ETHICS IN RESEARCH

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EDUCATION/TRAINING:

- Certificate on Flagship Course of Pharmaceutical Policy Reform, UK Department of International Development, World Bank and Harvard School of Public Health
- National University of Singapore *Outcomes Research and Pharmacoeconomics Training*
- Asian Institute of Management *Business Leadership Program*
- UP-PGH Department of Medicine Section of Cardiology *Fellowship Training in Cardiology*
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PRINCIPLES OF BIOMEDICAL ETHICS

- Respect for persons
- Nonmaleficence
- Beneficence
- Justice

RESPECT FOR PERSONS

- ***Respect for autonomy:*** those who are capable of deliberation about their personal choices should be treated with respect for their capacity for self-determination
- ***Protection of persons with impaired or diminished autonomy:*** those who are dependent or vulnerable should be afforded security against harm or abuse

NON-MALEFICENCE

- ***"Primum non nocere."***

- Non-infliction of harmful acts that may impair health or survival or lead to mental distress or loss of privacy

BENEFICENCE

- Potential benefits to subjects and to society should be maximized
- Protection of the welfare of patients and subjects, as well as the promotion of the common welfare
- Balance potential harms against potential benefits

JUSTICE

- ***Distributive justice:*** equitable distribution of both the burdens and benefits of participation in research

- ***Equity and fairness***

CODES OF CONDUCT FOR MEDICAL INVESTIGATIONS

- Nuremberg Code (1947)
- Declaration of Geneva (1948/1961)
- Declaration of Helsinki (1964/1989/2000)
- CIOMS & WHO: Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects (1982)
- Ethics guidelines for epidemiologists (1990)

CIOMS – Council for International Organizations of Medical Sciences – formed jointly by WHO and UNESCO in 1949

NUREMBERG CODE 1947

- Set of research ethics principles for human experimentation set as a result of the subsequent Nuremberg Trials at the end of WW 2
- Verdict in the “Doctors’ Trial” was delivered on August 19, 1947
- Opinion on medical experimentation on human subjects

NUREMBERG CODE 1947

1. Voluntary consent of the human subject is absolutely essential
2. The experiment should be such as to yield fruitful results for the good of society
3. The experiemnt should be so designed and based on the results of animal experimentation and knowledge of the natural history of the disease that the anticipated result will justify the performance of the experiment
4. Should be conducted as to avoid all unnecessary physical and mental suffering and injury

NUREMBERG CODE 1947

5. No experiment should be conducted where there is prior reason to believe that death or disabling injury will occur except where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment
7. Proper preparations should be made and adequate facilities provided to protect the subjects
8. Should be conducted only by scientifically qualified persons

NUREMBERG CODE 1947

9. During experiment, human subjects should be at liberty to bring the experiment to an end if he has reached the physical and mental state where continuation of the experiment seems to him to be impossible

10. During the course of the experiment, the scientist in-charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe that continuation might result in injury, disability, or death to the experimental subject

DECLARATION OF HELSINKI (1964, 1989, 2000)

- Set of principles regarding human experimentation developed by the World Medical Association (WMA)
- Considered as the cornerstone document of human research ethics
- Fundamental principles: respect for the individual, right to self-determination and the right to make informed decisions regarding participation in research

GENERAL OBSERVATIONS

- Unethical trials occurred in both developed and developing countries. In some cases, trials not approved by an ethical review committee/institutional review board
- Research organizations involved range from relatively unknown local companies to leading multinational corporations.
- Some of ethical trials are of recent dates (2005 or later)
- Nature of ethical concerns are diverse and relates to all paragraphs as specified in Declaration of Helsinki (DoH).

ETHICAL NORMS

Reference: Declaration of Helsinki (DoH) of the World Medical Association)

- Vulnerable research populations require special protection.
- Research must be based on knowledge of laboratory and animal experimentation.
- The protocol for clinical trials should be reviewed by an independent ethical review committee. The researchers must report any serious adverse events to this committee.
- The design of all studies should be publicly available.
- Investigations should be ceased if the risks are found to outweigh the potential benefits.
- The 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.
- Participation in a trial must be voluntary and participants must be informed.

Continuation..

