Ethical Issues in Clinical Research

Sibu Research Seminar
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Purpose of Research
- To produce generalizable knowledge about treatment efficacy by controlled experimentation in groups of patients with the aim of promoting improved medical, is therefore valuable to society.

Medical Ethics
- The Declaration of Geneva of the WMA binds the physician with the words, "the health of my patient will be my first consideration".
- The International Code of Medical Ethics declares that, "a physician shall act in the patient's best interest when providing medical care".

What is Ethics?
- Moral principles that govern a person's behaviour or the conducting of an activity
- About norms, values, right and wrong, good and bad, and what ought not to be done.
- Ethics of clinical research is about norms, values, right and wrong, good and bad, and what ought and ought not to be done in the context of clinical research.

Acknowledgement & Contents
- Slides are adopted and modified from the Malaysia GCP Training (Clinical Research Centre, MOH Malaysia)
- Define what is ethics and the background
- Discuss the principle and requirement of ethics in CR
- MOH guideline on CR ethics
- Ethics in writing and presentation of CR findings

The Dual Hat Problem

<table>
<thead>
<tr>
<th>Medical Care</th>
<th>Research</th>
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<tbody>
<tr>
<td>Purpose</td>
<td>Individualized care</td>
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<td>Methods</td>
<td>Routine care</td>
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<tr>
<td>Justification of Risks</td>
<td>Benefits to patients</td>
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Oxford Dictionaries Online
- Raphael DD Moral Philosophy Oxford University Press 1981

Malaysia GCP, page 74
Why Research Ethics?
- a few individuals are asked to accept burden / risk as research subjects in order to benefit others and society
- ethical concerns arise because of the potential for abuse &/or exploitation of these human research subjects”
  Grady C. in “Principles and Practice of Clinical Research”

Investigators' Discretion?
- Historically, observing research ethics and protecting human subjects - left to investigator's discretion.
- Investigators could be counted on to do the right thing.
- But, past research abuses confirmed the potential for exploitation and abuse of research subjects

Nazis Hypothermia Experiment
- Captured Russian troops submerged in ice water up to 5 hours - about 100 reported dead
- To determine how long German pilots would survive after parachuting into the cold North Sea

Nuremberg Code 1947
- Sets forth ten articles
  - Article 1: The voluntary consent of the human subject is absolutely essential
  - Article 9: Subjects have the right to withdraw at any time
  - Articles 2-8, 10: “Scientific value; favourable risk/benefit ratio; suffering by subjects be avoided”


World Medical Association's Declaration of Helsinki
- 18th General Assembly in Helsinki 1964
- Extend Nuremberg Code to include:
  - Research combined with medical care
  - Incompetent subjects & vulnerable subjects
  - Review by an independent review committee
  - International research (research in developing countries)
- Not a law!

Henry Beecher's Paper – Ethics and CR
- 22 examples of abuses (1966):
  - Withholding antibiotics from patients with rheumatic fever
  - Purposely infecting institutionalised children with hepatitis
  - Injecting live cancer cells into nursing home patients
  - Etc…

The New England Journal of Medicine
**Tuskegee Syphilis Study**

- Study in Tuskegee, Alabama: 1932 - 1972
- To determine natural history of untreated latent syphilis
- 400 black with syphilis vs. 200 without syphilis
- Never told they had syphilis, nor ever treated.
- End of investigators’ discretion and a weak protectionist era for human research
- US National Research Act 1974:
  - a national regulation with force of law
  - require independent IRB review

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**Three Ethical Principles for CR**

- The Belmont Report 1979
- Statement of 3 fundamental ethical principles
  1. Respect for person
  2. Beneficence and non-maleficence
  3. Justice

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**1. Respect for Person**

- 2 basic ethical convictions:
  1. individuals be treated as autonomous agents
  2. persons with diminished authority are protected
- Requirement of informed consent in research and respect for research subjects.

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**2. Beneficence and Non-maleficence**

- Two general complementary rules (Commission):
  1. do not harm
  2. maximize possible benefits and minimize possible harms
to help, or at least to do no harm *(primum non nocere)*

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**3. Justice**

- Requires us to treat persons fairly.

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**Seven Requirements and Ethical Principles**

<table>
<thead>
<tr>
<th>Requirements</th>
<th>Underpinning Principles</th>
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<tr>
<td>1. Societal/scientific value</td>
<td>Beneficence</td>
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<td>2. Scientific validity</td>
<td>Beneficence, respect for person</td>
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<td>3. Fair subject selection</td>
<td>Justice</td>
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<td>4. Favourable risk-benefit ratio</td>
<td>Beneficence and non-maleficence</td>
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<tr>
<td>5. Respect for subjects</td>
<td>Respect for person</td>
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<tr>
<td>6. Informed consent</td>
<td>Respect for subject autonomy</td>
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<tr>
<td>7. Independent review</td>
<td>Public accountability, avoid conflict of interest</td>
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</table>
1. Social or Scientific Value

- The treatment or hypotheses being tested should improve health and well being or increase knowledge about the research area.
- Why?
  - Research resources are limited
  - Avoidance of exploitation – not exposing human beings to potential harms without some possible social or scientific benefit.

2. Scientific Validity

- Clinical research should be well designed not only to ensure its scientific quality but also its ethical propriety.
- Only qualified researchers who can assume full responsibility for research on human subjects are permitted to conduct such work.

