

# CLINICAL & TRANSLATIONAL SCIENCE INSTITUTE

## Research Ethics – Concepts, Hot Topics and Help with Tough Decisions

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# Outline

Review of concepts

Hot Topics

- Consent in comparative effectiveness research
  - SUPPORT
- Consent comprehension
- Genetics

Sources for help with tough decisions

Questions/Discussion

# Biomedical Ethics Principles

## Classical Principles

- Autonomy
- Beneficence
- Nonmaleficence
- Justice

Research weighs these principles differently –  
the ethics are different

Beauchamp and Childress

# Nuremberg Code, 1949



1. Voluntary consent
2. Fruitful results for good of society, not otherwise obtainable
3. Well-designed
4. Avoid suffering and injury
5. No intended death
6. Benefit should outweigh risk
7. Proper preparation for ill effects
8. Conducted by scientists
9. Voluntary withdrawal
10. Ability to terminate

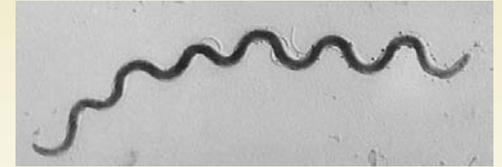
# The Belmont Report, 1979

## Basic Ethical Principles

- Respect for Persons
- Beneficence
- Justice

## Applications

- Informed Consent
- Assessment of Risk and Benefits
- Selection of Subjects



[www.microbeworld.org](http://www.microbeworld.org)

# Science and Ethics

Scientific Validity: Good science = good ethics

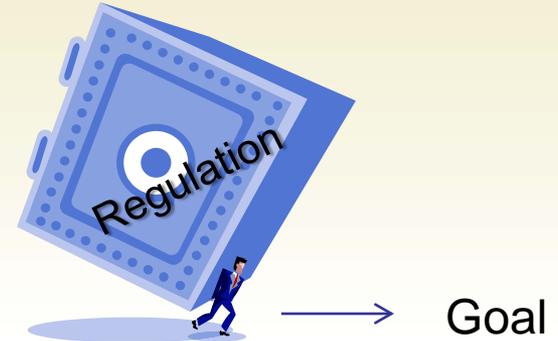
- Use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data.

“Scientifically unsound research on human subjects is *ipso facto* unethical in that it may expose subjects to risks or inconvenience to no purpose.”

# A word about investigator responsibility

## Traditional paradigms

- Physician  $\leftrightarrow$  Patient
- Investigator  $\leftrightarrow$  Science



## Rethinking the paradigm

- Patient/subject  $\leftrightarrow$  Investigator  $\leftrightarrow$  Science
  - Regulation as a guide or touchstone



# The SUPPORT Study

## *Background*

Retinopathy of prematurity (ROP) is a major morbidity among premature infants

- Data from 1950's showed that administration of oxygen improved outcomes among premature infants
- Use of oxygen led to an epidemic of blinding ROP among premature infants
- Advances over 50 years (e.g. measuring blood oxygen saturation) allowed precise administration of oxygen
- Cohort data from 1990's suggested that targeting lower blood oxygen saturation decreased ROP without affecting survival

# The SUPPORT Study

## *Design*

Randomized controlled trial of two oxygen saturation targets among premature infants

- 91-95% - “high saturation”
- 85-89% - “low saturation”

Conducted in 2005-2009

Both targets within “standard of care”

- 2006 AAP policy statement – 85-95%

Study masked by offset in reading built into oximeters

# The SUPPORT Study

## *Outcomes*

No difference in composite outcome of ROP or death

Lower saturation targets resulted in lower ROP rate

- High saturation – 17.9%
- Low saturation – 8.6%

Lower saturation targets resulted in higher death rate

- High saturation – 16.2%
- Low saturation – 19.9%

Results revolutionized oxygen management

# The SUPPORT Study

## *The Complaint*

Complaint to US Office of Human Research Protection (OHRP)

OHRP determination letter to University of Alabama at Birmingham (3/2013)

