University of Zambia Biomedical Research Ethics Committee

Introduction to Bioethics and Research Ethics

(Informed consent and Responsible Conduct of Research)

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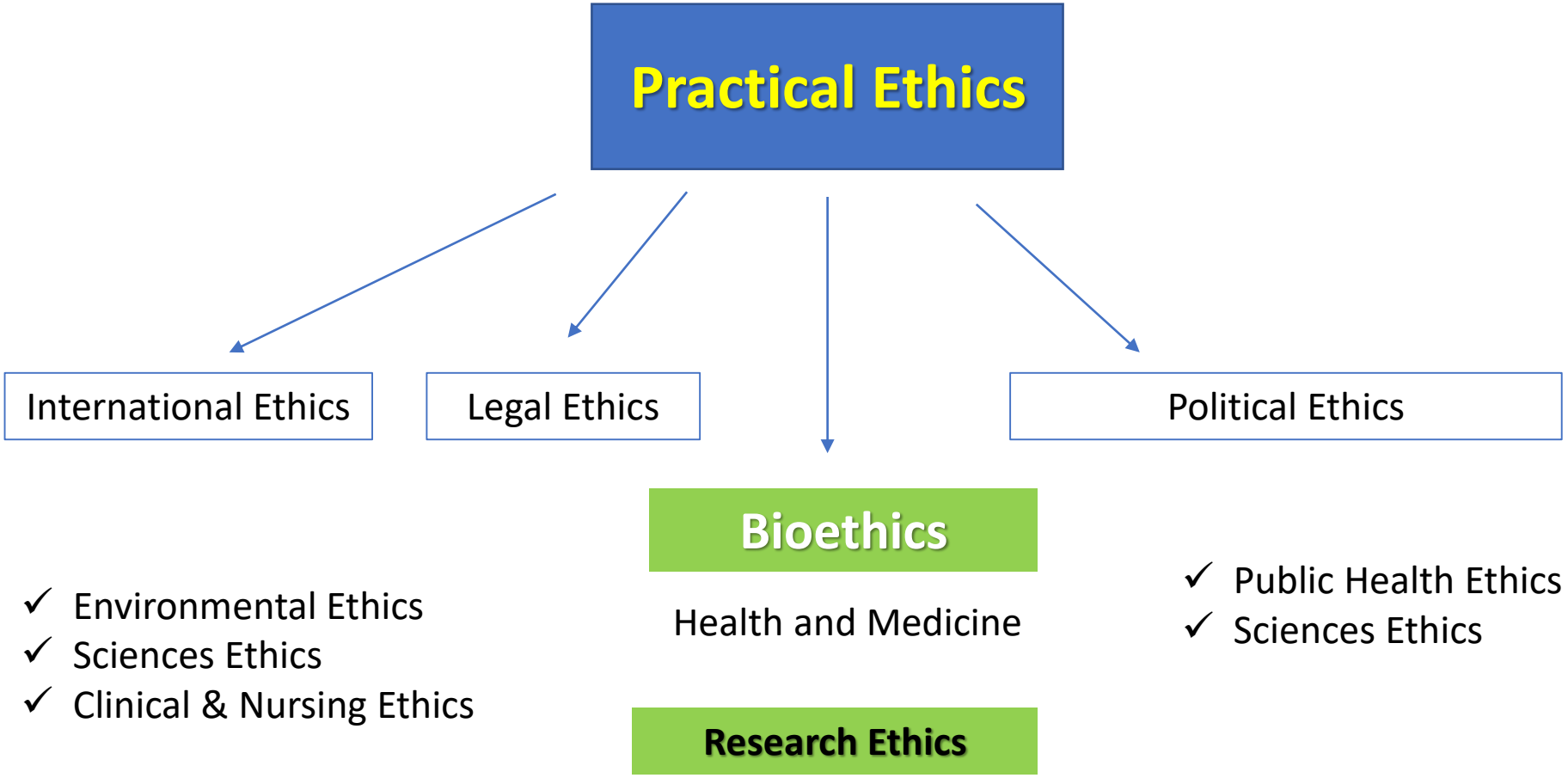
Where does Ethics come from?

