Operationalizing Ethics- A Focus on Informed Consent

HIV Cure Research Training Curriculum

Informed Consent Module Presented by:

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CUREiculum

The HIV CURE research training curriculum is a collaborative project aimed at making HIV cure research science accessible to the community and the HIV research field.

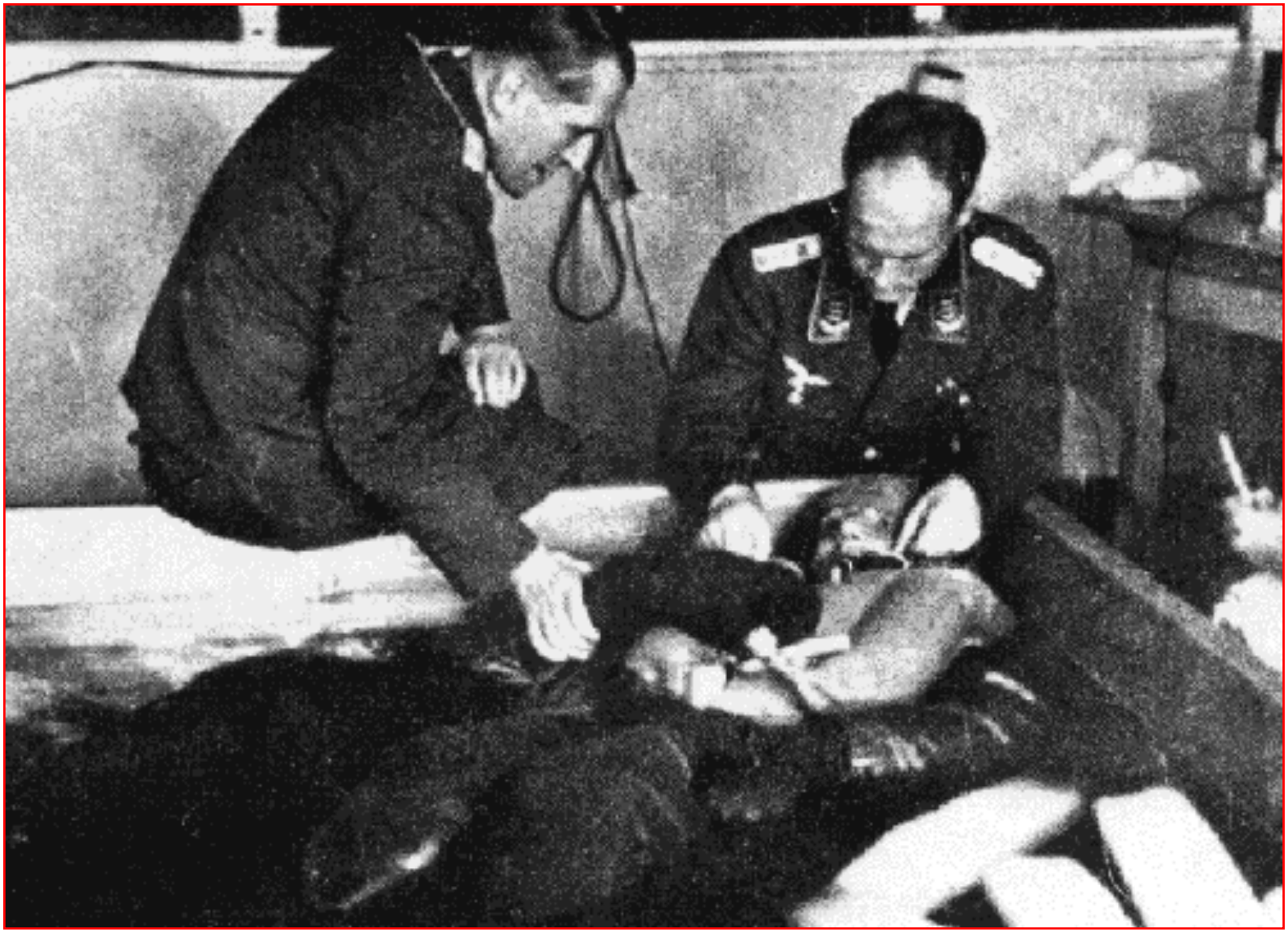
Objectives

Participants will be able to:

