Ethical issues in clinical trials

with a focus on COVID-19 vaccine trials

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Introduction

- Research has its own set of ethics guidelines
  - Research ethics is a subset of the broader field of bioethics, specifically addressing ethical issues that arise in research
  - Most often focuses on human resaerch studies
- Why are specific ethics guidelines needed? (aren't researchers ethical people?)
- Why wouldn't guidelines for doctors and medical practice also apply to research?

Medical care versus research

Medical care

Physicians are dedicated to the care of the patient:

"A physician shall be dedicated to providing competent medical care, with compassion and respect for human dignity and rights."

"A physician shall, while caring for a patient, regard responsibility to the patient as paramount."*

AMA Code of Medical Ethics

Research

Researchers' commitment is to generate sound scientific findings that contribute something valuable to society ***("social value")***

Researchers must also protect the individuals who participate in trials

At times, these two goals—advancing science, and protecting participants—could be in tension with each other, or even conflict

- For example, a researcher could learn valuable information conducting highly risky human trials;
- This might not be reasonable to do, or fair for the participants.

Public trust and research

- Trust is important in both medicine and research (lack of trust in physicians hampers the ability of doctors to deliver needed and beneficial medical care)
- Public trust in research is very fragile and also critical
- Research does not always bring benefits right away; a long sequence of research trials may be needed to get positive results;
- Public investment, and cooperation with, research is needed during these long periods of investigation
- The research process relies heavily on public trust, and sometimes public funding

Ethics guidelines for research: principles versus procedures

Guidelines and frameworks discuss ***ethical principles***

- Stipulating that research should be designed to produce useful knowledge (social value)
- Placing limits on risks to participants
- Emphasizing voluntariness and informed consent
- Addressing the fair distribution of benefits of research

Regulations largely specify ***procedures*** designed to support these principles:

- Institutional Review Board (IRB) review
  - Review of each research protocol by an independent committee to assess protections for study participants
- Informed consent process and documents
- Documentation of study activities

Ethics guidelines

- World Medical Association **Declaration of Helsinki**

WMA

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

- **CIOMS* guidelines**

*Council of International Organizations of Medical Sciences

CIOMS guidelines—partial list

GUIDELINE 1: SCIENTIFIC AND SOCIAL VALUE AND RESPECT FOR RIGHTS

GUIDELINE 2: RESEARCH CONDUCTED IN LOW-RESOURCE SETTINGS

GUIDELINE 3: EQUITABLE DISTRIBUTION OF BENEFITS AND BURDENS IN THE SELECTION OF INDIVIDUALS AND GROUPS OF PARTICIPANTS IN RESEARCH

