Anything Goes?: What are the limits to research without consent in a ‘learning healthcare system’?

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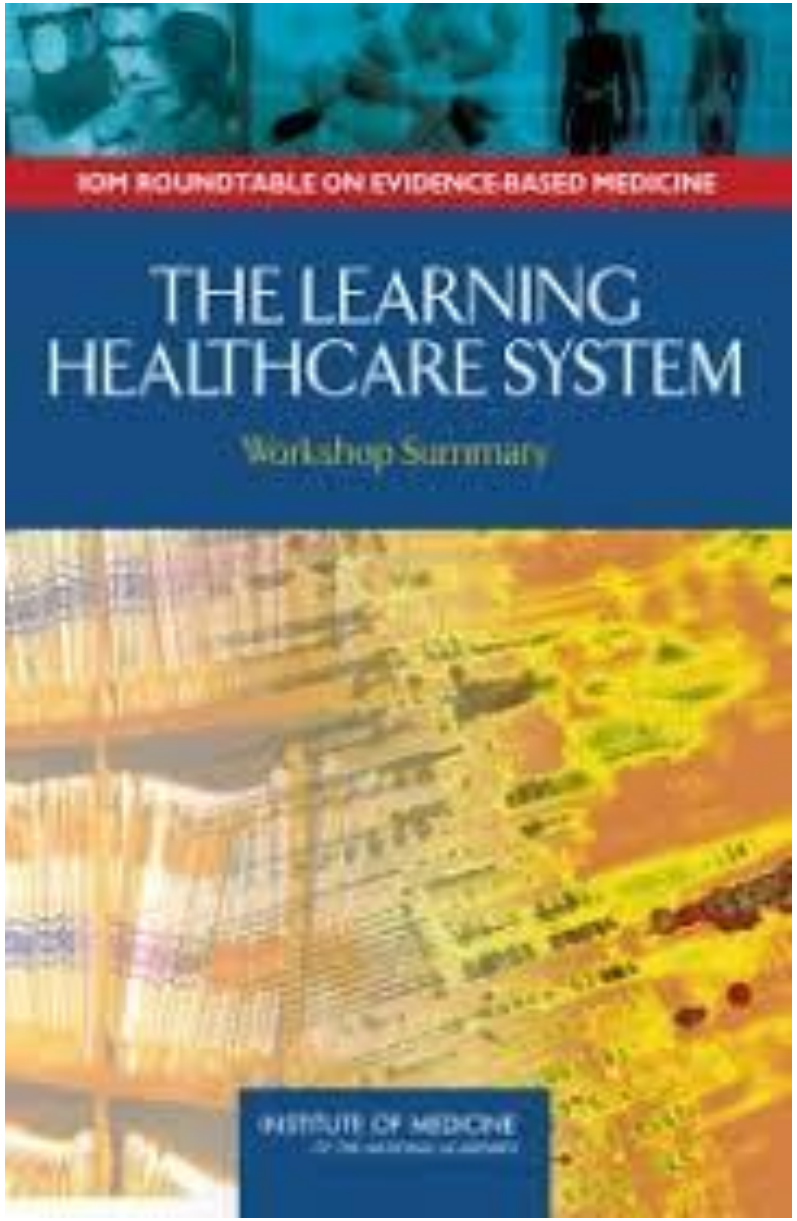
Disclosure

