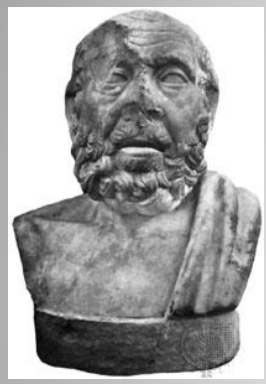
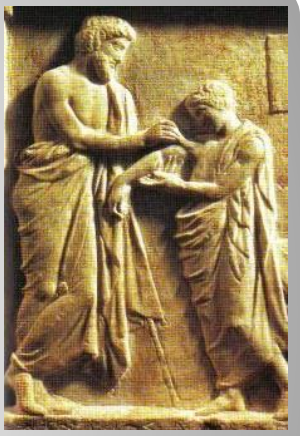


Thus, if anyone were able to light upon the truth by experiment…he would always be able to make the best pronouncements of all.
Hippocrates, Medicine, 420 BCE



Research with Human Participants: **IRB duties**

Steven H. Miles, Department of Medicine,
Center for Bioethics of the University of Minnesota.
SHM has no financial interests to declare.
No commercial products are mentioned
Content updated August 10, 2016.

Institutional Responsibilities for Ethical Research

- IRB Powers and Reviews
- Conflict of Interest
- Case Report Confidentiality
- Clinical Trial Registries
- Data Safety Monitoring
- Community Consent
- Avoiding Exploitation of Subjects and Host Countries
- Research Misconduct

Objectives:

IRB Functions and Operations

IRB Review

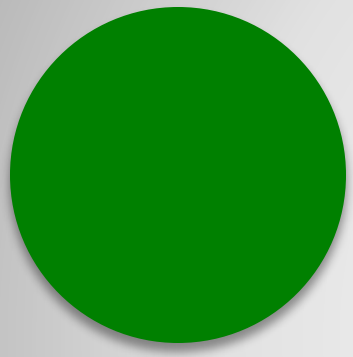
An IRB:

- Reviews and has authority to approve, require modifications to or disapprove all NIH studies.
- Note there are separate IRB rules for pregnant women, prisoners, animals.
- Notifies investigators and the institution of its decisions and gives the investigator an opportunity to respond in person or in writing.
- Reviews all studies, as appropriate to the degree of risk, but not less than once per year.

IRB Reviews

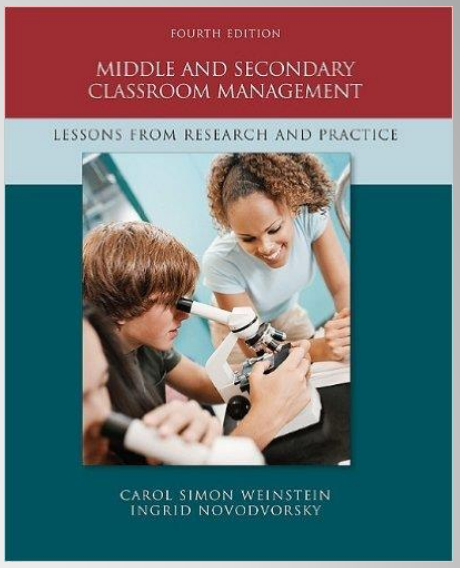
- Requires information given to subjects as part of informed consent.
- May observe or have a third party observe the consent process and the research.
- Requires documentation of informed consent or may waive documentation.
- May require a *Data Safety Monitoring* (DSM) plan with regular review of adverse events.

Exempt **Expedited** **Full Review**



The IRB, not the researcher, determines whether a project is exempt from IRB review.

- Research in schools of normal practices (e.g., studying instructional techniques or classroom management).



- Research with anonymous cognitive, diagnostic, aptitude, or achievement tests, surveys, interviews or observations of public behavior **unless subjects can be identified and disclosure places them at risk of criminal or civil liability or damage their financial standing, employability, or reputation.**

Situationally Exempt Research

Not more than *minimal risk.*

Minimal risk: the probability and size of anticipated harm/discomfort not greater than routine exams or tests.

Usual informed consent Requirements.

AND:

Noninvasive

- No sedation, x-rays, etc.)
- Hair, nail clippings, saliva, sweat, postpartum placenta, or blood collected by finger/heel/ear stick or venipuncture (volume restrictions).
- Research with data or specimens collected for non-research purposes.

AND:

Confidential when identified subjects would be put at risk of criminal or civil liability or damage to their financial standing, employability, insurability, reputation, etc,.

Expedited Review Criteria

The IRB (not the researcher) decides whether research is exempt or expedited.

The IRB may require full review of a study that seems to fit rules for "exempt" or "expedited" review.

IRB-Not Researcher Decides

Full IRB Review

Criteria for IRB Approval

IRB Risk Criteria

1. Risks are minimized:

   (i) by procedures consistent with sound research design

   (ii) when appropriate, procedures are already being performed for diagnostic or treatment purposes.

2. Risks are reasonable in relation to anticipated benefits.

   The IRB considers only risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).

   *The IRB should **not** consider.long-range effects of applying knowledge gained in the research as a benefit to the subject*

3. Selection of subjects is fair (e.g., enrolling and protecting vulnerable participants.)

4. Informed consent is properly obtained and documented

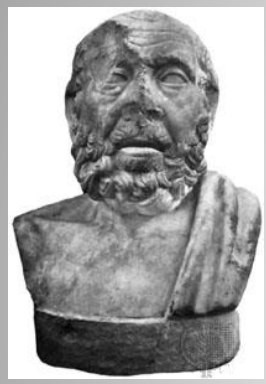
6. The research plan has data monitoring to ensure safety of participants.

7. There are provisions to protect the privacy of participants and the confidentiality of data.

IRB Participant Criteria

- IRB may suspend or terminate approved research that
  - Is not conducted in accord with IRB's requirements or
  - Is associated with unexpected serious harm to subjects.
- Suspension or termination shall be reported promptly to
  - Investigator and
  - Institutional officials and
  - NIH department or agency.

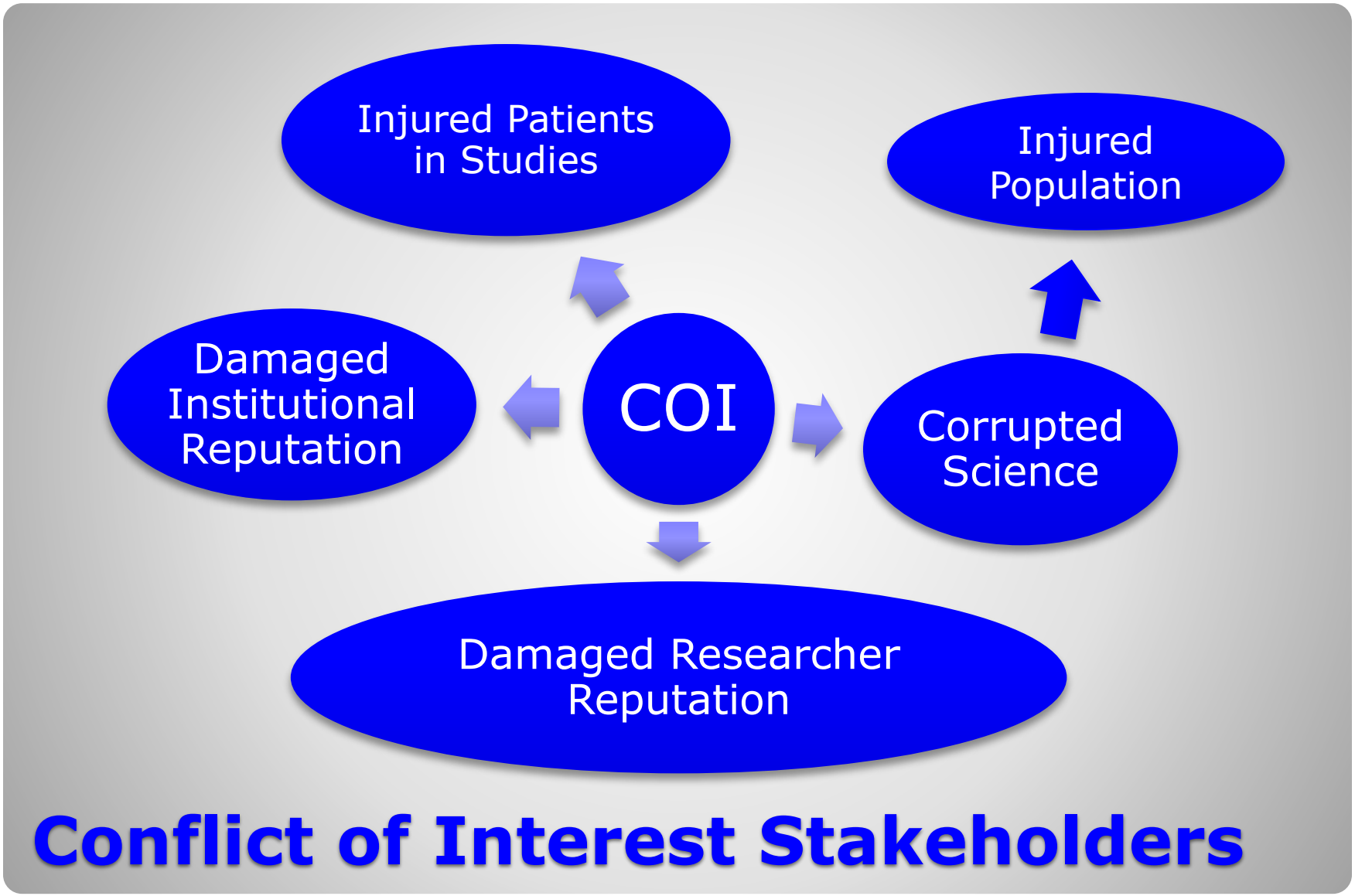
Suspension or termination of IRB approval.