Philosophy
(Study of logic and moral reasoning to explain human experience)

Theology
(God/Beliefs)

Ethics
(Study of moral principles that govern behavior)

Fields in Ethics



Ethical Philosophies/Theories

Be

Virtual Ethics/Theories

- ✓ **Morality is higher/above than law**
- ✓ **Character and virtue**
  - ✓ **Philosophers:**
    - ✓ **Socrates**
    - ✓ **Plato**
    - ✓ **Aristotle**
- ✓ Virtue ethics is person rather than action based: it looks at the virtue or moral character of the person carrying out an action, rather than at ethical duties and rules, or the consequences of particular actions.

Actions

Deontology/ Kantian Theories

- ✓ Rights
- ✓ Autonomy
- ✓ Dignity
- ✓ Respect
- ✓ Duty/rule principle
- ✓ *deon*, "obligation, duty"
- ✓ morality of an action should be based on whether that action itself is right or wrong under a series of rules, rather than based on the consequences of the action

Consequences

Utilitarian/ Consequentialist Theories

- ✓ Maximizing benefits
- ✓ Minimizing harms
- ✓ Maximize pleasure
- ✓ Minimize harms
- ✓ promotes actions that maximize happiness and well-being for the majority of a population

History of Research Ethics

- 1947 Nuremberg Code
  - Introduced voluntarism in research
- 1964 Declaration of Helsinki
  - Respect for person/autonomy
- 1978 Belmont Report (following Tuskegee Syphilis study)
  - Separation between practice and research
  - **Respect for persons**
    - Informed consent
    - Voluntarism
  - **Beneficence/Maleficence**
    - Assessment of risks and benefits
  - **Justice**
    - Participant selection

Ethical Principles

- **Respect for persons**: protecting the autonomy of all people and treating them with courtesy and respect and allowing for informed consent. Researchers must be truthful and conduct no deception; (Voluntarism) [**Deontology/ Kantian Theories]**

- **Beneficence**:/ **Non-maleficence:** The philosophy of "Do no harm" while maximizing benefits for the research participant and minimizing risks to the research participants; (Assessment of risks and benefits) [**Utilitarian/ Consequentialist Theories]**

- **Justice**: ensuring reasonable, non-exploitative, and well-considered procedures are administered fairly — the fair distribution of risks, costs and benefits to *potential* research participants — and equally (fair participant selection) [**Deontology/ Kantian Theories]**

Belmont Report of 1978

Informed consent

- Respect for persons/autonomy/voluntarism

- Challenges
  - Incomplete disclosure to accomplish goals
  - Undisclosed risks if they are no more than minimal risk
  - Plan for debriefing participants
  - Public health research/emergencies
  - Broad consent

Elements of informed consent

- **Comprehension/Understanding**
  - Foetuses, Infants, children, mentally disabled persons, comatose patients, terminally ill patients, elderly etc.

- **Voluntarism**
  - Free from coercion or undue influence
  - **Coercion** is when a threat for harm is intentionally presented to obtain compliance
  - **Undue influence** occurs when an offer for excessive reward to obtain compliance.
  - Acceptable inducements/compensation may be undue influence in vulnerable participants

Basic Elements of informed consent

- Statement of purpose of study and explanation of study procedures and duration
- Statement of foreseeable risks and discomforts
- Benefits to participants or others
- Disclosure of alternative procedures/treatments advantageous to participants **(ancillary care)**
- Privacy and confidentiality

Basic Elements of informed consent

- For more than minimal risk studies, compensation or treatment if injury occurred
- Contact information for questions or concerns or incase of injury
- Statement of voluntarism and that refusal to participate will not result in penalty or loss of benefits

Controversial issues in informed consent

- Information sharing after removal of identifiable personal information
- Biobanking of deidentifiable biospecimens
- **Broad consent**
  - **Zambian law prohibits broad consent**

Final Rule Revisions:
Understanding Broad Consent

Overview

Broad consent may be obtained in lieu of informed consent obtained in accordance with the basic and additional elements of consent, but only with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens. This is not a waiver, but an alternative.

