Historical research events and Human subjects protection in clinical research

Mr. Albert NDAGIJIMANA

Outline

- Definitions of Good Clinical Practice, Human Subjects Protection and Research
- Historical Background
- Current examples
- Ethical Milestones
- Regulatory Oversight

Good Clinical Practices (GCP‘s)

- International ethical and scientific quality standards for designing, conducting, recording, and reporting trials that involve the participation of human subjects.‖
- Purpose:
  - Protect human subjects during clinical studies
  - Protect patients who might receive approved products in the future
- Not just one document
- Several different components which vary by country and research setting

Human Subjects Research

DEFINITION:

- A human subject is a living individual about who an investigator obtains either:
  - data through interaction or intervention with the individual
  - bodily materials (cells, blood, urine, organs, nail clippings, hair) even if the investigator did not collect these
  - Private, identifiable information (Medical info)

Research Definition

- systematic investigation, including research development, testing and evaluation

- designed to develop or contribute to generalizable knowledge

Historical Perspectives

- Nazi War- Crimes (1940s)
- Thalidomide Event (1960)
- Willowbrook Study (1960s)
- Jewish Chronic Disease Hospital Study (1963)
- Tuskegee Syphilis Study (1970s)
- Constant Gardner (2000s)

The First Half of the 20th Century

A lack of adequate scientific rationale existed; inhumane experiments shaped modern day worldwide standards for human subject protection:

1946 Nazi War Crimes

1947 Nuremberg Trials

What was not right

- No informed consent
- No risk-benefit assessment
- Using vulnerable subjects

Nazi War Crimes

- ✓German physicians performed some experiments on concentration camp prisoners during World War II
- ✓Excessive harms and torture to participating human subjects.
- ✓Eg:
  - ✓Trying antityphus vaccine
  - ✓Trying anti-malaria drugs
  - ✓High Altitude Experiments
  - ✓Hypothermia Experiments

Nuremberg Trials

- ✓At the end of World War II, 23 Nazi doctors and scientists were put on trial for the torture and murder of concentration camp inmates who were used as research subjects.
- ✓Issue of section called "Permissible Medical Experiment “
- ✓Issue of Nuremberg code

Nuremberg code

1. "**The voluntary consent of the human subject is absolutely essential**“
2. The Research objective should be aimed for the good of the society.
3. Research should be based on prior animal work.
4. The risks should be justified by the anticipated benefits.
5. Only qualified scientists must conduct research.

Nuremberg code (cont')

6. Physical and mental suffering must be avoided.
7. Research in which death or disabling injury is expected should not be conducted.
8. Facilities and resources to conduct well-designed research should be available.
9. Subjects must be free to stop at anytime.
10. The investigator should stop the study if he/she believes that continuation of the study will result in serious injury, disability or death of the research subject.

Historical Events
Second half of the 20th century

- Thalidomide Event (1960)
https://www.theguardian.com/society/2012/sep/01/thalidomide-scandal-timeline

Thalidomide taken by pregnant women to treat insomnia leading to birth defects.

This incidence resulted in establishing of ICF as a requirement.

What was not right

- No IC
- Withholding information (subjects did not know they were taking a drug that was not approved)

Historical Events
Second half of the 20th century

1960s - The Willowbrook Hepatitis Study

Children with mental retardation were inoculated with a hepatitis virus to see how the disease progressed. There was evidence that parents were led to believe that due to overcrowding that their children would not get enrolled into the institution unless parents consented.

What was not right

- Coercion
- Risk-benefit ratio were not explained

Historical Events
Second half of the 20th century

1963 - Jewish Chronic Disease Hospital

Terminally ill patients were inoculated with live cancer cells without their knowledge.

What was not right

- No IC
- Subjects exposed to higher risks

Historical Events
Second half of the 20th century

1972 - Tuskegee Syphilis Trial

In a research study initiated by the US Public Health Service black American men from Alabama were left untreated with syphilis for years, from 1930 – 1970, to study the ―natural disease progression‖ of syphilis.