- Physicians should obtain freely-given informed consent from each participant
- Subjects who cannot provide informed consent themselves, for example children, should only be included in the research cannot be performed on other subjects instead.
- The benefits, risks, burdens and effectiveness of a new therapy should be tested against those of the best currently available therapy. Placebo-controlled trials are only allowed if not proven therapy exists or under special circumstances.
- At the conclusion of the study, all trial participants should be assured access to the best proven therapy identified by the study. Post trial access arrangements must be described in the trial protocol.
- When medical research is combined with medical care, the physician should inform the patient which aspects of the care are related to the research.

Unethical Trials Documented

- ART treatment interruption trials: Uganda, Zimbabwe, Cote d' Ivoire (2003-2006)
- Tenofovir trials on HIV transmission: Cameroon, Thailand, Nigeria (2004-2005)
- Hepatitis E vaccine trial in Nepal: Kathmandu, Nepal (2001-2003)
- Nevirapine PMTCT trials in Uganda: Uganda (1997-2003)
- SFBC Miami Test Centre: Miami, US (2000-2005)
- Letrozole trials: India (2003)
- Alosetron trials after marketing withdrawal: Various countries (2000)
- Streptokinase trials : Hyderabad, India (2003)
- Fortified ORS trials: Two hospitals in Peru (2004-2005)
- Risperidone trials: Gujarat, India (Probably, 2003)

Unethical Trials Documented

- VGV-1 trials: Ditan Hospital, Beijing (2003)
- TGN 1412 trials: London, UK (march 2006)
- Imatinib trials: S. Korea, HK, etc. (2001-onwards)
- Ragaglitazar trials: 32 countries including India (2002)
- Trovafloxacin trials: Kano, Nigeria (1996)
- Cilansetron trials: India (probably 2000)
- Trials on foster care children: NY, USA (1997-2002)
- Maxamine trial: Russia, Israel, Belgium and UK (around 2000)
- Cilostazol trials: India (probably1999)
- NDGA trials: Trivandrum, India (1999-2000)
- Cariporide trial: Nava Hospital, Buenas Aires, Argentina

ANTI-RETROVIRAL THERAPY (ART) TREATMENT INTERRUPTION TRIALS

Uganda, Zimbabwe & Cote d'Ivoire; 2002-2006

- DART was open, randomized trial to compare standard continuous therapy (CT) with structured treatment interruption (STI) of 12 weeks on and 12 weeks off ART.
- It recruited 3,000 volunteers
- On 14 March 2006, it was decided that all patients in the STI arm of the trial would be switched to continuous therapy as interim data demonstrated they had a greater rate of clinical HIV-related disease.

Unethical Aspects

- Relatively high number of fatalities in STI arm in Uganda but investigators said the critics' concerns are unfounded.
- Complaints on patients' enrollment who are desperate to get free treatment, insufficient arrangements for post-trial treatment access, the use of a drug regimen not readily available and omission of impt. risks in the consent forms
- Similar concerns apply to the Strategies for Management of ART (SMART) trial. Treatment interruption was associated with higher risk of disease progression
- Trivacan is another ART trial with two treatment interruption arms. It enrolled 840 patients in Cote d' Ivoire since 2002 and still ongoing.

Violated Norms

- Investigations may not have been ceased in time after a negative risk/benefit balance for STI was identified
- The population in w/c the research was carried out might not benefit from the results of the study, as tenofovir is not readily available in Uganda and Zimbabwe
- Voluntary informed consent was obtained for each patient but may have been compromised by patients desperate to get access to free treatment
- Post-trial access arrangements were unclear and not described in the trial protocol. This also inhibit patients to leave the trial.

Outcome

- Investigators denied lethal side effects of treatment interruption and ethical shortcomings
- An international workshop to discuss the conduct of STI and intermittent therapy trials was held in July 2006
- A review of available evidence confirmed that some trial participants were at increased risk of adverse events including death
- Concluded that STI trials cannot be recommended until the findings from past trials have been better understood.