In a pure and holy way, I will guard my life and my science.

Hippocrates, Oath, 420 BCE

Standards for Research with Human Participants: **Conflicts of Interest**.



Conflict of Interest Stakeholders

Conflict of Interest

- A "**Conflict of Interest**" is when a researcher is studying a product or process in which:
  - He/she or her/his spouse or minor children have a significant direct financial stake in the outcome of the research
  - The researcher is officer, director, trustee, business partner, employee of the public or private entity that has a financial interest in the outcome of the research,
  - The researcher is negotiating for prospective employment or has an arrangement for prospective employment.

NIH: Conflict of Interest

- **Real conflict**: an employee participates personally and substantially in matters that have a direct and predictable effect on a financial interest of the employee.
- **Appearance of a conflict**: an employee is involved in a particular matter involving specific outside parties under circumstances *where a reasonable person would question the employee's impartiality in the matter*. Such circumstances might include the involvement of a relative or former employer in the matter.
- Employees who have financial interests must disclose any conflict and work with the Ethics Coordinator to obtain a waiver or authorization, or be disqualified from participating in particular matters concerning the outside entity
  - https://ethics.od.nih.gov/Topics/coi.htm

Bounties and Finder's Fees

Bounties

- Capitation of fees based on numbers of subjects to research institutions for testing products.
- $5,000-10,000

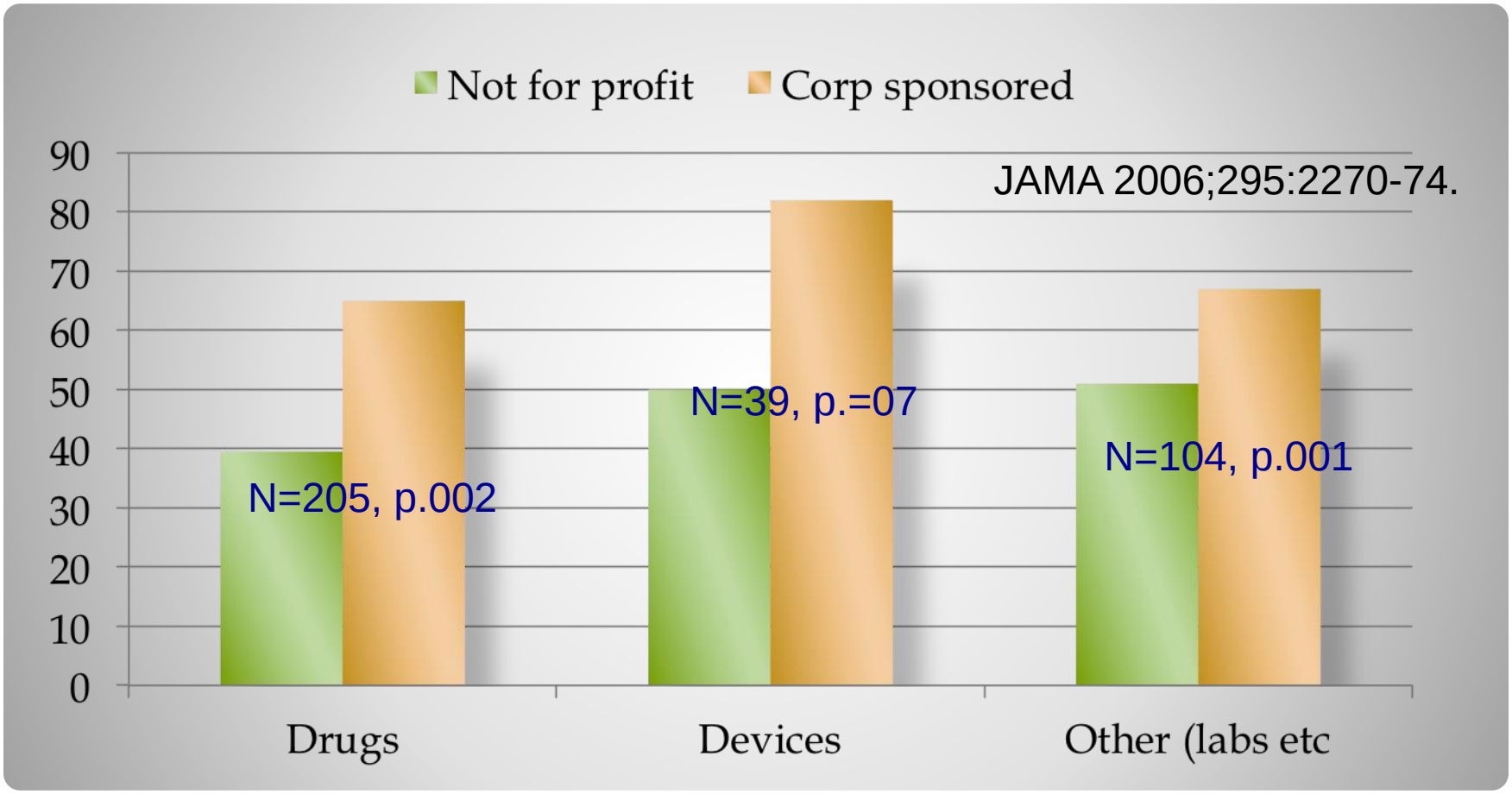
Finder's Fees

- Fees paid to residents, nurses, physicians to find and refer persons who enroll in studies.
- $250-500

Capitated reimbursement creates incentives to:
-short cut on research criteria.
-cause clinicians to pursuade patients to consent to research.

- 1996: Pfizer sent a team to northern Nigeria during an outbreak meningococcal meningitis to test a new antibiotic.
- The Nigerian principal researcher said that his office backdated an approval letter and this may have been written a year after the study had taken place.
  - BMJ. 2001 Jan 27; 322(7280): 194.

Corruption



CONFLICT OF INTEREST: Favorable Outcomes of Corporate Sponsored v Independent Research Published in JAMA, LANCET and NEJM

Publication Conflicts of Interest

- **Financial**: "I have a financial interest in this paper being published."
- **Intellectual**: "I cannot be intellectually fair to this topic." (e.g., I work an author or strongly differ with the point of view.)
- **Control of authorship**: ghostwriting.
- Disclose all.
- Violators will be punished.

Seek the Oracle. International Committee of Medical Journal Editors http://www.icmje.org/

‘WORST DRUG SAFETY TRAGEDY IN OUR LIFETIME’

Sales begin. Divided vote, poor data on risks. Minority report dissents.

WHO warns about heart effects.

GSK ordered to post unpub trials because of corporate suppression of data on anti-depressant suicides.

BMJ: Risks> benefits; withdraw it. BMJ 2010:341:c4848.

Europe stops sales.

FDA restricts sales; divided vote (Avandia speakers vote).

2004 **2006** **2010**

1999 **2005** **2007** **2012**

GSK internal study (that ignores some MIs) finds 31%↑ heart attack. P=NS. GSK conceals memo.

1 Million Rxs, ↑22%

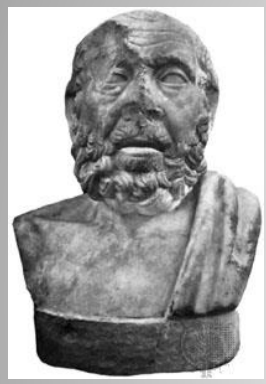
NEJM Meta-analysis shows 43% ↑ heart attack. Extra deaths~47,000. (**Peer reviewer** leaks mss to GSK.) FDA: Stronger label.

Sales ↓ from $3B to $1B/Yr.

GSK to **Euro’ Heart J:** “Withdraw this editorial (critical of Avandia) and refrain from publishing it in any way.”