Herman Shaw, Tuskegee Study participant,
after the White House ceremony.

What was not right

- No IC
- Withholding treatment
- Research on vulnerable population
- Putting men and their families at risk

Historical Events
Beginning of the 21th century

2000- Constant Gardener

It is about how large multinational phramaceutical companies exploit those in the third world, for profits in the "civilised societies". The research was conducted in kenya.

What was not right

- Treatment availability after research
- Vulnerable population

BORISON AND DIAMOND CASE- 1997

- Borison (MD)- former chair of Medical College of Georgia (MCG) Psychiatry Department.
- Diamond (PhD)- former MCG faculty, colleagues
- Systematically diverted $10 million in research funds from MCG to a private research company they had formed (in 10 years, over 100 studies conducted there)
- Irregularities in medical management, fraud, forgeries
- Untrained, clerical (non-clinical) staff performing clinical duties with no supervision
- Fines and restitution > $5 million, prison, debarment

FIDDES CASE - 1999

- Dr. Robert Fiddes: Fabricated participants, data, lab samples (multiple studies and multiple accounts)

– **Guilty – Conspiracy and faking false statements in** matter within jurisdiction of the FDA (18 USC 1001)

-Sentenced - 15 months in jail (see newspaper) & Fined - $800,000

– **Debarred by FDA**

"Drug Trials Hide Conflicts for Doctors“ Kurt Eichenwald and Gina Kolata New York Times, May 16, 1999, Section 1, page 1

"A Doctor's Drug Studies Turn Into Fraud“ Kurt Eichenwald and Gina Kolata New York Times, May 17, 1999, page A1

FDA Letter:http://www.fda.gov/OHRMS/DOCKETS/98fr/110602d.htm

GELSINGER CASE

- STUDY: A new way to replace defective genes in order to treat enzyme disorders
- STUDY POPULATION: 18 patients with mild genetic deficiencies
- WHAT WENT WRONG: Within hours of receiving his first injection of the genes, delivered by modified cold viruses, Jesse Gelsinger, 18, felt sick to his stomach. His immune system fought a pitched battle against the wildly proliferating viruses, but by the next day he had slipped into a coma. Three days later, Gelsinger's family made the agonizing decision to pull him off life support.
- The FDA argued that he should never have been given the genes.
- It was also troubled by the researcher's failure to report adverse reactions in other patients, and he has not been permitted to conduct any human trials since Gelsinger's.

Parascandola M: Five years after the death of Jesse Gelsinger: Has anything changed? Research Practioner: 2004:5(6) 191-200

Ellen Roche & Johns Hopkins – 2001

- Healthy lab technician volunteered for asthma study of hexamethonium bromide.
- Respiratory effects of hexamethonium bromide were not known to investigator prior to study.
- Previous participant had respiratory problems, solution was changed without IRB being informed.
- Johns Hopkins forced to halt $300 million in medical research
- Ellen Roche died. Compensation for her participation: $365.
- Johns Hopkins settled out of court with her family.

Robert Steinbrook; Protecting Research Subjects — The crisis at Johns Hopkins N Engl J Med 2002; 346:716-720

Uganda study to determine whether STIs increase risk of HIV infection

- Carried out in 10 clusters of rural villages in Uganda
- Residents of 5 of the 10 clusters given intermittent antibiotic treatment to reduce the prevalence of STIs.
- For up to 30 months, several hundred people with HIV infection were observed but not treated yet the investigators could easily assess treatment for them
- Many people who were found to have other sexually transmitted diseases were left to seek their own treatment.
- Should research conducted in developing countries be held to different standards from those applied in the developed countries?

