Initiatives in Research Ethics at Duke

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Overview

- The research environment
- Current initiatives
  - Building an ethics infrastructure
  - CECRE
  - Evidence based ethics & informed consent
- Next steps

A Changing Environment

- Increased calls for evidence in a system predicated upon trust
- Critiques and problems with the current system

Trust and Participation in Research

- Individual physicians and investigators
- Specific institutions
- The research enterprise as a whole

In Individuals

"There's not a lot that you can control when you're sick, so you have to rely on your doctors … if he suggests that you should go into a research project, I think you should really take his advice … because if you take the time to find yourself a good doctor and they're involved in research, they would never steer you wrong."

(552244-6)

In Institutions

"I think I've got the best treatment down there at [named hospital], I don't think I could get any better."

(333208-7)

In the Research Enterprise

"They know what they are doing. They wouldn't have you do this if they didn't know what they were doing,"

(332324-3)

Trust and Trustworthiness

"Not all things that thrive when there is trust between people…are things that should be encouraged to thrive…There are immoral as well as moral trust relationships."

Baier A, 1986

News You Can Use

Duke's hazards

Did medical experiments put patients needlessly at risk?

BY SHEILA KAPLAN
AND SHANNON BROWNLEE

In the hierarchy of the nation's elite research institutions, Duke University Medical Center has long ranked near the top. Nestled in the middle of a 210-acre campus in Durham, N.C., the center's gleaming glass tower has served as a beacon for top-flight researchers, who bring in $175 million of federal biomedical research funds annually, and for patients. More than 1 million come to Duke from all over the world each year.

But Duke's reputation suffered a big ding last week when the federal government forced the university to shut down all 2,000 of its medical experiments involving human subjects. In a stern letter that criticized the university for failing to adequately protect patients who enter research trials—either in hope of being cured or for altruistic reasons—the government ordered Duke to make drastic changes before admitting any more subjects. After medical school dean Edward Holmes and his associates flew to Washington and pledged to make immediate improvements, regulators told them they could resume a limited program. "Our concern was for the people in experiments facing risks they didn't know about or understand," said Gary Ellis, director of the Office for Protection From Research Risks (OPRR), which closed the program. Duke is not out of the woods yet. Another agency, the U.S. Food and Drug Administration, plans to inspect Duke's programs this week.

BOB SACHA

CURING ILLS. Duke was forced to improve its oversight over research on human subjects.

The deficiencies cited by OPRR, which ranged from failing to monitor ongoing research to ignoring federally mandated rules designed to protect children, are unusual for their sheer number—20 in all—and for their occurrence at such a prestigious institution. But similar problems are found with surprising frequency elsewhere. Federal audit reports obtained by *U.S. News* show that the safety net designed to protect patients in research trials is riddled with holes at scores of institutions around the country. Last year the FDA, which oversees research sponsored by private companies, cited nearly 150 institutions for problems ranging from neglecting to inform patients that an experimental treatment could blind them to recruiting patients by offering them money. And OPRR, which is investigating compliance with human protection rules at 60 institutions, has already noted violations at such well-known research centers as the City University of New York, Scripps Clinic in California, and Mount Sinai School of Medicine in New York.

Crackdown. Last week's suspension of Duke's research privileges lasted only five days. But the incident signaled a new toughness on the part of OPRR, a tiny office at the National Institutes of Health that oversees patient safety at more than 500 institutions. Duke's temporary closure follows disciplinary actions against Rush-Presbyterian-St. Luke's Medical Cen-

Problems in Research
Closure of Research Institutions

- University of Minnesota
- Rush-Presbyterian-St. Luke's Medical Center
- West Los Angeles VA/UCLA
- Duke University
- University of Colorado Health Sciences Center
- University of Alabama, Birmingham
- University of Pennsylvania
- Virginia Commonwealth University
- University of Oklahoma, Tulsa
- University of Illinois at Chicago
- Johns Hopkins University

Problems in Research
Deaths of Research Subjects

Johns Hopkins University

University of Rochester

Case Western Reserve University

University of Pennsylvania

PROBLEMS:Who is complaining?