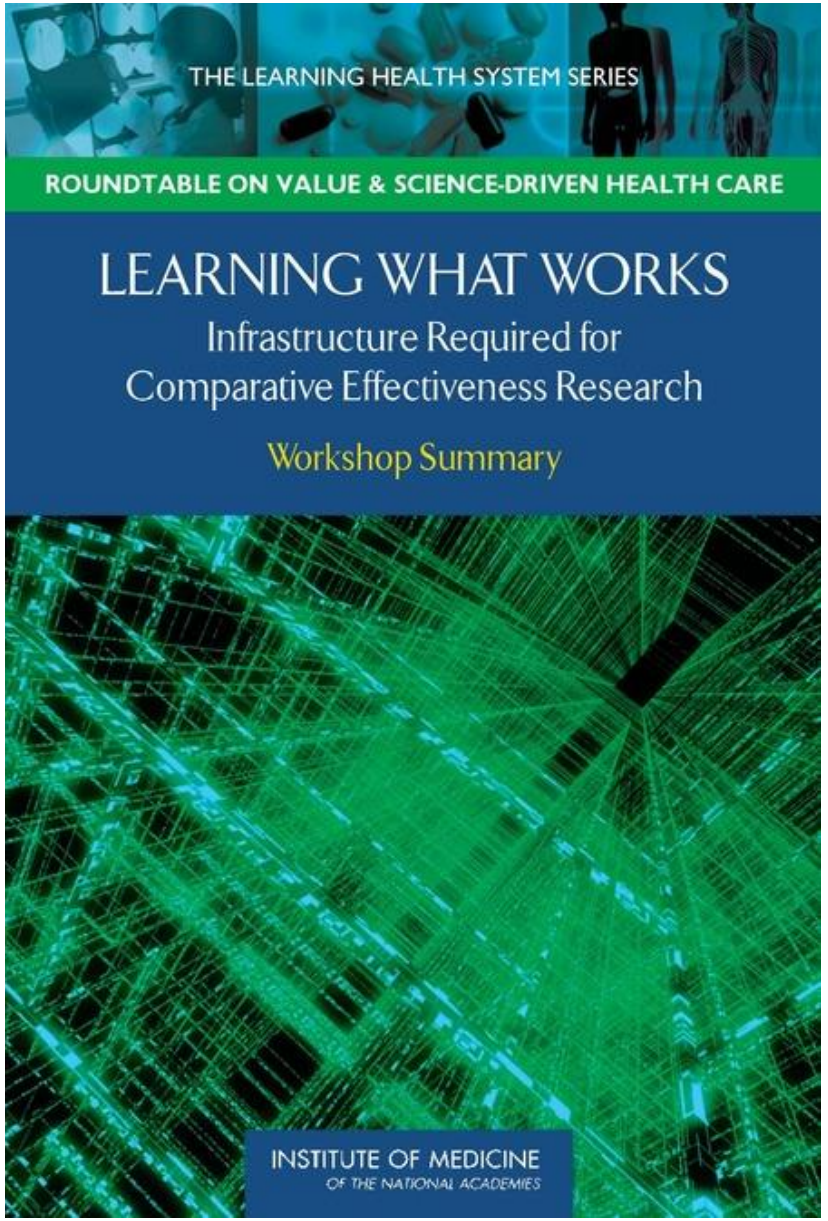
- Dr. Feldman has research funding from NHLBI, SBIR
  - Opinions are my own not IRB/HRPP

- Dr. Walkey has research funding from NHLBI, Gordon and Betty Moore Foundation and receives royalties from UptoDate

Learning Objectives

- Define a Learning Health Care system
  - Define comparative effectiveness (CE) research
- Review the regulatory definition of minimal risk research
- Describe the requirements for waiver of informed consent
  - Greater than minimal risk
  - Minimal risk research
- To present a model CE at BMC in the ICU
- To discuss concerns about CE research in a safety net hospital