Marcia Angell, M.D. Investigators' Responsibilities for Human Subjects in Developing Countries N Engl J Med 2000; 342:967-969

Placebo trials for PMTCT in developing countries

- Controversial issue in the conduct of clinical trials in developing countries – Should control group must receive the same intervention as that which would be provided if the study were conducted in a developed country?
- Trials compared a short course of AZT with placebo for PMTCT
- It was already known that a longer course of AZT reduced PMTCT but was very expensive and not available in developing countries

Peter Lurie, M.D., M.P.H., and Sidney M. Wolfe, M.D. Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries N Engl J Med 1997; 337:853-856

These trials are examples of why we need to particularly protect:

- minorities (untreated syphilis, no informed consent)
- women (untreated cervix carcinoma, uninformed patients)
- Inmates (involuntary experiments)
- Orphans
- Patients not capable of giving consent including
  - Children
  - Mental and/or physically incapacitated

Abstraction from History?

- In the past and in the present the burden of the study (ethical or not) fell upon the poor

  → whilst the advantages were reaped by the wealthy privately insured patients

- History of research abuse is the history of racism, class injustice, and other forms of bias and discrimination.

- Ethical starting point is not individual vs. society, but equality and human rights.

Ethical Principles

Dilemma of Principles

Fundamental Principles

Dilemma of Principles

- What is the source of today‘s ethical codes, ethical review, and regulation of experimentation on human subjects?

- Is research ethics a question of philosophy versus History
  - Philosophy: a set of universal, timeless principles?
  - History: a reaction to specific historical events that we resolve never to repeat

Dilemma of Principles

- Ethical Theories versus Ethical Principles
- We do not agree on any one theory
- We accept many principles, but we do not always agree on their priority
- There are many plausible sets of principles, differing in content and in number

International versus National guidelines

- National vs. international standards:
  - globalization and the drug industry
    - Practical need for uniform standards
    - Concern over exploitation
  - universal human rights
  - single vs. multiple standards

- For example what is the national Role of World Medical Association

- How do universal —Ethics translate into national —Regulation?

International guidelines and councils

Global perspective

International dilemma

International Guidelines

A wide range of national and international guidance, guidelines, declarations and regulations, including:

- **World Medical Association** (WMA): *Declaration of Helsinki*, last revised 2000; Note of
- **The Council for International Organizations of Medical Sciences** (CIOMS) in collaboration with the **World Health Organization** (WHO):
- **International Ethical Guidelines for Biomedical Research Involving Human Subjects,** last revised 2002.
- **Council of Europe** (CoE): *Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research*, prepared by the Steering Committee on Bioethics (CDBI) of the Council of Europe adopted by the Committee of Ministers, June 2004.

International Guidelines

A wide range of national and international guidance, guidelines, declarations and regulations, continued:

- **European Council and European Parliament** (EU): *Directive 2001/20/EC* on the approximation of the *laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use,* April 2001, brought into force by May 2004.

- **The European Group on Ethics in Science and New Technologies** (EGE): *Opinion Nr 17 on the ethical aspects of clinical research in developing countries*, published in Jan 2003.

- **Nuffield Council on Bioethics: The Ethics of Research Related to Healthcare in Developing Countries** Published: Wed, 24 April 2002

World Medical Association

- World Medical Association (WMA)
  - WMA created to restore integrity to the medical profession.
    - Focus: *physicians'* duties.
    - **http://www.wma.net**

- The International Conference on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use
    - Focus: *researchers'* duties
    - **http://www.ich.org**

Declaration of Helsinki

- Declaration motivated in part by desire for professional control of research enterprise between US, France and Japan.

- Adopted 1964; amended 1979, 1983, 1989, 1996, 2000.

- Last revised in October 2000 in Edinburgh, Scotland,

  Statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. (This includes research on identifiable human material or identifiable data)

Declaration of Helsinki

- Are principles, not rules
- 32 short clauses, no elaboration
- Advisory only, but recognized in national legislation and World Health Organization (WHO) practices.

