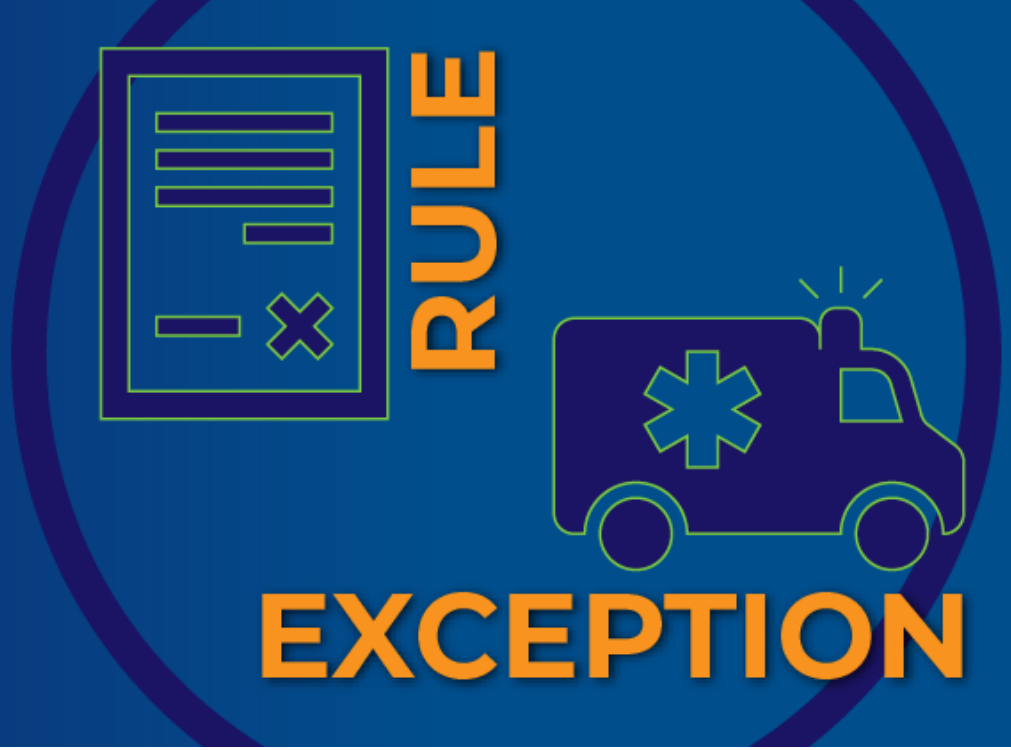
Office of Emergency Care Research

Regulatory Determinations related to Consent, EFIC and Waiver of Consent in Emergency Clinical Trials Workshop

An NIH hosted workshop for FDA, OHRP, IRBs, and Investigators



Welcome!

We will begin at 8:30 AM ET

Office of Emergency Care Research

Housekeeping Items

- This meeting is being **recorded** for internal NIH use only
- Please speak into the **microphone**
- Please state your **name** and **affiliation** before making a comment or asking a question
- Access the Workshop Website using the QR Code or visit **https://cvent.me/W8yeVy**

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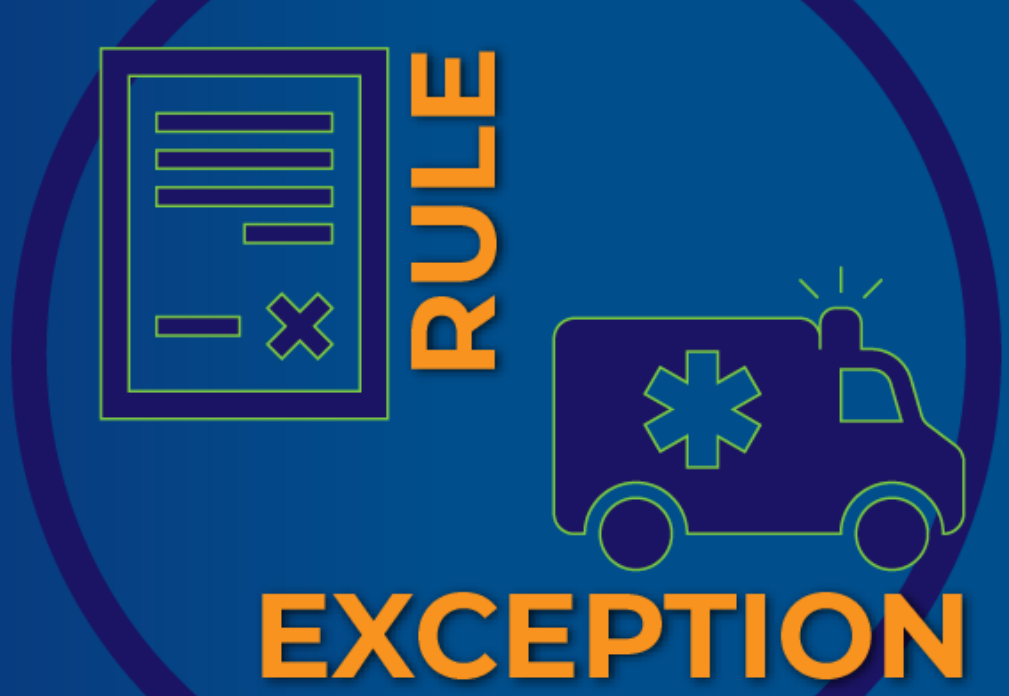

