

Ethical Issues in Clinical Trials

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Useful Definitions

- “Research means a systematic investigation to include research development, testing and evaluation, designed to develop or contribute some information or generalizable knowledge.”
- “Human subject is a living individual about whom an investigator (professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.”

Clinical Trial/ Study

Any investigation in human subjects intended

- to discover or verify the clinical, pharmacological and/or pharmacodynamic effects of an investigational product
- to identify any adverse reactions to an investigational product
- to study absorption, distribution, metabolism and excretion of an investigational product with the object of ascertaining its safety and/or efficacy



Objective of clinical trial

- Develop generalizable knowledge to improve health and/or increase understanding of human biology

Methodology

- Common research design
 - RCT – Randomized Clinical Trials
 - Single blind – Investigator knows what drug is taken by which patient
 - Double blind – Investigator and patient do not know which drug goes to whom (Gold standard)

Phases in Clinical Trials

- Animal studies
- Phase 1 – research among healthy subjects (10) to test the pharmacodynamics and safety of the drug
- Phase 2 – target population (50) to test safety and efficacy of the drug
- Phase 3 – target population (100) to test efficacy of the drug
- Phase 4 – target population (more than 100) for marketing purposes and to test drug across various populations

What makes clinical trials ethical?

1. Adds value – enhancement of health or knowledge must be derived from the research - positive contribution to knowledge about health and well being
 - Evaluates diagnostic or therapeutic intervention that could lead to improvements in health or well being
 - Focuses on important issues because research funds are limited – requires comparative evaluation of value
 - Sharing results both positive and negative

What makes clinical trials ethical?

2. Scientific validity – the methodology must be scientifically rigorous

“Scientifically unsound research is unethical”

- Clear scientific objectives
- Methods are valid and feasible
- Sufficient statistical power to prove hypothesis
- Have a plausible data analysis plan
- Clinical equipoise – absence of consensus about comparative merits of intervention

Research Objectives

- Purposeful
- Direct benefit/ indirect benefit/ benefit to science
 - Targeted to individual subjects/ community
 - By way of medical examination/ sharing information
 - Generation of knowledge, improvement in science
- Scientific soundness is essential to make a study ethically viable.
- ◆ Likely importance of the information which is sought.
- ◆ An investigator should describe the relevance of his/her research



Methodology Issues

- Appropriateness of the scientific design of a study
 - Endpoints defined
 - Adequate duration of participation of subjects
 - Appropriate selection of controls
 - Randomization to eliminate bias
 - Inclusion / exclusion criteria adequate
 - Subject size and statistical assumptions

What makes clinical trials ethical?

3. Fair subject selection – scientific objectives not vulnerability or privilege should be the basis for subject selection
 - Individuals and groups should also not be excluded from benefiting from research
 - Distribution of risks and benefits should determine selection of communities as study sites. Define the benefits that the study group will get.

Subject Selection

- Appropriateness of subject population
- Involvement of vulnerable groups
 - Is it necessity ?
- Secondary Subjects
- Inclusion/ exclusion criteria
 - Age
 - Gender
 - Pregnancy
- Selectively include subjects most likely to yield an answer
- Exclude subjects
 - who can predictably confound the answer
 - who might be at an increased risk



Vulnerable Subjects

- Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests.
- Informally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests.
- Provide protection and safeguards for vulnerable subjects.



Protection of Vulnerable Subjects

- ❑ Exclusion of vulnerable subjects
- ❑ Increased capacity of vulnerable subjects to give free consent
- ❑ Improvement of quality of consent process
- ❑ Creative and innovative ways of giving information and improving comprehension
- ❑ Institutional policies regarding recruitment of patients, students, etc.
- ❑ Careful calculation of fees paid to participants



Protection of Vulnerable Subjects

- Adherence to confidentiality rules
- Setting up physical structures to ensure protection of privacy
- Debriefing procedures after data gathering
- Counseling subjects at risks
- Avoiding circumstances that will expose subjects to social risks or stigmatization during the research process

What makes clinical trials ethical?

4. Favorable risk-benefit ratio –

- Potential risks must be minimized – opt for less risky interventions
- Potential benefits are enhanced – consider additional benefits to patients or communities (counseling, debriefing, access to medicine, etc.)
- Potential benefits to individuals and society outweigh risks
 - Knowledge gained for society should not be at the expense of patients.

