


Guidelines & Documents on the ethical aspects of clinical trials

Dr Melba Gomes
World Health Organization
Tropical Disease Research

Codes and Guidelines

- Nuremberg Code (1949)
 - Declaration of Helsinki (1964-2000, 2008)
 - Council for International Organizations on Medical Guidelines: CIOMS (1993, 2002)
 - International Conference on Harmonization - Good Clinical Practice (ICH-GCP)
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Development of ethical principles in research: response to poor practice

- Nuremberg Code of medical ethics - response to medical experiments -Nazi prisoners - precursor of Dec. of Helsinki
- Development /Agreement of principles that protect vulnerable people from exploitation & harm in research

- **Vulnerable because**

traumatized/comatose

terminally ill

elderly/aged

minorities

normal volunteers

poor, homeless

developing country population

unfamiliar with medical concepts

medical /nursing students

politically powerless

armed forces/police

unemployed

nomads, refugees, displaced

prisoners

patients with incurable disease

subordinate hospital/lab personnel



GCP- Objectives of ICH guidelines

- Unified standard - for research underpinning drug registration
 - EU, US, Japan
 - Facilitates mutual acceptance & clinical assessment
 - Consistent with existing standards in US, EU, Australia, Canada, Nordic Countries, and WHO
 - Guides conduct + enables assessment + evaluation & interpretation of clinical trial data
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Ethical oversight

- 1964 - Declaration of Helsinki - first reference standard for research on human subjects; 6 revisions to 2008
- Difference between Declaration of Helsinki & GCP

Requirements in last Declaration of Helsinki, absent in ICH-GCP

1. Investigators must disclose funding, sponsors & any conflicts of interest to IRBs (Ethics Review Committees) & in Informed Consent to study participants
2. Study design is publicly disclosed & results published - hence clinical trial registries
3. Research to benefit, and be responsive to health needs of, populations in which research is done
4. Restricted use of placebo controls even where there is no practical access - eg iv drugs, costly drugs in developing countries
5. Post-trial commitment to treatment access
6. Authors to report results accurately, and make public negative findings



Council for Int. Organizations of Medical Sciences

CIOMS Ethics Guidelines supplements DoH- for developing countries.

Differs from Declaration of Helsinki on placebo use ...

" ... it may be ethically acceptable to use an alternative comparator - placebo or no treatment" - when:

1. there is no established effective intervention
2. withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in symptom relief
3. using an established intervention as comparator would not yield reliable results & placebo would not add any risk of serious or irreversible harm
4. exceptional use .. the comparator is not available or likely to be available for economic /logistical reasons.. eg MOH tests an affordable intervention relevant to local population vs placebo, AS LONG AS -rights & safety of subjects are safeguarded.

