Emergency Research and the Regs: Why Ignorance is \textit{not} Bliss

James Feldman MD MPH FACEP CIP
Chair, BUMC IRB Panel Blue
April 12, 2013
Ignorance and bliss
Disclosure and Disclaimer

• No conflicts of interest to disclose

• Not official position for OHRP or FDA
Discussion Points

• IRBs approach research in emergency setting
• What an “FWA” means
• How an IRB reviews drug/device research
• How FDA and HHS regulations differ
• Exception from Informed Consent regulations
• Regulatory review of IRB decisions
Case Study

• Clinical controversy

• Rapid sequence intubation in sepsis
  – Midazolam
  – Etomidate
  – Other drugs
Etomidate

- Carboxylated imidazole derivative
  - anesthetic
  - amnestic properties
- Rapid onset ( < 1 min)
- No significant cardiovascular depression
- **BUT** adrenal reversibly inhibiting 11-beta-hydroxylase
- Concerns adrenal suppression

http://www.drugs.com/pro/etomidate.html
Methods: We performed a prospective, double-blind, randomized study of patients with suspected sepsis who were intubated in our ED during an 18-month period. Eligible patients who were critically ill and were suspected of having sepsis were randomized to receive either etomidate or midazolam before intubation.
Question

• What are the issues that an IRB would consider when reviewing a study like this?
Role of IRB

IRBs are rule enforcers not rule creators

Leonard Glantz, JD
Associate Dean Emeritus, Academic Affairs
Professor, Health Law, Bioethics & Human Rights
When the Institution becomes engaged in research to which the FWA applies,

the Institution and IRBs upon which it relies for review of such research will comply with the Common Rule.
exceptional

adjective

1. unusual; not typical
2. unusually good;
outstanding
Informed consent & emergency research
Informed Consent

- Except as provided elsewhere in this policy, **must** obtain the legally effective informed consent of the subject or the subject's LAR.

- An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative **sufficient opportunity** to consider whether or not to participate and that minimize the possibility of coercion or undue influence.
Sufficient time

- Tight glycemic control with STEMI to cath lab?
- Life threatening asthma compare NIV with heliox?
- Most of acute emergency medical care
OHRP and Emergency Research

• OHRP Guidance states that it is **IMPOSSIBLE** to obtain *legally effective informed consent* in an urgent or emergency care setting?

  – True?

  – False?
"It Depends."
OHRP Guidance

• Expected medical condition potential subject
• Nature of the research
• Sufficient time for subject/LAR to consider
• Circumstances minimize coercion or undue influence
OHRP FAQ Possible Informed Consent?

• IRB and investigator would have to consider:
  – Health and emotional condition?
  – Likely ability to:
    • Process information?
    • Ask questions?
    • Consider risk?
  – Timing of consent
    • So close to care blur treatment and research?
  – May need additional protections
Waiver of Informed Consent §46.116 C2

• No greater than minimal risk*

• Rights and welfare

• Practically

• Pertinent information
HHS v FDA Research Regs

- 46.116(c) and (d) state the conditions under which the IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirement to obtain informed consent.

- The conditions could not apply in FDA regulated research.

http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/educationalmaterials/ucm112910.htm
Local IRB Rationale

RCT trial poses no more than minimal risk if:

1. genuine clinical equipoise exists
2. all of the treatment options included in the research study fall within the current standard of care
3. there is no currently available treatment with a more favorable risk-benefit profile than the treatments included in the research study
4. the nontherapeutic components of the research are safely under the minimal risk threshold
5. the research protocol provides sufficient latitude for treating physicians to individualize care when appropriate
“The authors should be congratulated for completing such a difficult trial and presenting it in an elegant manner.”
approved drug is subject to all relevant requirements governing the investigational use of drugs, including the requirements of part 312. Specifically, “studies involving use of a marketed drug for a labeled indication... pose risks that patients’ interests will be subordinated to the interests of the study, and therefore implicate FDA’s responsibilities for the rights and safety of human subjects.” The FDA regulations do not allow for “waiver of informed consent” even if an institutional review board determines that research is not greater than “minimal risk.” This study required either an IND or the local institutional review board or the FDA finding that the 21 C.F.R.§ 312.2(b) IND exemption applied. The latter requires compliance with informed consent set forth in 21 CFR Part 50.
Dear James Feldman and Patricia A Bass

The two of you should be ashamed of yourselves. Your grandiose sense of self-importance leading to your letter to Annals regarding Etomidate, Sepsis and Informed Consent illustrates all that is wrong with over-officious IRB committees.

Really? You've got nothing better to do than troll journals for studies in which you take issue with the IRB approval that was already approved by another IRB committee?

We've come a long way from Nuremberg, you jackasses. People like you and the axe that you have to grind impedes research, frustrates clinicians, and does nothing to protect patients - only to harm them in the long run as academicians like myself get frustrated with your kind and move to private industry... but it won't stop you from hiding behind the "for the good of the patients" argument.

