

Emergency Research and the Regs: Why Ignorance is *not* Bliss

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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

The Case Study

INFECTIOUS DISEASE/ORIGINAL RESEARCH

A Comparison of the Effects of Etomidate and Midazolam on Hospital Length of Stay in Patients With Suspected Sepsis: A Prospective, Randomized Study

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

Federal Wide Assurance

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**

ex-cep-tion-al

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?



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
- Practicably
- 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**

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

Annals Editorial

“The authors should be congratulated for completing such a difficult trial and presenting it in an elegant manner.”

INFECTIOUS DISEASE/EDITORIAL

The Etomidate Debate

Alan E. Jones, MD

From the Department of Emergency Medicine, Carolinas Medical Center, Charlotte, NC.

Annals Letter

Etomidate, Sepsis, and Informed Consent

To the Editor:

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.”² 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.

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Sample “Fan” Mail

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 Nuremburg, 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

Chicago Tribune

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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

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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

Ads By Google

3 Early Signs of Dementia

Doctor: Know These 3 Warning Signs You're About to Suffer Dementia

www.newsmax.com



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)

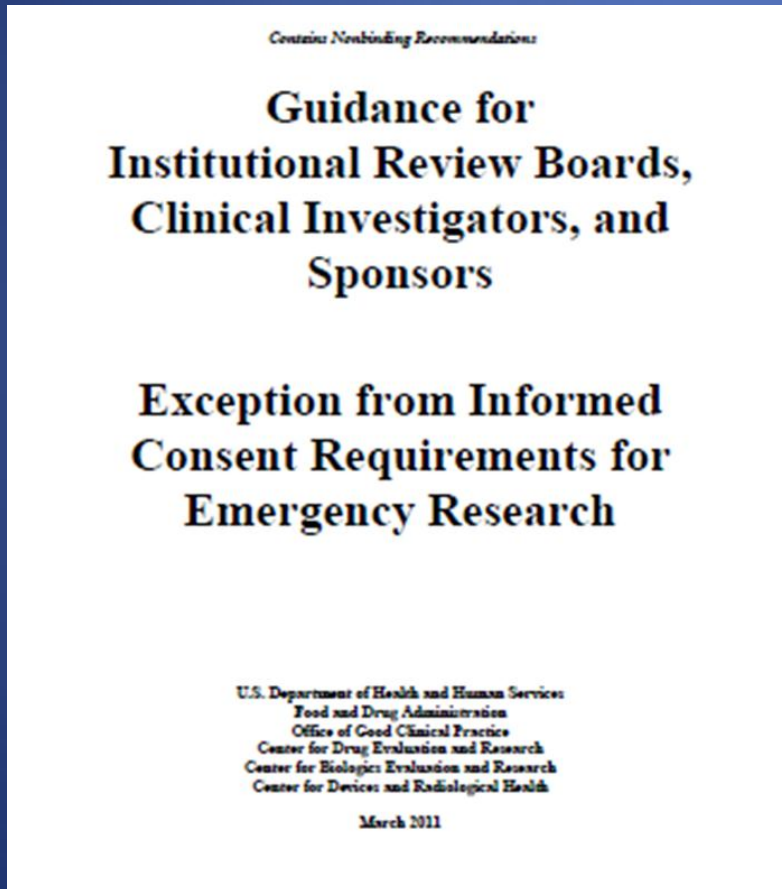
From our review of the establishment inspection report..., *we conclude that the IRB did not adhere to the applicable statutory requirements and FDA regulations governing the protection of human subjects.*

- 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...

IRB part of response!

- “... 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.”**

EFIC



- Exception from Informed Consent Requirements in Emergency Research
- 21 CFR 50.24 and 45 CFR 46.101(i)

APRIL 23, 2002

Powell's Mission Impossible



TIME

HOW
MEDICAL
TESTING
HAS TURNED
MILLIONS OF
US INTO ...

HUMAN
GUINEA
PIGS



www.time.com AOL Keyword: TIME

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

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VOLUME 346

FEBRUARY 21, 2002

NUMBER 8



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!