Introduction, Goals and Ground Rules

Housekeeping Items

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- Please speak into the **microphone**
- Please state your **name** and **affiliation** before making a comment or asking a question
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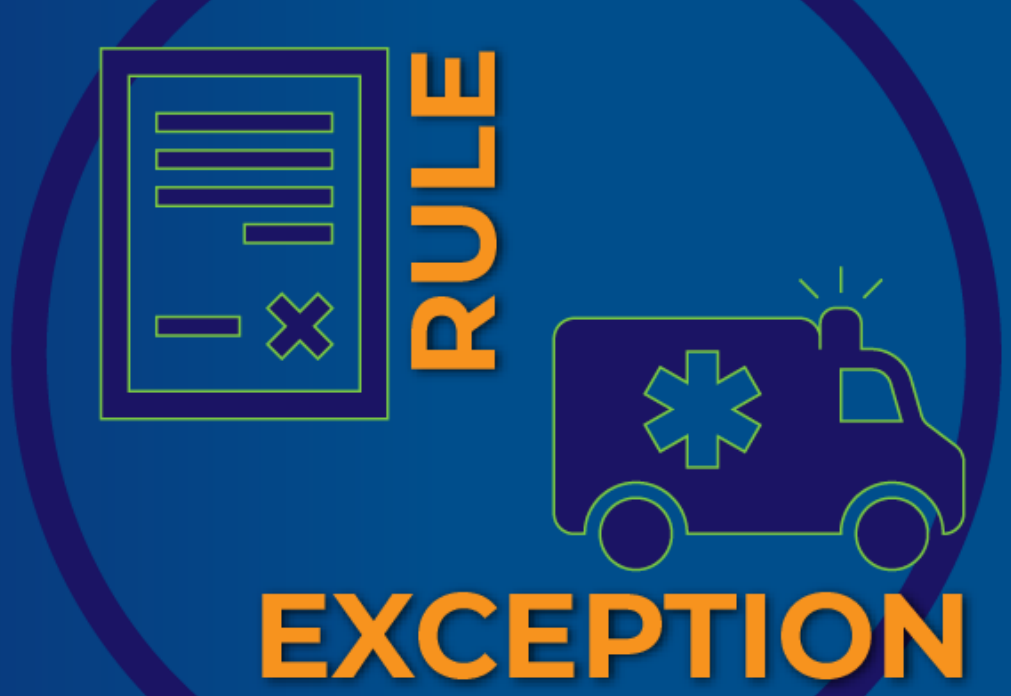

Brief FDA Overview of How They Do EFIC

Office of Emergency Care Research

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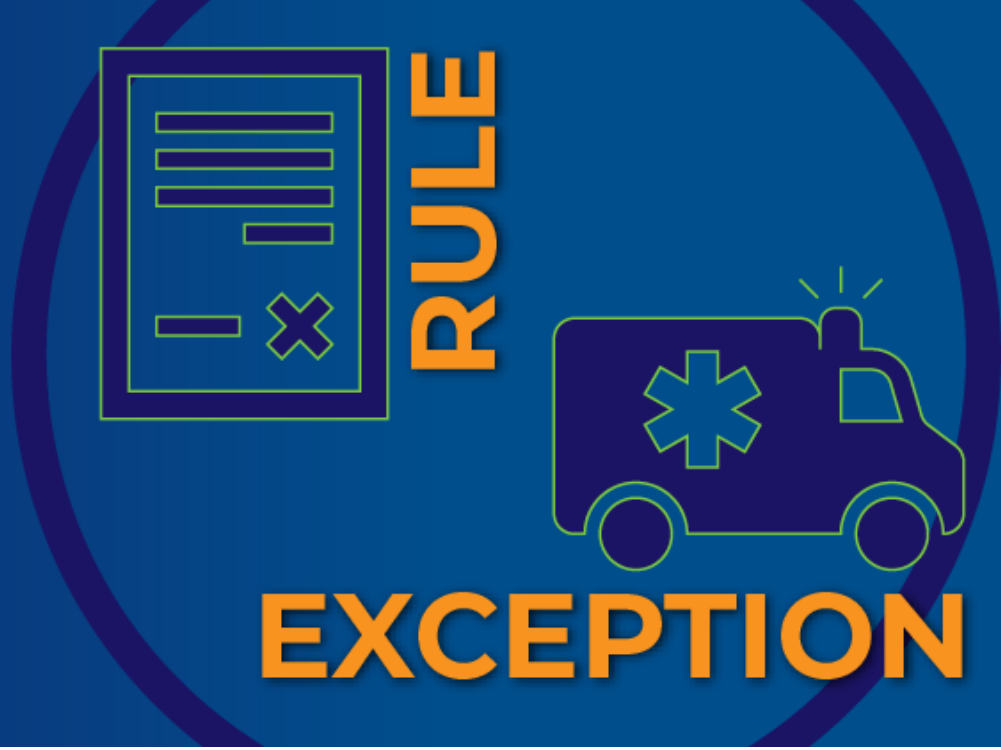


Agitated Delirium

Informed Consent and Investigational New Drug Applications when studying Acute Agitation

Jon B Cole, MD and Brian E Driver, MD

Hennepin Healthcare, Department of Emergency Medicine

Lessons from 10 Years of Studying Acute Agitation

- A case study in lessons learned about clinical research, ethics, and regulatory agencies

2012: Grant Application

ACAD EMERG MED • December 2005, Vol. 12, No. 12 • www.aemj.org

Management of Acute Undifferentiated Agitation in the Emergency Department: A Randomized Double-Blind Trial of Droperidol, Ziprasidone, and Midazolam

Marc Martel, MD, Ann Sterzinger, MD, James Miner, MD,
Joseph Clinton, MD, Michelle Biros, MD, MS

300 Emergency Department Management of Acute Undifferentiated Agitation: A Randomized, Double-blind Trial of Droperidol, Lorazepam, and Ziprasidone *Marc L Martel, Todd Gengerke, James R Miner, Michelle H Biros; Hennepin County Medical Center: Minneapolis, MN*

- Approached by fellowship mentor about a grant to study prehospital agitation, comparing ketamine and haloperidol
- My new institution, 8 years earlier had completed two trials studying IM agents for acute agitation in the ED
- AACT Grant Submitted

2013: Grant Awarded

AMERICAN ACADEMY OF CLINICAL TOXICOLOGY. INC.