What is paying research participants?

- Payment in cash (value) or in-kind (good) for participating in research
- Reason
  - Time
  - Travel
  - Incentive
  - Inconvenience
  - Reflect risk/burdens?
  - Discomfort
- Not a benefit

Models of paying research participants

- **Market model**
  - Provide incentives to facilitate recruitment
  - Approach: Escalate payment to meet recruitment

- **Wage model**
  - Compensate for time, effort and for discomfort
  - Approach: standardized wage like payments (Removes undue influence)

- **Reimbursement model**
  - Principle: Participating in research should be revenue neutral
  - Compensation to meet out-of-pocket expenses

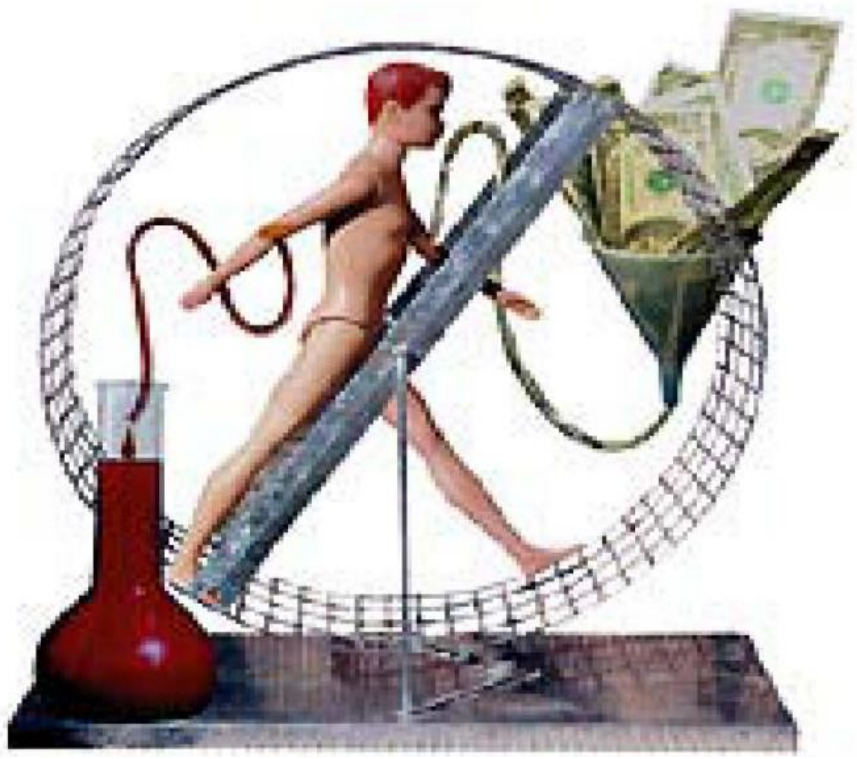
- **Appreciation model**
  - Token given for participation in research

Ethical issues of paying research participants

- May compromise voluntarism
- People may ignore benefits/risks/harms/burdens
- May cause participants to hide factors that may confound/compromise the study
- Participants may provide information that the researcher wants/introduce bias

Ethical issues

- Children
  - Payment goes to parents/guardians
- Patient participants
  - May benefit from the research
- Other vulnerable populations
  - Prisoners
  - military
  - Students
  - Homeless/poor
  - Foetuses
  - Drug abusers
  - Mentally ill patients



Forms of payment

- Money (cash)
- Gifts/Humpers
- Free care
- Travel vultures
- Gift certificates/Air time/Phones

Why pay research participants?