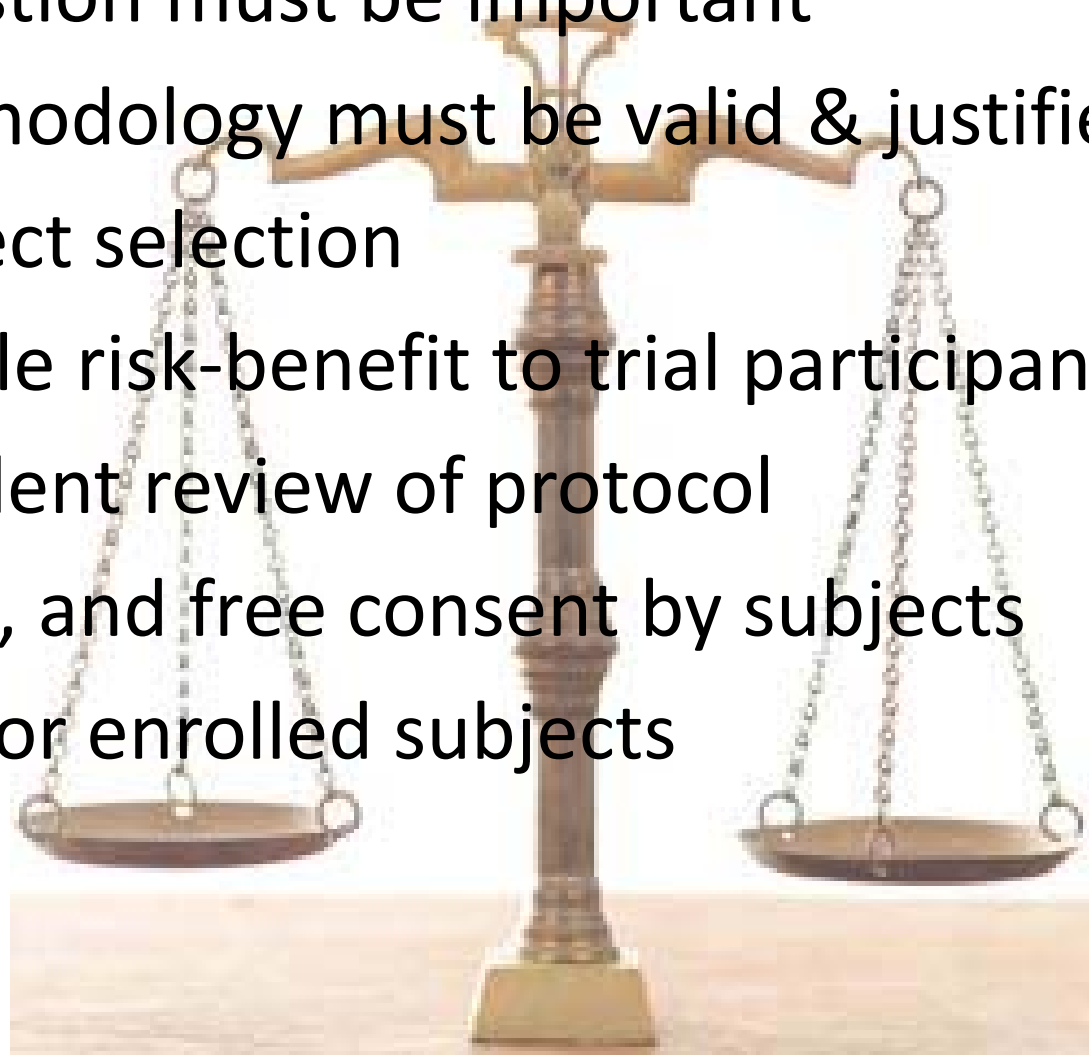
Common principles in Guidelines: Science & Ethics are linked

- *A clinical trial is not justified ethically* unless capable of producing scientifically reliable results
- *A clinical trial is not justified scientifically* unless executed ethically - ie protects trial participants from exploitation and harm
- **Poor ethics oversight invalidates trial results**
 - from Ethics Committee - membership, COI
 - from trial investigators- competence, procedures



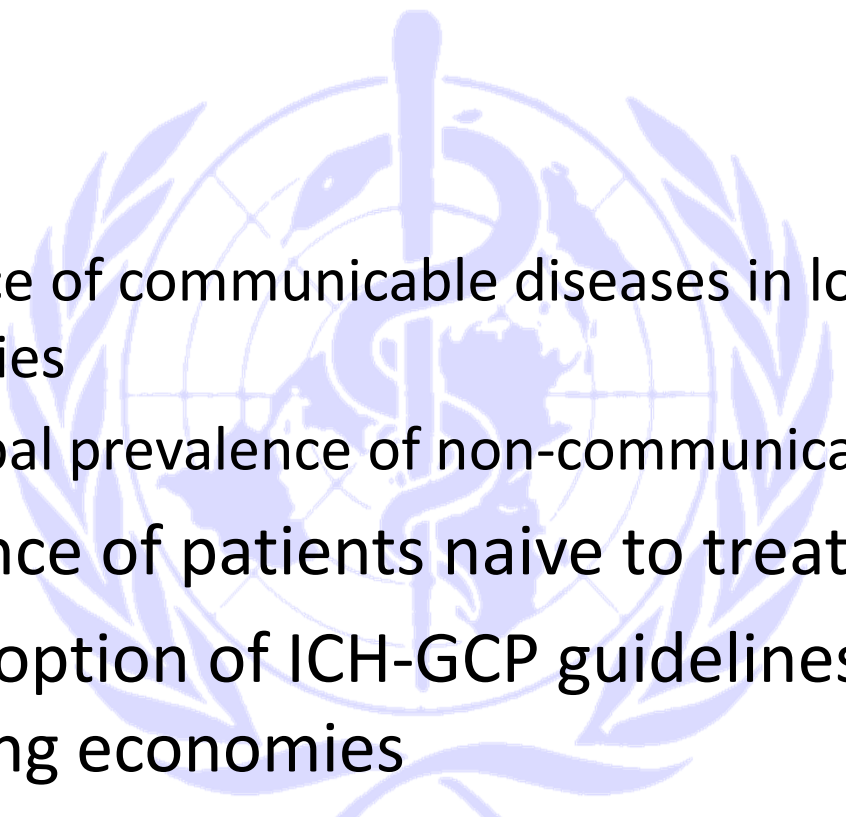
Common principles in Guidelines: Science & Ethics are linked