- Sponsors of research
- Clinical investigators
- IRB members and administrators
- Popular press
- Federal regulators

PROBLEMS: What is the complaint?

"The medical and research communities, including institutional review boards (IRBs), agree with the Department of Health and Human Services that this appalling state of affairs is unacceptable. We cannot tolerate or excuse inadequacies in our system of protection for human research subjects."

- Donna Shalala, 2000, NEJM

Disintegrating Trust?

- Nationwide Harris Interactive survey
- Conducted February 2002
- N=2,031 Adults

“How confident are you that patients in clinical trials…?”

- Get very good medical care
- Are treated as patients, not as guinea pigs
- Are told honestly and clearly of the risks of participating
- Are not recruited just so that the doctors and hospitals involved can make more money

- 32% Very Confident
- 24%
- 25%
- 20%

Building an Ethics Infrastructure

- Adequate resources
- Recognize IRB members
- Education
- Analyzing the current system

Adequate Resources

- Elements
  - IRB space
  - IT support for review and tracking
  - IRB staff
- Key question
  - Are these sufficient to ensure that the regulatory requirements for protecting human subjects are being met?

Recognize IRB Members

- Rationale
  - The activity is critical
  - Workloads tend to be heavy
  - Specific education is needed
- Hazards of inadequate support
- Possible recognitions

Education

- Target audience
  - IRB members and staff
  - Investigators
  - Research staff
  - Future investigators
- Rationale
  - Enhance the protection of human subjects
  - Encourage compliance
  - Enhance efficiency

Analyzing the Current System

- Participate in national deliberations about research ethics
- Lend expertise to efforts aimed at testing and certification
- Improve methods of protecting human subjects

An Empirical Imperative

- Clinical research is predicated on the notion that we need data to determine ‘truth’ and facilitate sound decision-making
- Ironically, methods of clinical research, including those designed to protect participants such as informed consent and the selection of subjects, are introduced without data regarding safety or efficacy
- We need to evaluate these protections as we would any proposed clinical intervention so that they can inform conceptual analyses and policy

Institutional Culture

"the leaders of research institutions set the tone for the ethical conduct of research under their institutions' auspices. Attentive and creative institutional leadership creates a culture in which both IRBs themselves and the function of protecting human subjects are held in high regard."

Gary Ellis, *JAMA* 1999; 282: 1963-5

Challenges to Success

- Lack of validated benchmarks and curricula
- Financial constraints

Consortium to Examine Clinical Research Ethics (CECRE)

- Examine past and present reform efforts in the oversight of clinical research to identify future needs
- Develop a method to generate previously unavailable data on the current characteristics of clinical research, including how it is conducted and subjected to oversight
- Begin a reexamination of the ethical framework and the goals of clinical research ethics
- Recommend ways to ensure that human research participants are protected and clinical research is ethical
- Engage public policy makers in dialogue about proposed reforms

http://cecre.duke.edu

CECRE

- Members
  - Ezekiel Emanuel, MD, PhD, National Institutes of Health
  - Alan Fleischman, MD, New York Academy of Medicine
  - Angela Bowen, MD, Western IRB
  - Kenneth Getz, MBA, Centerwatch
  - Carol Levine, MA, United Hospital Fund
  - Dale Hammerschmidt, MD, University of Minnesota
  - Ruth Faden, PhD, MPH, Johns Hopkins University
  - Jeremy Sugarman, MD, MPH, MA, Duke University Medical Center
- Staff
  - Lisa Eckenwiler, PhD, Duke University Medical Center
  - Carianne Tucker, MPH, Duke University Medical Center
- Consultants
  - Rob Califf, MD, Duke University Medical Center
  - Christine Grady, RN, PhD, National Institutes of Health
  - Robert Mayer, MD, Harvard Medical School
  - Joan Rachlin, JD, MPH, PRIM&R

CECRE Projects

- Evaluation of current efforts at reforming research ethics oversight
- Examination of the concept of vulnerability
- Survey of costs of IRB review in academic medical centers
- Exploring the landscape of clinical research