3. Fair Subject Selection

- Vulnerable individuals or “convenient” sample are not unfairly targeted for risky research; and the rich and socially powerful are not favoured for potentially beneficial research.
- Children, women, institutionalized populations, members of a group with a hierarchical structure (e.g. students, employees, armed forces, prisoners), etc.

4. Favourable Risk-Benefit Ratio

- Three conditions are fulfilled:
  1. Risks to individual subjects are minimised
  2. Benefits to individual subjects are enhanced
  3. Benefits to individual subjects and society are proportionate to or outweigh the risks

5. Respect for Research Subjects

1. Protect subject’s confidentiality and privacy
2. Provide opportunity to withdraw early, without penalty
3. Monitor subject’s well-being monitored - have procedures to manage adverse reactions, emergencies, change in clinical statuses
4. Inform subject of new information, and to re-consent if necessary.
5. Inform subject the study results, in recognition of his contribution to research.
6. Compensate subject for research injury.
6. Informed Consent: Definitions

A **process** by which a subject **voluntarily confirms** his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate.

Informed consent is **documented** by means of a written, signed and dated informed consent form.

**ICH GCP 1.28**

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**Valid Informed Consent**

The essential attributes in a **valid informed consent**?

- Competent
- Voluntary
- Comprehending or understanding
- Informed

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**Illiterate subject / legally acceptable representative (unable to read)**

- Investigator/designee must explain patient information and consent form point by point in the **presence of an impartial witness**.

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**Patient Information Sheet: 20 Elements**

- The trial involves **research**
- The purpose of the trial
- Probability for **random assignment** to treatment
- Trial procedures to be followed, including invasive procedures
- Subject’s responsibilities
- Experimental aspects of the trial
- Description of foreseeable risks/discomforts
- Expected benefits - subject made aware if no intended clinical benefit
- Alternative procedure(s) / treatment(s) available and their potential benefits and risks
- Subject compensation in trial-related injury

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**Patient Information Sheet: 20 Elements**

- Anticipated **prorated payment**, if any, to subject
- Anticipated expenses, if any, to subject
- Subject’s participation in the trial is **voluntary** - subject may withdraw at any time
- Direct access to subject’s original medical records without violating confidentiality
- Records identifying the subject will be kept confidential
- Will be updated if new information becomes available
- Person(s) to contact for further information and in the event of trial-related injury
- Circumstances for trial termination
- Duration of participation in trial
- Number of subjects involved in the trial

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**Practices for Assent - for who?**

- Assent must be obtained.
- Must first obtained the permission of the parents or guardians, and to solicit assent from the minor.
- Dissent of the minor must be respected even if the parent or guardian agrees.

Minors aged 7 to less than 18 years
Informed consent waiver in practice

The following would qualify:

1. Non-human subject research
2. Retrospective study based entirely on medical record
3. Registry or large-scale non-interventional population study

7. Independent review by IRB / IEC

A fundamental requirement for ethical research:
A key procedure for protecting human research subject:

1. minimise the impact of conflicts of interest.
2. is important for social accountability.

Ethical Issues in Scientific Publishing and Presenting

- Authorship
- Plagiarism

Vancouver Guidelines on Authorship

- Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data.
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published.
- Authors should meet conditions 1, 2, and 3.

International Medical Journal Editors' "Guidelines for Authorship" (http://www.icmje.org/)
Plagiarism

- The most common form of scientific misconduct
- "... a writer deliberately uses someone else's language, ideas or other original material without acknowledging its source."
- Council of Writing Program Administrators (www.wpacouncil.org)

- Often intentional.
- May be unintentional due to confusion regarding the definition of plagiarism and how to avoid it.
- A charge can have severe consequences:
  - loss of credibility and professional standing
  - expulsion from an institution
  - loss of a job

Plagiarism Detection Software


Acknowledgement

- Main financial support for the conduct of the study
  - Internal - i.e. own institution - salaries, facilities, space, utilities
  - External grant - big or small
- Technical helps contributed to the conduct of study (not to a point of authorship)
  - Aid by technician, research nurse
  - Specific use of special equipment/space/facilities
  - Input by students, trainees
  - Statistical/artistic/ICT assistance (if not authorship)
  - Ideas came out of discussion with other people
  - Critical review/improvement of quality of research or draft of writing
  - Provision of clinical details of patients

Acknowledgement - MOH Staff

We would like to thank Director General of Health Malaysia for his permission to publish / present this scientific paper / poster.

Further Reading

- Declaration of Helsinki (http://www.wma.net/)
- International Ethical Guidelines for Biomedical Research Involving Human Subjects (http://www.cioms.ch)
- Committee on Publication Ethics (http://www.publicationethics.org/)
- International Committee of Medical Journal Editors (http://www.icmje.org)

Circular on Publication and Presentation

Sibu Research Seminar 2013
CONCLUSION

The Ethics in Clinical Research
- Is about protecting the rights and safety of the subjects
- Observe the principles and requirement of ethical clinical research
- ICF & PIS – before study starts
- Must be approved by the Ethics Committee
- Practice ethical writing and publishing

References
- Malaysian Guideline for Good Clinical Practice, 3rd Ed

Thank You