6728 Old McLean Village Drive, McLean, VA 22101
Tel: 703 556 9222 Fax: 703 556 8729
WEBSITE: www.clintox.org

January 29, 2013

Jon B. Cole, MD
Medical Director
Hennepin County Medical Center
Poison Control Center
701 Park Ave
Minneapolis, MN 55415

Dear Dr. Cole:

The American Academy of Clinical Toxicology is pleased to announce that you are the recipient of the AACT Junior Investigator Award. A grant of $30,000 will be disbursed to Hennepin County Medical Center to conduct your study entitled "A randomized double blind controlled study comparing haloperidol to ketamine as a chemical restraint for "severe agitation" in the pre-hospital setting".

As part of the acceptance of this award, you as the grantee must comply with the following:

Mentors & Research Colleagues

- Senior Mentors:
  - James Miner, MD
    - Department Chair
    - Conducted previous agitation EFIC research
  - Michelle Biros, MD, MS
    - Chair of the SAEM Research Committee in 1994
    - Namesake of *Academic Emergency Medicine's* Biros Section on Research Ethics
    - Organized the Coalition for Acute Resuscitation and Critical Care Researchers to assist in the development of the Final Rule for Exception from Informed Consent (EFIC) Research (21 CFR 50.24).
    - In part because of her EFIC work, elected to the National Academy of Medicine in 2009.

Research Question

- Patients:
  - Severe prehospital agitation
    - (Altered Mental Status Scale = +2+3)
- Intervention:
  - Ketamine 5 mg/kg IM
- Comparison:
  - Haloperidol 10 mg IM
- Outcome:
  - Time to adequate sedation

Methodology

- Exception From Informed Consent (EFIC)
  - *FDA regulation 21 CFR 50.24*

A Randomized Double Blinded Trial Comparing Ketamine and Haloperidol for Severe Agitation in the Pre-Hospital Setting

Principal Investigator: Jon B Cole, MD

Plan for Community Consultation, Public Disclosure, and Contact of Legally Authorized Representatives

Department of Emergency Medicine
Hennepin County Medical Center

Concurrent Study in our ED

Ketamine vs. Etomidate for Rapid Sequence Intubation

Principal Investigator: Brian E Driver, MD

Plan for Community Consultation, Public Disclosure, and Contact of Legally Authorized Representatives

Department of Emergency Medicine
Hennepin County Medical Center

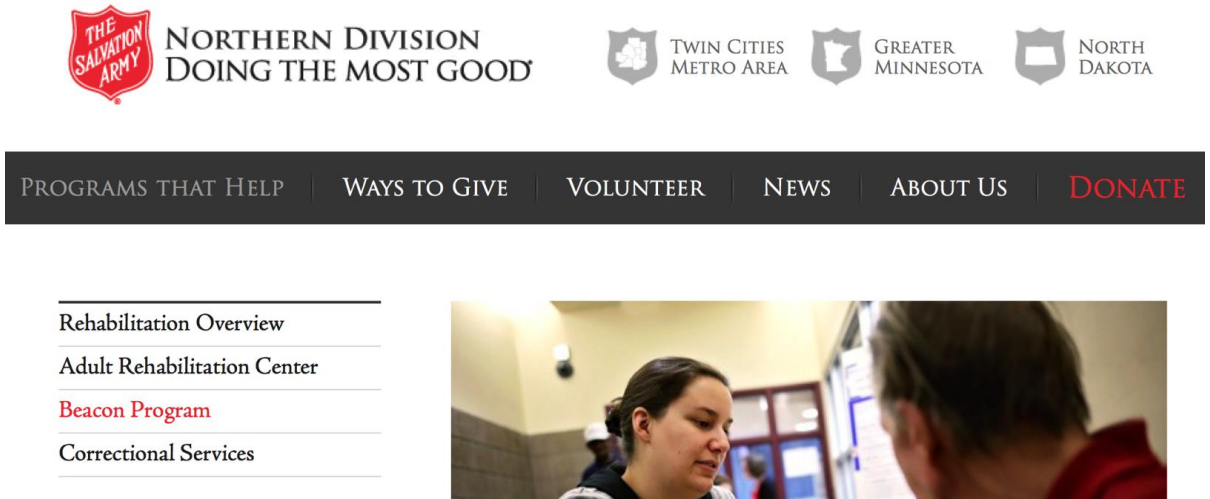
5 Elements of EFIC Completed Prior to Study

- Community Consultation (before final local IRB approval)
- Public Disclosure before & after the trial
  - including methods by which patients can “opt-out”
- Plan for contact of Legally Authorized Representatives (LAR) to seek informed consent
- Formation of a Data Safety Monitoring Board
- FDA Investigational New Drug (IND) application

Community Consultation: Completed

- Home Institution Emergency Department
  - In-person consultation with all ED workers
  - Random survey of 250 ED patients regarding the study

- The Beacon Program (multiple visits)
  - A chem dep program contained within Harbor Light Salvation Army Shelter