IOM ROUNDTABLE ON EVIDENCE-BASED MEDICINE
THE LEARNING HEALTHCARE SYSTEM
Workshop Summary
INSTITUTE OF MEDICINE


THE LEARNING HEALTH SYSTEM SERIES
ROUNDTABLE ON VALUE & SCIENCE-DRIVEN HEALTH CARE
LEARNING WHAT WORKS
Infrastructure Required for
Comparative Effectiveness Research
Workshop Summary
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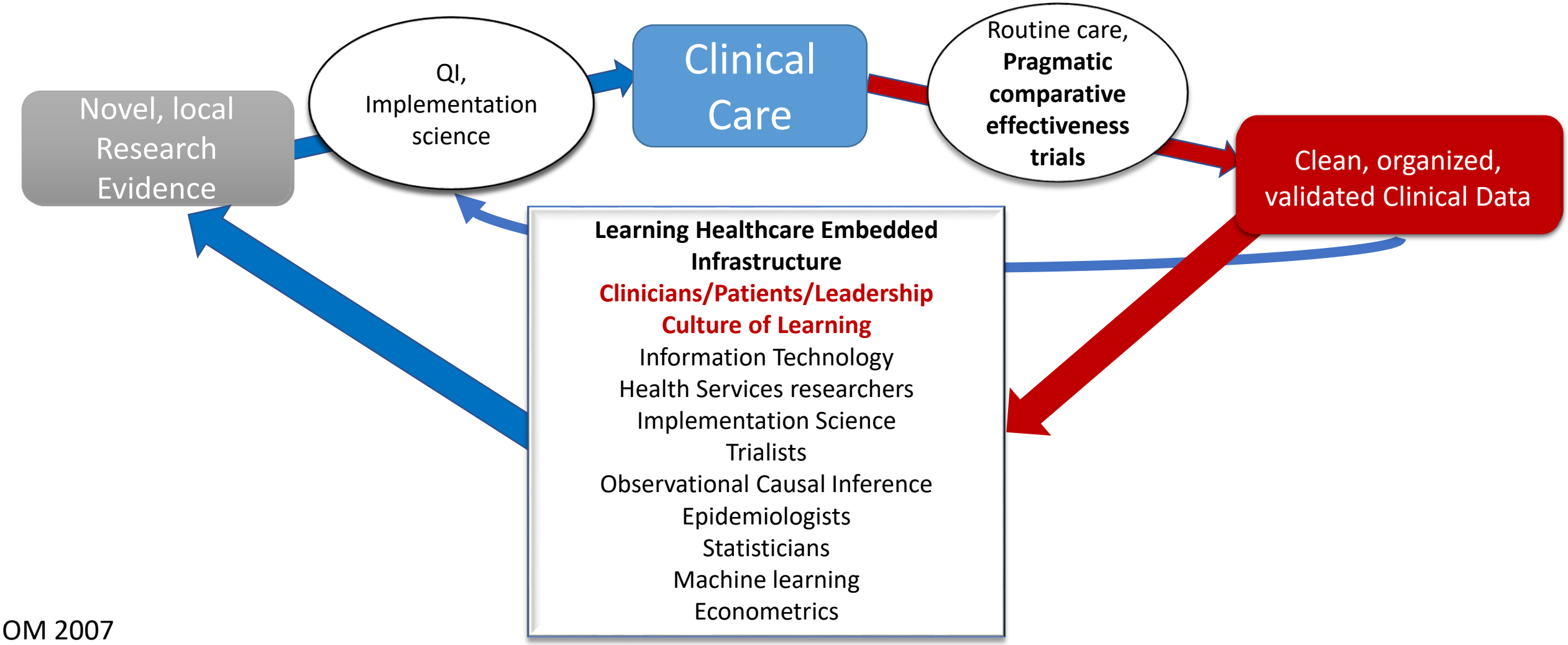
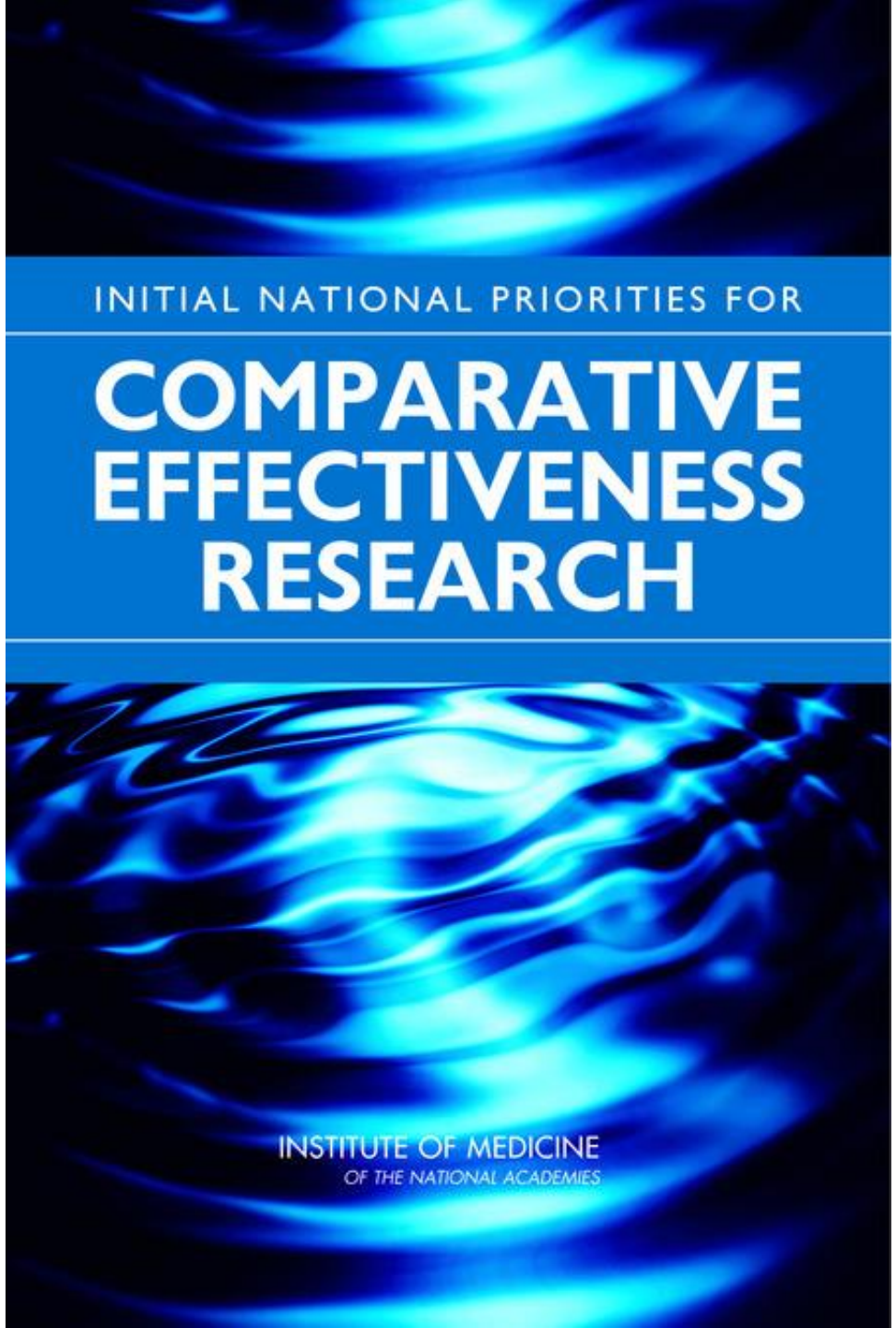
What is a Learning Healthcare System?