Defining risks and benefits

- ◆ The term risk refers both to the probability of a harm resulting from an activity and to its magnitude.
- ◆ `Risk' often stands for the combined probabilities and magnitude of several potential harms.
- ◆ A benefit refers to any sort of favourable outcome of the research to society or to the individual
- ◆ In practice, 'benefit' often stands for the combined probabilities and magnitudes of several possible favorable outcomes



Identifying Risks

- Physical risks
 - Bodily harm
 - simple inconvenience
- Psychological risks
 - Emotional suffering
 - breach of confidentiality
- Social risks
 - Employment or social discrimination
- Economic risks
 - Financial costs related to participation

Identifying benefits

- Physical benefits
 - Improvement of disease
- Psychological benefits
 - Comfort from suffering
 - Feeling of helping others in the future?
- Economic benefits
 - Financial benefits related to research participation?
- Benefit to science/society
 - Generalizable knowledge
 - Effective interventions in the future
 - Change in practice standards decreasing morbidity and mortality

What makes clinical trials ethical?

5. Independent review

- ❑ Individuals not affiliated with the research should review, approve, amend or recommend termination.
- ❑ Review committee should be made up of competent, ethical and properly trained people.
- ❑ Review committee should represent various disciplines.
- ❑ Conflicts of interests should be addressed.

What makes clinical trials ethical?

6. Informed consent

- ❑ Complete information - full disclosure of probable risks to include psycho-social risks
- ❑ Subject comprehension – understandable language
- ❑ Voluntary participation – avoidance of undue inducement

What makes clinical trials ethical?

7. Respect for enrolled subjects

- Respect for patient autonomy
- Privacy protected
- Opportunity to withdraw
- Well-being monitored
 - Placebo issue
 - Standards of care

Expertise and Training of the Research Team

- Necessary training and experience of the research team (doctors, biostatisticians, social scientists, etc.)
- Training to appreciate ethical components of the research
 - GCP trained
 - Subject selection
 - Risk/ benefit assessment
 - Informed consent
 - Confidentiality issues



Confidentiality Protection

- Recognize confidentiality issues in
 - Initial study design
 - Identification and recruitment of subjects
 - Consent processes for the study population
 - Security, analysis and final disposition of data
 - Publication or dissemination of data and results

Data protection plan

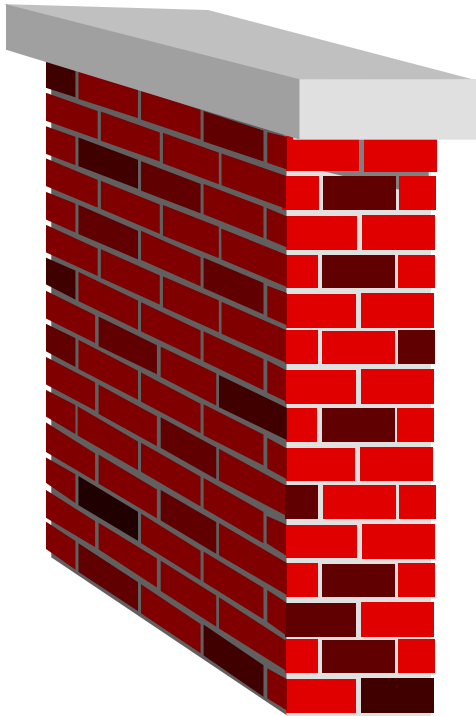
- Prepare plan for protection of identifiable data
- IRB review of data protection plan
- Describe appropriate level of confidentiality based on potential magnitude of risk from disclosure.
 - Physical security of data – lock and key, data disposal
 - Social measures – people in the know
 - Confidentiality training for research team
- Conduct training in privacy and confidentiality protection.



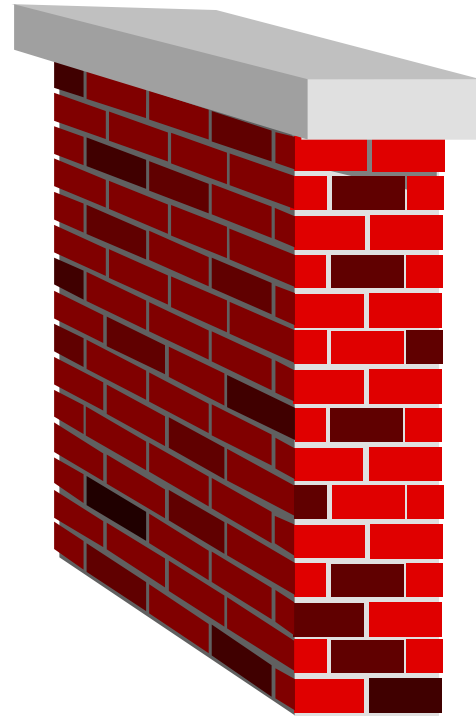
ICH GCP Guideline

A trial should be initiated and continued only if anticipated benefits justify the risks. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

