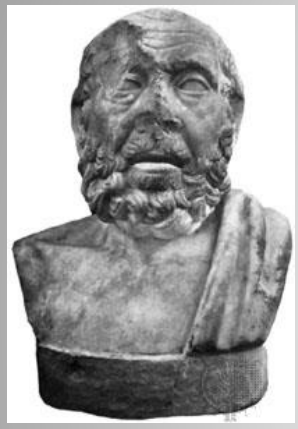


I do not believe that any clear knowledge of Nature can be obtained though any source other than a study of medicine and then only through a thorough mastery of this science.

Hippocrates, Medicine, 420 BCE

Standards for Research with Human Participants

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.

Ethical Research on Humans: A Very Brief History

The subject must give voluntary consent.

The subject is free to disenroll.

Qualified persons should conduct the experiment.

The study must be designed to yield fruitful results unprocurable by other means of study

The study should be based on animal experiments and a knowledge of the disease.

The study should be conducted to avoid unnecessary physical and mental suffering and injury.

No study may be conducted if there is reason to believe that death or disabling injury will occur (*except, perhaps, where the researcher serves as subjects*).

Preparations must be made to protect the subject from remote possibilities of injury, disability, or death.

The scientist must terminate the experiment if he has cause to believe that continuing the experiment is likely to result in injury, disability, or death.

Nuremberg Code: Nazi Doctors 1947

- Denying penicillin to men with strep throat.
- Giving carbon dioxide to patients during anesthesia to learn when ventricular arrhythmias develop.
- Giving Hepatitis A to children to learn the incubation period.
- Transplanting melanoma from a daughter to a mother who died of melanoma 455 days later. . . .

Beecher

- Never published names but spoke concerns to the public.
- Proposed that publishers evaluate whether researchers obtained informed consent and properly weighed the risks and gains.
- Noted government funding of research and thus put NIH in political hot seat to develop standards for research on humans.

1966 Henry K Beecher NEJM

Ethical Principles and Guidelines
for the Protection of Human Subjects of Research

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. HHS/NIH

- Respect for persons:
  - Protect autonomy and informed consent of all people.
  - Be truthful and conduct no deception.
  - Treat subjects with courtesy and respect.
- Beneficence: "Do no harm,"
  - Maximize benefits and minimize risks.
- Justice:
  - Fair, non-exploiting, non-coercive procedures for enrolling persons.
  - Fair distribution of costs and benefits to *potential* research participants.

Belmont Report 1979

What is Research?

Research: a systematic investigation designed to develop or contribute to generalizable knowledge.

