Ethical Issues in Research & Guidelines to Good Clinical Practice

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Objectives:

At the end of the session participants should know.
• Historical aspects & necessities for ethical guidelines involving human research
• Various documents, codes & Guidelines for the conduct of research
• Independent Ethics Committee & its role in the review of research.
• Informed Consent & Informed Consent Process
• Good Clinical Practice & its Components

What is ethics?
Ethics is an academic discipline which studies norms & morals of our actions. It is knowing how to apply moral principles & values in concrete situations.

What is Research?
Research refers to activities aimed at developing or contributing to generalized knowledge

History:
Hippocrates in 5th Century B.C. propounded the most important ethical principle for all the physicians: Primum Non Nocere (Do No Harm)
Ethical issues became extremely important during & after World War II when world realized the atrocities committed by Physicians under the Nazi regime. These Physicians were tried separately for their crimes. The trial is known as Nuremberg Trials & the code is known as the “Nuremberg Code”. It is the foundational document for all the later guidelines. The components are:
• Voluntary informed consent is essential
• Persons must have capacity to consent
• Freedom from coercion (Force, Compulsion)
• Comprehension & Understanding of Risks and Benefits
• Research should have
  • Proper design
  • Favorable benefit ratio
• Freedom to Withdraw for the participant “at any time”
• Research must be conducted by qualified persons.

There are many infamous cases which made the world take notice of the ethical & rights violations that took place in the name of research. The Tuskegee Syphilis study, The Jewish Chronic Diseases Hospital study, The Willowbrook study, The Radiation study on Children, The Monster Study are a few of the examples.

• World Medical Association also took notice & came out with “Declaration of Helsinki”.

• U.S.A came out with Belmont Report in 1979 incorporating the three principles of Respect for Person, Beneficence & Justice.

• All the guidelines emphasize Respect for Person, Beneficence, Non-Malficence & Justice.

• To achieve these laudable goals “Voluntary Informed Consent” became a must.

To monitor the research & review it to protect the rights of participants a system came into existence: the “Independent Ethics Committee” (IEC). Ethics Committee approval & Informed Consent are the two most important parameters of research involving humans.

All the countries have mechanisms / guidelines to achieve these goals. Good Clinical Practice is a set of guidelines specially formulated to oversee research specially the Clinical Trials (Phases I, II, III & IV). International Community after a conference on harmonization (ICH) came out with ICH – GCP. India too has a similar set of guidelines formulated initially by ICMR in 2000 & later as per the Drugs & Cosmetic Act 2005.

DCGI has made it mandatory to follow Schedule Y of this act for any trials to take place in India.

Why medical research?

Our knowledge has increased by leaps & bounds in the last 50 years. However we still do not fully understand the functioning of human body, the causes of diseases, the cure for these diseases, Hence we need to continue research to understand these to reduce human suffering but at the same do it with the safety & wellbeing of the participants in the mind.

3 Principles of Ethical Research:

Respect for persons:
• Autonomy (protection for those with reduced autonomy)
• Informed voluntary consent
• Privacy and confidentiality

Beneficence:
• Safety & well being of the participant paramount
• Maximize benefits Minimize risks
• Good research design

Justice:
• Equal chance to all
• Equitable risks & benefits to all the groups of participants.
• Inclusion & Exclusion Criteria

**Incorporating ethical principles in research is achieved by:**
• Informed voluntary consent
• Special precautions, especially for vulnerable group.
• Designing the research which has favorable benefits to risks ratio.
• Randomization for equal distribution.

**Monitoring & Reviewing Research**

**How is research regulated?**
• On the basis of the 3 principles Respect for persons, Beneficence and Justice
• Monitored by – IRBs or IECs
• ICMR / DCGI guidelines (In India)
• Appropriate guidelines have to be followed in International / Collaborative research in addition to the national guidelines of the participating countries.

**Independent Ethics Committee (IEC)**

**What is an IEC?**
• The IEC is an independent body which will review, monitor, supervise & regulate research to ensure that the proposed research involving humans will confirm to the ethical guidelines & regulations in force & to make sure that the safety & wellbeing of the participants is ensured & a valid Informed Consent has been obtained. It can decline to approve the research, can ask for modification 7 sometimes can ask for the stopping of the research.

**What is the composition of IEC?**
• Minimum 5 to 7 members (Not more than 15)
• Chairperson
• 1-2 basic medical scientists
• 1-2 clinicians
• One legal expert or retired judge
• One social scientist/ representative of NGO
• One philosopher/ethicist/theologian
• One lay person from the community
• Member secretary
• If needed an expert can be invited as an Observer
• Usually Volunteers
• IEC has an interactive role & ensures
• Protecting the participants
• Adequate protection from harm or basic rights violations
• To look after Safety & Well being
• Evaluation / resolution of ethical issues in research studies
What are the responsibilities of IEC?
- Ensuring an excellent Research design
- Risks minimized & expected benefits maximized
- Consent procedures are adequate
- Privacy & Confidentiality issues
- Injury & Compensation
- Special care if Vulnerable Groups are involved
- Declaration of conflict of interest
- Can order stoppage of the research anytime if the safety & wellbeing of participants are at stake.
- Reviews periodically the ongoing research
- IEC should be notified if any changes are made to the protocol, to recruitment procedures etc

Who can monitors research?
- Sponsor
- IECs
- Regulatory agencies
- Data Safety monitoring boards
- Public interest groups

What are researcher’s responsibilities?
- Protection of human participants
- Scientific correctness
- Appropriate informed consent
- Confidentiality protection
- Conduct research according to protocol
- Compliance with EC requirements

What are sponsor’s responsibilities?
- Ensure appropriate review, approval and supervision by an EC
- Monitor the research
- Select qualified researchers
- Provide policies and procedures
- In international research : Comply with the local ethical, regulatory and legal requirements

What is scientific misconduct?
- Fabrication, Falsification & Plagiarism

Informed Consent (IC)
**What is informed consent?**
Consent given by a competent individual who after receiving the necessary information has adequately understood the information & has arrived at a decision.

