

Review of International Research Ethics Guidelines

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History of Medical Research

- Medical research is as old as practice of medicine
- There was never a difference between practice and experimentation
- Rights and safety of patients have been recognized since the time of Hippocrates
- Besides the Hippocratic code of conduct, there was no formal medical ethics - The term “BIOETHICS” was first coined in 1970

Research Ethics: Codes & Guidelines

- Nuremberg Code – 1947
- UN - Universal Declaration of Human Rights - 1948
- WMA - Helsinki Declaration – 1964, Tokyo 1975, Venice 1983, Hong Kong 1989, South Africa 1996, Edinburgh 2000
- Belmont Report -1978
- CIOMS/WHO Guidelines – 1991 –Epidemiological Research
- CIOMS/WHO Guidelines – 1993 – Biomedical Research Involving Human Subjects
- WHO Guidelines for clinical trials on pharmaceutical products - 1995
- ICH – GCP Guidelines 1996
- Council of Europe – Convention for the Protection of Human Rights and Dignity with regard to Application of Biology & Medicine - 1997
- UNESCO – Universal Declaration on Human Genome & Human Rights 1997
- UNAIDS – 2000 Ethical Considerations in HIV Preventive Vaccine Research
- WHO – 2000 Operational Guidelines for Ethics Committees that Review Biomedical Research

Regulation → Reactionary

- Nazi experiments -1939-1945
- Radiation Exposure Experiments - 1950
- Tuskegee Study -1947-1976
- ACTG study 076 = Regimen 076 = 1994 & in 1997 the use of placebo became public
- Quinn et al Study in Uganda - 1997 NEJM & Lancet
- Oral cancer study - Kerala/Johns Hopkins - 2002

Focus on Tightening Guidelines

- The fifth amendment of Helsinki Declaration (October 2000)
- Revision of CIOMS/WHO guidelines (February 2003)
- The NBAC Guidelines for Research in Developing Countries (April 2001)
- Report of Nuffield Council of Bioethics on Research in Developing Countries (April 2002)
- Umpteen National and Regional Guidelines have been developed

Major concerns in developing countries

- Enormous disparities in economic development
- Huge difference in burden of disease and health outcomes
- Increasing globalization without requisite safeguards and protection of human rights
- Wide spread hectic research activity
- *The concerns are of*
 - Standards of care
 - Conceptualization of autonomy/difficulties in realizing informed consent
 - Vulnerable populations/gender/exploitation/abuse
 - Lack of local regulatory requirement

The stakeholders/Conflict Interest

- External funding agencies
- Researcher – National/International
 - Physician researcher
- Field worker
- Pharmaceutical/Biotechnology Industry
- Collaborating local institutions
- Community leaders/gatekeepers/politicians
- Governments

Contentious Issues

- Consent
- Standard of care
- What happens once research is over?
- Ethical Review Processes

Informed Consent

Capacity – Informed – Voluntary

- Illiteracy/Conflict of Interest of Stakeholders
 - Lack of genuine efforts – Legal vs. Moral
- Power relations/Peer Pressures
 - Male dominant/Elders/Gate keepers
- Hierarchical & paternalistic societies
 - “Doctor you decide what is best for us”
- Lack of healthcare
 - Therapeutic misconception – something vs. nothing
- Widespread poverty
 - Compensation vs. Coercion

Emphasis of changing FORMALITY of *informing* into PROCESS of *understanding*?

- Individual consent - written or verbal
 - Witnessed or recorded
- Simplified informed consent forms
 - Brief and crucial information
- Allocation of more monetary & human resources
 - Time, money and manpower
- Introducing innovations in the process
 - Flip charts, video animations, repetition, sleep over time, testing comprehension
- Administration of consent by an independent body
 - Ombudsman
- Post approval monitoring
 - High risk protocols
- **Voluntary?**

Standard of Care?

- Is commonly and widely accepted range of diagnostic interventions; preventive and curative treatments (or lack of them) for any given disease is called a standard of care
- Such a standard of care is routinely available to only a small proportion of the world's population
- A standard of care may be different between the developed and developing world; different within a country e.g. urban and rural areas; may be different between hospitals e.g. Private and public sector hospitals

WMA Helsinki Declaration 2000 on Standard of Care

“The benefits, risks, burdens and effectiveness of a new method should be tested against the best current prophylactic, diagnostic and therapeutic methods”

Paragraph 29

CIOMS/WHO Guidelines

‘If there is already an approved and accepted drug for the condition that a candidate drug is designed to treat, placebo for controls usually cannot be justified’.