- Discuss the protection of human research subjects in the United States
- Understand informed consent in a global health context
- Summarize international guidelines
- Addresses differences between HIV cure research and other fields

Informed Consent and the Protection of Human Subjects Research

Nazi Medical Experiments in WWII



Case No. 1 of the Nuremberg Military Tribunal
U.S.A. vs. Karl Brandt et al.

15 of 23 guilty, 7 hanged, 5 life sentences

Nuremberg Code 1947

- **Voluntary informed consent essential**
- Research should yield useful results
- Base research on prior work
- Avoid physical and mental suffering
- No expectation of death or disabling injury
- Risk must be outweighed by importance
- Subjects must be protected from injury
- Qualified scientists, adequate facilities
- Subject free to stop at any time
- Investigator must be ready to withdraw subject

"Before IRBs, the only consent required was that of a researcher's department head. ***The Nuremberg Code was ignored in practice****. As I look back on it, the interpretation of these codes was that they were necessary for barbarians, but not for fine upstanding people... In this prestigious unit we had a very strong obligation to behave in a civilized manner."*

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Dr. William Silverman, Columbia University pediatrician, on the postwar mentality (Sugarman interviews)

“Untreated Syphilis in the Male Negro”

US National Research Act, July 1974

- Established National Commission for Protection of Human Subjects
- Led to 1981 Code of Federal Regulations
  - Institutional Review Boards (IRBs)
  - Informed consent
- And the “Common Rule” harmonizing regulations protecting human subjects in research across all US Federal agencies, 1991

Public Law 93-348

Charge to the National Commission for Protection of Human Subjects

- Identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects
- Develop guidelines to assure that such research is conducted in accordance with those principles

National Research Act, 1974 (PL 93-348)

The Belmont Report:

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

- Respect for persons
  - Informed consent
  - Privacy & confidentiality
- Beneficence
  - Study design
  - Risk-benefit
- Justice
  - Selection of subjects
  - Recruitment
  - Populations under study

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979

How Do These Guidelines Get Enforced?

- Institutional Review Board (IRB) or Ethics Review Committee
  - A committee that reviews biomedical and behavioral research involving human subjects. The goal is to make sure participants understand they are in research, and the risk-benefit ratio is appropriate

- Data Safety and Monitoring Board
  - An independent group of experts that may be required to meet periodically, to evaluate the safety, study conduct and progress of a trial, and to make recommendations about continuation or termination

In World of Global Research, How Do We Harmonize IRB Review?

- International IRBs are often under-financed
- Members may lack training
- Lines of authority, communication, and relationships between IRBs and external parties often poorly defined
- Increased commercialization of research, proliferation of multi-site trials, more and new types of protocols present significant challenges

What is Required in Informed Consent?

