KCRI Kilimanjaro Clinical Research Institute

HEALTH RESEARCH ETHICS

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CONTENTS

- HRE
  - History of HRE : Europe, USA, Japan
  - Abuse of Human Research Participants in Africa
  - Why is Africa concerned?

Intro: History of HRE

- Biomedical research has made tremendous contributions to improvement of human health and welfare;
- **HRE as a discipline born in scandals and tragedies of biomedical research;**
- Codes, regulations and guidelines developed from public debates, or in response or anticipation of human abuses;
- **Examples: Europe, USA, Japan and South Africa**;
- Colonial/post colonial Africa (research)?

ORIGINS OF HRE

THE 1900 PRUSSIAN DIRECTIVE

- **Response to public debate on human subject experimentation.**
- Prohibited experiments in
  - minors
  - not fully competent.
- Unequivocal consent
  - Explicit explanation of the experiment and possible AE
    - Participants' information sheet
    - Consent form
- Only certain people were allowed to do research and must keep written records.
- Did not apply to medical treatment for diagnosis, therapy or immunization.

PROBLEMS WITH HUMAN SUBJECT EXPERIMENTATION

1900 Prussian Directive

- Response to "Case of Neisser"
- Dr. Neisser studied immunization of health persons against syphilis by inoculating them with serum from syphilitic patients.
- 3 prostitutes inoculated; all contracted syphilis.
- No consent obtained.

YELLOW FEVER EXPERIMENTS

- 1897 – In Italy
  - Guiseppe Sinareli (Italian) announced isolation of YF
  - Injected 5 persons to prove it. Criticized.
- 1900 – in the US
  - Surgeon General commissioned **Walter Reed** to identify the cause of YF. Done in Cuba.
  - Reed established several safeguards:
    - self-experimentation, ie on commission members;
    - involve only adults;
    - designed a written contract for local workers,
      - explain perils,
      - offered $100 to participate,
      - and another $100 if caught infection.
- **In Africa – Studies were underway to determine**
  - **Aetiology & transmission of tropical diseases**

PROBLEMS WITH HUMAN SUBJECT EXPERIMENTATION

Reich Health Council:

- 75 children died in experiments with tuberculosis vaccination.

Reich Council Regulations (1931)

- 14 points which demanded complete responsibility of the medical profession for carrying out human experimentations,
  - General technical and ethical standard,
  - Informed consent necessary,
  - Documented justification of protocol deviation,
  - Risk-benefit analysis required,
  - Justification for studying vulnerable population,
  - Necessity for written records.

PROBLEMS WITH HUMAN SUBJECT EXPERIMENTATION

Nazi Germany (1)

- Dr. Mengele's Experiments
- Infected one twin with a "germ". When s/he died, the other twin was **killed** and their organs compared at autopsy.
- Sewed twins together to create a Siamese twin.
- Studied subjects with genetic traits so as to better "**purify** the Aryan **super race**".
- Performed cross transfusions to "make boys into girls and girls into boys".

NAZI GERMANY MILITARY EXPERIMENTS

Study subjects:

200 Jews, 50 gypsies, 500 Poles, and 1,000 Russians, war prisoners:

- **High-altitude** (low-pressure) **experiments**: put prisoners in low-pressure tanks, how long could survive with little oxygen, autopsies followed;
- **Freezing exp**.: force prisoners to remain outdoors, naked, freezing, 9-14 hrs; or put in freezing water 3hrs; try re-warming bodies;
- **Malaria exp**.: infect prisoners, give drugs, many died;
- **Typhus exp**. Inject prisoners with antityphus “vaccine”. Then infect with typhus; controls infect with typhus no treatment;

NAZI GERMANY MILITARY EXPERIMENTS

- **Mustard Gas Exp**:
  - inhale gas, then try various treatments
- **Sulfanilamide exp**:
    - inflict wounds and infect with bacteria, apply sulfanilamide
    - control group: wound and infect, no sulfanilamide;
- **Poison exp**:
  - feed patients various poisons, many died;
  - kill survivors for autopsy;
- **Incendiary bomb exp**:
  - burn with phosphorus; study wounds;
- **Sterilization exp**:
  - use chemicals or x-rays instead of surgery.