GSK pleads guilty, pays $3 B fine.

Sales:$500 M/Yr.



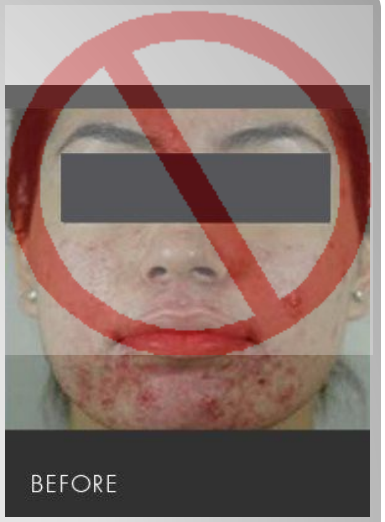
About whatever I may see or hear in treatment, or even out of treatment, in the life of human beings -- things that should not ever be blurted out outside --I will remain silent.

Hippocrates, Oath, 420 BCE

Case Report Confidentiality

CASE REPORTS

- Nonessential identifying details should be omitted. Authors should and editors should affirm before publication that changes do not distort meaning.
- Identifying information (e.g., initials, hospital numbers, pedigrees) should not be published unless essential for scientific purposes and the patient (or guardian) gives informed consent.
- Masking the eye region does not protect anonymity.
- The manuscript should be shown to the identifiable patient.
- Authors should disclose whether potentially identifiable material may appear on the Internet or print after publication.
- Patient consent should be archived with the journal, authors, or both and should be indicated in the article.



ICMJE
INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

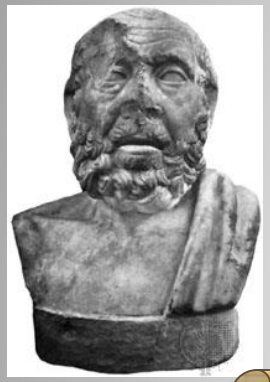
International Committee of Medical Journal Editors, Protecti of Research Participants.

- http://www.icmje.org/

CARE: Consensus-based Clinical Case Reporting Guideline Development

- http://www.equator-network.org/reporting-guidelines/care/

Bibliography: Journal Editors



Epidemics III: 16 Cases

1: In Thasos, the Parian who lay sick beyond the temple of Artemis was seized with acute fever, which at the beginning was continuous and ardent ...

Hippocrates. Epidemics III, 450 BCE

Standards for Research with Human Participants: **Clinical Trials Registries**.

To promote trust in health research, researchers, sponsors, research ethics committees, editors and publishers have an obligation to ensure public accountability for methods and results.

Researchers must prospectively register their studies, publish results and share data on which these results are based in a timely manner.

Negative and inconclusive as well as positive results of all studies must be published or otherwise be made publicly available.

- http://www.cioms.ch/index.php/guideline-24

CIOMS: Aims of Registries

ICJME: Aims of Registries

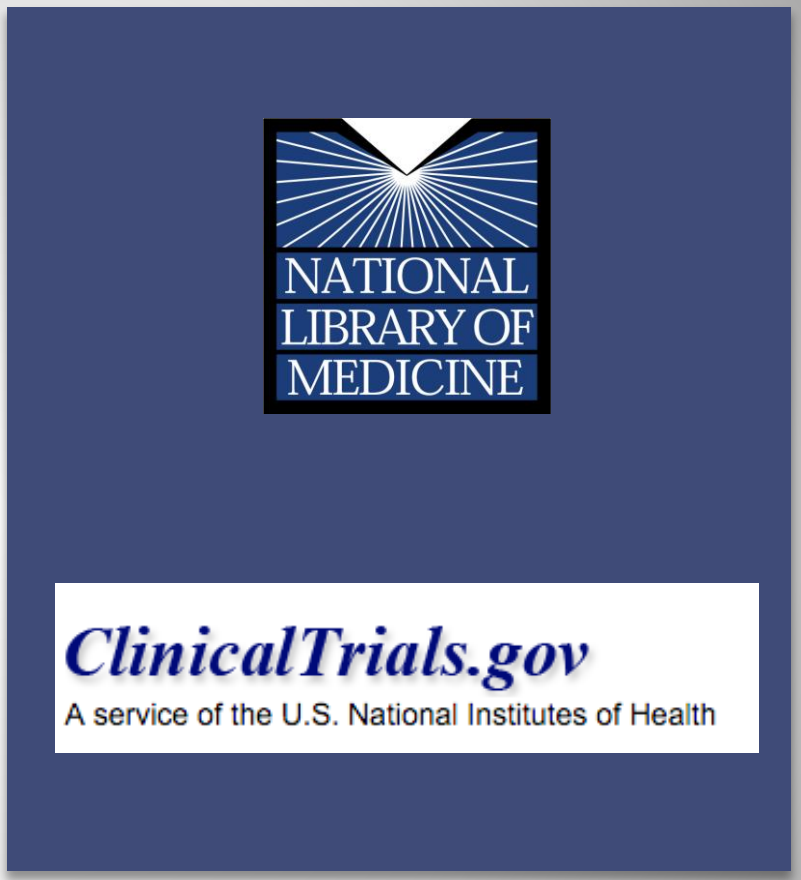
Clinical trial registration aims to:

- prevent selective reporting of research outcomes,
- prevent unnecessary duplication of research effort,
- help the public know what trials that are planned or ongoing into which they might want to enroll, and
- give IRBs a view of similar work and data relevant to the proposal being considered.
  - http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

Definition: Trial Registries

Registries are:

- Archives (libraries) of public data.
- Not an oversight mechanism for assessing data,
  - although independent secondary analysis of data serves as an oversight of science.



- 50% of research goes unreported.
- Reported studies are 2.5X more likely to show statistically significant positive results or highlight benefits over adverse effects.
- Biased non-publication is much more common in corporate-sponsored research.
- J R Soc Med 2011;104:532-8.

Research that does not shed light

Endorsed by health ministry.
Not for profit.
Sustainable.
Offers registry to public and private research.
Plan for data transfer if it closes.

Confirms registrations as real and complete.
Bars and corrects duplicate registration within or between registries.
Transparent auditing.

Certified Registry.

Uses ICJME 20 point data set.

Searchable. English.
Open to public.

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

ICMJE
INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

WHO

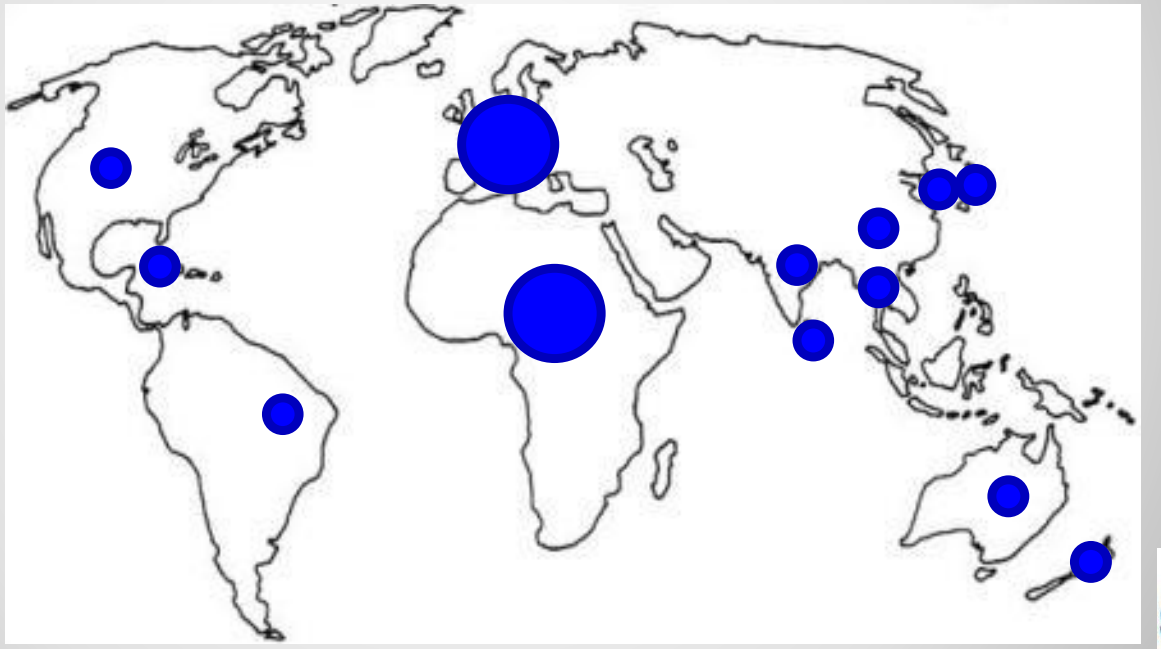
Certified Registry

International **C**linical **T**rials **R**egistry **P**latform.