Declaration of Helsinki

BASIC PRINCIPLES

1. Clinical research must conform to the moral and scientific principles that justify medical research, and should be based on laboratory and animal experiments or other scientifically established facts.
2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.
3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.
5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

Basic Principles of the Declaration of Helsinki

All subjects must volunteer

- Informed consent required:
  - aims, methods, sources of funding,
  - any possible conflicts of interest
  - anticipated benefits and potential risks
  - right to withdraw consent to participate at any time without reprisal.

Basic Principles of the Declaration of Helsinki

Ethical review committee required prior to study start

- Design of study to be publicly available
- No research unless the importance of the objective outweighs the inherent risks and burdens
- And unless reasonable likelihood that the populations in which the research is carried out stand to benefit

Basic Principles of the Declaration of Helsinki

Community Benefit

- Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.(article 19)

  - What are the criteria for determining likelihood?
  - What degree of likelihood is necessary?

Basic Principles of the Declaration of Helsinki

Protection of Incompetent Subjects

- Research on subjects incapable of consent requires:
  - Consent of parents or guardian
  - research is necessary to promote the health of the population represented
  - research cannot instead be performed on legally competent persons

Basic Principles of the Declaration of Helsinki

Placebo Controls

- A new method should be tested against the best current ... methods

- Placebo OK only where no proven prophylactic, diagnostic or therapeutic method exists.

Basic Principles of the Declaration of Helsinki

Obligations for Treatment

- At the conclusion ... every patient should be assured of access to the best proven methods identified by the study.

The International dilemma

- The world contains a vast number of cultures with varying customs and traditions
- Multinational research is a global enterprise
  - Sponsors include industry, industrialized country agencies, international organizations
- Can universal ethical principles be applied to these culturally diverse settings?
- Was the Declaration of Helsinki able to deal with this international perspective?

International dilemma

Cultural sensitivity

- A widely held view calls for researchers and sponsors to be curturally sensitive

- The general duty of respect implies a duty to be sensitive to other cultures….The variety of beliefs and practices that exist may challenge the notions of overarching ethical principles. This in turn prompts an analysis of the relationship between the requirement of sensitivity to cultural differences and the concept of moral relativism

Council for the International Organisation of Medical Sciences (CIOMS)

- NGO created by WHO and UNESCO
- Elaboration of Declaration of Helsinki
- 15 Guidelines with extensive explanations
- First version: 1993
- Revised version November 2002
- Taking into account the international dilemma of cultural differences

CIOMS for Developing countries

- No research in developing countries unless it could be carried out in developed countries
- research is responsive to the health needs and the priorities of the [host] community
- any product developed will be made reasonably available to inhabitants of the underdeveloped community

CIOMS: Dual Review

Guideline 3: Ethical review of externally sponsored research

- An external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country. The health authorities of the host country, as well as a national or local ethical review committee, should ensure that the proposed research is responsive to the health needs and priorities of the host country and meets the requisite ethical standards.

CIOMS 10: Research in communities with limited resources

- Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:
  - the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
  - any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.

CIOMS: The use of Deception

- Use of deception and lies acceptable only if:
  - No more than minimal risk
  - Deception necessary to achieve scientific goal
  - Scientific goal important
  - Deception not used to secure consent
  - Subjects debriefed after study ends
  - Subjects may refuse to permit use of data

CIOMS: Use of Deception

- Because of existing cultural, religious, political or legal constraints, it is sometimes impossible to achieve the ethical ideal and exceptions to this general principle may have to be accepted.…
  - In rare circumstances, it may be necessary for researchers to conform to local custom and request partner agreement.

The International dilemma

Criticism of CIOMS

- This guideline reflects a Western bias
  - It is based on the assumption that the circumstances…in the developed world are the norm. Thus, the developed world is envisioned as more advanced, not only technologically but also morally.