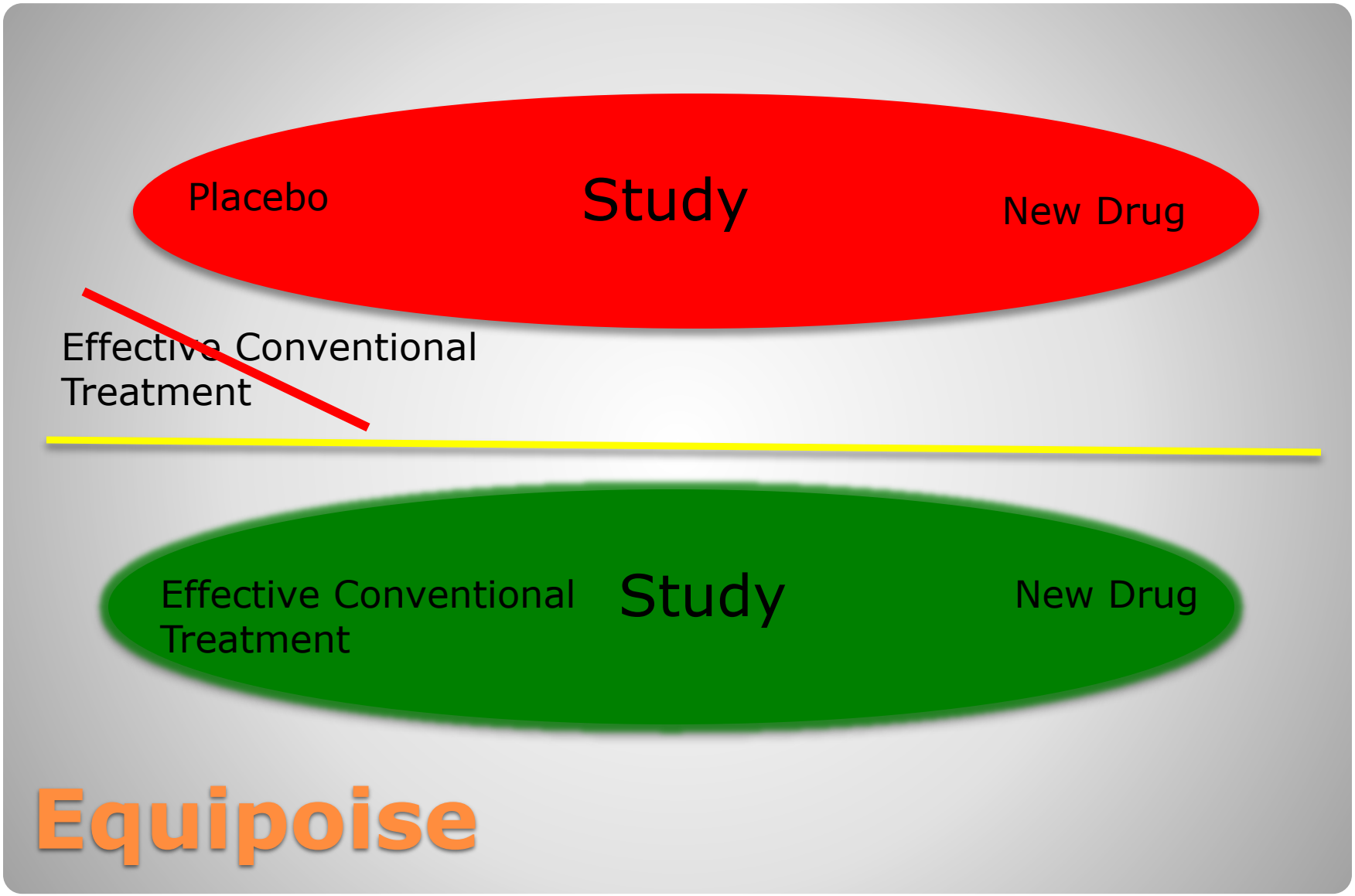
Clinical Research

Equipoise

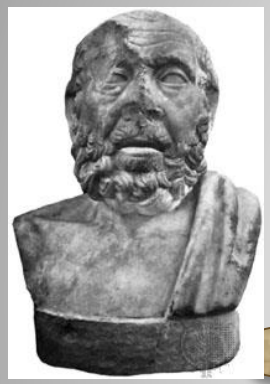
Ethical clinical research requires equipoise

- Genuine uncertainty regarding the comparative merits of each arm.
- Present or imminent controversy over the preferred treatment within the expert medical community about the preferred treatment.
- Permits randomization

If the investigator learns that one study arm is superior, the he/she is ethically obliged to not offer the other arm.

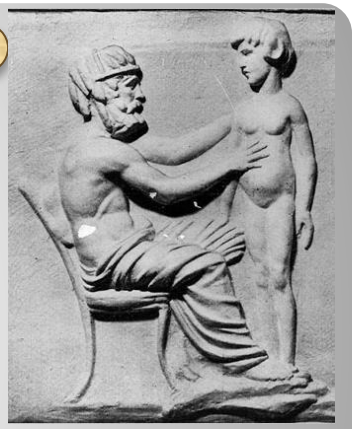

Placebo
Study
New Drug
Effective Conventional Treatment
Effective Conventional Treatment
Study
New Drug

Equipoise



It is incorrect to say that a disease differs from what it really is, to say that a major disease is minor, or to say that a minor disease is major; … or to say that what cannot be cured will be cured."