- Facilitates recruitment
  - Compensation for time and effort
  - Makes research revenue neutral
  - Incentive to overcome barriers
- Sign of respect
  - ‘time is money’
- Motivation

Why **not** pay research participants?

- **Commodification of research**

- **Skewed sample**
  - Money is more attractive to lower income individuals
  - **Defeats Justice**: disproportionate distribution of risks on lower income individuals

- **Coercion**
  - The action or practice of persuading someone to do something by using force or threats.
  - Money is an offer and not a threat; you cannot coerce someone with money
  - E.g. Inmates who may fear mistreatment for refusal to participate in research
  - E.g. A patient who may fear that care may be reduced if they refuse to participate in their doctor's research study

Why **not** pay research participants?

- **Undue inducement**
  - An offer one cannot refuse
  - A controlling and irresistible influence
  - Influence strong enough that one ignores risks/harms/interests
  - Can impair judgement
  - Can lie about information that may disqualify them or give incorrect information to get into the study
  - 70% could be induced by $500

Emanuel, *J Law Med Ethics*. 2004.

Casarett et al. *J Gen Intern. Med*. 2002

IRB Guide Book, OHRP

CIOMS International Ethical Guideline 13 and 14

Subjects may be paid for inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research; they may also receive free medical services. However, the payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment ("undue inducement").

– CIOMS International Ethical Guidelines

Compensation is not meant to compensate for risk that participants agree to undertake but rather, for inconvenience and time

Compensation is owed to research participants who are harmed psychologically, physically or socially, as a consequence of interventions performed solely to accomplish the purposes of research.

Emanuel, *J Law Med Ethics*. 2004.

Payment cannot be undue influence in an appropriately approved study

Models of paying research participants

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Conclusion
Paying according to risk

- Higher payment may attract people who may exercise poor judgement about a risk that may cause serious harm

- The appropriate form and level of compensation depends on the local economic and social context.

- **Focusing on undue inducement could reduce compensation and some of the benefits for participants and host communities. We should focus on fair compensation.** Emanuel, *J Law Med Ethics*. 2004.

- Paradoxically, balancing fair compensation and undue inducement may result in less compensation for members of impoverished communities.

- RECs should not approve studies that may expose participants to serious harm

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What makes Research Ethical

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PERSPECTIVE

What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research

Ezekiel J. Emanuel, David Wendler, Jack Killen, and Christine Grady

Department of Clinical Bioethics, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland

(See the editorial commentary by Kuritzkes, on pages 794–5.)

Slides adapted from Dr Gershom Chongwe Presentation

When is research ethical?

- (1) **Social Value**—enhancements of health or knowledge must be derived from the research; **[Utilitarianism/Beneficence]**

- (2) **Scientific validity**—the research must be methodologically rigorous; From Introduction, Literature review, design and methodology etc **[Utilitarianism/Beneficence]**

- (3) **Fair participant selection**—scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects; **[Deontology/Justice]**

Emanuel EJ, Wendler D, Grady C. What Makes Clinical Research Ethical? *JAMA.* 2000;283(20):2701–2711

When is research ethical?

- (4) **Favorable risk-benefit ratio**—within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks; **[Deontology/Justice]**

- (5) **Independent review**—unaffiliated individuals must review the research and approve, amend, or terminate it; **[Virtual ethics/Deontology]**

Emanuel EJ, Wendler D, Grady C. What Makes Clinical Research Ethical? *JAMA.* 2000;283(20):2701–2711

When is research ethical?

- (6) **Informed consent**—individuals should be informed about the research and provide their voluntary consent; and **[Deontology/Respect for person/autonomy]**

- (7) **Respect for enrolled participants** —participants should have their privacy protected, the opportunity to withdraw, and their well-being monitored. **[Deontology/Respect for person/autonomy]**

Emanuel EJ, Wendler D, Grady C. What Makes Clinical Research Ethical? *JAMA.* 2000;283(20):2701–2711

Table 1. Ethical principles and benchmarks for multinational clinical research.