Evidence Based Ethics & Informed Consent

- Informed consent for umbilical cord blood donation
- Improving informed consent for early phase trials in oncology
- Proxy decision making for research on dementia
- EQUIC

EQUIC

- Enhancing the Quality of Informed Consent
- VA Cooperative Studies Program (CSP)
- Palo Alto Coordinating Center

EQUIC Personnel

- Investigators
  - Phil Lavori
  - Jeremy Sugarman
- Research Team
  - Maryann Boeger, MBA - Program Manager
  - Andres Busette - Research Health Scientist
  - Carole Cain, PhD – Interviewer
  - Robert Edson, MS – Statistician
  - Patrick Nisco, MA- Interviewer
  - Lee Pickett, MS- Interviewer

Goals

- Create, field test, and validate an independent, real-time measure of the quality of informed consent encounters in actual clinical trials
- Develop specific interventions directed at improving the quality of informed consent
- Test interventions in CSP trials

Substudies

- EQUIC-DP (Development Phase)
- EQUIC-SM (Self-Monitoring)
- EQUIC-CC (Customized Consent)

EQUIC-DP

- Telephone interview after “parent” study consent
- Brief Informed Consent Evaluation Protocol (BICEP)
- Substrate for all subsequent EQUIC studies

EQUIC-SM

- Site-randomized comparison of standard and “self-monitored” consent process
- Self-Monitoring Questionnaire (SMQ) filled out by person obtaining consent
- Intent: activation, focusing on 5 critical aspects of IC

EQUIC-CC

- Site-randomized comparison of standard and “customized consent” including diagrams and pictures
- Brief assessment of patient’s cognitive status and educational level
- Interaction of participant’s cognitive status with effectiveness of CC

Status of Substudies

- EQUIC-DP
  - 632 participants enrolled (BICEP1=441; BICEP2=191)
  - 8 studies
  - 15 VAMCs
- EQUIC-SM
  - Currently enrolling
  - Obtaining approvals at additional sites
- EQUIC-CC
  - Instrument development and pilot

EQUIC-DP Parent Studies

1. CSP 027 FDG PET
2. CSP 403 Shingles Vaccine
3. CSP 410 FeAST
4. CSP 424 COURAGE
5. CSP 453 HOST
6. CSP 494 PTSD and Women
7. CSP 499 SELECT
8. CSP 719B Latent Prostate

EQUIC-DP Participating Sites

Site	Study	Site	Study
Ann Arbor, MI	CSP 424	Minneapolis, MN	CSP 403
Birmingham, AL	CSP 403	New York City	CSP 424
Buffalo, NY	CSP 027	Northport, NY	CSP 403
Durham, NC	CSP 424	Northport, NY	CSP 499
Houston, TX	CSP 410	Northport, NY	CSP 719B
Houston, TX	CSP 424	Reno, NV	CSP 410
Indianapolis, IN	CSP 027	Seattle, WA	CSP 424
Lexington, KY	CSP 410	St. Louis, MO	CSP 499
Mayo Clinic	CSP 424	St. Louis, MO	CSP 719B
Melbourne, FL	CSP 424		

EQUIC-DP
Site Coordinators' Reports

- 100% patient willingness to participate
- 98.9% "no difficulty with process"
- 99.5% "no difficulty with call"
- 94.5% "no difficulty reaching center"
- 98.4% "no interruption of clinic flow"
- 99.2% "no other difficulties"

Degree of Disruption of Parent Study

- None 66.3%
- Mild 32.8
- Moderate 1
- Severe 0

Incremental Burden

- Site coordinators
  - mean 14.2 min (std dev 9.6)
- Participants
  - mean 10.9 min (std dev 7.8)

Mean Timing of Interviews

- Completion of parent study IC and EQUIC IC: 19.8m (sd 28.0)
- EQUIC IC and initiation of call: 8.4m (sd 11.7)
- Duration of call: 8.8m (sd 3.6)

Respondents' Reports about Parent Study IC Process

- 96.5% received "just right" amount of information
- 99.3% remember signing consent form
- 99.8% "felt no pressure to consent"
- 98.4% "made a good decision to participate"
- 92.8% "completely satisfied with the IC process"