- “IRB approved informed consent documents for [the SUPPORT] study failed to include or adequately address the following basic element required by HHS regulations at 45 CFR 46.116(a)”
  - Inadequately explained ROP risk
  - Did not list risk of death
  - Did not address restrictions on physician discretion

# The SUPPORT Study

## *Fallout from OHRP Finding*

Public Citizen publicized OHRP finding (5/2013)

Editors of NEJM, NIH and dozens of ethicists sided with SUPPORT investigators (and others didn't)

OHRP clarification letter (6/2013)

- “Widespread misunderstanding about the risks that are required to be disclosed in obtaining informed consent ... [for] randomized studies of standard of care treatments”
- Recognized that some ethicists have proposed no consent for such studies
- Suspended compliance actions against UAB

# DHHS Meeting (8/2013)

## *Questions about “Standard of Care” Research*

1. How should an IRB assess risks?
2. What factors should an IRB consider in deciding which risks must be disclosed to subjects?
3. How should randomization be considered (i.e. should it be considered a risk)?
4. How does uncertainty about risk within the standard of care affect the answers to these questions?
5. Under what circumstances do potential risks qualify as reasonably foreseeable risks?

# Comparative Effectiveness Research

Comparative effectiveness research  $\approx$   
“standard of care” research

- Patients often receive one or another established therapy for reasons extrinsic to them
  - Availability
  - Physician preference
- Randomization assigns therapies differently, but no less arbitrarily

# Comparative Effectiveness Research

If therapy is assigned arbitrarily in either case:

- Are the risks of research different from those of standard care?
  - Do they need to be listed in a consent form?
  - Is consent needed at all?
- Does the difference in fiduciary responsibility of physician vs. researcher require consent (even if there will be no difference in outcomes)?
- What about respect for persons?

# Improving Consent

Among adults, with traditional consent process:

- 75% understand purpose of study
- Only 30% understand unproven nature of intervention

Among parents of newborns:

- 68% understand purpose of study
- 8% do not recall having enrolled infant in study

Joffe, Lancet, 2001; Ballard, J Perinatol, 2004

# Improving Consent

Multiple methods studied to improve comprehension:

- Altering wording, formatting, grade level of forms
- Alternate media – e.g. video
- **Shortened forms**
- **Verbal presentation**

Overall understanding remains a problem

Davis, J Natl Cancer Inst, 1998; Coyne, J Clin Oncol, 2003; Freer, Pediatrics, 2009; D'Angio, unpublished

# One Parent's View

## The Tampa Bay Times

### **The parental consent dilemma: Saving extremely premature babies by signing forms**

“I would not have read the form, because I did not read any of the forms, because the forms are for lawyers, not for parents. I had not slept in days. I was scared out of my mind. I had the mental capacity of a drunk being chased by bears. What kind of form can protect a parent in a situation like that?”

Benham, Tampa Bay Times, October 18, 2013



# Genetic Research

Whole genome/exome sequencing is now cheap-ish and easy

- Can we ever be anonymous again?
- Unintended consequences – incidental findings
  - Each human genome estimated to carry ~800 deleterious mutations and ~60 new, unique mutations
  - To report or not to report?
  - Duty to warn
  - Confidentiality, insurability

Chun, Genome Res, 2009; <http://www.sanger.ac.uk>

# CTSI Bioethics Key Function

The Bioethics Key Function of the CTSI provides independent ethics advice and facilitation for:

- Planning,
- Performance,
- Education for, and
- Regulation of

clinical and translational research at the University of Rochester.

# CTSI Consultation Clinic

Provides a host of research-related advice (resources, statistics, trial design), including research ethics consultation

- Path: URMC » CTSI » Research Help » Resources and Services » Request a Consultation
- <http://www.urmc.rochester.edu/ctsi/research-help/>

# Other Opportunities

## 2014 CTSI Symposium – “Ethics in Research: Consent Quandaries”

- March 13, 2014
- Preliminary Agenda
  - New Approaches to Research Consent
  - Consent Comprehension
  - Consent in Special Populations
  - Consent in Community Participatory Research
  - Consent in Comparative Effectiveness Research
  - The Federal Emergency Research Consent Exception
  - Research Education for Community Partners

# Questions/Discussion



# THANK YOU