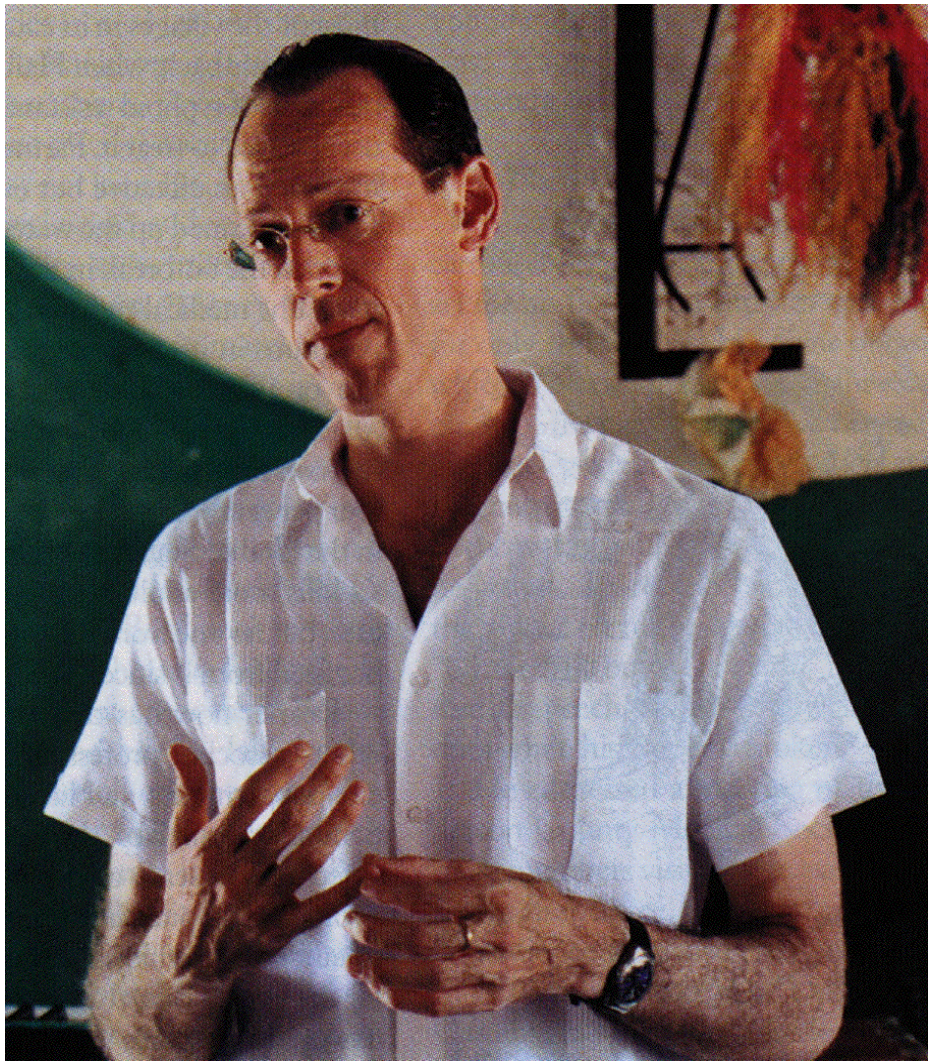
US Federal Regulations Spell Out

- The study involves research; explanation of study purpose, procedures and duration
- Reasonably foreseeable risks/discomforts
- Benefits to subject/others; lack of direct benefit should be stated. Include potential societal benefits
- Alternative should be described
- Confidentiality of identifying records
- Explanation of compensation and/or treatments if injury occurs when risk is greater than minimal
- Participation is voluntary, can discontinue; refusal will involve no penalty/loss of entitled benefits

Challenges of Poverty and Inequality Underlie Need for More Protections

- Incomplete ‘transitions’ – demographic, nutrition, and epidemiologic
  - New & persisting infectious diseases, especially AIDS
  - High child mortality in Africa
  - Simultaneous rise of chronic diseases and risk factors
- Persisting or increasing inequality and negative consequences of globalization in the poorest parts of the world

Social Inequalities Underlie Individual Health Outcomes



The inequalities of outcomes are biological reflections of social fault lines…inequality itself constitutes our modern plague

-Paul Farmer, MD, PhD

Vulnerability & HIV Prevention Research

"HIV disproportionately affects vulnerable populations, and because social determinants of the AIDS pandemic encompass poverty, stigma, discrimination, and injustice … From a scientific perspective, the most desirable populations for HIV prevention research are often the most vulnerable. These most vulnerable populations have a profound need for protection against exploitation."

MacQueen, K and Sugarman, J. HIV Prevention Trials Ethics Guidance for Research. HPTN Ethics Working Group, 2003.