IOM 2007


INITIAL NATIONAL PRIORITIES FOR
COMPARATIVE EFFECTIVENESS RESEARCH
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Federal Regulations and Policy stemming from Belmont Principles

45 CFR 46 – DHHS Policy for Protection of Human Research Subjects

21CFR50, 56, etc. – drugs, devices, biologics

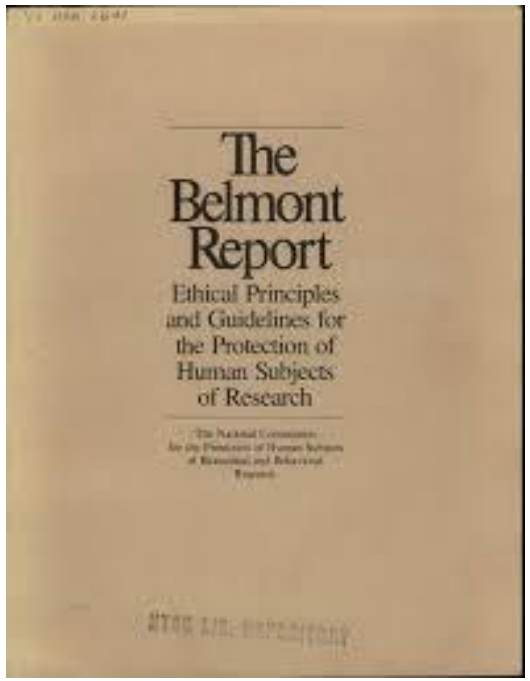
Common Rule, DOD, DOE ……

Minimal Risk

What is the definition of minimal risk?

According to the federal regulations at §46.102(i), *minimal risk* means that the probability **and** magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

"The requirement for informed consent for human research is based on the bedrock ethical principle of respect for persons."



