The Development of the Final Rule; Exception from IC in Emergency Research

Michelle H. Biros, MD, MS
Dept. of Emergency Medicine
Research Director, HCMC
Editor in Chief, AEM
Informed consent

Protects from

Research abuse
Unnecessary risks
Additional costs (financial / other)

Is meaningful

Educated permission
Voices understanding
Is not coerced
Problems with the regulations

- Consent is not always feasible
  *Surrogate is not always available*
  *Patient is critical*

- Therapeutic time window is short
  *Research is evolving*

- Inconsistent regulations among agencies

- IRBs get little guidance

- The Regs carry the weight of the law
“Working Solutions” (1991 FDA/ DHHS)

• FDA emergency treatment regulations applied to research
• Liberal interpretation of “minimal risk”
• Alternative consenting mechanisms
  - Deferred/ delayed consent
  - Two tiered consent
  - Implied consent
The Problem Crystallizes

- The radiation experiments
  - Clinton’s directive- 1992
- FDA shuts down the vest CPR study- April 1993

- The PEG- SOD study
  U. Of Nebraska IRB 1993
  - approves with FDA treatment regs. 4/93
  - FDA mandates IC only enrollment , 7/93
  - deferred consent is discounted 8/93
  - FDA allows exception from consent 9/93
- A new OPRR director, 8/93
  - letter of the regs, and not the spirit
  - Dear Colleague letter

- Wyden’s document and hearing
  - “Human Guinea pig research in ERs; How some drug and device manufactures use patients who can’t say no”- 3/94
  - hearing set for 5/94
The Issue

“All human subject research studies approved by institutional review boards with multiple projects assurances and all projects funded by NIH require prospective informed consent....”

Director of the OPRR,
Summer 1993
The Research Community Responds

- Testimony at Wyden’s hearing - May 1994
- Promise of a public forum – May 1994
- Coalition of Acute Resuscitation Researchers formed

Consensus conference - Oct. 1994
Consensus published – April 1995
Development of consensus

Problem identified

Organizational Buy – in

Process development

Consensus

Conference

Coalition

Development
Consensus
  ↓
Position paper
  ↓
Dissemination of Recommendations
  ↓
Problem resolution

Coalition
  ↓
Image development
  ↓
Leadership organization
  ↓
Other strategies
Consensus Conference

- American Assoc. for Clinical Toxicology
- American Assoc. for Surgery of Trauma
- American College of Cardiology
- ACEP, ENA, SAEM
- AHA
- National Head Injury Foundation
- Society of Critical Care Medicine
The 1995 Government Proposal

- Was likely driven by research community
- Emergency Medicine was the spearhead

- Secretarial override
- Local IRB authority
- Community Involvement
Key Aspects of the Final Rule

• The ethics of the proposal
• Pre-emptive effect of state’s laws
• Public notification/ disclosure
• Community consultation
• IND/ IDE must be filed with FDA
• Life threatening vs debilitating
• Provisions for proxy consent in place at all times
• Use of placebos/ equipoise allowed
• Independent DSMC
Exception from Informed Consent Requirements for Emergency Research
(21 CFR 50.24)

For research for which an IND or IDE is in effect

Involving human subjects who cannot give informed consent because of their emerging life-threatening medical condition (for which available treatments are unproven or unsatisfactory)
Exception from Informed Consent Requirements for Emergency Research
(21 CFR 50.24)

Where the intervention must be administered before informed consent from the subject’s legally authorized representative is feasible

Cannot move forward without sponsor has received written permission from the FDA

Have additional patient safeguards beyond those usually required
Community Consultation

“…providing the opportunity for discussions with and soliciting opinions from the community(ies) in which the study will take place (geographic area) and from which the study subjects will be drawn (similar demographics of patients with the emergent condition under study). These communities may not be the same; when they are not the same, both communities should be consulted…”
Community Consultation

Allows an information exchange
Ensures that the community is (are) involved with IRB decision making
Occurs prior to study start
Sponsors usually bear the costs
IRB and investigator plan appropriate means
Number of attendees depends on research plan
Community Consultation

**Should include:**

- Fact that IC will not be obtained in most subjects
- Risks and benefits of the research
- Individual’s right to refuse
- Ways in which patients wishing to be excluded could indicate this preference
IRBs must

- Provide a chance for feedback
- Decide if CC is adequate
- Consider community discussions
- Document discussions and resolutions of controversies
- Decide if the study can go forward
Public Disclosure

“…Dissemination of information about the emergency research sufficient to allow a reasonable assumption that the communities are aware that a study will be conducted and, later, that the communities and scientific researchers are aware of the study’s results.”
Public Disclosure (pre study)

Must disclose

– That IC will not be obtained
– The nature and purpose of the study
– Risks and benefits
– Summary of the protocol
– How attempts will be made to contact representatives
– How those not wanting to participate can communicate their wishes
Public Disclosure (post study)

- General information about results should be disclosed
- IRB ensures adequacy
- IRB must document its occurrence
- In a “timely fashion”
- Comprehensive data for researchers
Contacting Legally Authorized Representatives or Family Members

**Commitment** (prior to test article being administered)

- Must be described
- IRBs must document
- Requires IC document
- Family members can object
- Attempts must be summarized and IRB informed
Contacting Legally Authorized Representatives or Family Members

After the test article has been given

– At “earliest feasible” opportunity
  ▪ to the subject if the subject recovers
  ▪ to the legally authorized representative
  ▪ to the family
  ▪ after death, if feasible
– No time limit is set
– Attempts should be documented
Data Monitoring Committee (DMC)

“…Group of (independent) experts established by the sponsor to access at intervals the progress of a clinical trial… and to recommend to the sponsor whether or not to continue, modify, or stop a trial…"
Lessons Learned

• It takes lots of time and money to change federal regulations
• What makes sense to you doesn’t count; you need to prove it with data
• Consensus approach is highly regarded
• In general, IRBs are not creative
• In general, IRBs require explicit guidance
Lessons Learned

• Revisions of the Final Rule will be up to the research community
• When possible, use data to justify any called for change
• Suggestions regarding revisions should come from many specialties