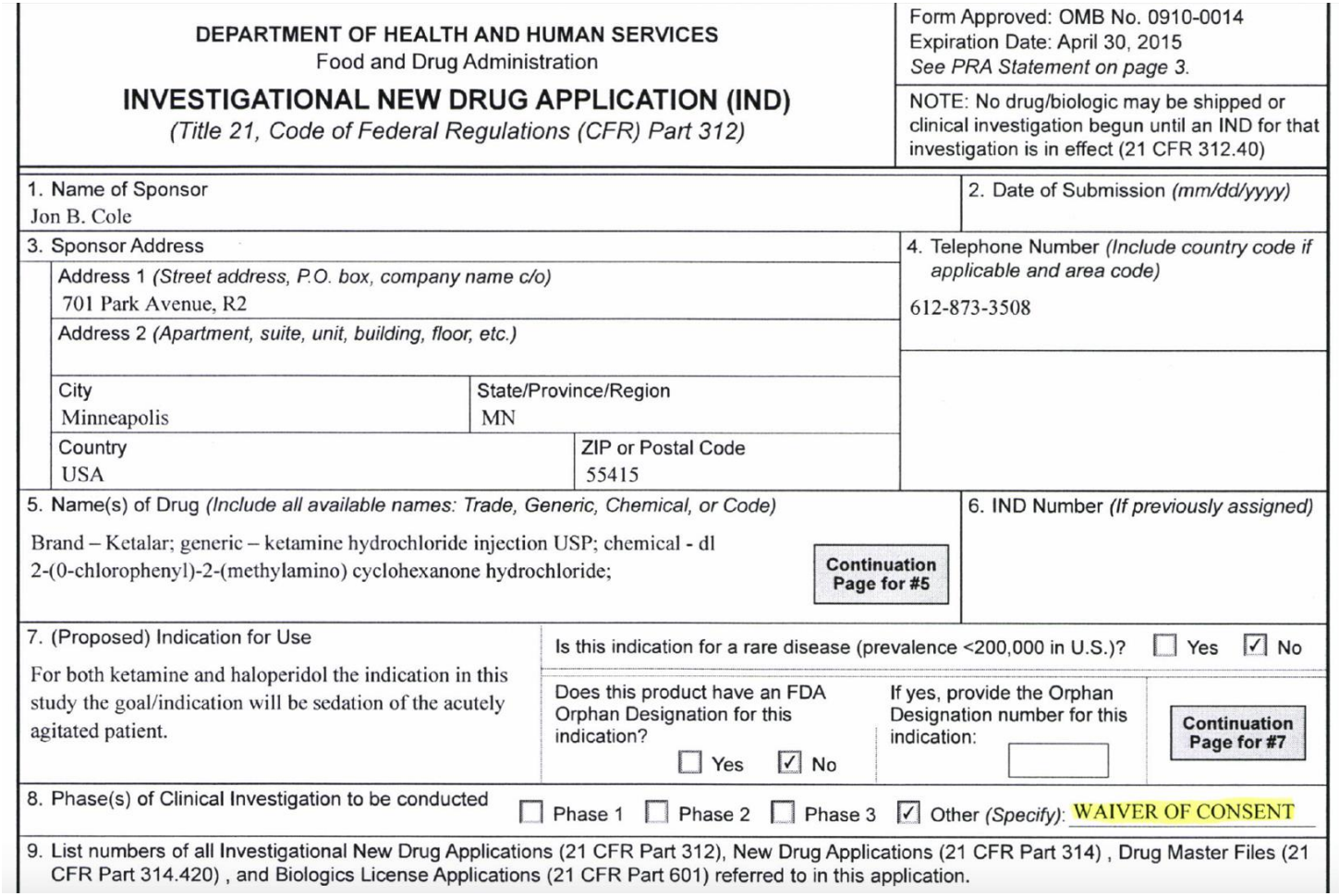


Community Consultation: Feedback

- Why no previous studies?
- Concern about consent…
- Concern about “allergic” reactions…
  - Could we add “Benadryl” ahead of time?
- Concerns about modesty
  - Specifically, incontinence
  - What happened while I was “out?”
- Concerns about disclosure
  - “you just saved their life! …they’re going to sue you…”

LAR Plan and DSMB formed

- Website created for public disclosure
- LAR for consent plan in place
  - Little expectation of use
- Data Safety Monitoring Board created
  - 3 research physicians at HCMC
- FDA IND filed 4/3/14



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: April 30, 2015
See PRA Statement on page 3.

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. Name of Sponsor
Jon B. Cole

2. Date of Submission *(mm/dd/yyyy)*

3. Sponsor Address

Address 1 *(Street address, P.O. box, company name c/o)*
701 Park Avenue, R2

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City
Minneapolis

State/Province/Region
MN

Country
USA

ZIP or Postal Code
55415

4. Telephone Number *(Include country code if applicable and area code)*
612-873-3508

5. Name(s) of Drug *(Include all available names: Trade, Generic, Chemical, or Code)*
Brand – Ketalar; generic – ketamine hydrochloride injection USP; chemical - dl 2-(0-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride;

Continuation Page for #5

6. IND Number *(If previously assigned)*

7. (Proposed) Indication for Use
For both ketamine and haloperidol the indication in this study the goal/indication will be sedation of the acutely agitated patient.

Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☑ No

Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☑ No

If yes, provide the Orphan Designation number for this indication:

Continuation Page for #7

8. Phase(s) of Clinical Investigation to be conducted ☐ Phase 1 ☐ Phase 2 ☐ Phase 3 ☑ Other *(Specify)*: WAIVER OF CONSENT

9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314) , Drug Master Files (21 CFR Part 314.420) , and Biologics License Applications (21 CFR Part 601) referred to in this application.