Commentary on Guideline 14

Issues of Standard of Care in Research

- What standard of care should be provided to control arm in research?
- When does an intervention become a standard of care?
- Is there a universal standard of care?
- Universal standard of care or local standard of care?
- Does allowing local standard of care means exposing vulnerable populations to exploitation?
- Most cases the local standard may be nothing. Does this mean placebo should be provided to control arm?
- Is the researchers responsibility the same in clinical & epidemiological studies?

Issues of Standard of Care in Research

- Should there be minimal standard of care or a national standard of care?
- Should externally sponsored research be expected to provide the standard of care of the sponsoring country ?
- Should researcher from premier institutes doing research in rural areas be expected to provide the care at the level of their hospitals?
- Or should the standard of care be contextual?

Marcia Angell set out at least three principles: one concerned with the importance of **avoiding the exploitation** of people in developing countries; one concerned with the **responsibilities of researchers** and sponsors of research; and one concerned with the need to **avoid making the standard of care depend upon the local context**

Angell M. Investigators' responsibilities for human subjects in developing countries. **New England Journal of Medicine** 2000;342(13):967-9.

Standard of Care

- Universal standard of care = if NOT attainable- and many believe despite guidelines that it is not attainable
- There are no national standards of care as there are; urban and rural; public and private sector differences in care and we all know the lowest standard of care or nothing exists in the public systems of developing countries
- Recommendations suggest that for, externally-sponsored research, the level of care that ought to be offered to participants should, as a minimum, be the standard that the country endeavors to provide nationally and if they provide less than they need to justify to local ethics committees

Does it not make a mockery of everything and does it not open doors to exploitation and leaving it on to local ethics committees to decide.....?

Post Trial Access

Helsinki Declaration 2002

“Medical research is only justified if there is reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.”

Commentary on CIOMS

“As a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research will be made reasonably available to the inhabitants of the host community or country at the completion of the successful testing. Exceptions to this general requirement should be justified and agreed to by all concerned parties before the research begins.”

Guidelines 8 & 15

Post research benefits

- Guidelines narrowly focused on clinical trials
 - All types of research should be included
- Phase II/III trial
- Affordability/Accessibility
- Participants to receive life long treatment
 - Acute vs. chronic diseases
 - Trial participants – Subjects/controls/community
 - Registered/Unregistered drug/Compassionate use
 - How long? Who pays?
- Inducement to participate
- Practically and feasibility

Post research benefits

- All agree that some benefits should accrue to the subjects/Communities – Exploitation?
- Drugs/Vaccines/other interventions/local capacity building/health center/value
- Benefits to be negotiated before by ERB's & Govt's
- Bargaining/strict with externally funded research
- Double standards/Lack of consistency
- Mechanisms whereby prevent ERB Shopping – How?

Ethical Review Processes

- ERB's ???
- Independent ??
- Competent ??
- Capacity ??
- National Guidelines ??
- Monitoring ????
- ERB Audits ????

AKU & HSPH Study

- Questionnaire based study
- Institutions 25
- Non Responders 12
- Responders 13 = 10(No)+3(Yes)
- Only one ERB which was actually functioning according to the internationally recommended guidelines
- Ghost ERB's

AKU Ethics Review Board

12 Members

AKU staff

- Clinicians 3
- Nursing 1
- Epidemiologist 1
- Social Scientist 1
- Pharmacist 1
- Hospital Admin 1
- IED 1

Public Members

- Lawyer 1
- Journalist 1
- Judge 1

Sub-Committee of URC

Reports to URC

Ethics Review Boards

- Every guideline has dumped the final decision on all contentious issues in the hands of the local ERB's
- There is lack of capacity and expertise to have quality reviews in developing countries
- They are under lot of pressure and their independence is questionable
- Recommendation are to strengthen this area by major capacity building exercise
- But what happens to the other part of my question.....Independence of ERB's?

Silver lining

- Capacity building measures
 - Fogarty International Center, NIH, USA
 - Wellcome Trust, UK
- NIH & CDC have now a requirement to have ERB's approved for their sponsored research
- Members expected to undergo an online evaluation of research ethics understanding
- More and more international Medical Journals now require ERB approvals
- Bioethics is now part of many curricula of medical schools in developing countries
- National/institutional guidelines/policies

Independence.....???

So where do we stand with all these guidelines?

- There are over a dozen international guidelines and what difference have they made?*
- Has the research ethics world become more ethical?*
- Will there be repeat of anymore unethical studies or have all this noise over last 5 years with plethora of guidelines put an end to miscreants?*

I think nothing much has changed or will change only the issues have been brought to the forefront, the focus and responsibility has shifted to local ERB's

Geographical Morality

- Global Health Inequities – the 10/90 gap – Huge burden of disease and poor health outcomes - all so glaringly linked to economic growth and development
- Illiteracy
- Poverty

Unless these real issues are not sorted out the cosmetic debate on the issues and the language & semantics of recommendations or guidelines is not going to change anything

Thank you