Conducting Research on Ethical Issues

Ezekiel J. Emanuel, M.D., Ph.D.

Department of Bioethics
The Clinical Center
National Institutes of Health

Previous Pandemics

- 1918-19—Spanish flu ~40 million deaths
- 1957—Asian flu 2 million deaths
- 1968—Hong Kong flu 1 million deaths

Prospects for Influenza Pandemic

- Experts disagree about chances of a new pandemic.
- 3 in last 88 years—3-4% chance per year.
- "Experts at WHO and elsewhere believe that the world is now closer to another influenza pandemic than at any time since 1968."

Prospects for Influenza Pandemic

	Moderate 1957 & 1968	Severe 1918 like
Illness	90 million	90 million
Outpatient visits	45 million	45 million
Hospitalization	865,000	9.9 million
ICU care	129,000	1.5 million
Respirators	65,000	743,000
Deaths	209,000	1.9 million

Current Health Care Resources

- Hospital beds (USA 2007) 947,000
- ICU beds (USA 2007) 90,400
  (includes all types
  medical, neonatal, burn)

DISCLAIMER

The views expressed in this presentation do not represent the views of the NIH, DHHS, or any other government agency or official. These are not their views.

DISCLAIMER

These views merely represent
The Truth.

Influenza Vaccines

- 500 million doses, but it is thought each person will need two doses. Thus, only 250 million people world wide will be vaccinated under optimal conditions.
- Each country will nationalize its vaccine—that is ensure all its citizens are vaccinated before permitting any vaccine to be exported.

Influenza Vaccine

- In the United States, there is only 1 influenza vaccine manufacturing plant.
- This plant is capable of manufacturing 3 to 5 million 15 µg vaccines per week.
- Each person requires 2 doses. (This is an optimistic estimation. Recent NIAID studies suggest people may need higher doses.)

Influenza Vaccine

- Hence a maximum of 2.5 million people per week vaccinated.
- Over 6 months, a maximum of 20% of the population could be vaccinated in the first year.

Many Allocation Questions

Who should get a scarce influenza vaccine in a pandemic?

Who should get a scarce respirator?

Allocating Values

- **Equal opportunity**
  - First-come, first-served
  - Lottery
- **Helping the worst-off**
  - Save the sickest first
  - Save the youngest first

Allocating Values

- **Maximizing benefits**
  - Save the most lives
  - Save the most life-years
- **Promote social value**
  - Instrumental value
  - Reciprocity

A Case

Asthma Study with Children

- Children will be enrolled in a placebo controlled trial of a new immune modulator for moderate to severe asthma.

A Case

The trial will last 12 weeks, involving

- At least 17 office visits
- 3 physical exams
- Daily diaries for spirometry
- 3 quality of life assessments
- 23 blood draws
- 2 sputum inductions
- CXR, EKG, skin tests, vaccines

A Case

- It is proposed that children be paid $1,460 for participating in this trial.
- Is paying children to participate in research ever ethical?
- When is paying children excessive?

A Charge

[I]t is difficult to avoid coercing subjects in most settings where clinical investigation in the developing world is conducted. African subjects with relatively little understanding of medical aspects of research participation, indisposed toward resisting the suggestions of Western doctors, perhaps operating under the mistaken notion that they are being treated, and possibly receiving some ancillary benefits from participation in the research, are very susceptible to coercion.

Nicholas Christakis

A Charge

- When is research coercive?
- What makes research coercive?
- Are participants in developing countries necessarily coerced into participating in research?

Distinctions

It is important to distinguish:

- The ethics of conducting research
- Conducting research on ethics questions

Research on ethics questions is obtaining information on ethical issues that arise either in clinical care or in research setting.