TENOFOVIR TRIALS ON HIV TRANSMISSION
Cameroon, Thailand & Nigeria (2004-2005)

- **Cameroon:**
- Five women became HIV-infected while enrolled in the Tenofir-study.
- 400 sex workers participants t in the trial not adequately informed on the risks and only English info was given to mostly French-speaking volunteers
- Lack of ARVs for patients infected during the trial
- **Thailand**:
- Community groups not consulted about the trial design and conduct until a very late stage
- Intravenous drug users participating in the trial won't have access to free, clean syringes through needle exchange programs
- In case drug is effective, researchers not ensured a roll over study to take care of trial participants
- Only one year of free post-trial access was negotiated, even though at least two years of post-trial drug would be the norm.
- **Cambodia:**
- Local union of sex workers protested of insufficient medical insurance for trial participants

Violated Norms

- Vulnerable subjects may not have received the required special protection
- Participants had not been adequately informed
- Post-trial access arrangements were insufficient

Outcome

- Trials were cancelled in Cameroon in 2005 and in Cambodia in 2005.
- Impending study in Nigeria was also cancelled. Community groups asked for establishment of broad committee to address HIV issues, involvement in trial outreach and education & ensuring at least two years of post-trial tenofovir access to trial participants.

TRIALS ON FOSTER CARE CHILDREN
New York; (1997-2002)

Unethical Aspects

- Phase I & II trials conducted on HIV-infected children & infants in the guardianship of NY Agency for Children's Services. Children were forced to take the experimental medication that made them severely ill and had potentially lethal side effects.

Violated Norms

- Children were vulnerable subjects & did not receive required protection
- Research shouldn't have been performed on children w/o justification
- The US Code of Federal Regulations prohibits the use of children who are wards of the state to experiments involving greater risks

Outcome

- Trials halted in 2002. Investigation confirmed non compliance with legal regulations

What is GCP ?
Good Clinical Practice

“A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.”

GCP APPLIES TO ALL RESEARCH

- ***All investigators:*** commercial, non-commercial clinical trials
- ***All sponsors:*** private, government, university, industry
- ***All study designs:*** double-blind, open-label, comparator, etc
- ***All study phases:*** Phase I to IV
- ***All investigational products:*** new drugs, new indications, biomedical device, new methodology, new surgical techniques, etc

FDA REGULATIONS

21 CFR (Code of Federal Regulations)

- Part 50 – Protection of Human Subjects
- Part 56 – IRB
- Part 312 - Investigational New Drug (IND)
- Part 314 - New Drug Application (NDA)
- Part 601 - Biologic License Application (BLA)

FDA GUIDANCE

- Compliance Program Guidance Manuals
  - Sponsors, CROs and Monitors – 7348.810
  - Clinical Investigators - 7348.811
  - Institutional Review Board (IRB) - 7348.809
- Guideline for the Monitoring of Clinical Investigations
- Information Sheets
  - Informed consent