**Informed Consent Process**
A communication process between researcher and the participant, starts before the research has started & continues throughout.

Prospective participants must understand the:
- Purpose
- Procedures
- Potential risks and benefits
- Alternatives to participation
- A consent document giving this is a vital part of the process
- Opportunity to discuss any questions is necessary
- Obtaining signature on consent document is important
- But it is just one step
- IC is about people’s understanding and willingness to participate in study and not about signing a form.

**Informed Consent Document is:**
- Read by participant
- Or read to the participant
- In local language
- Should be simple & comprehensible
- There should be time for questions
- Give adequate time to consider
- Signature / Thumbprint
- Must be witnessed usually by a family member

**What are the essential components of I.C?**
- Research Purpose
- Research Procedures
- Risks
- Benefits
- Alternatives
- Privacy & Confidentiality
- Disclosure of Potential Conflict of Interest
- Research-Related Injury
- Compensation
- Contact Information
- Withdrawal
- Authorization to publish research

**When is I C taken?**
• Prior to participation in a trial
• Before ANY trial procedure
• Including the taking of blood to screen patients if it is not part of normal clinical practice
• Before giving a questionnaire to access health etc

**How to consent someone?**
• The consent form must have been approved by IEC
• No coercion to enter the trial
• Non-technical language must be used
• Information presented in the most appropriate way
• Must have “ample” time to consider the decision

**Who can consent a Participant?**
• A medically qualified person (usually)
• Declaration of Helsinki states “Physician”
• Consent may be delegated to a Sub - Investigator (needs documentation)
• The investigator retains overall responsibility

**I.C & Vulnerable Groups**

Special precautions & justification needed if research involves Vulnerable Population:
• Children
• Prisoners
• Mentally ill & Mentally challenged persons
• People Incompetent to give I.C
• Disabled persons etc
• They may require a Proxy to consent for them (usually a family member)
• But these participants can refuse to consent even if the proxy has consented
• Some other participants belonging to groups like:
• Employees
• Students
• Subordinates
• May have reduced autonomy &
• Hence I.C Process may have to be more transparent

**Good Clinical Practice:**

**What is Good Clinical Practice?**
• Good Clinical Practices (GCP) provide
• Operative guidelines for ethical and scientific standards for the designing of a trial protocol including conduct, recording and reporting procedures
• Should be strictly adhered to while carrying out a trial.
How does GCP work?
- Sets minimum standards
- Defines mechanisms required to deliver standards
- Describes monitoring and assessment arrangements

ICH – GCP
- Provides Unified Standard
- Facilitate mutual acceptance of data by the regulatory authorities
- Guidance document must be followed when generating clinical data
- Principles established applied to other clinical investigations that may have impact on safety & wellbeing of human subjects

Good Clinical Practice Indian Scene
- Drugs & Cosmetic Act 1940
- ICMR Guidelines 2002
- Indian GCP Guidelines 2001
- Drugs & Cosmetic Act (2nd Amendment) Rules 2005
  - Amended Schedule Y
  - Regulate
    - Import
    - Manufacture
    - Distribution of New drugs

Good Clinical Practice: Components
- Definitions
- Protocol
- Data Handling & management
- Quality Control & assurance
- Finance & Insurance
- Ethical Principles
- Ethics Committee
- Informed Consent process
- Sponsor
- Monitor
- Investigator
  - Principal Investigator
  - Co Investigator
  - Coordinating Investigator
- Adverse Event
- Serious adverse Event
- Reporting of AE & SAE
- Investigational Product
- Investigator Brochure

Responsibilities of Principal Investigator & Research team
- Developing proposals that are ETHICAL
• Seeking ethical committee approval
• Notifying ALL relevant organizations
• Conducting research to agreed protocol
• Ensuring participant welfare throughout
• Feeding results to participants, sponsors and host organizations

Duties of the Research sponsor
• Quality assurance
  • Proposal safe, worthwhile
  • Ethics approval
  • Research environment
  • Trials registration
  • PI and researchers
• Resources to deliver
  • Data quality
  • R&D to protocol
• Agreement on
  • Responsibilities
  • Management
  • Monitoring
  • Intellectual property
  • Compensation
  • Dissemination
• Review safety, design
• Independent expert advice

Conclusions
• Ethical issues in research will increase in complexity
• Regulatory requirements will multiply
• Preferred approach back to basics (e.g., Belmont Report)
• Culture of concern for ethics in practice
• Constructive prospective engagements between IECs and investigators throughout the research process

Further Reading:
• http://www.icmr.nic.in  ICMR
• http://www.fhi.org  FHI
• http://www.cdc.gov/od/ads/  CDC
• http://www.nih.gov/sigs/bioethics/  NIH
• http://www.wma.net/  WMA
• http://www.who.int/  WHO

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