Review of Waiver of Informed Consent

21 CFR 50.24 or 45 CFR 46.101 (i),

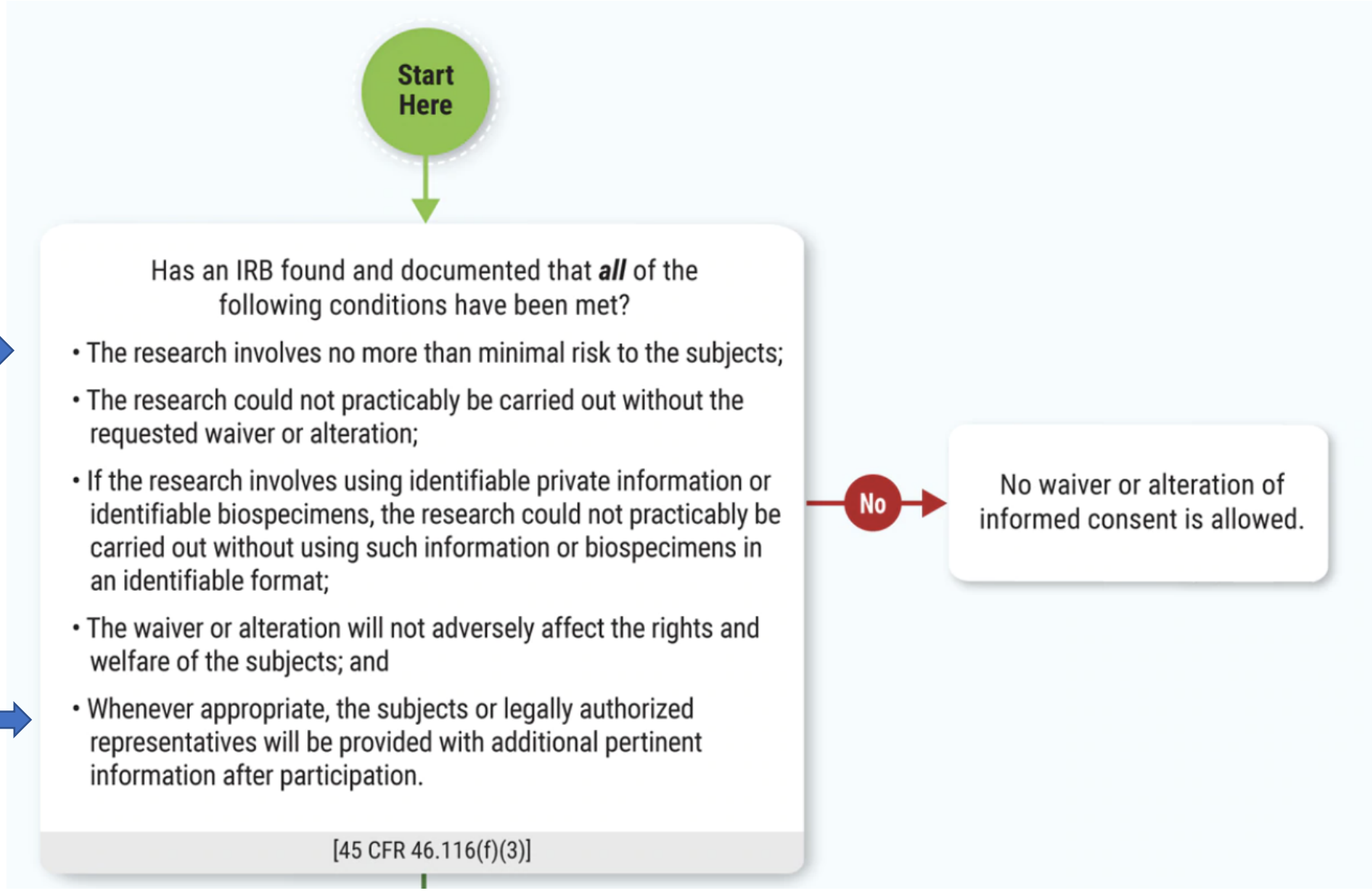
EFIC

- Potential subjects are in a **life-threatening situation**, and available treatments are **unproven or unsatisfactory**

- and

- collection of scientific data is required to **determine the safety and effectiveness of the experimental intervention**

Chart 13: When Can Informed Consent Be Waived or Altered Under 45 CFR 46.116(f)?



Risks in Comparative Effectiveness Research

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 27, 2010 VOL. 362 NO. 21

Target Ranges of Oxygen Saturation in Extremely Preterm Infants

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network*

ABSTRACT

Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care

Draft

Date: October 20, 2014

The draft guidance addresses the following topics:

1. **What are "standards of care"?**
2. **What are "risks of research" in studies evaluating risks associated with standards of care?**
3. **When is evaluating a risk in a research study considered to be a "purpose" of the research study?**
4. **Are the risks of research associated with the purposes of studies of standards of care "reasonably foreseeable risks" that must be disclosed to prospective subjects in the informed consent process?**

IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects

Guidance for Sponsors, Investigators, and Institutional Review Boards

This guidance is for immediate implementation.

Case studies

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

Karis L. Tekwani, MD, Hannah F. Watts, MD, Rolla T. Sweis, PharmD, Kathleen H. Rzechula, RN, Erik B. Kulstad, MS, MD
From the Department of Emergency Medicine, Advocate Christ Medical Center, Oak Lawn, IL.

Feldman J, Bass PA. Etomidate, sepsis, and informed consent. *Ann Emerg Med*. 2011;57(6):705-706. doi:10.1016/j.annemergmed.2011.01.026

Ketamine Versus Midazolam for Prehospital Agitation

Sponsor:

Hennepin Healthcare Research Institute

Information provided by (Responsible Party):

Hennepin Healthcare Research Institute

MINNEAPOLIS

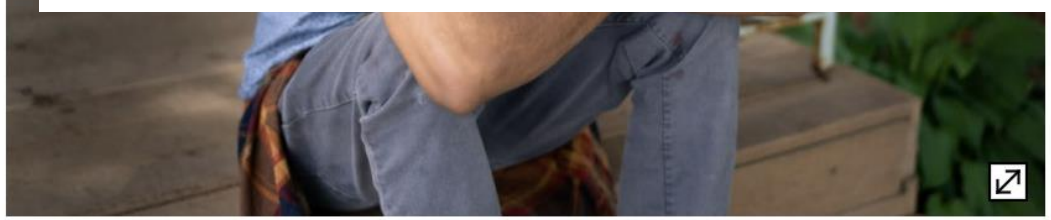
Patients sedated by ketamine were enrolled in Hennepin Healthcare study

Forced sedation in their best interest, hospital says.

By **Andy Mannix** Star Tribune | JUNE 23, 2018 — 7:51PM

Confusion turned to anger when the hospital staff gave her a document saying they'd enrolled her in a study for a sedative called ketamine: "You are receiving this form because you or someone you care for was included in a research study examining patients with agitation."

"This is all I got," she said. "Just this form saying that I'm part of their little test."