GUIDELINE 4: POTENTIAL INDIVIDUAL BENEFITS AND RISKS OF RESEARCH

GUIDELINE 5: CHOICE OF CONTROL IN CLINICAL TRIALS

GUIDELINE 6: CARING FOR PARTICIPANTS' HEALTH NEEDS

GUIDELINE 7: COMMUNITY ENGAGEMENT

GUIDELINE 8: COLLABORATIVE PARTNERSHIP AND CAPACITY-BUILDING FOR RESEARCH AND RESEARCH REVIEW

GUIDELINE 9: INDIVIDUALS CAPABLE OF GIVING INFORMED CONSENT

GUIDELINE 10: MODIFICATIONS AND WAIVERS OF INFORMED CONSENT

GUIDELINE 11: COLLECTION, STORAGE AND USE OF BIOLOGICAL MATERIALS AND RELATED DATA

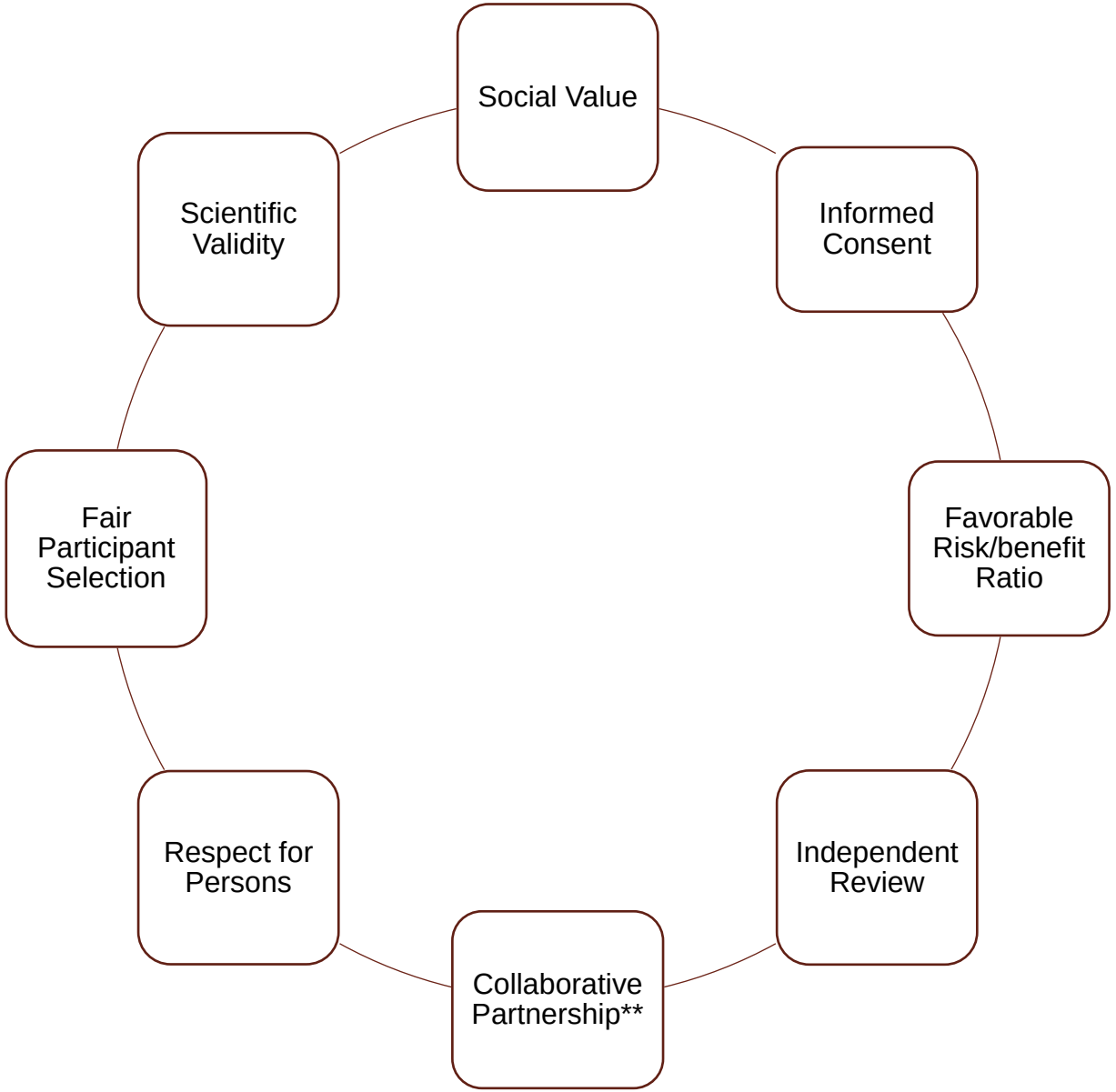
GUIDELINE 12: COLLECTION, STORAGE AND USE OF DATA IN HEALTH-RELATED RESEARCH

GUIDELINE 13: REIMBURSEMENT AND COMPENSATION FOR RESEARCH PARTICIPANTS

GUIDELINE 14: TREATMENT AND COMPENSATION FOR RESEARCH-RELATED HARMS

GUIDELINE 15: RESEARCH INVOLVING VULNERABLE PERSONS AND GROUPS

Ethical framework for evaluating research*



***Emanuel, Wendler, Grady, *What makes Clinical Research Ethical?* JAMA 2000**

****Emanuel, Wendler, Killen, Grady, What makes clinical research in developing countries ethical? The benchmarks of ethical research. JID 2004**