Principles	Benchmarks
Collaborative partnership	Develop partnerships with researchers, makers of health policies, and the community.
	Involve partners in sharing responsibilities for determining the importance of health problem, assessing the value of research, planning, conducting, and overseeing research, and integrating research into the health-care system.
	Respect the community's values, culture, traditions, and social practices.
	Develop the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise.
	Ensure that recruited participants and communities receive benefits from the conduct and results of research.
	Share fairly financial and other rewards of the research.
Social value	Specify the beneficiaries of the research—who.
	Assess the importance of the health problems being investigated and the prospective value of the research for each of the beneficiaries—what.
	Enhance the value of the research for each of the beneficiaries through dissemination of knowledge, product development, long-term research collaboration, and/or health system improvements.
	Prevent supplanting the extant health system infrastructure and services.

Scientific validity	Ensure that the scientific design of the research realizes social value for the primary beneficiaries of the research.
	Ensure that the scientific design realizes the scientific objectives while guaranteeing research participants the health-care interventions to which they are entitled.
	Ensure that the research study is feasible within the social, political, and cultural context or with sustainable improvements in the local health-care and physical infrastructure.
Fair selection of study population	Select the study population to ensure scientific validity of the research.
	Select the study population to minimize the risks of the research and enhance other principles, especially collaborative partnership and social value.
	Identify and protect vulnerable populations.
Favorable risk-benefit ratio	Assess the potential risks and benefits of the research to the study population in the context of its health risks.
	Assess the risk-benefit ratio by comparing the net risks of the research project with the potential benefits derived from collaborative partnership, social value, and respect for study populations.

Independent review	Ensure public accountability through reviews mandated by laws and regulations.
	Ensure public accountability through transparency and reviews by other international and nongovernmental bodies, as appropriate.
	Ensure independence and competence of the reviews.
Informed consent	Involve the community in establishing recruitment procedures and incentives.
	Disclose information in culturally and linguistically appropriate formats.
	Implement supplementary community and familial consent procedures where culturally appropriate.
	Obtain consent in culturally and linguistically appropriate formats.
	Ensure the freedom to refuse or withdraw.
Respect for recruited participants and study communities	Develop and implement procedures to protect the confidentiality of recruited and enrolled participants.
	Ensure that participants know they can withdraw without penalty.
	Provide enrolled participants with information that arises in the course of the research study.
	Monitor and develop interventions for medical conditions, including research-related injuries, for enrolled participants at least as good as existing local norms.
	Inform participants and the study community of the results of the research.

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Responsible Conduct of Research and Research Misconduct

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What is ‘Right’?

What is ‘Wrong’?

What is ‘Ethics’?

“Ethics primarily concerns the effects of our actions on others.”

Randy Cohen

Responsible Conduct of Research

- The practice of scientific investigation with integrity
- Involves awareness and application of established professional norms and ethical principles in the performance of all activities related to scientific research.
- Encompasses the following areas:
  - research misconduct,
  - research with human participants,
  - research involving animals,
  - data acquisition, management, sharing and ownership,
  - mentor/trainee responsibilities,
  - publication practices and responsible authorship,
  - peer review,
  - collaborative science, and
  - conflicts of interests
  - Privacy, confidentiality and informed consent

Research Misconduct

- *Research misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.*
  - ***Fabrication*** is making up data or results and recording or reporting them.
  - ***Falsification*** is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.[3]
  - ***Plagiarism*** is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.

  - Research misconduct does not include honest error or differences of opinion.

Data acquisition, Management and Sharing

- ***Fabrication*** is making up data or results and recording or reporting them.
- ***Falsification*** is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.[3]
- ***Plagiarism*** is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.
- Failing to get **approval** from an ethics committee for research

- Research misconduct does not include honest error or differences of opinion.