Hippocrates. Diseases I:6. 405 BCE



Informed Consent.

Consent: Clinical Care v Research

Informed Consent: Clinical and Research

Clinician-Patient Relationship	Researcher-Participant Relationship
Goal: Advance patient's well-being (fiduciary duty).	Goal: Create generalizable knowledge.
Consent confirms that the clinical decision serves the patient's interest and values.	Consent is ***a gift*** to accommodate personal interests to science. It does not remove the person from a clinical relationship.
Regulation & laws.	Regulation and laws.

Consent Requirements

- No investigator may enroll a person without obtaining informed consent by the person or his/her surrogate.
- Information given shall be *understandable*.
- Investigators must give possible subjects (or surrogate) *opportunity* to consider whether or not to participate and minimize coercion or undue influence.
- Consent must be *documented*.
- Informed consent *may not* release the investigator, funder, or institution from liability for negligence.

Content of Informed Consent

- Aims, process.
- *Foreseeable risks*, discomforts are….
- Reasonably expected *benefits* to you are….
- This is how your privacy is affected
- Participation is *voluntary*. Refusing or discontinuing will not lead to penalty or loss of benefits.
- You may incur these extra *costs* ….

Content of Informed Consent

- If *new information* is found during the study that may affect your consent, we will tell you about it so you may reconsider.
- Who to contact for questions about the study, and if an injury occurs.
- As needed:
  - Risks to you/your fetus if you get pregnant.

Pitfalls in Communication

Therapeutic Misconception

- The potential subject's belief that a study will provide a personal benefit.

So, you are telling me there is hope for me?

Illiteracy and Readability

Functional Illiteracy

- ¼ of American adults are Level I proficient (illiterate).
- ¼ are Level I proficient (able to make low level inferences from simple text).
- 1/3 are Level III.
- 1/6 are Level IV (highly proficient).
  - National Adult Literacy Survey 2013.

Readability

- Consent forms are written at grade 12.2 and can run to 4,000 words.
  - Perspect Clin Res. 2015;6:104–8.
  - J Fam Pract. 1996;42:606-11.
  - Am J Clin Oncol. 2010;33:387-92.

Withdrawing Consent

Person Withdrawing from Study.

Participants must be told that they may quit the study at any time without penalty or loss of benefits.

Investigators must:

- Create a plan for prompt, orderly and safe withdrawal.

Dropping Study Participant.

Potential participants must be told that the study may be terminated without regard to consent because of:

- Positive or negative results.
- Poor compliance.

Impaired Consent Capacity

Definition of Impaired Consent Capacity

Impaired consent capacity means that the person cannot decide whether the study is

- A risk that they want to take.
- A gift to science that they wish to give.
- Benefits that they wish to seek even though no one knows that the study will help.

Impaired consent capacity occurs in many toxic, metabolic, situational and disease states.

Impaired consent capacity may be

- temporary (e.g., **intoxication**),
- fluctuating (e.g., **delirium**) or
- progressing (e.g. **dementia**) or
- permanent.

When does impaired Consent Capacity happen?

Consent capacity is task-specific relative to the nature and complexity of the decision.

- The capacity may vary relative to the complexity of consent required of various studies.
- It is not simply present or absent.

Characteristics of Consent Capacity

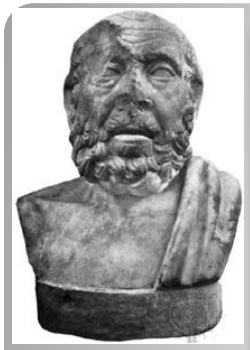
Procedures for Managing Impaired Capacity or vulnerable subjects

- Speaks for the potential subjects values when the subject is unable to.
- Guard the subject during the study.
- Is a person with loving familiarity with the subject.
- Every person with impaired consent ability must be represented by a surrogate.
- Persons with impaired consent ability should only be used as subjects when other persons can not serve the study goal. (e.g., it is permitted to study treatment of delirium in persons with delirium.)