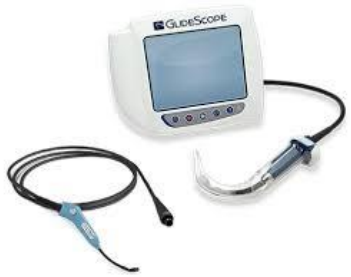


GLEN STUBBE – STAR TRIBUNE

Before he was given ketamine, Thomas Hosley "was not combative at all," said his mother, Katie Hosley, who called 911 when she found her 18-year-old son, Thomas, having a seizure in his room last October.

Vanderbilt model

vs



NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies ▾ Al

Home > Search Results > Study Record Detail

Preliminary Investigation of optimaL Oxygen Targets Trial (PILOT)

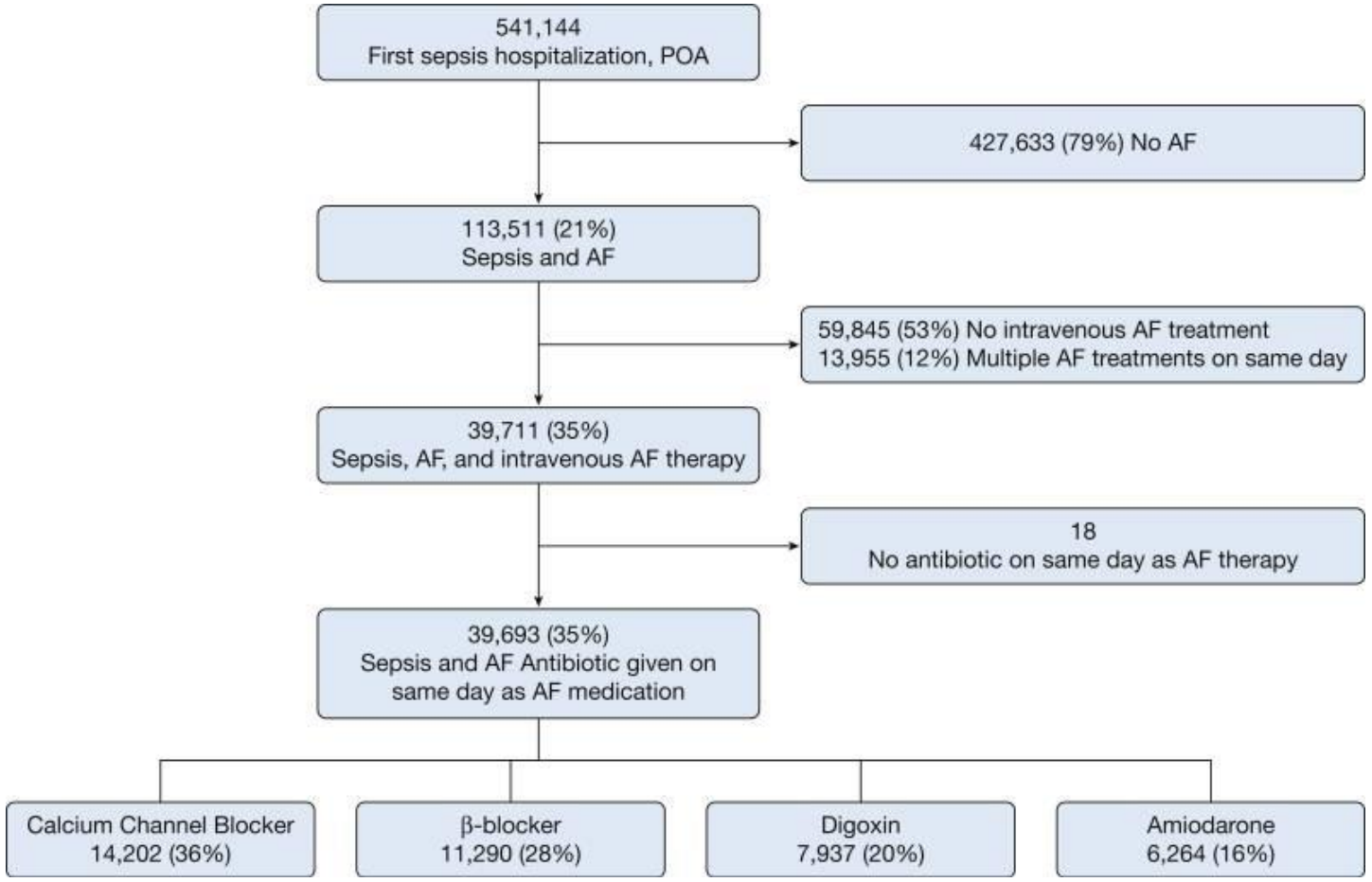
Condition or disease ℹ	Intervention/treatment ℹ
Respiratory Failure	Other: Lower SpO2 Target Other: Intermediate SpO2 Target Other: Higher SpO2 Target