Not a Clinical Trials Registry.

A search engine of certified registries:

- Australia-New Zealand
- Brazil
- Cuba
- China
- European Union
- Germany
- India
- Iran
- Japan
- Pan Africa
- Netherlands
- South Korea
- Sri Lanka
- Thailand
- United States



World Health Organization: ICTRP

WHO

Country	Trials
US: ClinicalTrials.gov	150,551
EU: CTR	21,060
Japan: JPRN	12,728
UK: ISRCTN	11,794
Australia/New Zealand: ANZTR	8,216

Five Largest Registries 2013.

Standards for Using Registries

Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

Negative and inconclusive as well as positive results must be published or otherwise made publicly available. . . .

Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

- http://www.wma.net/en/30publications/10policies/b3/

Declaration of Helsinki

What studies must be registered?

Require Registration

Controlled clinical trials of drugs or devices subject to FDA regulation that:

- Are conducted in the USA
- Are conducted under an FDA investigational new drug application or investigational device exemption
- Involve a drug, biologic, or device manufactured in the US and exported for research.

Exempt from Registration

- Phase 1.
- Small device feasibility studies.
- Observational studies.
- Many sponsors and investigators voluntarily registered their studies.

- The Responsible Party for a trial must register the trial and submit results.
  - The sponsor of the clinical trial or
  - The principal investigator if so designated by a sponsor, grantee, contractor, or awardee, as long as the PI has access to and control over the data, has the right to publish the results and is able to supply clinical trial information.

NOT THE IRB!

Who registers?

When to register a study

- Applicable Clinical Trials must be registered within 21 days of enrolling first participant.
- A study can be registered on ClinicalTrials.gov any time.
- Journal editors require registration of clinical trials before enrolling the first participant.

- A study may be registered before getting IRB approval if it is not yet recruiting participants.
- When IRB approval is obtained, Registry "Recruitment Status" should be changed to Recruiting.

Sequence IRB and Registration

Publication and Certified Registries

Medical Journals and Registries

- All medical editors should require registration at or before participant enrollment as a condition of publication.
- The ICMJE accepts any WHO ICTRP certified registry.
- The ICMJE recommends that journals publish the trial registration number with the abstract.
  - http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

ICMJE
INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

FDA Transparency Illustration!

The ICMJE encourages posting clinical trial results in registries. Posting of trial results in a registry is not prior publication if the results are given as a brief structured abstract or tables.

Registry Posting and Press Embargoes

ICMJE
INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

NEJM lifts embargo on blindness gene therapy study early after BBC breaks it

leave a comment »

The *New England Journal of Medicine* (NEJM) lifted the embargo early yesterday on a study of a rare form of blindness following a break by the BBC.

The NEW ENGLAND JOURNAL of MEDICINE

Keeping an eye on how scientific information embargoes affect news coverage

Embargowatch.com

How to make an editor really mad!

NIH: ClinicalTrials.gov

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

WHO International Clinical Trials Registry Platform.

- http://apps.who.int/trialsearch/

Slides contain redacted transcriptions of policies and laws.
Always refer to the original and most recent texts.

WHO

Bibliography: Registry Standards

International Committee of Medical Journal Editors: Clinical Trials Registration.

- http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

Bibliography: Publication Standards

Bibliography: Ethics

World Medical Association: Ethical Principles for Research with Human Subjects (Declaration of Helsinki).

- http://www.wma.net/en/30publications/10policies/b3/

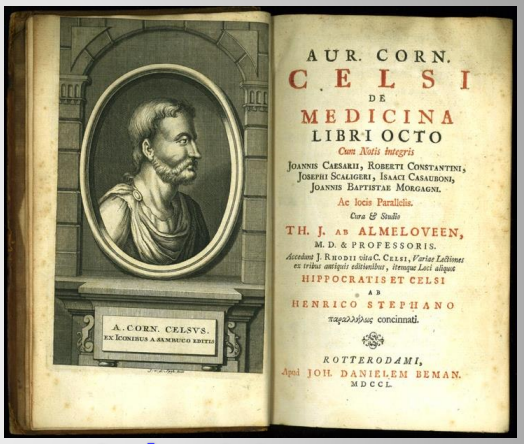
Council for International Organizations of Medical Sciences [UNESCO, WHO] CIOMS. Public Accountability for Health Related Research.

- http://www.cioms.ch/index.php/guideline-24

Dickersin K, Chalmers I. Recognizing, investigating and dealing with incomplete and biased reporting of clinical research from Francis Bacon to the WHO. J R Soc Med. 2011;104:532-8.

this sincere confession of an [adverse event by an ancient Greek MD,450 BCE] befits a great mind that will accept many responsibilities, especially in handing down knowledge for the advantage of posterity that no one else may be deceived again."

Celsus. De Medicina IV:5. ~45 CE.



Standards for Research with Human Participants: **Data Safety Monitoring**

1979, NIH Clinical Trials Committee:

- "every clinical trial should have provision for data and safety monitoring."
- "a variety of types of monitoring may be anticipated depending on the nature, size, and complexity of the clinical trial."
- "In many cases, the principal investigator is expected to perform and accountable for performing the monitoring function."

1994, NIH Office of Extramural Research:

- "all trials, *even those that pose little likelihood of harm*, should consider an external monitoring body."

DSM History

DSMs: Aims and Overview

- The purpose of **D**ata and **S**afety **M**onitoring (**DSM**) is to ensure that research trial is safely managing the health of human participants.
- DSM is a person or board, often distinct from the investigators, that oversees a clinical trial to review:
  - potential risks to human subjects,
  - actual adverse events seen during a study
  - external scientific events that bear on the design or rationale for the trial.
- DSMs recommend to continue, modify, or stop a trial to:
  - The NIH sponsoring Institute or Center.
  - The IRB

DSM and Risk

DSM should be commensurate with risks assuming that risks are minimized.

- A phase I trial of a new drug or agent may involve increasing risk, to a small number of participants, as the drug is escalated in dosage.
- A phase II trial may discover unanticipated risks as the recruitment proceeds.

In such cases, DSM assesses those risks and may recommend

- Terminating the trial when significant benefits or risks have developed or if the trial is unlikely to be concluded successfully.
- Informing current subjects about the emerging data so that they can exercise their option to make an informed decision about whether to continue to consent or to withdraw from the study.

EXEMPTIONS TO DSM

- An IRB or NIH may rule that DSM is not required for an observational trial without any behavioral, pharmacologic, or physiologic intervention if standard care is not withheld or modified.

DSM Meetings

- **Open Meetings:**
  - Lead investigator and biostatistician attend.
  - Open to DSMB members, NIH staff and ad hoc experts, including industry.
  - Discuss study progress, accrual, characteristics of enrollees, comparability of groups, protocol compliance, site performance, adverse events. Data must be presented without grouping by treatment assignment and must mask all subjects. Outcome results must not be discussed.
- **Closed Executive Session:**
  - Only DSMB voting members
  - Discusses outcomes and makes recommendations.
  - The Report containing data on outcomes, safety and group efficacy. If this report is provided to non-voting members, the reason and to who will be included in the Report.

DSM: Conflict of Interest

- No member of the DSMB
  - May have direct involvement in the conduct of the study.
  - May have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB.
- DSMB members disclose Conflicts of Interests at joining and at each meeting.
- The DSMB determines how to handle conflicts of interest by restricting voting or replacing a member.
- NIH may dismiss a DSMB member in the event of unmanageable potential conflict or appearance of conflict.

Does a study need DSM?

DSM and "Minimal Risk"

"***Minimal risk*** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

- www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.102.

Some minimal risk studies (e.g., blood drawing, vision checks), especially when a test cannot

reveal any immediate health risk or

when done at a single institution

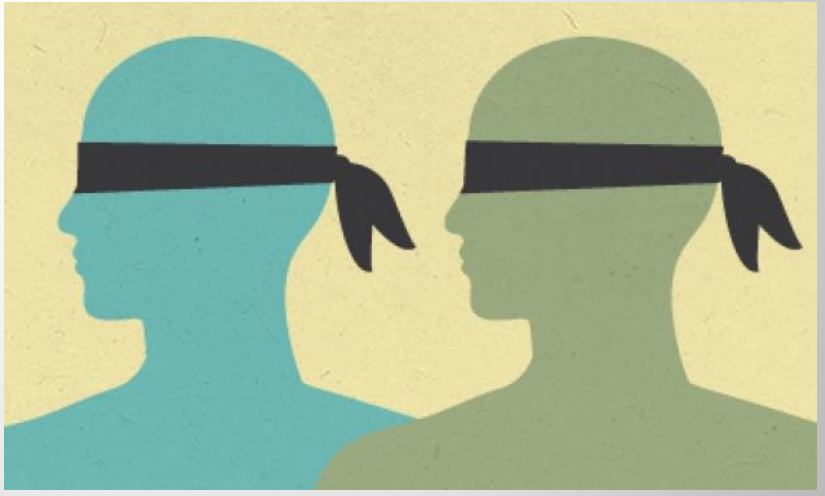
do not require DSM. Consult the IRB or NIH sponsor!