You embarrass my specialty, Feldman. Full professor or not, retire already, and get out of the way so the rest of us can truly serve patients.

Dr. James Kanter
Associate Professor
FDA rebukes Advocate Health Care
Feds say state's largest health system failed to get ER patients' consent for drug study

June 16, 2012 | By Deborah L. Shelton, Chicago Tribune reporter

The U.S. Food and Drug Administration has sharply criticized Advocate Health Care, the state's largest health system, for enrolling emergency room patients in a clinical trial without their permission.

In a warning letter made public this week, the FDA questioned a study designed to evaluate the effectiveness of a sedative called etomidate. The subjects were patients at Advocate Christ Medical Center in Oak Lawn who needed intubation, an emergency procedure in which a tube is inserted down the throat to open the airway or deliver medication.

The study proposal originally stated that the patients being intubated would receive whatever drug the doctor preferred and clinical outcome data would be collected from their
The U.S. Food and Drug Administration has sharply criticized Advocate Health Care, the state's largest health system, for enrolling emergency room patients in a clinical trial without their permission.
FDA Response

This letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your Institutional Review Board (IRB).

From our review of the establishment inspection report..., we conclude that the IRB did not adhere to the applicable statutory requirements and FDA regulations governing the protection of human subjects.
• The Advocate Health Care IRB failed to comply with 21 CFR 56.111 when it approved Study 4257, “The Effect of Etomidate on Patient Outcomes after Single Bolus Doses,” without requiring that informed consent be sought in accordance with and to the extent required by 21 CFR Part 50.

• The IRB approved ...a clinical investigation for which informed consent was not sought from prospective subjects or their legally authorized representatives...
• “... your response is unacceptable ... the IRB did not review the letter provided to subjects, to determine whether it provided appropriate information to subjects regarding the study....

• “In addition, we find the clinical investigator’s letter to the subjects to be deficient because, among other things, it did not

• (1) inform the subject unambiguously that he/she was enrolled in a research study

    or

• (2) include details of the study and other information that should have been contained in the informed consent document, including information about risk to the subject.”
Exception from Informed Consent Requirements in Emergency Research

- 21 CFR 50.24 and 45 CFR 46.101(i)
Powell's Mission Impossible

How medical testing has turned millions of us into...

HUMAN GUINEA PIGS
Brief History EFIC

• “Deferred consent”
  – Brain hypothermia 1993
• JAMA 1995

Informed Consent in Emergency Research

Consensus Statement From the Coalition Conference of Acute Resuscitation and Critical Care Researchers

Michelle H. Biros, MD, MS; Roger J. Lewis, MD, PhD; Carin M. Olson, MD; Jeffrey W. Runge, MD; Richard O. Cummins, MD, MPH; Norman Fost, MD, MPH

• FDA issues rules Oct 1996
Required for EFIC

1. Life threatening situation necessitates urgent intervention available rx *unproven* *or* *unsatisfactory*

2. Informed consent not feasible b/o medical condition

3. Prospect of DIRECT BENEFIT

4. Not practicable without waiver
   Prospective ID not reasonable

5. Treatment window not allow LAR consent

6. IRB approves consent procedures and document

7. *Additional protections*
Other EFIC requirements

- Additional protections:
  - Community consultation
  - Public Disclosure before/after

- Independent DMC
- IRB approve consent process and document
- Information to subject, family, LAR ASAP
- IND/IDE (FDA)
- Other
INVESTIGATOR RESPONSIBILITIES

21 CFR 50.24 and 45 CFR 46.101(i)

Identify how criteria are met

a. Life threatening situation
b. Clinical equipoise exists
c. This research is needed now (basic science and animal work are supportive)
d. Consent is not feasible
e. Benefit : Risk assessment
f. Study with consent not practicable
Issues with EFIC

• Life threatening
  – Mortality rate?

• Therapeutic benefit
  – Placebo trials allowed?

• Unsatisfactory
  – “e.g. high incidence AE, efficacy, limitations in setting (refrigeration, portable, IV, surgery needed)”

• “Community consultation”
  – What community?
Other EFIC Concerns

• Time, cost burden?
• International translation?
• Violates “JUSTICE”
  – Equitable risks for benefit
    • Hypothermia in cardiac arrest?
    • Resuscitation in shock?
  – Need for international standard
The New England Journal of Medicine

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

participating center. For all patients, the requirement of informed consent was waived in accordance with the ethical standards of the local institutional review board and the guidelines for good clinical practice of the European Agency for the Evaluation of Medicinal Products.24 The patient’s family was informed about the tri-
Case Summary

• Investigators
  – Consider requirements for informed consent
    • Legally effective
    • Sufficient time

• Investigators and IRBs
  – Drug or Device study?

• EFIC or written consent subject/LAR
Failure to follow the LAW
• Comments?
• Questions?
• Discussion?
• Thank you!