Christakis, Nicholas A. and Levine, Robert J. (1995). "Multinational Research." In Encyclopedia of Bioethics, ed. Warren T. Reich. New York: Simon & Schuster Macmillan.

The International dilemma

- There has been significant criticism of all the aforementioned guidelines as they are often inconsistent and inappropriate for the developing country setting.

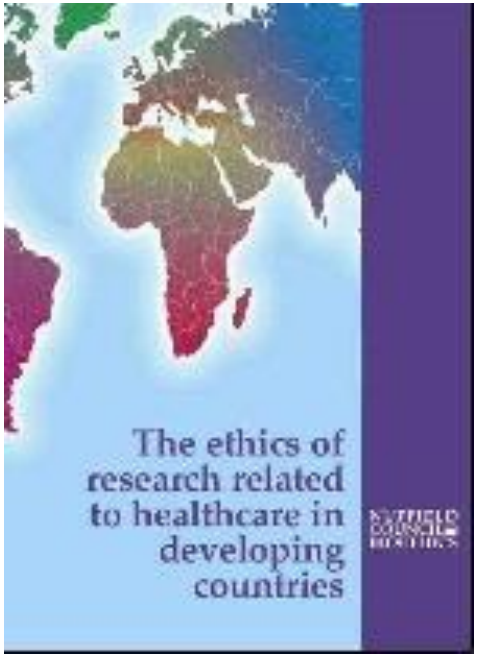
  - Making interpretation and application of international guidance in a specific context often extremely difficult.

  - Therefore it is recommended that developing countries produce their own national guidance to promote ethically sound research.

Nuffield Council of Bioethics

- Nuffield Council on Bioethics, *The Ethics of Research Related to Healthcare in Developing Countries* (London: Nuffield Council on Bioethics, 2002)

- A follow-up Discussion Paper 2005
  Nuffield Council on Bioethics
  The ethics of healthcare related
  research in developing countries:



Nuffield Council of Bioethics

- Following a number of international controversies:
  - the Nuffield Council on Bioethics established a Working Party to consider the issues in 1999.
  - The Report, *The ethics of research related to healthcare in developing countries*, was published in 2002.
  - A follow-up Discussion Paper, based on a Workshop held in Cape Town to discuss practical issues faced when implementing guidance, was published in 2005.

Nuffield Council of Bioethics

- More and more developed countries sponsor healthcare-related research involving populations and patients in developing countries.

  → Although, many of the issues raised by such research, such as what treatment should be provided to participants following research, are not confined to trials in developing countries.

  →They tend, however, to be exacerbated when only very limited resources are available, as may be the case in developing countries where basic healthcare is not widely available and research ethics committees are often underdeveloped or absent.

Nuffield Council of Bioethics

the inequalities that exist between developed and developing countries create significant risks of exploitation when externally sponsored research is carried out.

The Nuffield Council of Bioethics took the international differences further and dealt with actual experiences of international research controversies and addressed these.

Nuffield Council of Bioethics

Ethical framework

—We recognize that it would not be possible to formulate a robust set of guidelines for all situations. However, we identify four principles which should be taken into account by anyone who is designing or conducting healthcare research in developing countries:

- the duty to alleviate suffering;
- the duty to show respect for persons
- the duty to be sensitive to cultural differences; and
- the duty not to exploit the vulnerable.

Nuffield Council of Bioethics

Social and cultural issues

- Misunderstandings can occur when sponsors of research are unfamiliar with the cultural traditions of the country in which it is conducted.
  - Differing perspectives on respect for family and individuals, and the role of the community.

- Prospective participants in research may have experience of very different traditions of healthcare and hold varying beliefs about illness and disease.
  - Views about the causation of illness may differ from the _western‘ medical model.

- Participants will often be unfamiliar with the concept of research and may be sensitive to some practices, such as taking blood samples.
  - It is critically important that the local social, cultural and economic context is taken into account when research is designed

Nuffield Council of Bioethics

- **Setting priorities**
  - We recommend that all countries should set national priorities for healthcare research. If external sponsors propose research which falls outside the national priorities, the research should be justified to the appropriate research ethics committees [paras 2.31-2.32].