“The Twin Pillars of Human Protection”

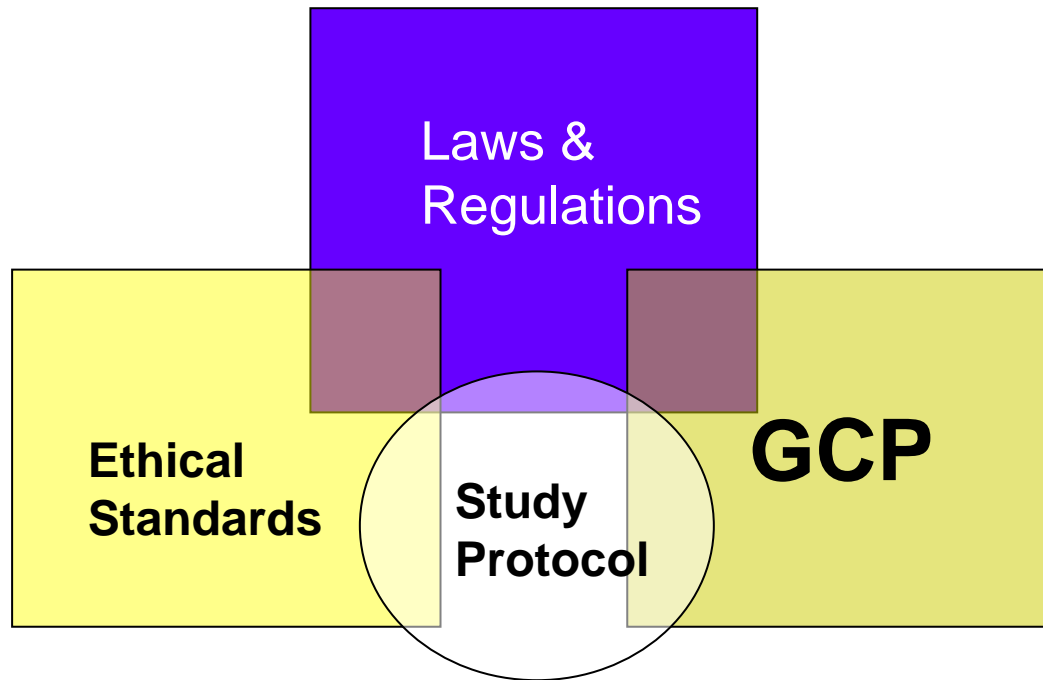


**Independent
Review**



**Informed
Consent**

Clinical Research Requirements



Developed vs Developing Countries



Any Choice?

Standards of Care

- **“benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods” (Helsinki 2000)**
- **“.. Best available and sustainable ..” (UNAIDS 2000)**
- **“.. Established effective therapy, whether or not such therapy is available in the host country..” (NBAC 2000)**
- **Commentary and exceptions (CIOMS 2002)**
- **“Must be seen in context ... “ (NCB 2002)**

Ethical issues in international health research

- How ethical is it to undertake “new” research, when existing knowledge and interventions remain under-utilised?
- How can the ethical regulation of research reduce the equity gap?
- Reduce the dysfunction in public health?
- ? Differential Standard of care permitted

What Makes *Multi-National* Clinical Research Ethical?

- Social Value
- Scientific Validity
- Fair Selection of Subjects & Communities
- Favorable Risk-Benefit Ratio
- Independent Review
- Individual Informed Consent
- Respect for Enrolled Subjects & Communities
- Collaborative Partnership



Helsinki Declaration – Point 29

- The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.
- This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

Helsinki Declaration 2004 - Clarification to Point 29

- A placebo-controlled trial may be ethically acceptable, even if proven therapy is available
 - Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
 - Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.



Helsinki Declaration – Point 30

- At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

Helsinki Declaration 2004 – Clarification to Point 30

- Reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

Post Trial Benefits

- *a priori agreement*
- Distribution of burden and benefit of research
- Focus on health needs of participating community
- After completion of trial product availability free/subsidized cost
 - Availability to the participants/ whole community
- Care of participants during and after the trial
 - Care between the time of trial completion and marketing of the product
 - Provision of drug by sponsor until marketed
- Affordability and accessibility issues



CIOMS (2002): Clinical Trials in Developing Countries

- Phase 1 drug studies and Phase I and II vaccine studies should be conducted only in developed communities of the country of the sponsor.
- In general, Phase III vaccine trials and Phase II and III drug trials should be conducted simultaneously in the host community and the sponsoring country