Surrogate decisionmaker

Consent Monitor:

- An impartial observer to reduce coercion or assure complex decisions are well communicated to vulnerable potential research participants.
- Use when
  - staff have little experience obtaining consent, or
  - Where there are concerns about the consent process including where there are problems with an investigator or project.



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

Community Consent

Goals of Community Consultation

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

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.)

CONSENT

Allows communities to approve or reject a project

CONSULTATION

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

A Fundamental Distinction

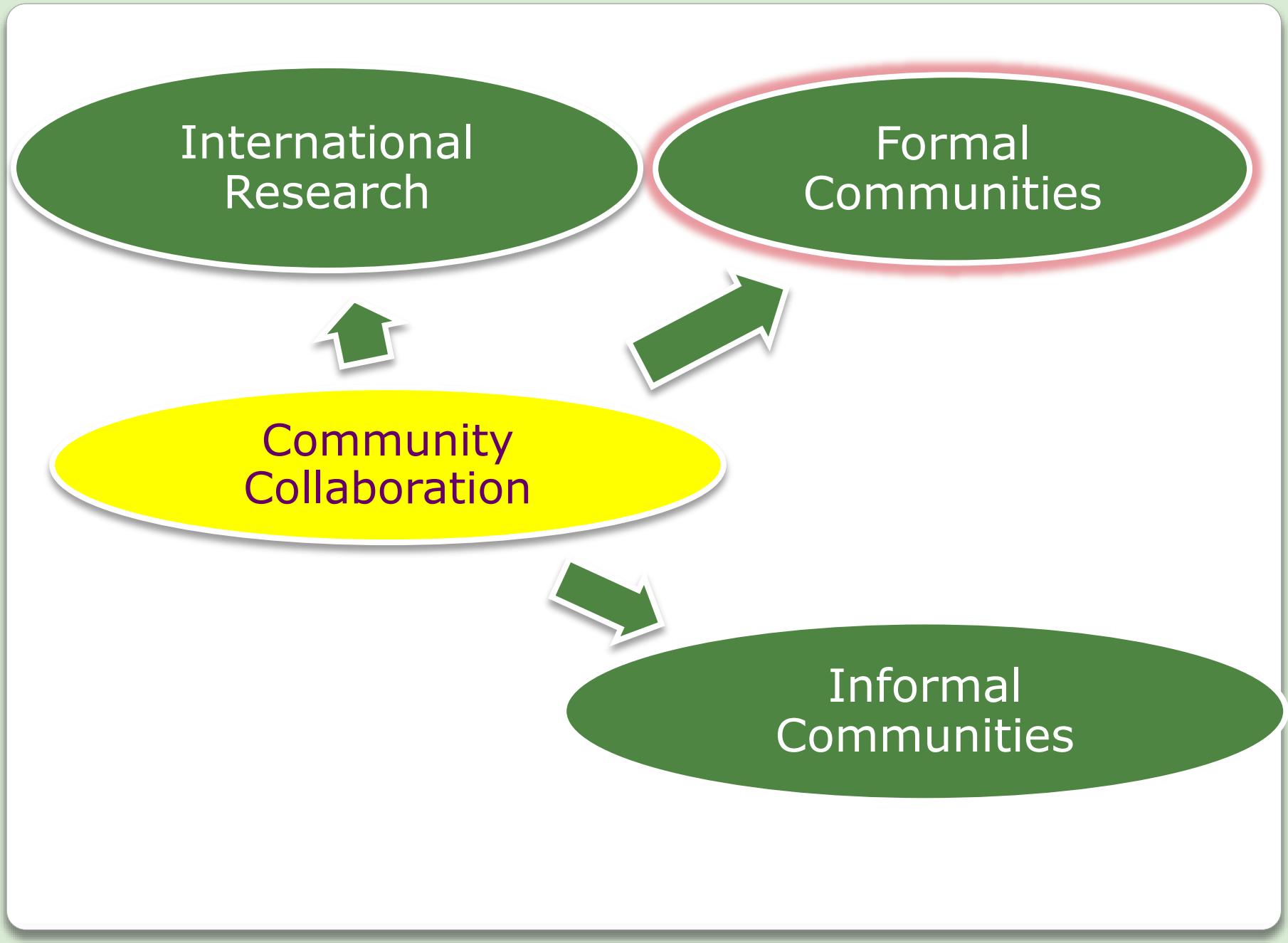
Community

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.