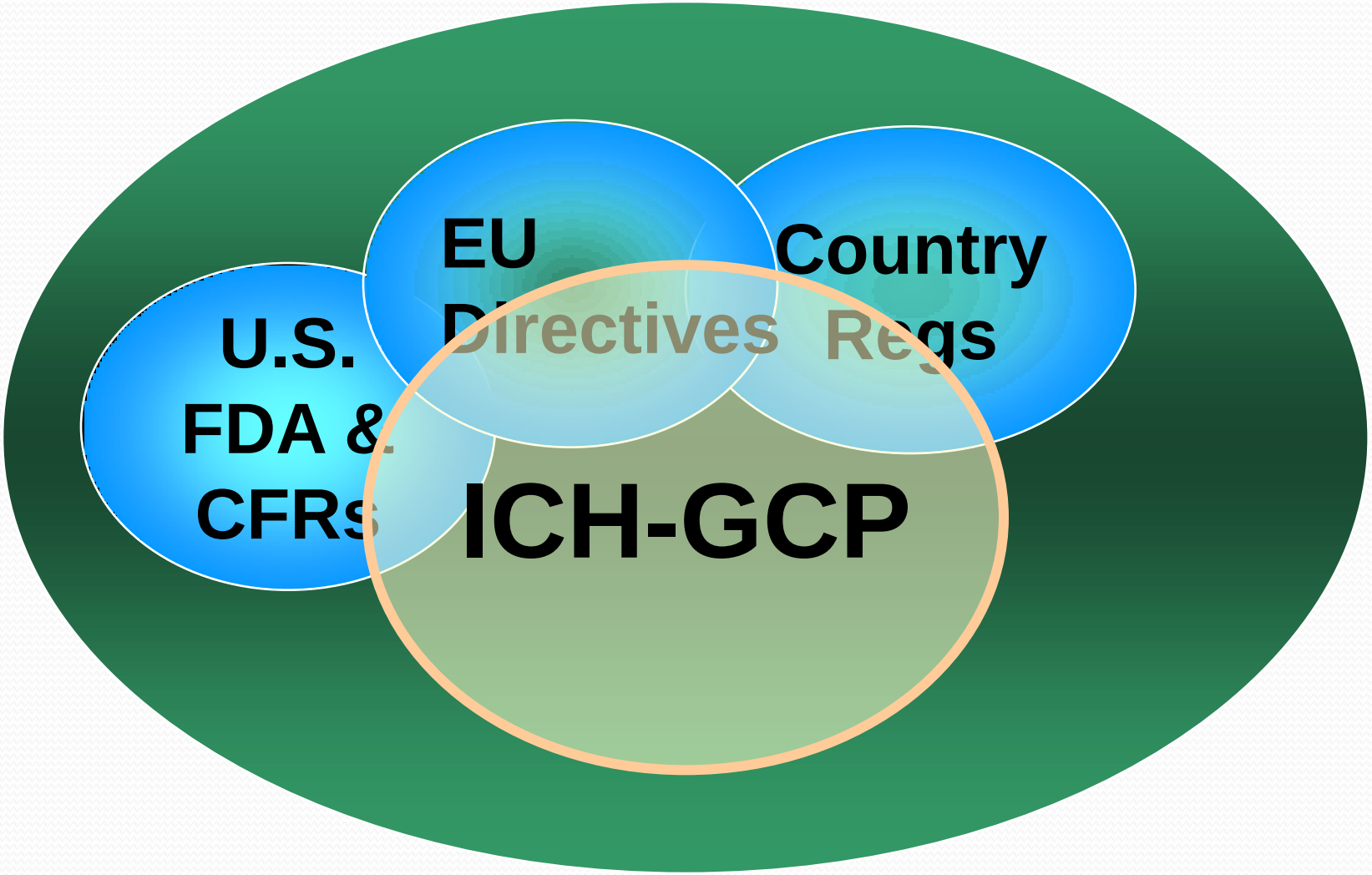
EUROPEAN LEGISLATIONS

- European Clinical Trial Directive 2001/20/EC and associated guidance documents
- European GCP Directive 2005/28/EC and associated guidance documents
- European Directive 2003/94/EC (GMP Investigational products)
- Annex 13 to Good Manufacturing Practice (GMP)
- Local legislation

GLOBAL ETHICAL STANDARDS

- Declaration of Helsinki
- CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects

GCP: THE MINIMUM REQUIREMENTS



however……GCP is a process, not just a book

ICH Harmonized Tripartite Guidelines for Good Clinical Practice (ICH-GCP)

- Introduced in 1996
- Provided pharmaceutical companies and investigators with a framework for conducting clinical trials -
  - Globally,
  - Following the same requirements,
  - Conforming to high ethical and scientific standards.

INFORMED CONSENT

To understand:

- Purpose and intent of Informed Consent
- Requirements for Informed Consent process
- Required elements of the Informed Consent Form
- Requirements for documenting Informed Consent

INTERNATIONAL CONFERENCE ON HARMONIZATION (ICH)

ICH-GCP

Section 4.8.1 - 4.8.15 which references originating from Declaration of Helsinki

INFORMED CONSENT

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 Guideline for GCP 1.28

INDIVIDUAL INFORMED CONSENT

For all biomedical research involving subjects, the investigator must obtain the ***informed consent*** of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the ***proxy consent*** of a properly authorized representative.

INFORMED CONSENT PROCESS

Intended to:

- Give a subject all the information he or she reasonably would want about a study
- Ensure that the subject understands this information
- Ample time and opportunity to consider the information and decide
- All questions to be answered to patients satisfaction
- Updated information provided

ELEMENTS OF INFORMED CONSENT

- ***Disclosure*** –adequate disclosure of information enabling the patient to make an informed choice
- ***Understanding*** – ability to understand what he/she is told to make a reasoned choice
- ***Consent*** – voluntary decision or agreement on the part of a capable person

VOLUNTARINESS

- He/she wills the action without being under the control of another influence
- Categories:
  * coercion
  * persuasion
  * manipulation