FDA Correspondence

- 4/10/14: FDA writes:
  - *"…met all requirements for exemption from the IND regulations, and, therefore… the FDA will not accept your application."*

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 122418

ACKNOWLEDGE/EXEMPT IND

Jon B. Cole, MD
Medical Director, Hennepin Regional Poison Center
701 Park Avenue, Mail Code R2
Minneapolis, MN 55415

Dear Dr. Cole:

We acknowledge receipt of your Investigational New Drug Application (IND), submitted April 3, 2014, received April 7, 2014, under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ketamine injection and haloperidol injection.

After reviewing the information contained in your submission, we have concluded that your study, entitled "A Randomized Double Blind Controlled Study Comparing Haloperidol to Ketamine as a Chemical Restraint for Severe Agitation in the Pre-Hospital Setting", meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct your investigation. In accordance with 21 CFR 312.2(b)(4) of the regulations, FDA will not accept your application.

FDA Correspondence

- 5/8/14: FDA writes, “we inadvertently missed this information (EFIC)…an IND *will* be required”
  - IND re-submitted
- 5/21/14: FDA re-acknowledges IND
  - Long list of revisions asked for with 6/14/14 deadline
- 5/28/14: FDA writes again, wants to “discuss this application” (phone meeting 6/12/14)
  - Local and national experts engaged

FDA Correspondence

- 6/3/14: FDA writes again to move up the teleconference to 6/10/14.
- 6/6/14: Phone request from FDA Division of Psychiatric Products (DPP) to provide:
  - Stability and safety data for the drugs
  - Labels for the randomization vials
  - Pictures of the randomization vehicles
    - We used RAMPART mechanism
  - An updated research protocol (3rd version)

FDA Correspondence

- Phone meeting, June 10, 2014
  - FDA Team: MD, PhD, PharmD, Ethicist, 2 others

- DPP group decides the study does not qualify for EFIC because, due to the large number of patients in our system, ***we should be able to obtain consent.***
  - Either from the patient themselves, or
  - From a legally authorized representative
    - Appointed health care surrogate, judicially appointed guardian, or closest adult relative in absence of the former (MN definition).
- DPP also concerns with supervision after ketamine administration

IND Closure & Study Re-design

- 6/13/14: IND withdrawn from FDA
- Study re-designed as unblinded before/after EMS protocol change
  - IRB now deems study “minimal risk”
    - I.e., local IRB determined study qualified for “Waiver of Consent.”
- Changes from initial study design:
  - No blinding, randomization, or additional blood draws
  - One additional data point collected:
    - ***“Was a legally authorized representative (LAR) available at the scene to provide informed consent?”***

Waiver of Informed Consent (WIC)

- 45 CFR 46.116d (rather than 21 CFR 50.24)

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

2015: Study Finished & Presented

CLINICAL TOXICOLOGY, 2016
VOL. 54, NO. 7, 556–562
http://dx.doi.org/10.1080/15563650.2016.1177652

Taylor & Francis
Taylor & Francis Group

CLINICAL RESEARCH

A prospective study of ketamine versus haloperidol for severe prehospital agitation

Jon B. Cole[a,b], Johanna C. Moore[b], Paul C. Nystrom[b], Benjamin S. Orozco[a,b], Samuel J. Stellpflug[c], Rebecca L. Kornas[b], Brandon J. Fryza[b], Lila W. Steinberg[b], Alex O'Brien-Lambert[b], Peter Bache-Wiig[b], Kristin M. Engebretsen[c] and Jeffrey D. Ho[b]

[a]Minnesota Poison Control System, Minneapolis, MN, USA; [b]Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, MN, USA; [c]Department of Emergency Medicine, Regions Hospital, St. Paul, MN, USA

ABSTRACT

Context: Ketamine is an emerging drug for the treatment of acute undifferentiated agitation in the pre-hospital environment, however no prospective comparative studies have evaluated its effectiveness or safety in this clinical setting. **Objective:** We hypothesized 5 mg/kg of intramuscular ketamine would be superior to 10 mg of intramuscular haloperidol for severe prehospital agitation, with time to adequate sedation as the primary outcome measure. **Methods:** This was a prospective open label study of all

ARTICLE HISTORY
Received 5 February 2016
Revised 3 April 2016
Accepted 7 April 2016
Published online 21 April 2016

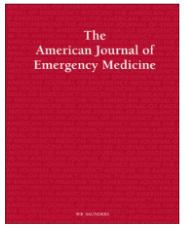
- 2016: study published (LARs present in 6% of cases)

2016-2017: Intoxicated ED Patients – Consent?