Nuremberg War Crimes

- Trial of Nazi doctors for inhuman acts
- Medical experiments during the war
- Without consent of the individual
- Among civilian and war prisoners

POST WAR RESPONSE (1)

"The Case Against the Nazi Physicians"

***Nuremberg Doctors' Trial – 1946 –47**

- 23 defendants
  - 3 non-physicians
- 15 found guilty
- 7 were hanged
  - 4 physicians
- 5 sentenced to life in prison
- 4 sentenced to 10-20 years in prison
- 7 were acquitted and freed.

***Separate Trial:**

- 31 "underlings" were also found guilty;
  - 22 – hanged.

POST WAR RESPONSE (2)

Nuremberg Code of Medical Ethics (1948)

- **Adopted by the World Medical Association 1964**
- True voluntary consent
  - freely given; prior to experimental procedures
- Truly necessary
  - well thought out experiments in which the expected benefits justify the risks
  - No unnecessary psychical or mental suffering or injury.

POST WAR RESPONSE (3)

- The person performing the task is qualified
- No experiment shall be undertaken where death or disabling injury will likely occur.
- Proper preparation & adequate facilities to protect subjects must be present to prevent further injuries.
- Subjects should be allowed to discontinue participation at anytime.
- Upon observing the likely risk of injury, disability or death, the researcher should terminate the experiment (DSMB, CRO – monitors (internal, external)

INTERNATIONAL ACCEPTANCE OF THE NUREMBERG CODE (WMA)

- **Helsinki Declaration (1964)**
  - Praised the code
  - Rejected it for widespread use
  - Modified the code
- **Further modifications (1975,1983, 1989, 1996, 2002, 2008)**

INTERNATIONAL CONVENTION ON CIVIL AND POTILICAL RIGHTS

Article 7 of 1966

"No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment.

In particular, no one shall be subjected without his free consent to medical or scientific experimentation"

US ACCEPTANCE OF THE NUREMBERG CODE (1)

Dr. HENRY BEECHER – NEJM (1966)

- Criticized lack of sincerity in implementing basic concepts of informed consent,
- Cited 50 episodes of potential "Code" violations which were published in peer-reviewed scientific journals in the US.
- **Suggested that journal editors reject articles based on violation of patient rights.**
- 1966 – NIH required establishment of IRBs for institutions receiving funding for medical research.

DESPITE REGULATIONS MAJOR PROBLEMS REMAIN: 1932-1972

PHS study of the effects of untreated syphilis on black men in Alabama (**"Tuskegee Study"**)

- 399 men who were already in late stages of syphilis
- 201 Negative controls
- **Treatment was available but not used**
- No formal protocol located
  - procedures evolved
  - Not a treatment study
- **Study objective:**
  - **The effects of spontaneous evolution of syphilis (Morbus Luis) on black males**

Tuskegee Study

- Study participants poor and illiterate
  - most had never seen a doctor before
- Free physical examination
- Free transport to the clinic
- Hot meals on exam days
- Free treatment for minor ailments
- Burial stipend
- Nurse Rivers – tracked participants/patients
- Press later labeled it "racial medicine";
- Late 1970s US Gov compensation authorized;1997 Pres. Clinton apologized.

US ACCEPTANCE OF THE NUREMBERG CODE (2)

PHS Policy modified 1974:

- Nat. Res. Act: IRB review and approval of all research involving human subjects;
- Nat. Comm. Protection of Human Subjects of Biomedical and Behavioral Res. created:
- Fed. Regulations governing research with humans promulgated;

1979-Belmont Report

1985- Act amended

BELMONT REPORT (1979)

Sets out Ethics Principles:

- Respect of person's **autonomy**
- **Beneficence** – protect research subjects from harm.
- **Justice** – who bears the burden?