Council for International Organizations of Medical Sciences (CIOMS)

- 2002 revisions aim to “reflect conditions and needs of low-resource countries, and implications for multinational research in which they may be partners”
- Revisions currently under discussion
- Example of how to define ‘benefits’

Example: Define Benefits

1990 US Federal Regulations: Benefit to subjects or society

2002 CIOMS - *Guideline 10:* *Research in populations and communities with limited resources*

CIOMS: Guideline 10

- "Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:
  - the research is **responsive to the health needs** and the priorities of the population or community in which it is to be carried out; and
  - any intervention or product developed, or knowledge generated, will be made **reasonably available** for the benefit of that population or community"

How do differences between HIV prevention, treatment and cure affect informed consent?

Difference Between HIV Prevention, Treatment and Cure

Research type	Participant status	Research goal	Selected ethical issues
HIV treatment	HIV positive	Effective suppression of virus, boosting immune system	All phases; risk of drug side- effects; adherence problems
HIV prevention	HIV negative	Effective methods of preventing HIV acquisition	Seroconversion of participants during trial; behavioral disinhibition
HIV 'cure'	HIV positive	Interventions to permanently suppress or eradicate HIV	**Early phase;** risk of intervention side-effects; existence of known effective treatment

Clinical “Cure” Trials Are Small, Early Phase Studies

- Many are first-in-human studies, testing toxicity, with **no prospect of direct medical benefit and many, potentially significant risks**
- In contrast to volunteers for other early phase trials (e.g., cancer) who may be very ill, HIV ‘cure’ trials recruit people who are relatively **healthy on ART** medication
- Some may be asked to **interrupt treatment**, which will have additional risks

Managing Expectations for Informed Consent

- How can we ensure understanding that “this study won’t cure your HIV”?
- Acquiring knowledge can happen before, during, and after the initial contact with study staff.
- What kinds of studies should be undertaken to investigate whether consent is truly informed?
  - Baseline data, prior to recruitment
  - Interviewing both joiners and decliners
  - Over time

The Language of HIV Cure Trials Matters

- How trials are described:
  - Experiment vs. “study”?
  - Goals? “Cure, Remission, Eradication, Functional cure, Sterilizing cure…”
  - Early phase research may not look for a functional cure, just for **safety** in humans
  - Remission, which implies that HIV could return, may be the **most informative** word to use

How Does Language Play a Role in Informing?

- Unknown risks- common in early phase trials; honest portraits are hard to understand
- Analysis of 13 ‘cure’ consent forms documented 4-13 risk types, listed in no particular order, often without mention of severity or likelihood

Protocol Sample

"There may be adverse effects that are presently *unknown and unforeseeable…* Possible consequences of [intervention] are unknown. It could have no effect or a positive effect… [It] could also possibly cause cancer, or even spread to your reproductive organs and be passed on to any future children you may have. However, to date no such events have been reported… so this risk is still theoretical… a test to monitor this will be run at various times points during the study."

Henderson, Gail E. AIDS Research and Human Retroviruses

Seductive Messages About Benefits?

- The study purpose can be described as
  - “to prevent HIV from killing CD4+ T cells”
  - “to achieve HIV remission”
  - “to eradicate hidden virus… unmask or flush out the latent HIV in your cells”
- This contrasts with the clear, “no benefit” message in benefit section of consent forms
- Language use in study purpose section and in recruitment conversations is key

Will Participation Be Truly Voluntary?

Concerns for HIV ‘cure’ studies in South Africa:

- Conducting early phase trials among populations that are particularly vulnerable because of structural inequalities and low literacy
  - Studies show that people join trials to get health care, often not a voluntary choice
  - Despite legal focus on informed consent, long documents are unreadable by ordinary people
  - Shortcomings in understanding elements of informed consent undermine voluntary choice.

Staunton, C. BMC Medical Ethics 15,16:3, 2015

Conclusions

- Tools can be developed by Research Ethics Committees, providing additional safeguards (Staunton, 2015)
- Be vigilant in messages from consent forms and education of volunteers throughout study participation (Henderson et al., 2006)
- Initiate research that collects baseline data on people before recruitment, follows joiners and decliners longitudinally, and collect data after study is over (Peay & Henderson, 2015)

Questions

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