International Research
Formal Communities
Community Collaboration
Informal Communities

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.

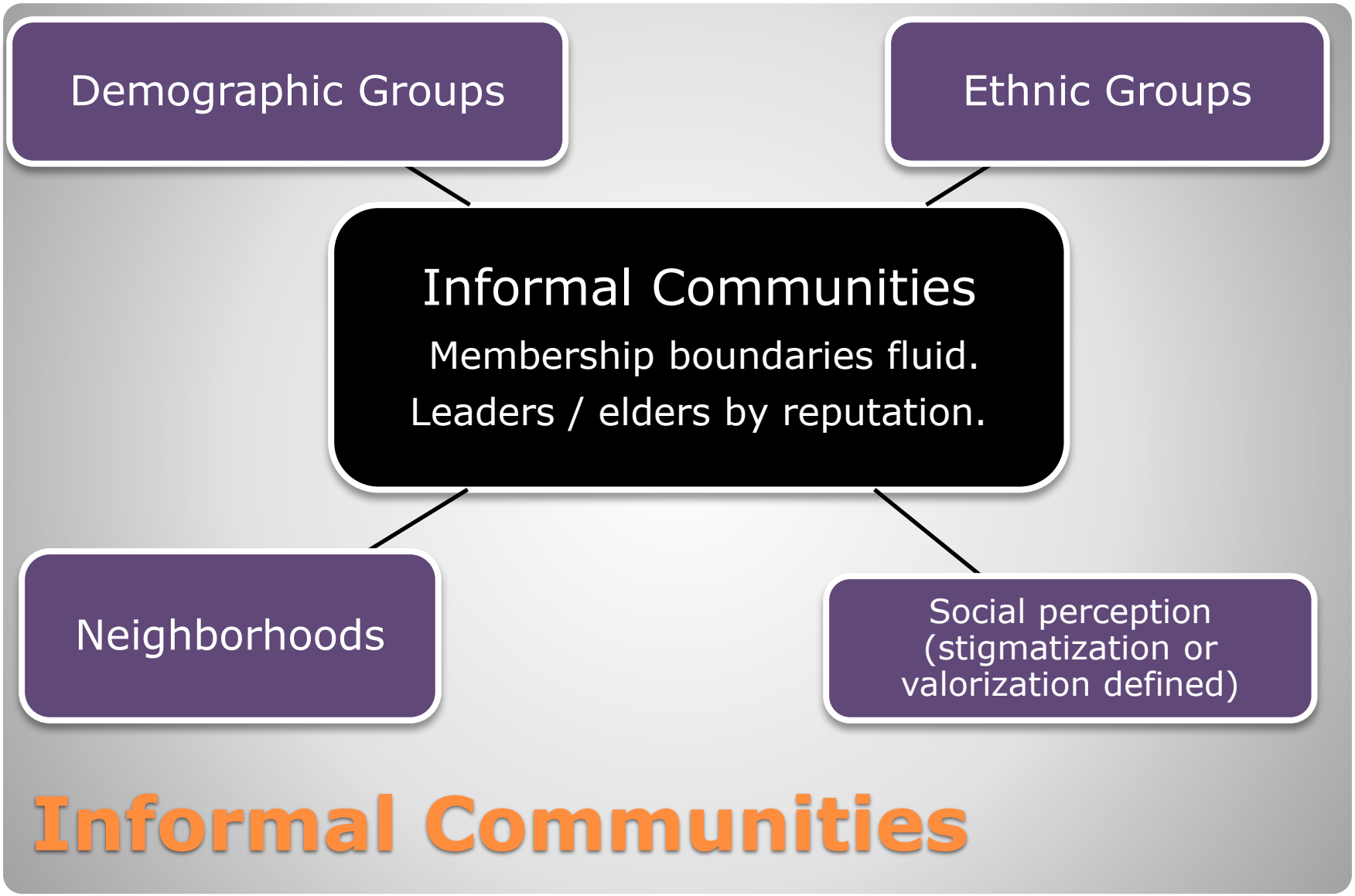
The Indian Health Service' Health Program for American Indians and Alaska Natives (in NIH not BIA) requires Tribal Council/Government approval for research on Native American communities regardless of funding source or tribal affiliation of the researcher.