LEADING ETHICS GUIDELINES

- Declaration of Helsinki, 2008 (www.wma.net)
- CIOMS (2002) International Ethical Guidelines for Biomedical Research Involving Human Subjects (www.codex.uu.se/texts/international.html)
- CIOMS (2008) Internatinal Ethical Guidelines for Epidemiological Studies. Provisional Text <http:www.cioms.ch/080221Feb 2008.pdf>
- ICH GCP Guidelines 1996 (www.ifpma.org)
- **National Bioethics Advisory Commission (www.bioethics.georgetown.edu/nbac/human/overvol1/html).**
- **Nuffield Council on Bioethics (www.nuffieldbioethics.org/filelibrary/pdf/errhdc-fullreport.pdf).**
- **WHO/TDR Operational Guidelines for Ethics Committees that Review Biomedical Research (2000).**

WAR CRIMES BY JAPANESE PHYSICIANS

- **Japanese massive program of bio warfare during WWII**, eg Unit 731 had 100 buildings;
- **Exps on disease dissemination** (eg STDs, cholera, bubonic plague and malaria);
- **Civilian water supplies infected;** bombs carrying infected fleas dropped;
- **Many exps on prisoners**
  - Combatants
  - captured Chinese, Russian and Korean,
  - some civilians including comfort women

ABUSE OF HUMAN RESEARCH PARTICIPANTS IN AFRICA (1)…

SOUTH AFRICA CABINET, 1985: PW BOTHA

“ …I wish to announce a number of new strategies that should be put to use to **destroy this Black bug**. We should now make use of the **chemical weapon**. Priority number one, **we should not by all means allow any more increases of the Black population** lest we be choked very soon. I have exciting news that our scientists have come with an efficient stuff. I am sending out more researchers to the field to identify as many venues as possible where the chemical weapons could be employed to combat any further population increases. The hospital is a very strategic opening, for example and should be fully utilized. The food supply channel should be used. We have developed **excellent slow killing poisons and fertility destroyers**…

”

TROVAN TRIAL IN NIGERIA

- Pfizer trial on a new drug
  - Trovan on 200
    - children in Kano, Nigeria
    - in middle of a meningitis epidemic
- Govt approval/clearance not obtained;
- Informed consent from parents not obtained, not told could withdraw;
- 11 children died, many others injured;
- Control group received low doses of an effective drug, some in control group - died.

MALARONE TRIAL

- **In Zambia, Gabon, Kenya, Uganda, etc**
- Malarone, a new antimalarial prophylaxis tested in Zambia and Gabon;
- Because it was very expensive SKB (now GSK) donated 1M doses to developing countries: donation tested in Kenya and Uganda;
- SKB withdrew donation;
- Malarone a leading malaria prophylactic for short-term travellers, costs +$60/dose.
- Malarone cannot be manufactured in Developing Countries

RECENT ABUSES IN AFRICA

- Virodene trial in Tanzania
- Tenefovir Trial in Cameroon
- Mefloquine, halofantrine trials
- HIV vaccine trial U Nairobi/Oxford U/comm sex workers
- etc

ARE ABUSES IN AFRICA LIMITED TO TRIALS?

- Plague studies in Tanzania, Thomas Buttler
- Removal of eyes from cadavers in Malawi
- HIV infections in Libya
- Unnecessary delays in implementing research results
- Research on orphans, Nairobi,
- etc

AFRICAN CHARACTERISTICS LEADING TO ETHICS CONCERNS

- Deteriorating health situation, high disease rates, scarce and poor health facilities
- High poverty, ignorance rates
- Human rights abuses rife
- Poor research systems
- Biomedical and Genomic revolution producing many new candidate drugs, vaccines, diagnostics, and devices needing testing
- Rich biodiversity, increasing bioprospecting / biopiracy
- etc

HIGH LIABILITY TO EXPLOITATION, COERSION, ENTICEMENT, INDUCEMENT

COMPROMISED VOLUNTARINESS

PART II: GCP

GCP DEFINITION

"Good Clinical Practice :-

is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects."