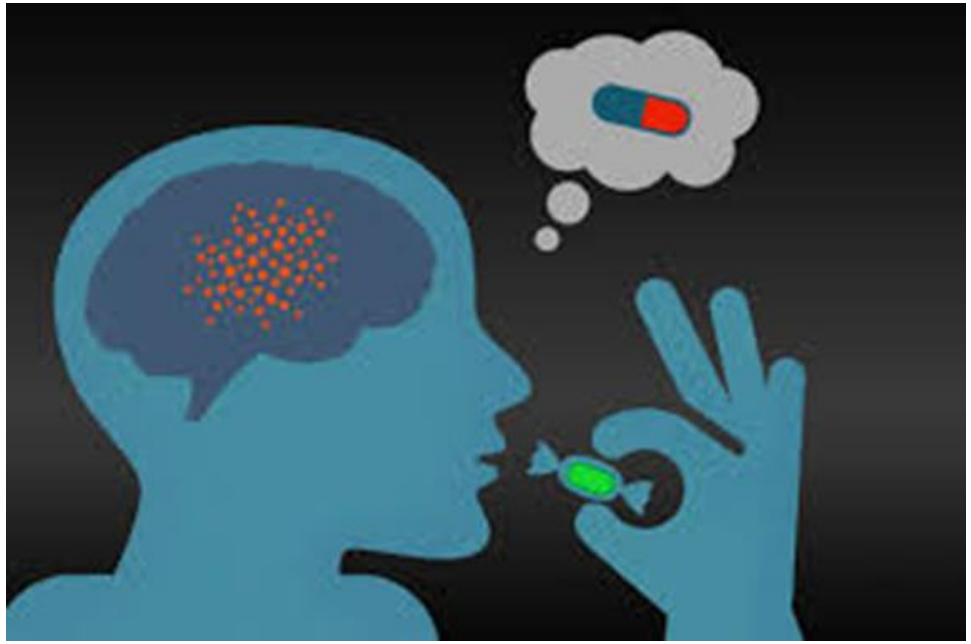
Requirement	Justifying Ethical Values	Example Benchmarks
Collaborative Partnership	Beneficence, nonexploitation, and respect for communities	Involve partners in sharing responsibilities for determining the importance of health problem, assessing the value of research, planning, conducting, and overseeing research, and integrating research into the health-care system.
Social Value	Scarce resources and nonexploitation	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.
Scientific Validity	Scarce resources and nonexploitation	Ensure that the scientific design realizes the scientific objectives while guaranteeing research participants the health-care interventions to which they are entitled.
Fair Selection of Study Population	Justice	Select the study population to minimize the risks of the research and enhance other principles, especially collaborative partnership and social value.
Favorable Risk/Benefit Ratio	Nonmaleficence, beneficence, and nonexploitation	Assess the potential risks and benefits of the research to the study population in the context of its health risks.
Independent Review	Public accountability, minimizing influence of any conflicts of interest	Ensure public accountability through reviews mandated by laws and regulations.
Informed Consent	Respect for participants' autonomy	Disclose information in culturally and linguistically appropriate formats.
Respect for Participants	Respect for participants' autonomy and welfare	Develop and implement procedures to protect the confidentiality of recruited and enrolled participants.

Ethical issues in COVID vaccine trials: examples for discussion

1. Is it ethical to continue to use placebo controlled trials now that effective authorized vaccines are available?
2. Which groups should be targeted for enrollment in clinical trials at present?
3. Do research sponsors have an obligation to provide vaccine doses to countries that participate in clinical trials?

(1) Placebo controlled trials

Are placebo-controlled trials still ethically acceptable once proven vaccines are available?



<u>Placebo controlled trial</u>: for scientific reasons, the new vaccine being studied is compared to an inactive product (placebo). Study participants don't know whether they got the real thing or the placebo.

Placebo control versus active control

Pfizer, Moderna, and J&J vaccines have been given authorization by the FDA for widespread use

One alternative to a placebo controlled trial is to test a new vaccine by comparing directly to an existing vaccine (“active control trial”)

- Placebo:
  - Faster and more clear cut answer to research question,
  - But some participants do not receive active vaccine
- Active control:
  - Every participant receives active vaccine,
  - Trials are much more complicated, lengthy, may be difficult to interpret results

Ethical Guidelines

- **Helsinki article 33**
  - Placebo use only when effective treatment does not exist or
  - "for compelling and scientifically sound methodological reasons… *and* patients will not be subject to risks of serious or irreversible harm"
- **CIOMS guideline 11**: control groups in clinical trials
  - Extensive discussion of rationale and justification for placebo controls

CIOMS: choice of control in clinical trials

- Participants in control groups generally should receive an established effective intervention

- A placebo may be given to control groups when:
  - There is **no** established effective intervention, OR
  - There is an established effective intervention, BUT
    1. There are compelling scientific reasons to use a placebo, *and*
    2. Delaying/withholding the effective intervention will not significantly increase risks to participants in the control group.

Arguments against placebo controlled trials

- The EUA vaccines are effective and widely recommended, so they are the “standard of care”
  - Ethics guidelines say study participants deserve to get treatments that are at least as good as the standard of care

- People in placebo group are at risk of getting infected with COVID due to exposure in the community
  - These participants could experience an *avoidable harm*: not caused by the trial, but it could have been prevented by researchers

Two arguments for continuing trials with placebo controls

Social value argument

- Even when a new vaccine is proven effective, trials should continue with placebo controls
- The social value of the information is high:
  - Additional vaccines are needed;
  - The demands of a public health emergency allow researchers to continue with placebo controls due to urgent need for data from these trials
  - Study participants always given option to discontinue, but no promise of vaccine in midstream

Public health standards/health policy argument

- In some countries, even when first vaccines are proven effective, they are not widely available
- Obligation to provide vaccines to the population is a health policy question;
- Standard of care in some places has not yet shifted to universal vaccination;
- Trials can continue, even while some high risk groups may be prioritized to receive first vaccine.