(Greater than "minimal risk" studies usually require some form of DSM.)

DSM and Multi Center Trials

All Phase I or Phase II trials where the subjects or clinicians are blinded to the intervention must have a DSM.

DSM



DSM and Multi Center Trials

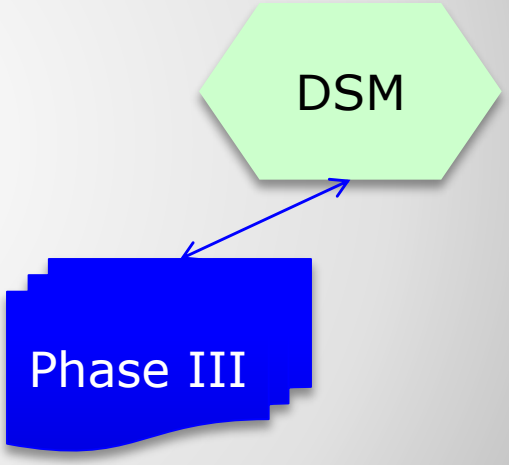
All "greater than minimal risk" *multicenter* trials must have a DSM plan.

DSM

Greater than Minimal Risk Multi-center Study

DSM and Phase III Clinical Trials

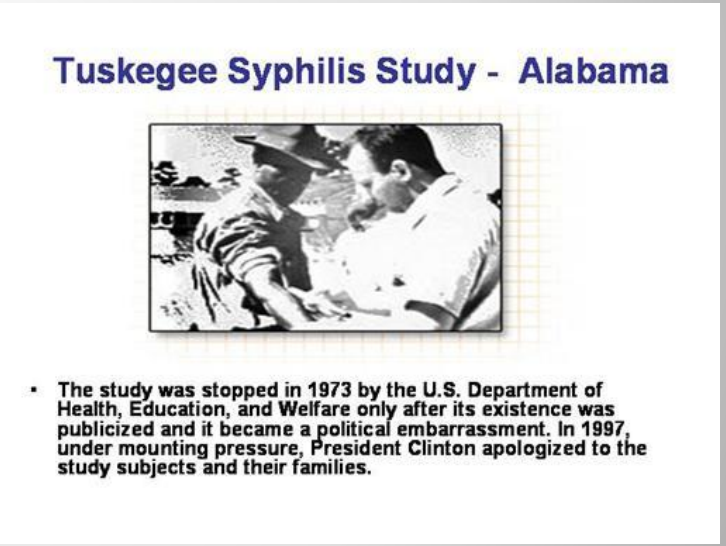
All Phase III clinical trials must have a DSM plan.



DSM and Vulnerable Subjects

- Vulnerable participants are persons at risk of exploitation by research.
  - Regulations define children, pregnant women, neonates, human fetuses, and prisoners as vulnerable subjects.
  - Other potentially vulnerable subjects include University students and employees, indigent persons who are motivated by financial incentives.
- DSM is required for vulnerable participants. Guidance should be sought from the sponsor and IRB.

DSM



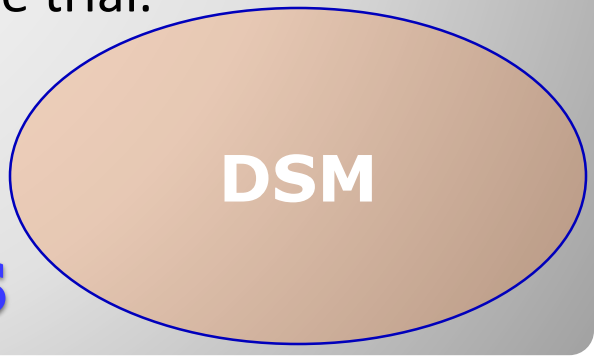
DSM Structure, Meetings, Powers

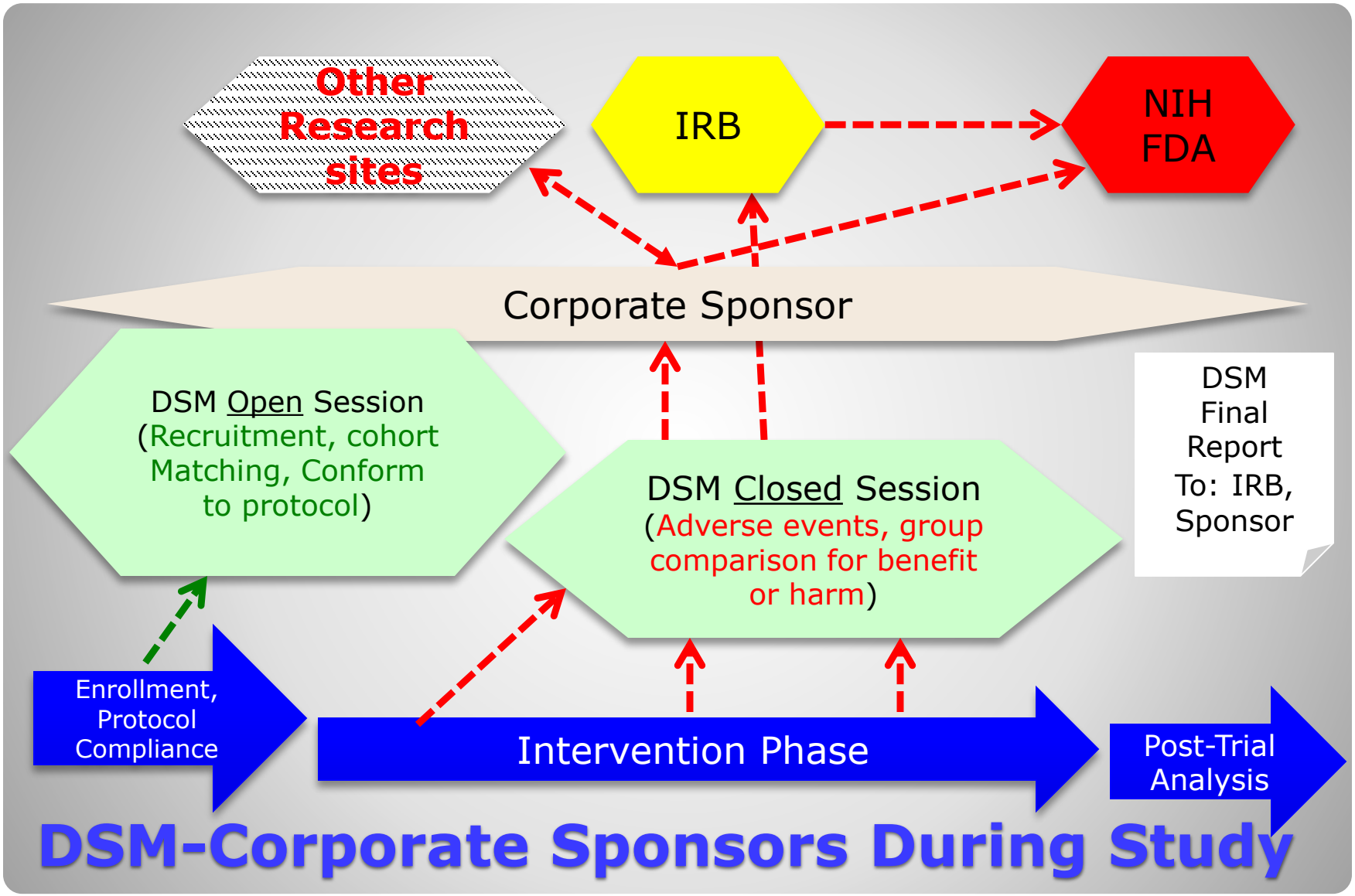
- DSM must be independent from the trial.
  - Conflicts of interest must be managed.
- For multi-center trials by a cooperative group, most of the DSM review team should be external to the research team.

DSM Independence

DSM Responsibilities

- Review research protocol and plans for data/safety monitoring.
- Ensure compliance of all sites with monitoring and reporting.
- Evaluate trial progress, including regular assessments of data quality; subject recruitment and retention; participant risk versus benefit, and other factors affecting study outcome.
- Consider external scientific developments that may change the relative safety of risks to the participants or conduct of the study.
- Identify, assess, and report adverse events to the IRB, NIH.
- Make recommendations to the NIH or the IRB and investigators concerning modification or termination the trial.