Taking a Deeper Look

- Verbatim responses to selected items
  - What is the primary purpose of the [parent study]?
  - What are the benefits to you of participating in [parent study]?
  - When can you stop participating in the [parent study]?
- Coding developed and refined during BICEP-1

“What is the primary purpose of [parent study]?” (n=191)

Code	Percent
Addresses a research question?	89
Directed at an outcome to ultimately benefit others?	31
Directed at an outcome to ultimately benefit self?	6
Other?	2

“What are the benefits to you of participating in [Parent Study]?

Code	Mean of count
Direct	.35
Indirect	.71
Aspirational	.73
Uncategorizable	

“When can you stop participating in the [Parent Study]”

Code for clear appreciation of voluntariness

- Yes
- No

- 127
- 62

Reliability of Verbatim Coding

- 3 interviewers, each coding verbatim responses from interviews in BICEP2 and parent studies concerning research on a therapy (n=42)
- ICC for coded responses: .75
- Variable components analysis
  - Subjects (true)=.94
  - Residuals (rater)=.32

IC Aggregate Score (Mean=9.8; sd=1.29)

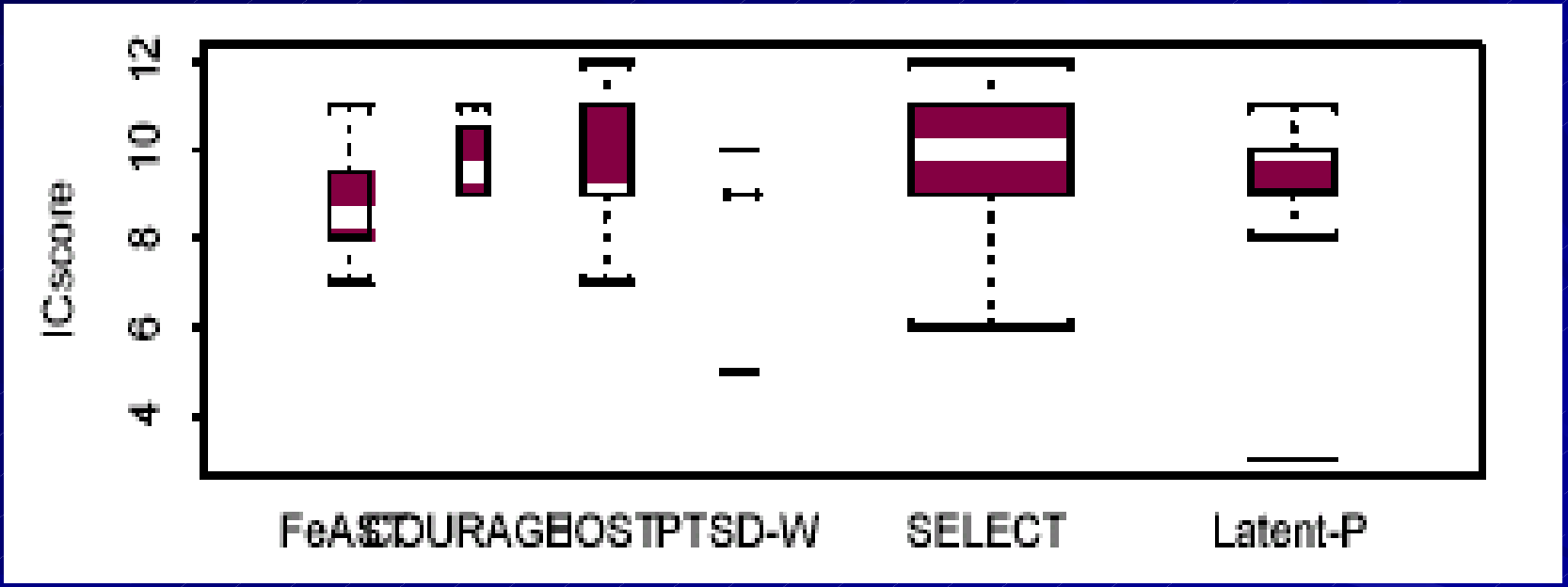
Positive

- All information needed
- Sign form
- Aspirational benefit
- Satisfaction
- Address research question
- Ultimately benefit others
- Voluntariness