- Trial question must be important
- Trial methodology must be valid & justified
- Fair subject selection
- Favourable risk-benefit to trial participants
- Independent review of protocol
- Informed, and free consent by subjects
- Respect for enrolled subjects



Why are ethical guidelines important?

Why is ethics oversight important?

- Increased number of clinical trials in developing countries
 - Last decade
 - Cost savings :
 - High prevalence of communicable diseases in low/middle income countries
 - Increasing global prevalence of non-communicable diseases
 - Higher prevalence of patients naive to treatment
 - Widespread adoption of ICH-GCP guidelines increases trials in emerging economies
 - All this increases responsibility of IRBs & regulatory bodies in participating countries
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Increased No of FDA- NDA submissions based on non-US clinical trial data

Table 1: FDA Marketing Applications for Drugs and Biologics Containing Clinical Data Approved in FY 2008

Marketing Applications	Drugs	Biologics	Drugs and Biologics
Applications With Only Domestic Data	15	9	24
Applications With Foreign and Domestic Data	82	5	87
Applications With Only Foreign Data	9	1	10
Totals	106	15	121

Note: These numbers are based on 121 applications with sufficient information to determine whether the data were foreign or domestic.

Source: OIG analysis of FDA marketing applications approved in FY 2008.

Increased No of FDA- NDA submissions based on non-US clinical trial data

Table 2: Number and Percentage of Foreign Subjects and Sites From Clinical Trials Supporting Drug- and Biologic-Marketing Applications Approved in FY 2008

	Drugs	Biologics	Drugs and Biologics
Number of Foreign and Domestic Subjects	92,859	208,842	299,701
Number of Foreign Subjects	52,820	179,712	232,532
Percentage of Foreign Subjects	56.9%	86.0%	77.6%
Number of Foreign and Domestic Trial Sites	11,227	717	11,944
Number of Foreign Trial Sites	6,129	358	6,485
Percentage of Foreign Trial Sites	54.6%	49.7%	54.3%

Note: These numbers are based on data from 193 clinical trials with complete subject and site information.

Source: OIG analysis of FDA marketing applications approved in FY 2008.

FDA regulation of foreign trials

- Today FDA explicitly relies on ICH-GCP, not Helsinki
- Trial conduct under ICH-GCP, 21 C.F.R - which refers to Helsinki
- FDA requires that foreign trials be allowed FDA inspection
- For scientific data to be accepted ethically, FDA requires adequately constituted Ethics Review Committee
 - at least 5 members
 - at least 1 independent member
 - evidence protocol used was reviewed before trial commencement
 - evidence of voting without Conflict of Interest
 - diverse background
 - maintenance of IRB records for inspection
- Adequate maintenance of trial records for inspection

ICH GCP Principles of the Informed Consent Process

- Prior written IRB/IEC approval of the consent form + other information given to participant
- IC process must be free of coercion or undue influence
- The investigator must provide ‘want to know’ information, including risks and benefits
- Clinical trial information must be presented in a way that ensures understanding
- Subjects must have adequate time to ask questions and get answers

Informed Consent- Principles

- Disclosure of information
- Understanding
- Voluntary
- Authorized
- Respect
 - Protect confidentiality
 - Monitoring welfare
 - Right to withdraw
 - Provide new information
 - Informing re findings
 - Post trial planning



Links to more information

- <http://www.wma.net>
 - <http://www.cioms.ch>
 - <http://ohrp.osophs.dhhs.gov>
 - <http://ohsr.od.nih.gov/>
 - <http://www/fda.gov>
 - <http://cme.nci.nih.gov/>
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