Other Research sites
IRB
NIH FDA
Corporate Sponsor
DSM Open Session (Recruitment, cohort Matching, Conform to protocol)
DSM Closed Session (Adverse events, group comparison for benefit or harm)
DSM Final Report To: IRB, Sponsor
Enrollment, Protocol Compliance
Intervention Phase
Post-Trial Analysis
DSM-Corporate Sponsors During Study

Open Meetings

- DSMB members, NIH staff, ad-hoc experts, including industry.
- Discuss general study progress.
- Data must be presented without grouping by treatment assignment.
- Outcomes may not be discussed.

Executive Session

- Only voting members.
- Discuss interim analysis by groups.
- Blinded safety data only goes to members.
- The members may unblind data (e.g. for safety assessment).

https://grants.nih.gov/grants/guide/notice-files/not98-084.html

DSM Meetings

Open Sessions

Investigators, NIH/IRB staff, industry sponsor review whether study is:

- Following the design,
- Recruiting subjects as expected,
- Producing matched arms etc.

Closed Sessions

Review emerging outcomes.

- Differences between arms that might lead to a recommendation to terminate study early.
- Unanticipated problems, harms or risks.

No one with a proprietary interest in an outcome may attend when data is presented or discussed.

DSM Meetings

NATIONAL INSTITUTES OF HEALTH

- Must be ensured for reviewing and tabulating interim results and making recommendations.
- The only persons who see interim analyses of outcome data are:
  - Voting DSM members,
  - Statisticians,
  - NIH/IRB program staff

  Except in instances where the DSM deems that serious adverse events warrants broader disclosure.

DSM Confidentiality

Changed because:

Needs revised informed consent because of

- Availability of a new therapy,
- Adverse effects
- Changes in the risk benefit ratio etc.

Terminated due to:

- Unanticipated risks,
- Is unable to answer research question (e.g., fails to recruit enough subjects).
- Research question has been settled elsewhere

DSM may recommend that a trial be:

1. Data Safety Monitoring may be done by:

A. Board or Committee

B. A Principal Investigator (in small, single institution studies with simple monitoring activities)

C. A qualified independent consultant.

D. Any of the above.

Continuing Education Question

3. In a corporate sponsored trial, a representative **may or may not** be present as adverse events as the DSM votes on matters pertaining to adverse drug reactions.

a) May

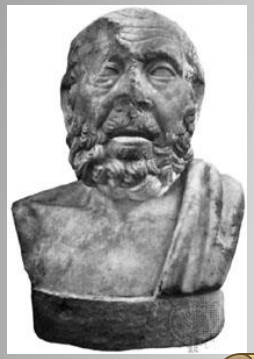
b) May not

Continuing Education Question

4. In a clinical trial, a DSM may report and the NIH or IRB may suggest that a trial be prematurely ended because of:

a) An unexpected high rate of adverse events
b) A significant superiority or inferiority of one of the study arms.
c) New scientific evidence suggesting that an alternative treatment is superior to any of the clinical trial arms.
d) A or B
e) A or B or C.

Continuing Education Question



On arrival at a town with which he is unfamiliar, a physician should examine ... how the natives are off for water, whether they use marshy soft water or hard such as comes from rocky heights ... the soil too, whether bare and dry or wooded and watered ... the mode of life...

Hippocrates. Airs, Waters, Places. 450 BCE

Standards for Research with Human Participants: **International Research**.

Steven H. Miles, Department of Medicine,
Center for Bioethics of the University of Minnesota.

SHM has no financial interests to declare.
No commercial products are mentioned.

Regulatory Benchmarks for International Research

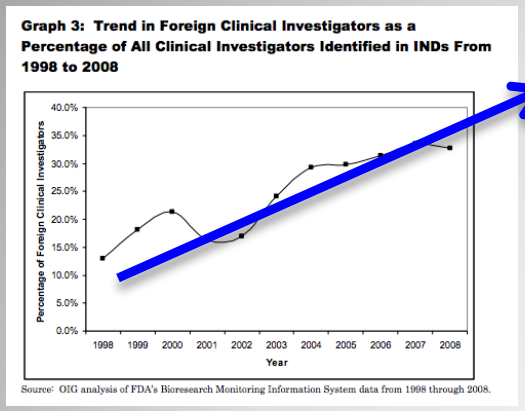
Revisions to NIH policy?

Local Laws

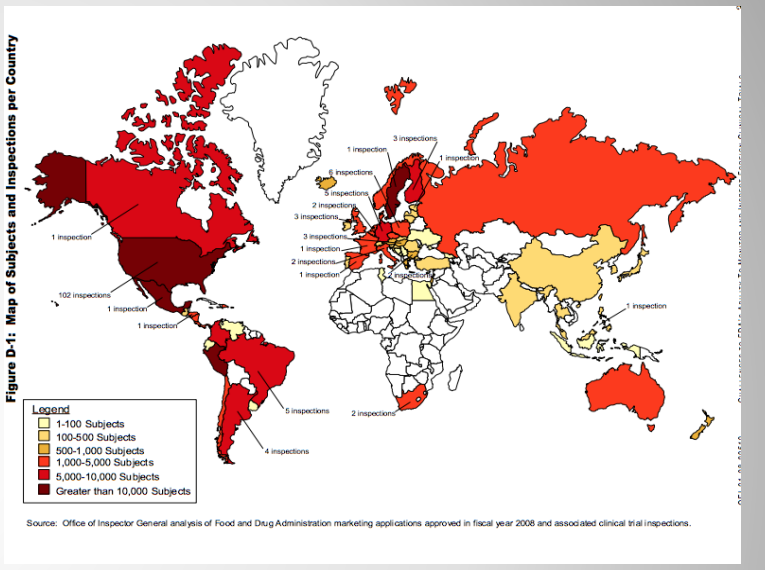
Journal Policies

Guidance on Good Clinical Practice
Standards to facilitate acceptance of studies for obtaining drug approval.

Guidelines Affecting the Publication and Acceptability of International Trials.



FDA Investigations are increasing



Off shore, *corporate-sponsored* studies are outside of US regulatory framework.

Academic researchers should use caution in collaboration.

- OIG. 2010

Peru: 13,000 subjects, 2008, No US inspections.

FDA Oversight of Foreign Corporate Research is rare but increasing

Local laws and Regulations

- The export of some technology or software to carry out studies may be subject to US laws.

- Project Registration & Permits
- Work Visas /Personnel licensing
- Importing Drugs
- Importing/use of satellite phones or internet

- Medical dispensing
- Research regulations
- Disposition of materials at end of Project
- Taxes

Have Local Legal Assistance

IRB: International Research

- University investigators' research in foreign countries must comply with University policies.
- Requirements for ethical conduct and consent apply.
  - Local customs and norms may affect consent formats. Research proposals should explain cultural norms requiring accommodation (e.g., societies without written language).
  - The IRB may waive some or all requirements for written consent.
- Research projects must be approved by the local equivalent of an IRB (or experts or community leaders) **before** being presented to the University IRB.

Ethics Standards for International Research

Opinion of Peers/ Media

Local Customs

Voluntary Ethics Standards

NATIONAL BIOETHICS ADVISORY COMMISSION

WMA

CIOMS

NUFFIELD COUNCIL ON BIOETHICS

Ethics Standards for International Research

World **M**edical **A**ssociation A congress of national medical associations.

- Content is similar to US policy.
- NIH commends it for studies outside of its regulatory jurisdiction.
- A prestigious standard of care; not law or regulation.

Helsinki Declaration

WMA

Council for **I**nternational **O**rganizations of **M**edical **S**ciences:

- A voluntary non-governmental organization created by WHO and UNESCO in 1949.
- 49 international, national and associate member organizations of national academies of sciences and medical research councils.
- Facilitates international activities in the biomedical sciences especially when participation by several international and national institutions is necessary.
- A prestigious statement of the standard of care but it is not law or regulation.

CIOMS

International Trials: Local Benefit

- Sponsors should ensure that:
  - The research is responsive to the health needs and priorities of the local community; and that
  - Any new product or knowledge will be made reasonably available to benefit that community. When an intervention has important potential for host country health care, the sponsor should consult with national stakeholders to determine the practical implications of "reasonable availability."
- If a study drug is shown to be beneficial, the sponsor should provide it to subjects.

CIOMS: Local Benefit

[By justice and beneficence] a population should not be the focus of research unless some of the potential benefits of the research will accrue to that group after the trial.

- Study proposals should explain how proven therapies will become available in the host country beyond research participants.
- If applicable, investigators should describe pre-study negotiations among sponsors or host country officials aimed at making such interventions available.
- When investigators do not believe that successful interventions will become available to the host country, they should explain how the research benefits the health needs of the country.

