study participants are minimized
- Risks are reasonable in relation to anticipated benefits
- Selection of study participants is equitable
- Informed consent is obtained and appropriately documented for each participant
- Adequate provisions for monitoring data collection to ensure safety of the study participants
- Participant privacy and confidentiality is protected



The IRB/IEC should obtain the following documents

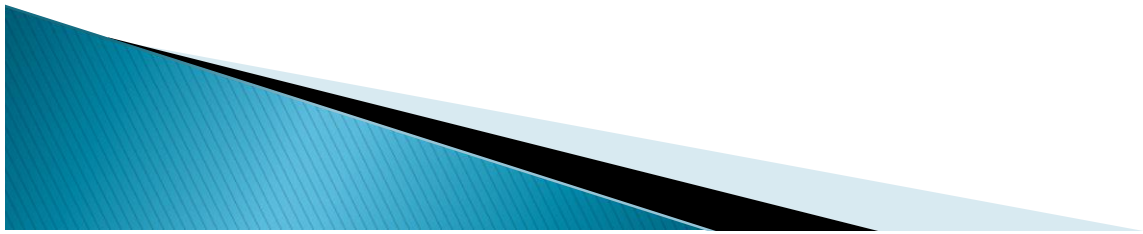
- Trial protocol(s)/amendment(s),
- Written informed consent form(s)
- Consent form updates that the investigator proposes for use in the trial
- subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB),

- Available safety information,
- Information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications,
- Any other documents that the IRB/IEC may need to fulfill its responsibilities.

What Projects Need Ethical Approval?

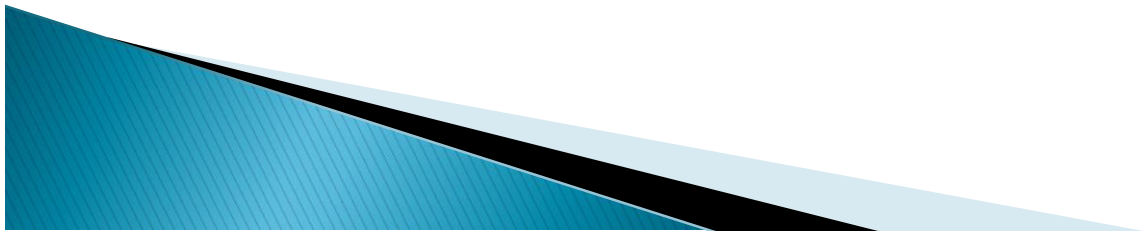
- Human participants
- Use of the ‘products’ of human participants
- Animal participants
- Work that potentially impacts on human participants

- *Where ethical approval is deemed unnecessary a disclaimer may be signed by researcher (and supervisor)*



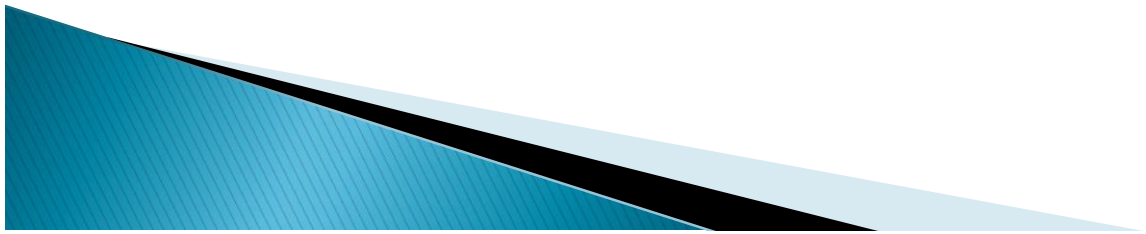
Key Ethical Issues

- Informed Consent – special consideration for minors
- Deception
- Need for debriefing
- Right to withdraw
- Confidentiality
- Safety and risk



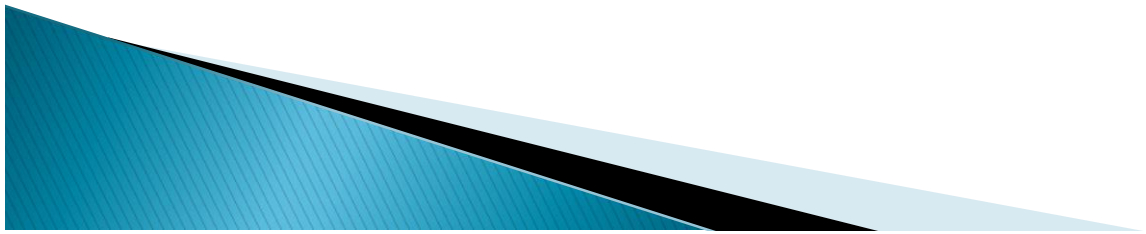
What Is GCP?

Good Clinical Practice (GCP) is defined as a ‘standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are rotected’



Under GCP, the FDA Requires That People be Informed:

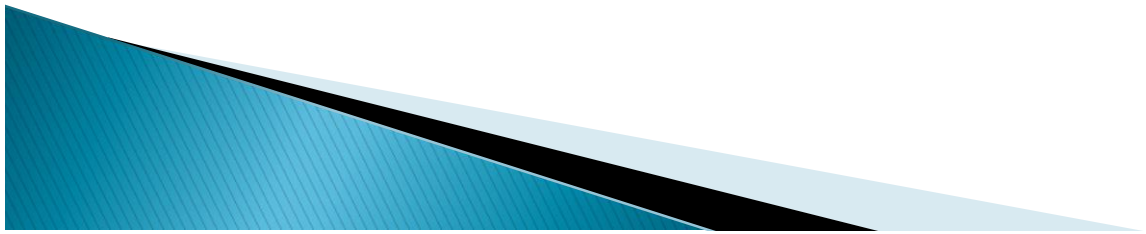
- The study involves research of an unproven drug, the purpose of the research
- How long the participant will be expected to participate in the study
- What will happen in the study
- Possible risks/benefits to the participant
- Participation is voluntary and that participants can quit the study at any time without penalty or loss of benefits to which they are otherwise entitled.



Informed Consent

- Definition: A legally-effective, voluntary agreement that is given by a prospective research participant following comprehension and consideration of all relevant information pertinent to the decision to participate in a study.

- The HHS regulations require that investigators obtain legally effective informed consent from prospective participants in a way that allows them to consider whether or not to participate and that minimizes the possibility for coercion or Undue influence.



Coded Private Information and Human Subjects Research

- Research with coded private information or specimens does not involve human subjects if:
  - The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
  - The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens

Case Study: Research With Anonymized Data

- You are an investigator proposing to use data from a colleague's database to conduct secondary analyses. Your colleague will provide coded data for your proposed studies, and you and he enter into an agreement by which he will keep the key to the code and will have no other involvement in the research.

- Does this study involve human subjects?
- Yes, this study involves human subjects .
- No, this study does not involve human subje