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem



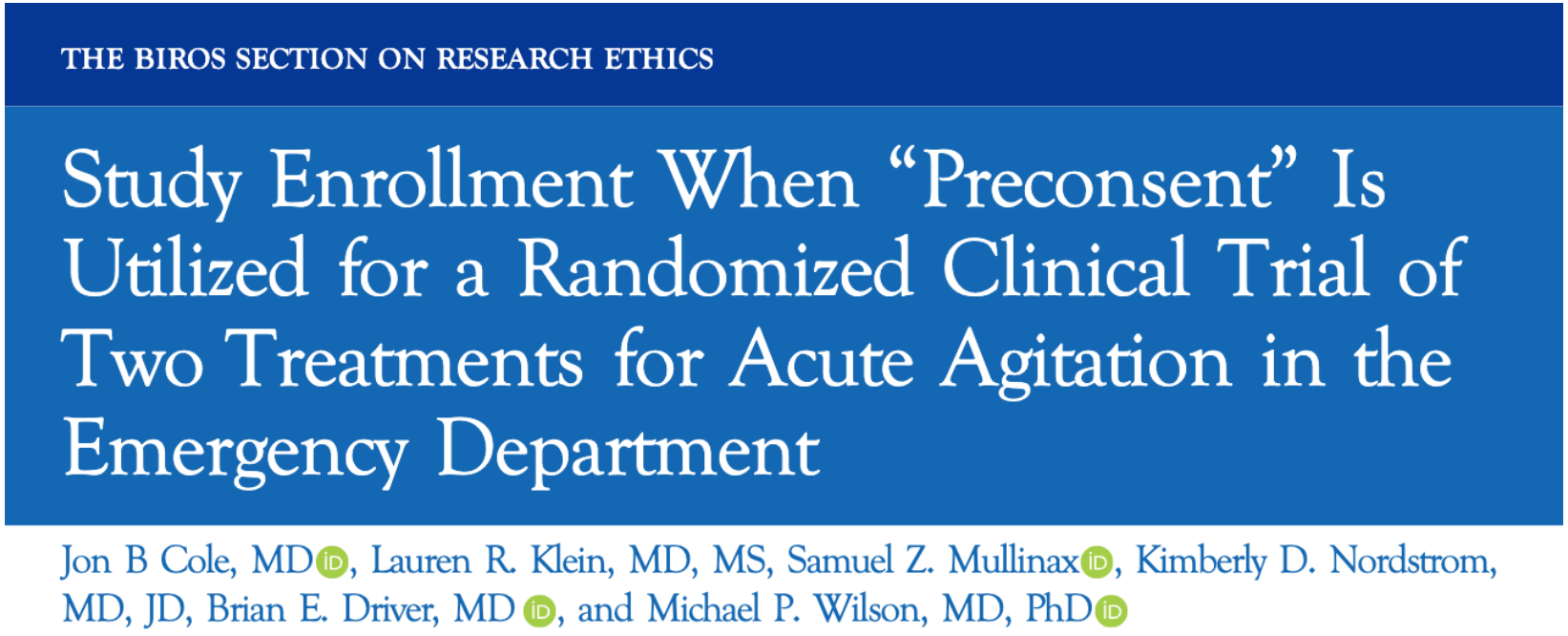
A brief assessment of capacity to consent instrument in acutely intoxicated emergency department patients

Marc L. Martel, MD [a,*], Lauren R. Klein, MD [a], James R. Miner, MD [a], Jon B. Cole, MD [a], Paul C. Nystrom, MD [a], Kayla M. Holm, BS [a], Michelle H. Biros, MS, MD [a,b]

[a] *Department of Emergency Medicine, Hennepin County Medical Center, 701 Park Avenue, Minneapolis, MN 55415, United States*
[b] *Department of Emergency Medicine, University of Minnesota, 717 Delaware Street SE, Suite 508, Minneapolis, MN, 55414, United States*

- A validated tool showed that only 1.9% of intoxicated ED patients had the capacity to provide informed consent.
- Half the patients who demonstrated capacity did not recall the test

2017: Study of “Pre-consent”



- Only 2 patients enrolled after screening >1,000

2017: Follow-up study in the ED

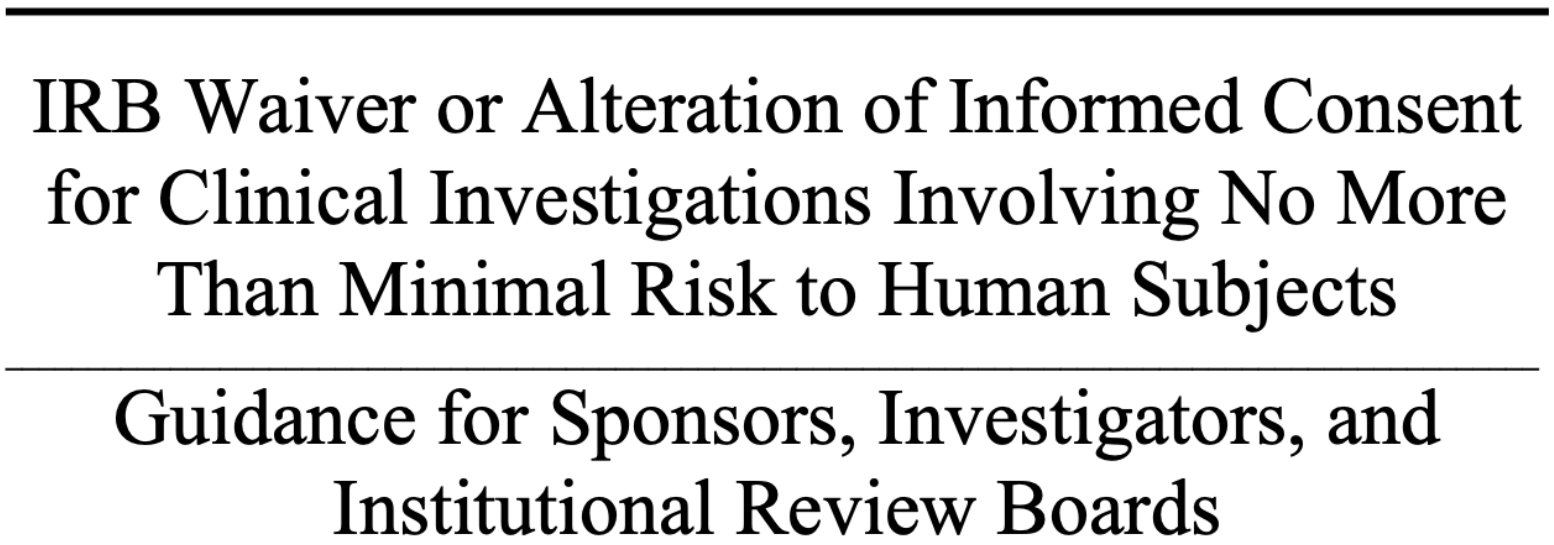
- IND again sought for an ED trial; design identical to previous trials from 2004 - 2005
- Again, denied due to “consent possible,” placed on Full Clinical Hold
- Again, re-designed as before/after open label