CATEGORIES OF INFLUENCE

- ***Coercion:*** when one intentionally uses a credible and severe threat of harm or force to control another
- ***Persuasion:*** convinced through merit of reasons advanced by another person
- ***Manipulation:*** various forms that are neither persuasive nor coercive

INFORMED CONSENT: Essential information

- language that patient can understand
- invitation to participate; aims/methods
- expected duration of participation
- benefits to subject or others as an outcome of the research
- foreseeable risks or discomfort
- alternative procedures or courses of treatment that might be as advantageous, associated with participation in the study

INFORMED CONSENT: Essential information

- Confidentiality
- Extent of investigator's responsibility, if any, to provide medical services
- Therapy to be provided free-of-charge for specified types of research-related injury
- Compensation for disability or death resulting from such injury
- Freedom to refuse and to withdraw at any time without penalty or loss of benefits

INFORMED CONSENT FORM

- Must include
  - ICH-GCP required elements
  - other applicable requirements
- Must be approved by IRB/IEC and Sponsors prior to use
- New written Informed Consent may be required

WRITTEN INFORMATION

- Must be understandable to the subject
  - practical
  - nontechnical
  - in the subject's language
- May not cause subject to waive legal rights

INFORMED CONSENT: Investigator's Obligations

- give subject full opportunity and encouragement to ask questions
- exclude possibility of unjustified deception, undue influence, intimidation
- seek consent only after adequate information given
- ***General rule: signed form***
- renew informed consent if there are material changes in the conditions or procedures of the study

INFORMED CONSENT: SIGNATURES

- Consent form must be signed and personally dated by the:
  - subject (or subject's legal representative)
  - person who conducted the informed consent discussion
- Subject should receive a copy of the signed informed consent form and any updates

INFORMED CONSENT: SIGNATURES

- Subject's legal representative can sign for subject if:
  - subject not legally competent
  - emergency situations

  Local laws must be followed.

- If subject, or legal representative, is unable to read, an impartial witness must be present and must sign and date the ICF to confirm the process

INFORMED CONSENT: VULNERABLE SUBJECTS

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy, in case of refusal to participate.

VULNERABLE SUBJECTS

- Children
- Persons under discipline (soldiers, army, police)
- Laboratory assistants
- Medical students
- Ethnic minorities
- Persons in nursing homes
- Those mentally incapacitated (poor understanding)
- Persons with incurable diseases or in emergency situations
- Those economically disadvantaged (unemployed, impoverished, homeless, nomads, refugees)

INDUCEMENT TO PARTICIPATE

- subjects may be paid for inconvenience and time spent
- reimburse them for expenses incurred in connection with participation
- may also receive free medical services
- ***But: not "undue inducement"***
- all payments, reimbursements, medical services provided to subjects should be approved by an ethical review committee

INFORMED CONSENT

- Informed Consent process is a fundamental way to protect subjects
- Investigator may delegate but is ultimately responsible
- Informed = understood
- Process begins when subject is first contacted

CONFIDENTIALITY & PRIVACY PROTECTION

PRIVACY

- withdraw from public view
- having control over what one discloses and withholds

CONFIDENTIALITY

- being entrusted with private/secret matters
- breach: failure to protect the info or deliberately disclosing it to someone without consent

CONFLICT

- responsibility to keep the info secret -vs-
- legal or moral duty to reveal to 3rd parties

Depends on:

- balance of the nature and magnitude of public benefit
- degree of restriction of individual rights
- distribution of both benefits and risks

SUGGESTIONS FOR PRIVACY PROTECTION

- remove all identifiers
- limit access for clinical purposes only
- obtain prior consent for any other user/s
- passwords and encryption
- direct receipt of faxed outputs
- prominently mark material as confidential
- regularly re-emphasize & train study personnel in confidentiality procedures

RCT's & EQUIPOISE

- genuine uncertainty about the comparative therapeutic merits of each treatment arm in a clinical trial
- ***Clinical equipoise:*** based on the available data, a community of physicians would be content to have their patients pursue any of the treatment arms in an RCT, since none of them has been clearly established to be preferable
- control arm: best available standard Rx

SUMMARY

- risks to subjects are minimized and proportionate to the anticipated benefits & knowledge
- data are monitored to ensure safety
- selection of subjects is equitable
- if subjects are vulnerable, additional safeguards are included
- informed consent is obtained
- confidentiality is adequately protected