Negative

- Pressure to participate
- Not participating affect medical care
- Direct benefit
- Ultimately benefit self
- Uncertainty about signing form

IC Score by Parent Study



TM Aggregate Score (Mean 1.62; SD=.93)

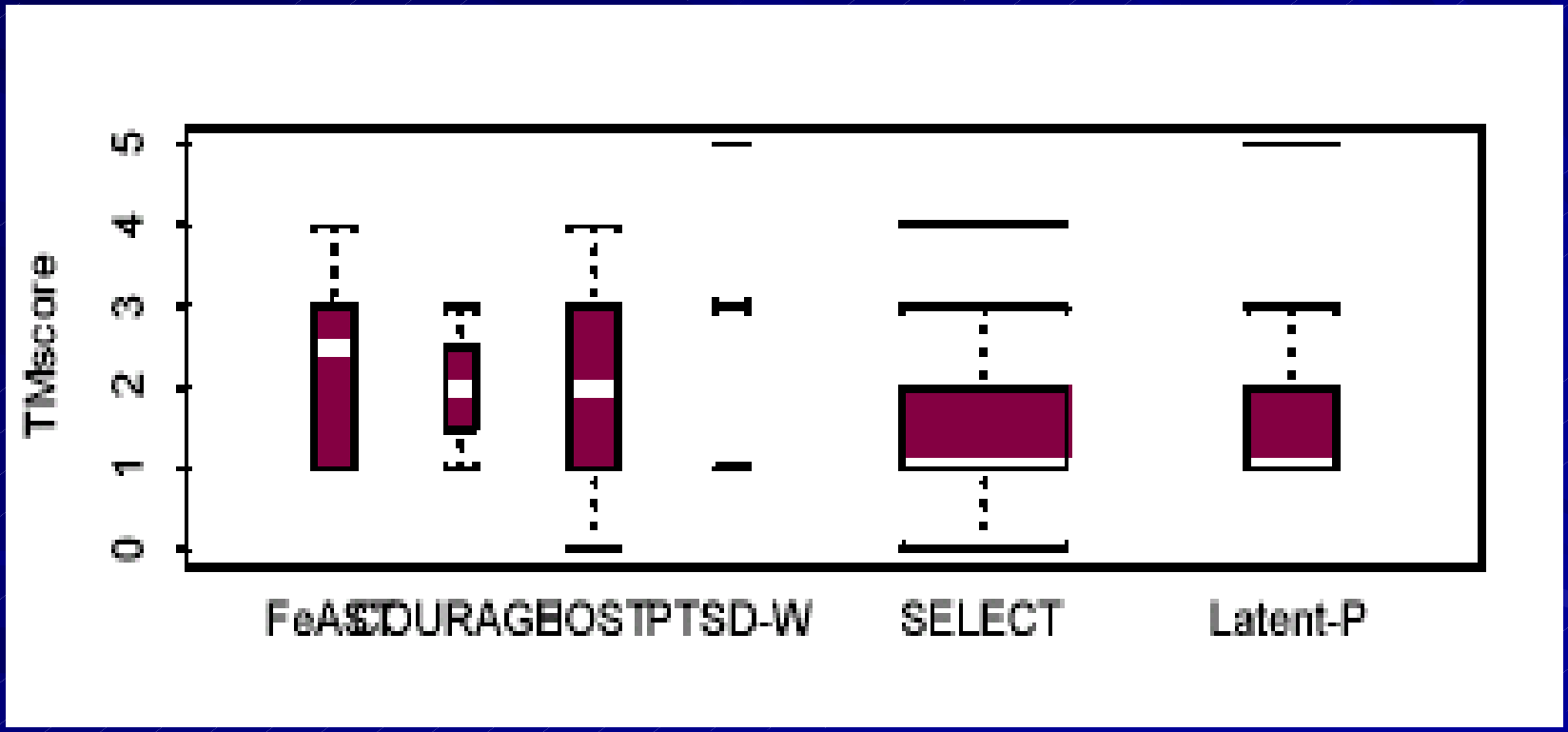
Positive

- Direct benefit
- Ultimately benefit self

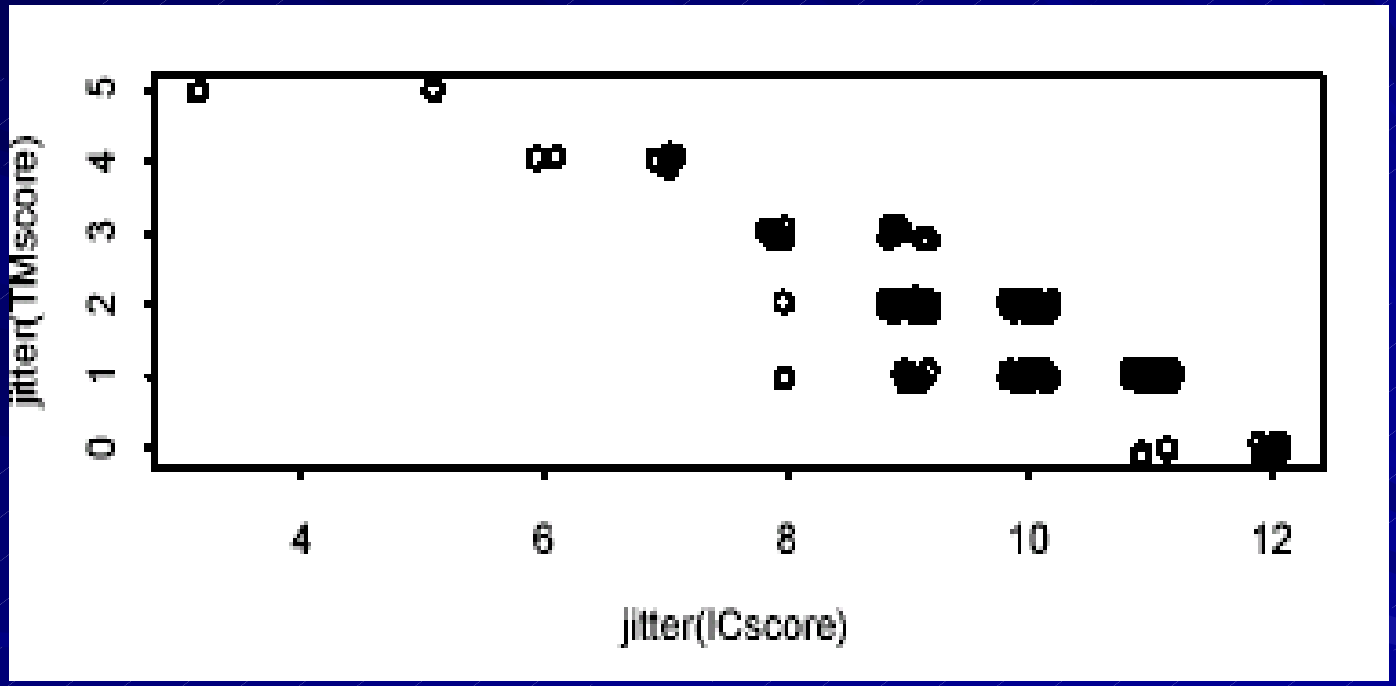
Negative

- Aspirational benefit
- Addresses a research question
- Ultimately benefit others

TM Score by Parent Study



IC vs TM Score



Conclusions

- BICEP is well-tolerated, by participants and staff
- BICEP imposes minimal burden
- Verbatim coding is reliable
- Patients who consent are uniformly satisfied with the process, but inspection of verbatims reveals considerable room for improvement, especially in the “therapeutic misconception”
- Innovations have scope to work

Closing Comments

- Recent attention to the ethics of research ethics has highlighted the need to improve methods and approaches to oversight
- Including a multitude of perspectives and using empirical approaches can contribute to this important task