- Poster in ICU
  - Could be enrolled ED/ICU
- Participants / surrogate **notified via flyer of trial**
- Could opt out use of data

The Problem with atrial fibrillation (AFIB)

- Afib occurs in 25% of patients with critical illness
- New-onset afib during critical illness = worse outcomes
- Optimal treatment of Afib with high heart rates during critical illness is unclear
- Treatments for Afib during critical illness vary widely
  - (10% of variation driven by hospitals of admission)

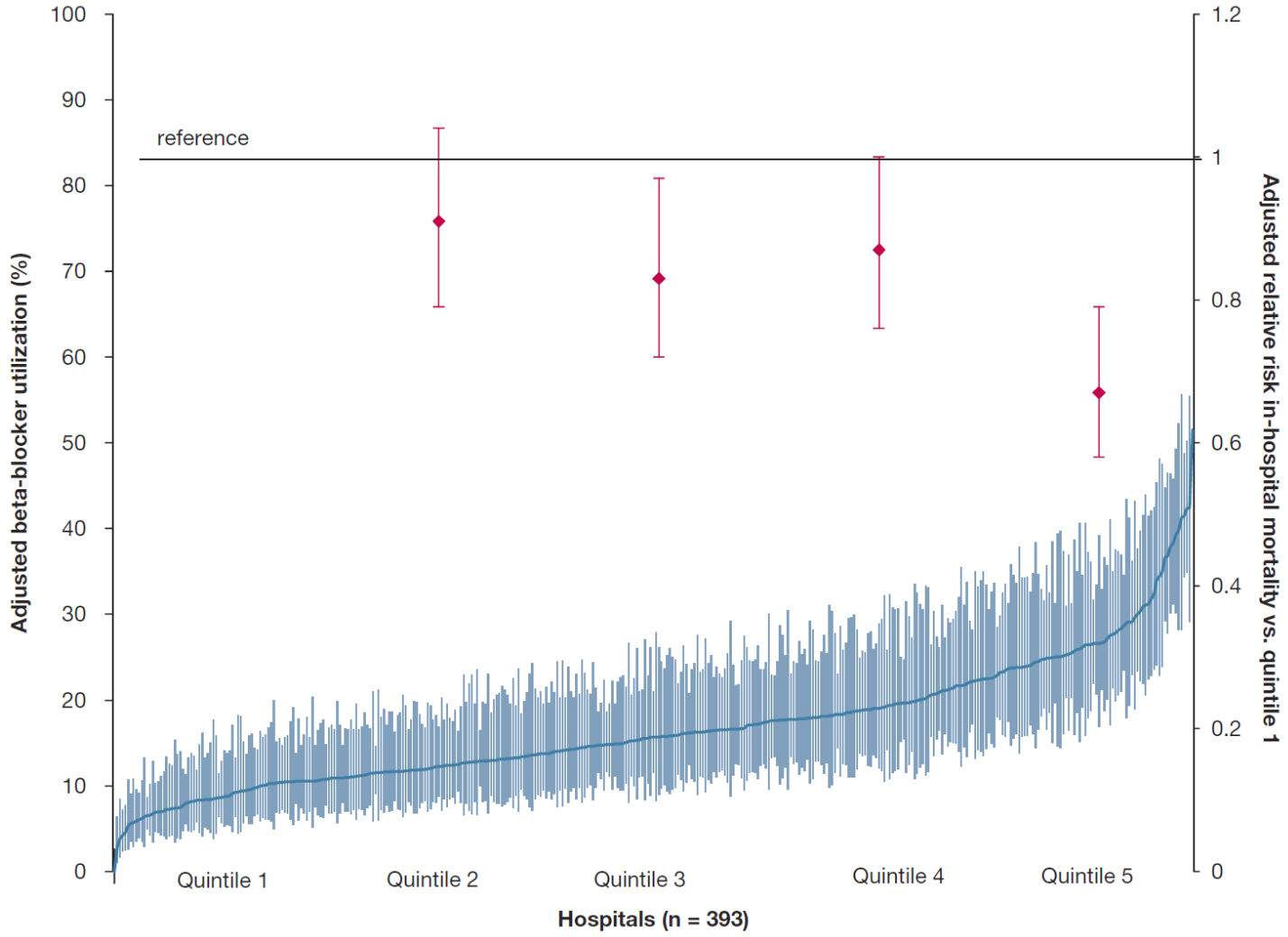
Comparative effectiveness of medications for atrial fibrillation during critical illness