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

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.)

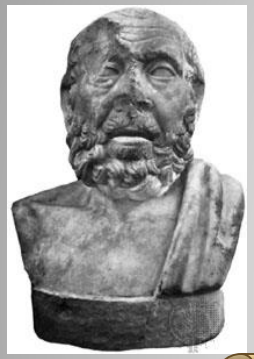
Assent / Consent

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

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



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

International Research.

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

Health Canada Santé Canada

European Union

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

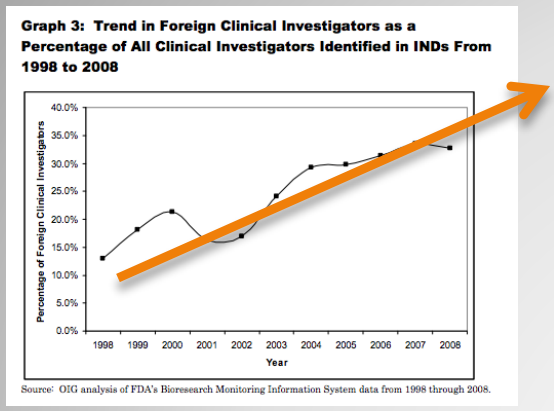
- https://bioethicsarchive.georgetown.edu/nbac/clinical/Vol1.pdf

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

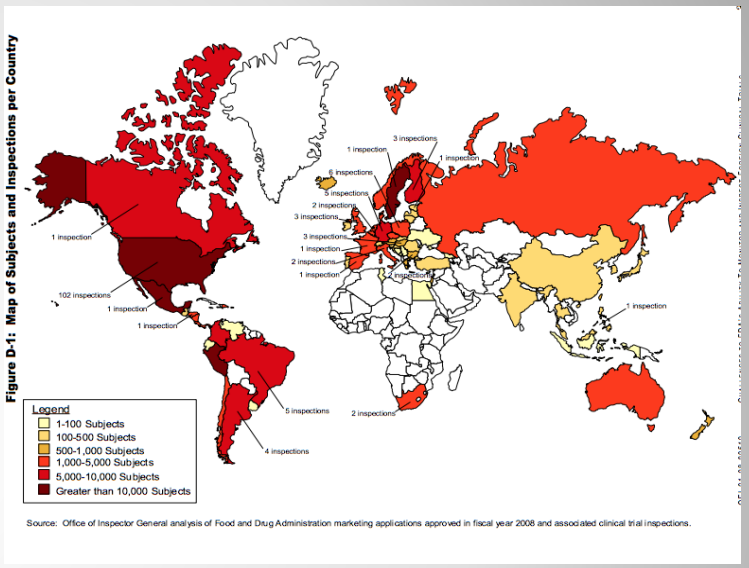
- http://apps.who.int/prequal/info_general/documents/GCP/gcp1.pdf

Bibliography: Ethics Standards: II

Regulatory Benchmarks for International Research



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

UMN 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.
- There is a special IRB form for international research.
  - http://www.research.umn.edu/irb/guidance/international.html

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

CIOMS: 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.

[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

Continued treatment

- 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.

- 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

International Trials: Capacity Building

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

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

Steven Miles, MD
Center for Bioethics
University of Minnesota