Placebo arguments, cont'd

Participant choice

- Participants can choose not to join, or can choose to leave, a trial at any time.
- Participants can use other measures to protect themselves against COVID (masks, social distancing, etc).

Lower risk in the community (depends on local context)

In our DMV area specifically:

- Cases are going down and high vaccination rates in the population help prevent widespread transmission

(2) Which populations or groups should be targeted for enrollment in current COVID-19 vaccine trials?

Fall 2020: there were no authorized COVID vaccines available

Research groups conducting COVID vaccine trials sought diversity in clinical trial enrollment:

- Reflect the groups hardest hit by the pandemic
- Provide both direct and indirect benefits to diverse groups, including Black communities, LatinX communities, front line workers, and others with high risk of exposure to COVID
- Help to dispel mistrust about vaccines and about clinical research in general
- Facilitate transition to health care when approved vaccines are available

SpFN trial enrolling healthy, unvaccinated individuals

July 2021: authorized vaccines now widely available across the US for all groups ages 12 and older

- New vaccine trials need to enroll unvaccinated people so they can measure the immune response to the new vaccine
- At this stage, authorized vaccines (Pfizer, Moderna) have been offered to all residents over age 18; Pfizer for those over age 12

Vaccination rates in the DMV area*		
Location	1st dose	2 doses
Maryland	75.7%	58%
• Montgomery Co.		63%
• Prince George's Co.		47%
• Frederick Co.		58%
DC	62.1%	53.3%
• Wards 7 and 8		24 – 30%
• All other Wards		Over 40%
VA	53.1%	59%

* https://coronavirus.dc.gov/data/vaccination ; https://coronavirus.maryland.gov/#Vaccine; https://www.vdh.virginia.gov/coronavirus/covid-19-vaccine-summary/

Groups less likely to be vaccinated

- African Americans and LatinX communities have lower rates of vaccinations compared to whites in Maryland, DC and VA
- DC: wards 7 and 8 have lowest coverage
- MD: PG County has lower rate than Montgomery and Frederick

- Age group 18 to 29 has lowest rate of all adult age groups (not counting those under 18)
- Vaccination rates are lower in Republican districts compared to Democratic (MD District 1 at 50% versus District 8 at 62%)*
- * https://geographicinsights.iq.harvard.edu/vaccineuscongress

Targeting unvaccinated groups

- Does it make a difference *why* someone did not get vaccinated?
- Is there a chance someone would prefer an authorized vaccine but is swayed by the compensation to join the trial?
- Does the clinical trial possibly exploit individuals who have few choices for earning extra income?
- Does it make a difference if the groups that may be targeted for clinical trial enrollment have systematic difficulties accessing health care?
- ***Does the clinical trial contribute to ongoing injustice, or help to reduce it?***

(3) Who benefits from clinical trials?

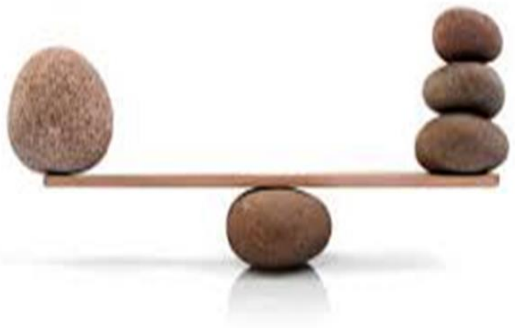
- Some large international COVID vaccine trials have been conducted in multiple countries
- Access to approved vaccines in these countries may be limited
- Should companies or organizations conducting trials in these participating countries make specific commitments to provide vaccine doses if the product is proven effective?

Public trust and vaccine trials

- In low and middle income countries, despite more favorable attitudes towards vaccines in general, mistrust can be generated in the context of vaccine trials
- Community engagement work in Ebola trials addressed issues of community trust

If people do not have confidence in you, [...] you will not succeed. Yes, the first thing is confidence building – trust. People need to have trust in you that presented the message. If they do not have trust in you, even when you present the message, they will sit down and listen to you, [but] these people do not accept the messaging. . (CLT008).

Dada, Sara, et al. "Lessons learned from engaging communities for Ebola vaccine trials in Sierra Leone: reciprocity, relatability, relationships and respect (the four R's)." *BMC public health* 19.1 (2019): 1665.



Summary

- Ethical issues frequently involve tradeoffs (multiple ethical commitments at the same time; need to balance the various commitments)
- Each situation involves interpreting and apply ethical guidelines
- Research has the possibility to deliver great societal benefit; maintaining public trust in research is essential
- Protection of individuals who participate in research is paramount