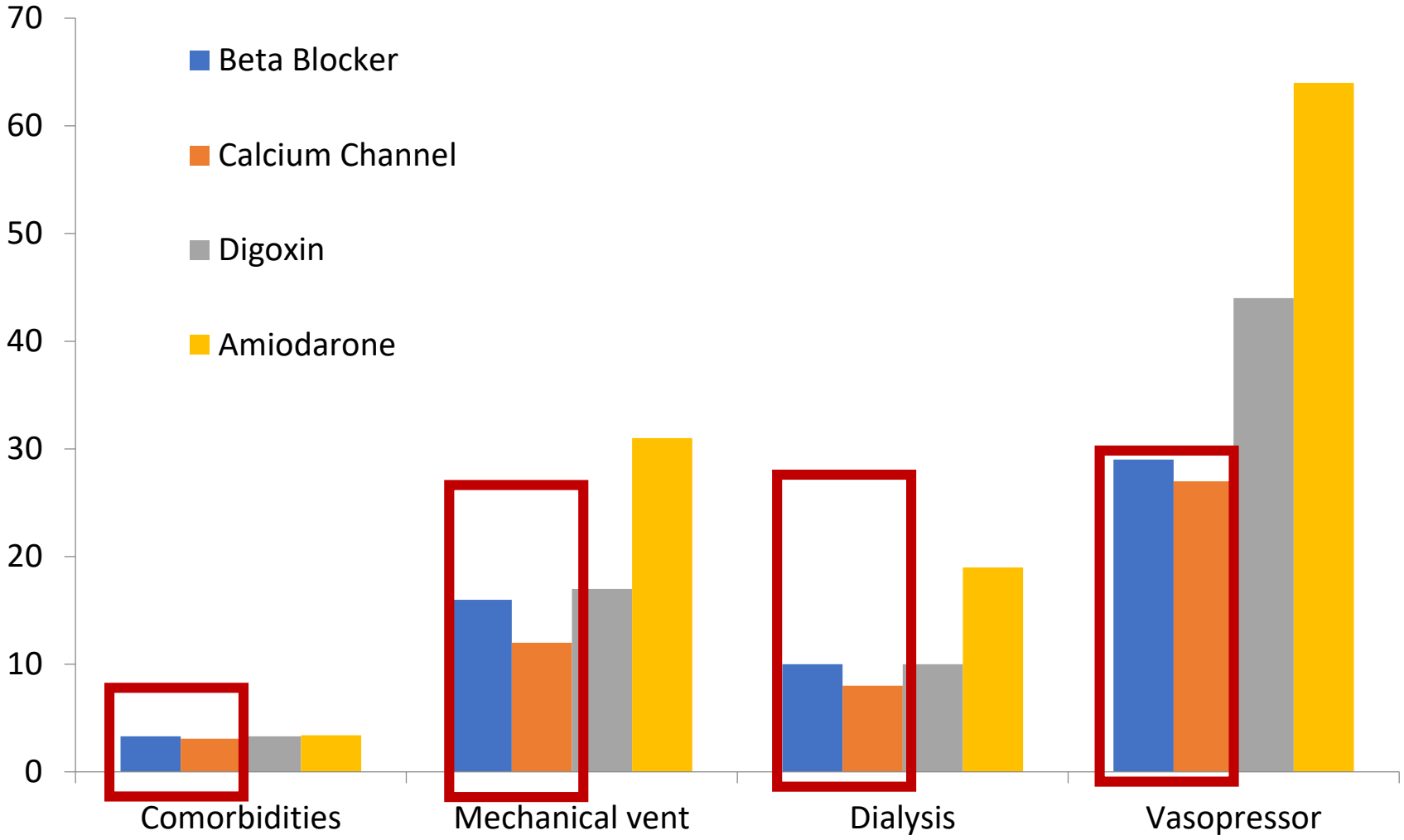
At BMC:
Survey 36 ICU physicians
83% choose Bblock 1st
17% Calcium channel block

Walkey et al CHEST 2016

Beta-blocker use may be associated with better outcomes



Beta-blocker and calcium channel blockers used in similar clinical situations



97% of physicians felt there was equipoise for trial of Bblocker vs CCB

How can we design a RCT to learn if BB vs CCB is the best treatment for AF during critical illness?

- AF in critical illness happens suddenly and without warning
- Treatment generally needs to be given immediately
- Critically ill patients with AF are decisionally-impaired

- How should informed consent occur in such a situation?

A. Waive informed consent after community consultation and public notification under exception from informed consent (EFIC)
B. The study should not occur as it is not minimal risk
C. Waiver of informed consent, cluster randomization, notification via flyer (similar to Vanderbilt model)
D. Other? Write in

How should pragmatic trials comparing standards of care in decisionally-impaired patients ethically proceed?

- Please UNMUTE and offer your opinion
  (as a possible patient, researcher or member of the BUSM/BMC community)

  1. What about a study comparing a beta blocker to a calcium blocker for AFIB in the ICU makes you think it should be approved or not approved at BMC?

  2. How concerned are you with allowing research without informed consent for studies comparing accepted treatments at BMC as a safety net hospital?