Intro: GCP

HISTORY OF GCP:

- Traces back to one of the oldest enduring traditions in history of medicine: The Hippocratic Oath.
  - **Primum, non nosere (first, do no harm)**
    - **The Guiding code of Ethics**

YET:

- Syphilis Study on Blacks - despite know treatment available
- Voltage study – Level of voltage that can be withstood
- World War episode – Duration of exposure in cold weather before death.
- Other Atrocities relating to “Nuremberg” trials

Intro: GCP

World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects.

Adopted by the 18th WMA General Assembly

Helsinki, Finland, June 1964

and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

FUNDAMENTAL TENETS OF GCP

FUNDAMENTAL TENETS OF GCP:

- In research of man:
  - interest in science and society should never take precedence over considerations related to well being of the study participant

- Aims to ensure that
  - studies are scientifically and ethically sound
  - clinical properties of the (pharmaceutical) substances under investigation are properly documented

GCP CARDINAL PRINCIPLES

1. ***PROTECTION*** **OF**

   Rights

   Safety

   Well-being/ Dignity

   of Trial Participants

2. ***Credible Clinical Trial Data***

GCP BASIC PRINCIPLES

1. It is the duty of the physician in medical research to protect the life, health, privacy and dignity of the human subject (***Helsinki Declaration; para 10***).
2. Physicians should **cease** any investigation if the **risks** are found to outweigh the potential benefits (***HD; para 17***)
3. The **right** of research subjects to safeguard their integrity must always be respected …. (***HD; para 21***).

The Requirements for Biomedical Research

"Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality"

(*Declaration of Helsinki, Intro, Paragraph 6*)

WHY COMPLY

- To obtain regulatory approval, clinical studies on drug/vaccines must be planned &conducted to meet relevant regulatory requirements and guidelines.

- The guidelines and regulations concerning clinical research put together, constitute what has come to be known as “Good Clinical Practices” (GCP).

- In some cases where registration of product does not apply, the results of clinical studies are expected to support the recommendation of use.

ICH and it's AIM

The International Conference on Harmonization of Technical Requirements for Registration of pharmaceuticals for Human Use

The aim of the International Conference on Harmonisation (ICH) is to develop common standards to facilitate the mutual acceptance of clinical data by regulatory authorities in European Union, Japan and the United States.

ICH OBJECTIVES

- To avoid (useless) duplication of testing and trials
- To allow sponsors to prepare one set of 'Core Technical Data' on Safety, Quality, and Efficacy for a new drug application which will be acceptable wherever the dossier is filled (Global Dossier)
- To allow through the submission of the 'Global dossier' the 'mutual acceptance' of foreign data

THE TASK OF GCP

To create a research environment that is in the interest of public health

- for the research participants & their communities
- in support of national health priorities
- in the interest of regional health development

GCP DEFINES RESPONSIBILITIES

- for Ethics Committees
- for Sponsors
- for Researchers
- for Competent (Regulatory) Authorities

CHALLENGES: ICH GCP

- **Protection of Participant :** is it given a high place in the document?
- A document regularly applied in practice by sponsors: Often disregarded by **Researchers** and **IECs/IRBs**
- **No systematic consultation** with partners outside the three regions and the observers;

CHALLENGES: ICH GCP

- **Clearly limited to pharmaceuticals:**
  - Inadequate consideration is given to
    - Device
    - Radiation
    - Psychological
    - Epidemiological
    - Social science studies
- **Specific questions of developing countries not addressed**
  - community consultation
  - informed consent
  - capacity building
  - product development and availability
  - publication of trial results

FINAL THOUGHT

It is not just to know what the ICH GCP principles are,

but to know what it means to apply ICH GCP to a trial.

"Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible."

Acknowledgement

KCRI

AMANET

AHRI