PAIN MANAGEMENT AND SEDATION/ORIGINAL RESEARCH

Intramuscular Midazolam, Olanzapine, Ziprasidone, or Haloperidol for Treating Acute Agitation in the Emergency Department

Lauren R. Klein, MD, MS*; Brian E. Driver, MD; James R. Miner, MD; Marc L. Martel, MD; Michelle Hessel, PharmD; Jacob D. Collins, BS; Gabriella B. Horton; Erik Fagerstrom, BS; Rajesh Satpathy, BA; Jon B. Cole, MD

2017: FDA Issues IRB Guidance


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

- FDA does not object to a local IRB approving a “minimal risk” trial at the local level

2018: ED Study & Editorial Published

PAIN MANAGEMENT AND SEDATION/ORIGINAL RESEARCH

Intramuscular Midazolam, Olanzapine, Ziprasidone, or Haloperidol for Treating Acute Agitation in the Emergency Department

Lauren R. Klein, MD, MS*; Brian E. Driver, MD; James R. Miner, MD; Marc L. Martel, MD; Michelle Hessel, PharmD; Jacob D. Collins, BS; Gabriella B. Horton; Erik Fagerstrom, BS; Rajesh Satpathy, BA; Jon B. Cole, MD

PAIN MANAGEMENT AND SEDATION/EDITORIAL

Ethics and Regulatory Barriers to Research in Emergency Settings

Neal W. Dickert, MD, PhD*; Jeremy Sugarman, MD, MPH

*Corresponding Author. E-mail: njr@emory.edu.

2017 – 2018: The Follow-Up Prehospital Study

2 **Ketamine Versus Midazolam for Out-of-Hospital Agitation: A Prospective Study**

Cole J, Klein LR, Scharber SK, Simpson NS, Driver BE, Arens AM, Nystrom PC, Olives TD, Moore JC, Ho JD/Hennepin County Medical Center, Minneapolis, MN; Duke University School of Medicine, Durham, NC

Premature Study Closure

MINNEAPOLIS

StarTribune

Ketamine cases raise questions

MINNEAPOLIS

StarTribune

Patients sedated by ketamine were enrolled in Hennepin

nature

NEWS · 25 JULY 2018

Controversial US ketamine trial sparks ethics complaint

Advocacy group alleges that emergency medical workers in Minnesota gave patients ketamine injections without consent, despite known risks.

To Your Health

Hospital's experi

without consent raises ethical

Politicians called study of sedative "unconscionable and unethical."

By Andy Mannix Star Tribune | JUNE 26, 2018 — 11:38AM

HennepinHealthcare

Summer 2018: Local IRB audited by FDA

Fall 2018: Litigation

SECTIONS | 🔍 StarTribune

LOCAL

Lawsuit alleges hospital improperly sedated woman with ketamine, enrolled her in study

She alleges paramedics unnecessarily injected her with ketamine after 911 call.

NOVEMBER 8, 2018 — 9:52PM

Forbes

FORBES > BUSINESS > POLICY

Forcibly Sedating An Innocent Woman Doesn't Violate The Fourth Amendment, Federal Court Rules

Nick Sibilla Senior Contributor ⓘ

I cover criminal justice, entrepreneurship, and offbeat lawsuits.

Follow

Sep 2, 2021, 02:45pm EDT

April 2019: Investigator Audit

- April 2019: Form 483 received
- May 2019: Form 483 response
- May 2021: Warning Letter received
  - FDA determined study should have had IND
- October 2021: Notification of Compliance

Criteria for IND Exemptions: 21 CFR 312.2(b)(1)

- (b) *Exemptions.* (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:
- (i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
- (ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
- (iii) ***The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks*** (or decreases the acceptability of the risks) associated with the use of the drug product;
- (iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and
- (v) The investigation is conducted in compliance with the requirements of § 312.7.

Nov 2021: Request for Disqualification

- April 2022: FDA denies Citizen Petition

Questions for the future

- Who can and who cannot consent, especially for time-sensitive conditions?

- If EFIC is only for life-threatening conditions (not directly defined), then presently it is not possible to conduct drug studies without consent for time-sensitive conditions that impair cognition but rarely result in death (e.g., moderate to severe agitation, severe alcohol withdrawal, moderate traumatic brain injury).

- Is either EFIC *or* a waiver of consent at the local IRB acceptable for future trials comparing two standards of care in common use in such conditions?

Reflections

- FDA was concerned with *enrolling intoxicated patients* who were unable to give consent; this is, however, the exact population we wished to study, as they receive these treatments routinely.
- Our experience and data suggest real-time informed consent is likely not feasible; moreover, if a patient is in such a state as to be able to consent, that is not the high-risk population of interest.
- Patients with agitation at high risk for intoxication are at risk for death or permanent disability, but not the same risk as patients in cardiac arrest; as such, does/should EFIC apply?
  - Is there currently a regulatory limbo? – “too sick to consent, not sick enough for EFIC?”

Department of Health and Human Services: Secretarial Waiver for Emergency Research

Julie Kaneshiro

Acting Director
HHS Office for Human Research Protections (OHRP)

OASH | Office for Human Research Protections

Disclosure: I have no relevant personal/professional/financial relationship(s) with respect to this educational activity.

Disclaimer: The opinions expressed are those of the presenter and do not necessarily reflect the policy of the U.S. Department of Health and Human Services.