Types of Research on Ethical Issues

Four Types of Research

- Historical Research
- Conceptual Research
- Empirical Research
- Policy Research or Policy Analysis

Types of Ethical Issues

- Physician-Patient Relationship
  - Truth Telling
  - Confidentiality
  - Informed Consent
- End of Life Care
  - Euthanasia and PAS
  - Withdrawing Life Sustaining Care

Types of Ethical Issues

- Allocating Health Care Resources
  - Socio-economic differences in Resource Utilization
  - Defining Basic Health Services
- Human Subjects Research
  - Informed Consent
  - Randomization
  - Placebo Controls
  - Phase I Oncology Trials

Types of Ethical Issues

- Genetics
  - Defining Genetic Defects
  - Defining Enhancements
  - Effects of Genetics Tests
- Reproductive Health Care
  - Cloning
  - Stem Cells
  - Abortion
  - Selling Embryos

Types of Ethical Issues

- Methods of Medical Ethics

Research on Ethical Issues

	Historical	Conceptual	Empirical	Policy
Phys-Pat Relation		Is consent without understanding ethical?	Do oncologists tell patients the truth?	
End of Life Care	History of euthanasia debates		How often do dying patients get chemo?	
Clinical Research		Are Phase I trials ethical?	Do Phase I patients understand?	

Research Process

- Define the question and specify the objectives
- Review the relevant literature

Research Process

- Establish the methodology
  - What is the sample population?
  - What are the data collection instruments?
  - What are the problems and how should they be address?

    Frequently no gold standard instruments

Research Process

- Statistical Considerations
  - Sample size and power
  - Modeling and linear regression models
- Pilot Studies
  - Work out problems
  - Assess feasibility

Research Process

- Conduct
  - Develop protocol
  - IRB Review
  - Compliance issues

An Example

- Informed consent is less than perfect.

Purpose

Study	Participants	Understanding
Lynoe 1991	Swedish women in gynec. study	98% research study
Joffe 2001	US oncology studies	30% drugs unproven
Pitisuttithum 1997	Thai HIV vaccine study	80% vaccine might not work
Ciriscione 2003	US rheumatoid arthritis drug study	100% research experiment

Randomization

Study	Participants	Understanding
Hietanen 2000	Finnish women breast cancer	23% randomization
Harrison 1995	US HIV vaccine	21% everyone get vaccine
Howard 1981	US men cardiac Beta blocker	42% randomization
Pace 2003	Thai HIV IL-2 treatment	42% randomization

Risks

Study	Participants	Understanding
Bergler 1980	U.S. Hypertension	28% not recall 2 risks 2 hours after consent
Miller 1994	Analgesia	52% not recall even one risk 60 days later
Dougherty 2000	US oncology	100% recall at least 1 side effect
Leach 1999	Gambian mothers vaccine	56% recall 1 or more risks

Right to Withdraw

Study and Year	Country	Subjects	Knew they could Withdraw
Pitisuttithum 1997	Thailand	33 HIV vaccine	88%
Karim 1998	South Africa	56 perinatal HIV prevent	93% (freedom to quit)
Lynoe 2000	Bang-ladesh	105 iron for pregnancy	48%

How can we Improve Informed Consent?

- What are the possible interventions?

How can we Improve Informed Consent?

- Four main approaches:
  - Video or computer-based disclosure
  - Shorter, more readable forms
  - More time spent on discussion
  - Using short tests to confirm understanding and guide discussion

Video or Computer-Based Presentation

- Only 3 out of 12 trials showed an improvement in understanding due to video or computerized presentation (P<.05)
- Although videos and computers may improve understanding sometimes, they usually have not worked

Shorter, More Readable Consent Forms

- 6 out of 15 trials showed an improvement in understanding (P<.05)
- But 5 of the 6 trials that showed improvement were simulated consent processes
- Improved consent forms may be no better than multimedia

Extended Discussion

- 3 out of 5 trials showed an improvement in understanding (P<.001)
- The other 2 trials showed trends toward improvement (P=.054, P=.08)

Using a Test to Confirm Understanding

- 5 out of 5 studies showed an improvement in understanding ($P<.05$)
- But these studies may have mistaken rote memorization for understanding