US BAC: Local Benefit

- Researchers and sponsors should make reasonable efforts before starting a study to secure continued access to proven effective interventions for participants after the trial.
- Research protocols should describe the duration, extent and financing of such continued access.
- When no arrangements have been negotiated, the researcher should justify to the ethics review committee why this is the case.

Continued treatment

- Medical research is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group.
- This group should stand to benefit from the knowledge, practices or interventions that result from the research.

Helsinki: Local Benefit

US BAC: Capacity Building

- To enhance research collaborations between developing and developed nations, it is important to increase the capacity of resource-poor countries to become more meaningful partners in international collaborative research.
- Capacity building to conduct research could include:
  - During a clinical trial, enhancing the host nation's researchers ability to conduct research (e.g., training) or
  - Providing research infrastructure (e.g., equipment) or
  - Building capacity to conduct scientific and ethics review of studies.

Many countries lack capacity to assess or ensure the scientific quality or acceptability of biomedical research in their jurisdictions.

Sponsors and investigators are ethically obliged to ensure that research projects adds to national/local capacity to conduct and monitor research.

Capacity-building may include (among other things):

- Developing technologies appropriate to health-care and biomedical research.
- Educating the community from which research subjects are drawn.
- Strengthening independent IRBs.
- Strengthening research capacity.
- Training research and health-care staff.

CIOMS: Capacity Building

International Trials: Compensation for Injury

- If required by regulation, a sponsor should insure a investigator/institution against claims arising from the trial, except for claims arising from malpractice and /or negligence.

Compensation for injury.

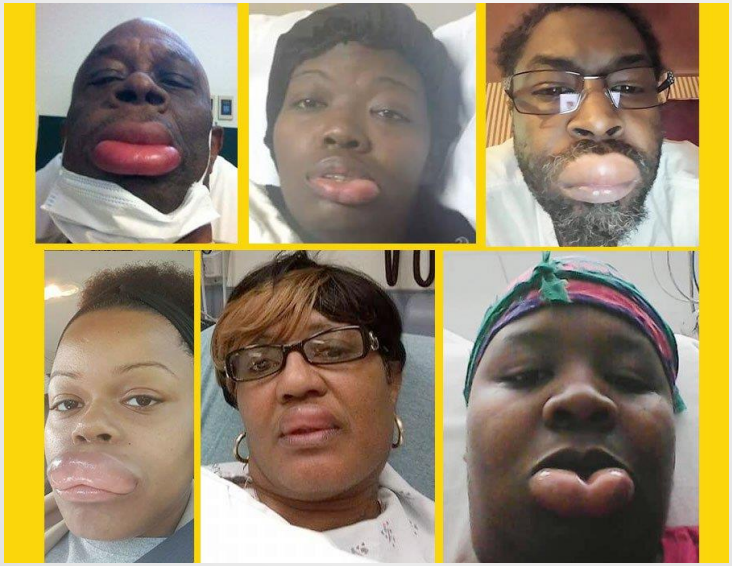
- During and after a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events related to the trial.
- A sponsor's policies should address the costs of treating trial subjects for trial-related injuries in accordance as required by local laws or regulations.
- The method and manner of compensating trial subjects should comply with applicable regulations.

Compensation for injury.

- Subjects who are injured solely as a result of the experimental intervention should receive free treatment and other assistance to compensate them for resulting disability. (Also in FDA/EU/Japan Guidance on Good Clinical Practice)
- Compensation / free treatment is not owed to subjects who suffer foreseeable adverse reactions to study interventions when such reactions do not differ from those known to be associated with established interventions in standard medical practice.
- In Phase I & early Phase II studies, subjects who are injured/ disabled should be compensated because it is unreasonable to expect a study drug to benefit.
- In case of death from participation, dependents are entitled to compensation.

CIOMS: Compensating for injury

- Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.



Helsinki: Compensation

Control groups in low-resource countries

- General poverty cannot justify a placebo-controlled study in a country of limited resources when it would be unethical to conduct a study with the same design in a population with general access to the effective intervention.
- The ethical standards applied should be no less stringent than for research carried out in the donor's country.

India Cervical Cancer study.

1. Pap test, if positive refer. Mod death rate.
2. Vinegar test, if positive refer. Mod death rate.
3. Inform about pap screening (putative standard of care). High death rate.

CIOMS [WHO concurs]: Poverty as a control

- Clinical trials should provide control subjects with established effective treatment, whether or not such treatment is available in the host country.
- Any proposed study that would not provide the control group with an established effective treatment should justify the design to the sponsor and IRB.
- Representatives of the host country (e.g., scientists, officials and persons with the condition under study) should have a strong voice in determining whether a proposed trial is appropriate.

US BAC: Controls

The benefits, risks, burdens and effectiveness of a new intervention must be tested against the best proven intervention(s), except in the following circumstances:

- Where no proven intervention exists or
- Where for scientifically sound reasons the use of a less effective intervention is necessary to determine the efficacy or safety of an intervention and such subjects are not subject to additional risks as a result of not receiving the best proven intervention.

  Extreme care must be taken to avoid abuse of this option.

Helsinki: Comparator

Universal Standard for Comparators: the best standard control used anywhere in the world (regardless of where the research is conducted).

- Comparator treatments should not depend on where the research is performed . . .
- The investigators' responsibility to the subjects' well being should not be influenced by local political and economic conditions. Such conditions do not justify providing a lower standard of care for some subjects than they would have received had they taken part in the same study in a different place.
- Any other position could lead to the exploitation of people in developing countries, in order to conduct research that could not be performed in the sponsoring countries.
  - New England Journal of Medicine, 342(13) 967–9.

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Non-universal standard for comparators:

- All people within study arms must always be treated identically, but a relevant reason should be offered for difference between a comparator arm and the best international standard.
- Assess the local context of the research to establish whether or not it provides a morally relevant reason for offering a different standard of care.

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Control groups should generally receive a universal standard of care.

In externally-sponsored research, comparators should at least equal the comparator that the host country endeavors to provide nationally. It may be appropriate to offer a higher comparator while keeping the research relevant to the local setting.

These issues must be defined in consultation and after acceptance by local authorities, IRBs, and the sponsor.

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Controversial International Trials

Perinatal HIV Transmission

Multiple studies over several years showed that antiretroviral drugs prevented perinatal HIV transmission.

There was interest in finding less expensive protocols.

- Is a shorter regime as effective as standard duration of a couple of weeks to cover prenatal and breast feeding period?
- What drugs work best?

NIH funded studies used placebo controls in poor counties of Africa and Asia with the following rationale

- Met local standard of care.
- Produced results faster.
- Did not require as large N as equivalency trials.
    - N Engl J Med 1997; 337:853-856September 18, 1997

Standards for international clinical trials to facilitate acceptance of results by European Union, US, Japan (as well as Australia, Canada, the Nordic countries, and the WHO) for drug approval.

- http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf

FDA

pmda JAPAN

Australian Government
Department of Health
Therapeutic Goods Administration

Bibliography: Guidance on Good Clinical Practice

Council for International Organizations of Medical Sciences (CIOMS).

- International Ethical Guidelines for Biomedical Research Involving Human Subjects
  - http://www.cioms.ch/publications/layout_guide2002.pdf
- International Ethical Guidelines on Epidemiological Studies
  - http://www.ufrgs.br/bioetica/cioms2008.pdf

World Medical Association.

- Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki).
  - http://www.wma.net/en/30publications/10policies/b3/

Bibliography: Ethics Standards I

US National Bioethics Advisory Commission:
Ethical and Policy Issues in International Research:
Clinical Trials in Developing Countries

- https://bioethicsarchive.georgetown.edu/nbac/clinical/Vol1.pdf

WHO: Handbook for Good Clinical Research Practice (Similar to CIOMS).

- http://apps.who.int/prequal/info_general/documents/GCP/gcp1.pdf

Bibliography: Ethics Standards: II

Nuffield Council on Bioethics: The Ethics of Research Related to Healthcare in Developing Countries

- http://nuffieldbioethics.org/wp-content/uploads/2014/07/Ethics-of-research-related-to-healthcare-in-developing-countries-I.pdf

UNAIDS: Ethical Considerations in Biomedical HIV Prevention Trials.

- http://www.unaids.org/sites/default/files/media_asset/jc1399_ethical_considerations_en_0.pd

Bibliography: Ethics Standards: III

Continuing Education Questions

1. Control groups: The best description of the expectation for control groups for international trials in low resource countries is:

A) A control group should generally meet the standard for the global standard of care or at least the National Health Service' aspiration for standard care in the country where the research is conducted.

B) A control group may customarily equal the local standard practice.