US Commission on Research Integrity (1996)

- *Research misconduct is significant misbehaviour that improperly appropriates the intellectual property or contributions of others, that intentionally impedes the progress of research, or that risks corrupting the scientific record or compromising the integrity of scientific practices. Such behaviours are unethical and unacceptable in proposing, conducting, or reporting research, or in reviewing the proposals or research reports of others.*

Smith R. www.bmj.com/talks

A preliminary taxonomy of research misconduct (ranked by seriousness) 2/4

Not admitting that some data are missing

Ignoring outliers without declaring it

Not including data on side effects in a clinical trial

Conducting research in humans without informed consent or without justifying why consent was not obtained from an ethics committee

Smith R. www.bmj.com/talks

Fabrication

- Intentionally creating records that do not exist and for which there is no truth with the intent to mislead or deceive:
  - Interviewer completing a questionnaire for a fictitious participant that was never interviewed
  - Preparing records for follow-up of participants who were really lost to follow-up
  - Creating notes for a participant visit that never took place

Falsification

- Alteration of data collected in the conduct of scientific investigation
- Omission/deletion/suppression of conflicting data without scientific justification
  - Back-dating interviews to fit within the timeline provided in protocol
  - Changing a participant's age in data records by an unimportant amount to fit enrollment criteria

Plagiarism

- Intentional use of someone else's words, thoughts, or ideas, as though they are your own

- Also includes "self-plagiarism" – author using his/her own published material in another work without citation

Research Misconduct

- National Health Research Act 2 2013

"20. (1) A health researcher commits misconduct if the health researcher—

(k) fabricates, falsifies or knowingly plagiarises data;

..\Health Research Act 2013.pdf

Research Involving Animals

- The guiding principles for the use of animals in research are the three R's:
  - **Replacement**: Use alternative, non-animal methods to achieve the same scientific aim
  - **Reduction**: Use statistical methods so that a smaller number of animals are required
  - **Refinement:** Improve the experiments so that animals do not suffer

Discussion

Mentor-Mentee Relationships

- What are the grey areas?

Peer review Processes

- What are the grey areas?
  - Manuscripts/Publications
  - Grants

Authorship

- Authorship
- First author vs Last author
- Ghost authorship
- Gift authorship

- ‘Publish or Perish concept’

A preliminary taxonomy of research misconduct (ranked by seriousness) 3/4

- Publication of post hoc analyses without declaration that they were post hoc
- Gift authorship
- Not attributing other authors
- Not disclosing a conflict of interest

Smith R. www.bmj.com/talks

A preliminary taxonomy of research misconduct (ranked by seriousness) 4/4

- Not attempting to publish completed research
- Failure to do an adequate search of existing research before beginning new research

Smith R. www.bmj.com/talks

Collaborative Research

- North-South Partnerships/Collaborations
- Movement of Samples
- Intellectual property

Privacy and Confidentiality

- What are the applicable laws?
- What are the grey areas

Research Ethics Course

- History and Principles of Research Ethics
  - Nuremberg Code
  - Declaration of Helsinki
  - Belmont Report

- Principles of Research Ethics
  - Respect of persons (autonomy)
  - Beneficence (Non-maleficence)
  - Justice

https://gcp.nidatraining.org/

- Research Ethics Course
  - International laws
  - National Laws (National Heath Research Act of 2013)
  - Institutional Guidelines
  - Institutional Review Board (IRBs)/ Research Ethics Committee
  - Informed Consent
  - Privacy and Confidentiality
  - Documentation and Record Keeping
  - Participants recruiting, retention and follow-ups
  - Participants safety and adverse events reporting
  - Writing a Research Protocol
  - Research Misconduct

Discussion

Acknowledgement

Some slides modified and adapted from **Christine Grady** presentation, Department of Clinical Bioethics, National Institutes of Health, USA.

Most of the material is taken from: Emanuel, E.J., Wendler, D., Killen, J. and Grady, C., 2004. **What makes clinical research in developing countries ethical?** The benchmarks of ethical research. *The Journal of infectious diseases*, *189*(5), pp.930-937.