– introductory lectures in bioethics –

Experimentation on Human Subjects

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Fraught with Tension

- Huge benefits from research. Indispensable in developing good treatments. “Historical” and nonhuman animal studies not sufficient.
- Informed consent. If medical treatment requires informed consent, greater reason to require consent to research – exposure to risk, less reason to think it benefits patient.
- No competing right. No future patient has a *right* to the benefits of research.
- Loyalty, oath. Experimental treatment is often administered by patient’s physician.

The Nuremberg Code

- Horrific Nazi doctor experiments: typhus vaccine, bone TXs not needed, infection with gangrene to study it, etc. Two of resulting code's provisions:
  - Voluntary consent is essential.
  - Experiment is prohibited if reason to think death or disabling injury will occur.
- Some experiments in U.S. were also horrific – Tuskegee syphilis study, e.g.
- Underlying rationale of code: Never treat a person merely as a means .... (Kant)

Questions Beyond Consent

- How much information, of what sorts?
  - OK to withhold information that subjects will irrationally misinterpret?
- Consent required even if no harm risked?
- If subjects receive less than “standard of care” but they would not have received it anyhow, have they been harmed?
- Do randomized clinical trials (RCTs) violate physician loyalty to patients?
- Are placebo-arm trials ethical? New drug trials, especially.

Withholding Misleading Information

Jewish Chronic Disease Hospital

- Brooklyn NY, 1963, debilitated patients.
- Purpose: measure rate of rejecting foreign cancer cells by persons with non-CA illnesses. Previous studies: People with CA take longer than healthy people to expel foreign CA cells.
- Injecting CA cells was non-therapeutic research, but arguably harmless.
- To ensure sufficient enrollment, researchers avoided saying "...cancer cells." No matter how misleading, such info was 'material.'

Comparative Harm

Willowbrook Hepatitis Studies (1956-71)

- Gamma globulin injections thought to generate immunity to hepatitis.
- In separate ward at Willowbrook State School for developmentally disabled, injected children with gamma globulin and exposed them to milder hepatitis strain than was normal at WSS. Were arguably better off for being in study.
- Parents not told of hepatitis exposure.
- Study led to arguably significant advances.

‘Study in Nature’ Gone Awry

Tuskegee Syphilis Experiment (1932-72)

- Study of black men with advanced untreated syphilis by U.S. Public Health Service, to discern natural course of the disease.
- Told they would receive treatment for “bad blood” with medications that were the only treatments at time (not regarded as very effective). Were it not for study, very unlikely they would have had any treatment.
- Received low-dose treatment, aspirin, iron ointments, burial stipends – sufficient to get them into study.

Tuskegee (continued)

- Spinal taps and autopsies on some.
- Did not receive marginally better treatments that became known by 1940.
- When truly effective penicillin arrived by 1945, USPHS took active steps to insure subjects did not receive it.
- Continued until 1972, when exposed by researcher who was not part of study.
- Would this ever have been done on whites?
- Legacy: distrust among African-Americans.

Randomized Clinical Trials (RCTs)

- Very important in effectiveness trials after basic safety trials are completed.
- Active-control trial (ACT): new therapy, existing therapy, and perhaps placebo.
- Placebo-control trial (PCT): new therapy, placebo.
- Gold standard is a double-blind RCT. Neither researchers, caregivers, nor subjects know which arm patient is in.

RCTs – the Need for ‘Equipoise’

May a provider, acting in best interest of patient, participate in a RCT? YES, if

- Provider is in ‘equipoise’ – reasonably believes that patient is served no worse or no better by any one arm of trial than any other.
- Patient is accurately informed of nature of trial, including randomization.
- Description of randomization is not deceptive (nothing glossed to portray it as equipoise).
- Provider has no conflict of interest.

When Should a Trial Be Stopped?

- ECMO (extracorporeal membrane oxygen-ation), now standard of care for children.
- Initial trials of ECMO faced this question: early positive results, but sample still too small for statistical confidence.
- Then already, treatment likely more effective than existing therapy, but uncertain.

  HOW MUCH CERTAINTY ARE WE JUSTIFIED IN TRYING TO ACHIEVE if current subjects in the non-ECMO arm would likely be better served if trial were stopped?

International Trials: What Is Appropriate 'Standard of Care'?

- Context: difficult to recruit subjects (AZT in use), but subjects available in poor country.
- Standard of Care (SoC) in rich country (AZT) determined by effectiveness. Lower SoC in poor country (no AZT) is determined by lack of resources, not medical opinion differences.
  - Placebos justified if No AZT is SoC, but not justified if AZT is SoC
  - Which SoC is proper reference for researcher?
  - Precise effectiveness cannot be determined without PCTs

International Trials – Exploitation and Fairness

- Does it make a difference if benefits of the trial are primarily for rich country's citizens, not poor country's?
- Suppose benefits are potentially for both, but only if poor country gets assistance. Does fairness require financial "compensation" of poor country by rich one so poor country's citizens can benefit, too?

Trials for New Drug Approval

- When may PCTs be used in trial of new drug for condition that has an existing treatment?
- USFDA allows PCTs when and only when
  - Compelling scientific reasons – "assay sensitivity" because of existing therapy doubts.
  - Delay/withholding of existing Rx would be no more than minor increase above minimal risk.
  - Subjects are informed of PCT design.
- NOTE: pharmaceutical companies badly want to use PCTs so "me-too" drugs get approved.

Drug Trials (continued)

- Informed consent: Is information accurate when purpose is said to be "for benefit of patients"?
  - New drug may be only a me-too drug.
  - Trial results may be kept secret.
  - Trial may be stopped early, to co's gain.
- Is patient benefit really the goal if only "surrogate outcomes," not real benefit-to-patient outcomes are used?
  - E.g., PCSK9 inhibitors: lower blood cholesterol, not cardiac incidents or longevity.

Summary

- Experimentation poses conflict between treating individual subject not merely as a means and large potential benefit to others.
- A firm right to informed consent still leaves decisions at the edges about
  - How much and what information
  - Alternative reference points for standard-of-care that determine whether there is risk or harm
  - When to stop a trial with good early results
  - What is true “equipoise” in a RCT
  - When, if there is existing therapy, may placebos be used to test a new therapy