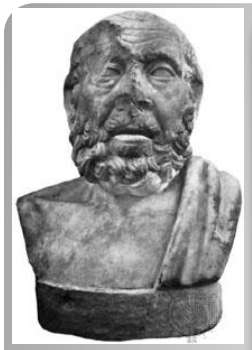
Continuing Education Question

2. Which is the best description of the expectation for local benefit for international trials in low resource countries?

a) Research is inherently beneficial to host countries. It generates wealth and employment. It is unrealistic to expect that trials of costly medications or expensive drugs will be immediately usable or affordable to poor host countries.

b) A trial should be relevant to the needs and capabilities of countries where the research is done. Drugs that are proven to be effective should continue to be available to study volunteers. Well off countries should improve the capacity of poorer host countries where research is done to collaborate with biomedical research.

Continuing Education Question



In Europe, there are tribes differing one from another in stature, shape and courage. The differences are due to the same causes which I will now describe more clearly.

Hippocrates. Airs, Waters, Places. 450 BCE

Standards for Research with Human Participants: **Community Consent**


Emergency Research
Formal Communities
Community Collaboration
International Research
Informal Communities

CONSENT

Allows communities to approve or reject a project

CONSULTATION

A dialogue that seeks to identify and address misunderstandings and concerns.

A Fundamental Distinction

Community

Consultation

- Aims to recognize and accommodate relevant specific values and concerns.
- Seeks advice, reactions, concerns, suggestions.
- Must be responsive in study design.
- Is a dynamic process.
- Is fair. All relevant groups are consulted (i.e., not excluding disempowered or minority constituencies.

Assent / Consent

- Solicits permission/approval by the community to allow its members to be approached for enrollment.
- May occur after community consultation.
- Requires a legitimate such that representatives are properly empowered to consent on behalf of the community.
- Does not void need for individual consent.

Goals of Community Consultation

- Improving design to respect community' values/beliefs.
- Negotiate and enhance benefit sharing to participants or community.
- Establish legitimacy and trust for researchers.
- Negotiate collaboration at the community level.

Formal Communities

Formal Communities

Consultation

- Formal governance, bureaucracy.
- Strong procedural requirements.
- Fairness is contingent on fairness of political system. (This can be a problem.)

~~Assent /~~ Consent

- Explicit consent of organization / nation, government required.
- Does not void need for individual consent.

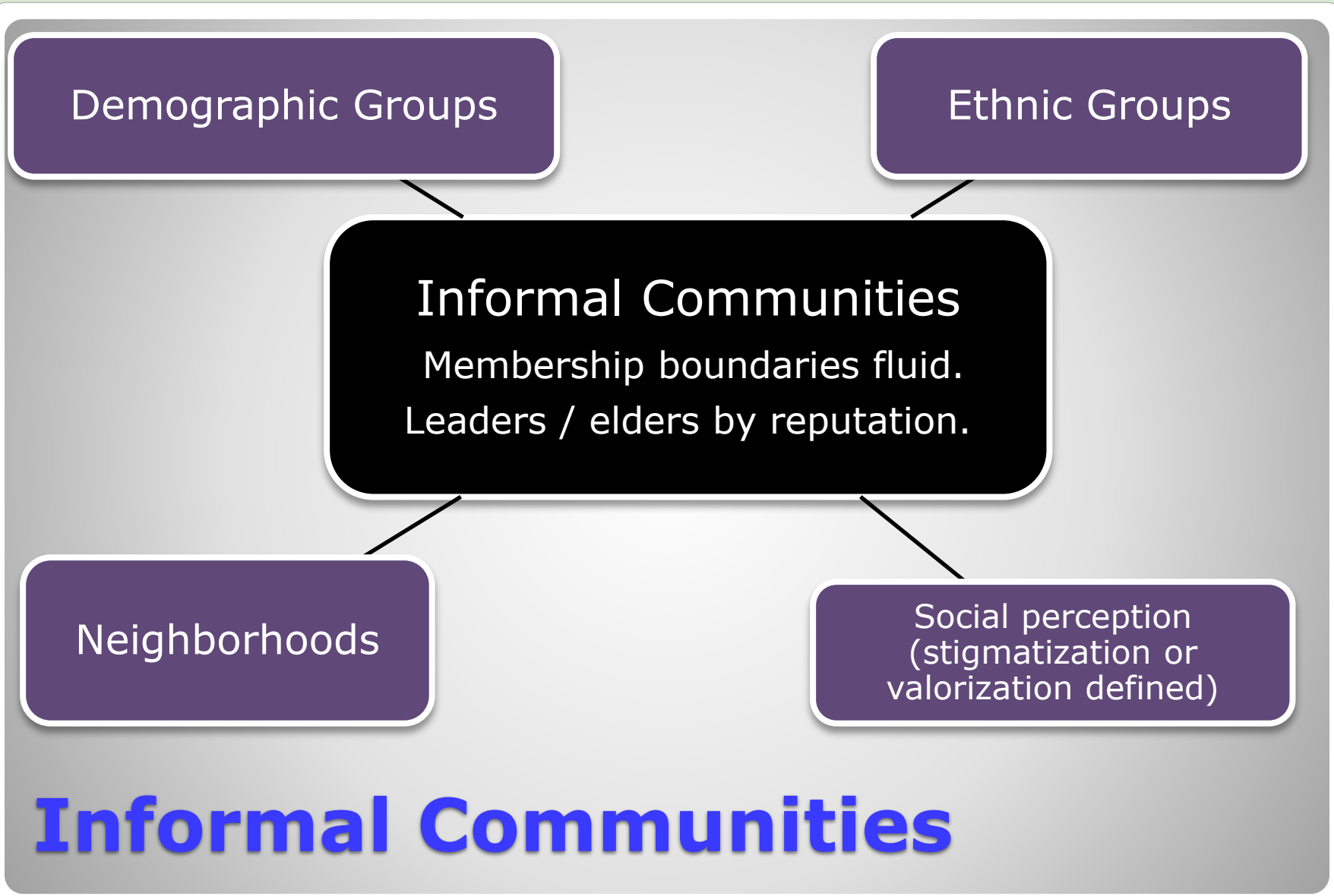
The Indian Health Service' Health Program for American Indians and Alaska Natives (in NIH not BIA) requires Tribal Council/Government approval for research on Native American communities regardless of funding source or tribal affiliation of the researcher.

Tribes may require their own IRBs to approve studies.

When more than one nation or band is involved, separate permission from each entity may be required.

See IRB Policy 510.

Native American Communities.



Informal Communities

CONSENT

Allows communities to approve or reject a project

CONSULTATION

A dialogue that seeks to identify and address misunderstandings and concerns.

A Fundamental Distinction

Informal Communities

Consultation

- Informal and relational negotiation with elders, opinion leaders.
- Implicit rather than explicit procedures requirements.
- Fairness is contingent on fairness of society. (This can be a problem.)

Assent / Consent

- Authorized assent of leaders is sought. Does not void need for individual conse

International Community Consultation

- Research teams should develop culturally appropriate ways to communicate unfamiliar research concepts (e.g., randomization) to foster informed consent and compliance.
- IRB may ask for community consultation to:
  - Assess whether study is responsive to local needs and values.
  - Evaluate potential intermediaries between investigators and subjects.
  - Ensure that consent is open to all. voluntary and private.
- The purpose of community consultation should be specified in the protocol.
- Permission from community leaders does not substitute for individual informed consent. (Leaders should understand that consent will be individually sought from individuals enrolling in research, lest this practice be seen as unanticipated disrespect for his or her authority.)

Bibliography: Ethics Standards I

Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines on Epidemiological Studies. (2008)

http://www.ufrgs.br/bioetica/cioms2008.pdf

World Medical Association. Declaration of Helsinki.

http://www.wma.net/en/30publications/10policies/b3/

Bibliography: Ethics Standards: II

US National Bioethics Advisory Commission. Ethical and Policy Issues in Research Involving Human Participants. 2001.

- https://bioethicsarchive.georgetown.edu/nbac/human/overvol1.pdf

WHO: Handbook for Good Clinical Research Practice. 2002. (Similar to CIOMS).

- http://apps.who.int/prequal/info_general/documents/GCP/gcp1.pdf

Bibliography: Ethics Standards: III

Nuffield Council on Bioethics: The Ethics of Research Related to Healthcare in Developing Countries.

- http://nuffieldbioethics.org/wp-content/uploads/2014/07/Ethics-of-research-related-to-healthcare-in-developing-countries-I.pdf

Useful Articles

International Research.

- Dickert N, Sugarman J Ethical Goals of Community Consultation in Research. Am J Public Health. 2005;95: 1123–27.
  - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1449329/
- Diallo DA1, Doumbo OK et al. Community permission for medical research in developing countries. Clin Infect Dis. 2005;41:255-9.
  - http://cid.oxfordjournals.org/content/41/2/255.full.pdf