Nuffield Council of Bioethics

- **Consent**
  - Who should give consent?
  - How should consent be obtained?
  - How should consent be recorded?
  - Are inducements acceptable?

Nuffield Council of Bioethics

- **Standards of care**
  - What level of care should be provided for those in the control group?
  - Provision of care to all trial participants
    - *Research into preventive measures*
    - *Care for other conditions*

- Definitions:
  - Universal standard of care: the best current method of treatment available anywhere in the world for a particular disease or condition.
  - Non-universal standard of care: the treatment available in a defined region.

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- **After the research is over**
  - Should an intervention be provided after the trial?
  - Who should be responsible for making a successful intervention available?
  - Where participants have chronic diseases, who should be responsible for providing continuing care after the research is over?

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- **Ethical review**
  - Research ethics committees
    - What types of review should be required?
      - relevance to healthcare priorities within the country;
      - scientific validity; and
      - ethical acceptability.
    - Where should ethical review take place?
    - Who should fund research ethics committees?
  - Developing capacity

In Summary

- There is an urgent need for externally sponsored research in developing countries. However, rigorous ethical safeguards must be in place to prevent the exploitation of those who take part in the research. The report aims to provide a framework for anyone who is designing or conducting healthcare research in developing countries.

- Research must be appropriately planned, taking account of the local context, and effectively reviewed on scientific and ethical grounds. Externally sponsored research also provides the opportunity to assist developing countries to strengthen expertise in conducting and reviewing research.

From declaration and reports to local regulations and laws

Medical Ethics Review

What is Ethical Review?

- *Protect* Human Subjects?
  - Individual over group?
- Treat Human Subjects *Fairly*?
  - No risk-taking without consent and without scientific justification
- Treat Human Subjects *Equally*?
  - No discrimination (racism, bias)

What is Ethical Review?

- Done by a Medical Ethics Committees (MEC) or Insitutional Review boards (IRB)
  - Reviews proposals and protocols for medical research
  - **Keeps a register** of Medical Ethics judgments

According to LOCAL or REGIONAL LAWS !!!!

Guidelines for Review of Research Proposals by MEC– WHO, 2000

1. Scientific design and conduct of the study
2. Recruitment of research participants
3. Care and protection of research participants
4. Protection of research participants confidentiality
5. Informed Consent practices
6. Community considerations

Open Discussion

The Rwandan Situation

Open discussion

- Discuss how the ethical principles presented here are translated to local principles?
- How are these principles translated into guidelines in Rwanda?
- How are these guidelines translated into local law?
- Discuss the difference between these guidelines and laws?
- What laws are there is Rwanda presently concerning Medical Ethics?
  - Do these include Ethical review?
  - Does this include informed consent?
  - How are other ethical principles dealt with in Rwandan law?

Basic Protections for Human Subjects

- Ethics
  - Regulations (ethics operationalized)
  - Oversight (Culture of conscience)
- Science
  - Design/Important question
  - Conduct/Validity

IRB/EC : its purpose is to protect the rights and welfare of human subjects

IRB/EC REVIEW

- Appropriate Informed Consent
- Acceptable Risk/Benefit ratio
- Privacy and Confidentiality Protection
- Data and Safety Monitoring
- Scientific Validity
- Equitable Subject Selection

Summary of Ethical issues

Three ethical principles guide research with human participants:

- Respect for Persons
- Beneficence
- Justice

Summary of Ethical issues

Seven Requirements:

1. Social or scientific value
2. Scientific validity
3. Fair subject selection
4. Favorable risk-benefit ratio
5. Independent review
6. Informed consent
7. Respect for potential and enrolled subjects

Emanuel et al, JAMA 2000;20:2701