Ethical Considerations In Protocol design and

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GCP Clinical Trial Protocol and Protocol Amendment Requirements

- General Information
- Background Information
- Trial Objectives and Purpose
- Trial Design
- Selection and Withdrawal of Subjects
- Treatment of Subjects
- Statistics

Clinical Trial Protocol and Protocol Amendment (s)

- Direct Access to Some Data/Documents
- Quality Control and Quality Assurance
- Ethics
- Data Handling and Record Keeping
- Financing and Insurance
- Publication Policy
- Supplements.

Research Objective issues

- 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

The Question?

- What's the outcome?
- What's the intervention?
- When and for how long?
- For whom?
- How many participants are needed?
- How can we optimize potential benefit while minimizing potential harm?

Study design issues (1)

① Designing the study

- Endpoint, randomization?, adequate duration

② Appropriateness of study population

③ Inclusion/Exclusion criteria

Study design issues (2)

4. Vulnerable participant
5. Selecting a Comparison
6. Balancing risk and benefit
   - Enhance benefit, minimise risk

Eligibility Criteria

- Consider
  - –Potential for effect of intervention
  - –Ability to detect that effect
  - –Safety
  - –Ability for true informed consent

Inclusion/Exclusion criteria

- Selectively include subjects most likely to yield an answer
- Exclude subjects who can predictably confound the answer
- Exclude who might be at an increased risk

Sample Size (1)

- The study is an experiment in people
- Need enough participants to answer the question
- Should not enroll more than needed to answer the question
- Sample size is an estimate, using guidelines and assumptions

Sample Size (2)

- Approaches for early phase studies
  - Dose escalation schemes
  - Decision that intervention is unlikely to be effective in XX % of participants
  - Decision that intervention could be effective in XX% of participants
- Standard ways of estimating for phase III

Sample Size (3)

- Assumptions depend on
  - Nature of condition
  - Desired precision of answer
  - Availability of alternative treatments
  - Knowledge of intervention being studied
  - Availability of participants

Withdrawal Criteria

- Define the conditions that the investigational intervention be stopped, safety or efficacy issues e.g.
  - Pregnancy
  - SAE
  - No clinical response within ? Day
  - Etc.

Designing the study

CIOMS:

"Scientifically unsound research on human subject is *ipso facto* unethical in that it may expose subject to risk or inconvenience to no purpose"

Helsinki:

"Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature"

Inclusion and Exclusion Criteria

CIOMS:

Individuals or communities to be invited to be subjects of research should be selected in such a way that burdens and benefits of the research will be equitable distributed. Special justification is required for inviting vulnerable individuals and, if they are selected, the means of protecting their rights and welfare must be particularly strictly applied

Vulnerable participant

- 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.

Selecting a Comparison

- Fundamental principle
  - ✓Groups must be alike in all important aspects and only differ in the intervention each group receives
  - ✓In practical terms, “comparable treatment groups” means “alike on the average”

- Randomization and Blinding
- Placebo VS Active control

Balancing Risk/Benefit:
Guidelines for Risk/Benefit Assessment

1. The potential risks to participants
   - identified
   - minimized
2. The potential benefits to participants and society are proportionate to or outweigh the risks

Risk/benefit analysis

- To assess the probabilities/magnitude of possible harm and anticipated benefits
- To assess whether the risk or inconvenience is justifiable in relation to the value of information sought
- To determine a balance between personal risk borne by participant and potential societal benefit
- Constitutes a key ethical dilemma

Importance of Risk-Benefit Assessments

- Clinical research develops generalisable knowledge that improves health & increases understanding of disease.

- Risk-Benefit assessment is to minimize possibility of exploitation by ensuring
  - that the ratio is appropriate
  - sufficient value of the research
  - research not too unfavorable to individual

Ethical considerations in the protocol

- State the guidelines or directives
- Discuss – Benefit / risk consideration
- Discuss – measures to protect participants

Monitoring of the study – Why?

- Monitoring system
  - Monitoring team from sponsor
  - DSMB
  - IRB/IEC

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.