HHS Secretarial Waiver of Informed Consent in Certain Emergency Research

- HHS Secretary may waive some or all of the provisions of 45 CFR part 46. 45 CFR 46.101(i).
- October 2, 1996, HHS published a *Federal Register* notice waiving the informed consent requirements for certain emergency research.
- Few differences between FDA's regulation and the Secretarial Waiver for emergency research.

What Research is Covered by the HHS Secretarial Emergency Waiver?

- Research conducted or supported by HHS -- even if also FDA regulated.
- Research involving adults or children.
- **Not** research involving pregnant women or fetuses, or prisoners

Key Differences Between HHS Secretarial Emergency Waiver and FDA's Regulations (21 CFR 50.24)

- The HHS Secretarial Emergency Waiver cannot be used to waive the informed consent of pregnant women or prisoners.
- OHRP does not prospectively approve an institution's use of the Secretarial Waiver.
- OHRP is only notified of an institution's use of the Secretarial waiver when the research is not subject to FDA regulations at 21 CFR 50.24.

Possible Paths Forward?

- **Consent:**
  - Possible to prospectively recruit from facilities treating patients most likely to be eligible for the study (e.g., homeless shelter's inpatient chemical dependency program where community consultation occurred)?
  - Only enroll people who have an LAR available and there is sufficient time to obtain consent.

Possible Paths Forward?

- **Waiver of consent/minimal risk (45 CFR 46.116(f)):**
  - Key Point: If the research changes the treatment that a person would have received if they were not in the research, then the treatment is a research intervention, and its risks need to be considered.
    - This is the case even if the study involves assigning people to one or more versions of “usual” or “standard care.”
  - Look for collaborating sites where the treatments to be evaluated are being used clinically for the intended study population.

Possible Paths Forward?

- **Secretarial Waiver for Emergency Research/EFIC:**
  - Limit enrollment to those in a life-threatening situation (e.g., those with excited delirium syndrome or profound agitation).

  - **A New Secretarial Waiver?**

OHRP Contacts

- Contact us or submit your questions to OHRP@hhs.gov
- Visit OHRP website at www.hhs.gov/ohrp
- Education page: https://www.hhs.gov/ohrp/education-and-outreach/index.html
- Policy and Guidance page: https://www.hhs.gov/ohrp/regulations-and-policy/index.html

Regulatory pathways to permit clinical research beyond EFIC

Barbara E. Bierer, MD

Faculty Director, MRCT Center
Department of Medicine, Brigham and Women's Hospital
Professor of Medicine, Harvard Medical School

bbierer@bwh.harvard.edu
(617) 827-7413

12 March 2024

- I have no significant financial relationships with industry to disclose relevant to the content of this discussion.
- No Commercial Support was provided for this discussion.

Case Study and question

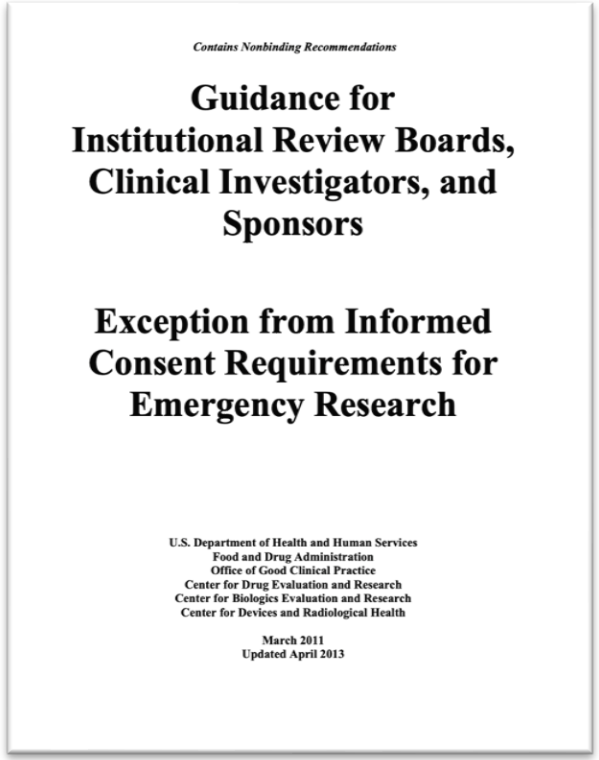
- Acutely agitated individuals in need of urgent sedation
  - Narrow therapeutic window for timing of treatment
  - Treatments exist, but optimal treatment is unknown
  - By virtue of the condition, the individual is unable to give informed consent nor does the timing allow for appropriate informed consent discussion and process
  - LAR may or may not be in attendance, but the likelihood is small

  Notably:
  - Not life-threatening situation
  - Clinical judgment is used as to whether an agitated individual requires sedation
  - Not a minimal risk intervention

I do not intend to litigate or re-litigate this case.

FDA EFIC Guidance

- 21 CFR 50.24 Conditions to be met:
  - Life-threatening situation that necessitates urgent attention
  - Available treatments are unproven or unsatisfactory
  - Valid scientific evidence is necessary to determine safety and effectiveness
  - Obtaining informed consent is not feasible
    - Participants unable to give informed consent as a result of medical condition
  - Intervention must be administered before consent can be obtained from LAR
  - Cannot prospectively identify eligible potential participants
  - Clinical investigation could not be carried out without the waiver
- Must hold out the prospect of direct benefit to participants
  - Risks are reasonable in relation to the medical condition, the risks and benefits of standard therapy, and what is known of risks and therapies of proposed intervention or activity.


Contains Nonbinding Recommendations

Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors

Exception from Informed Consent Requirements for Emergency Research

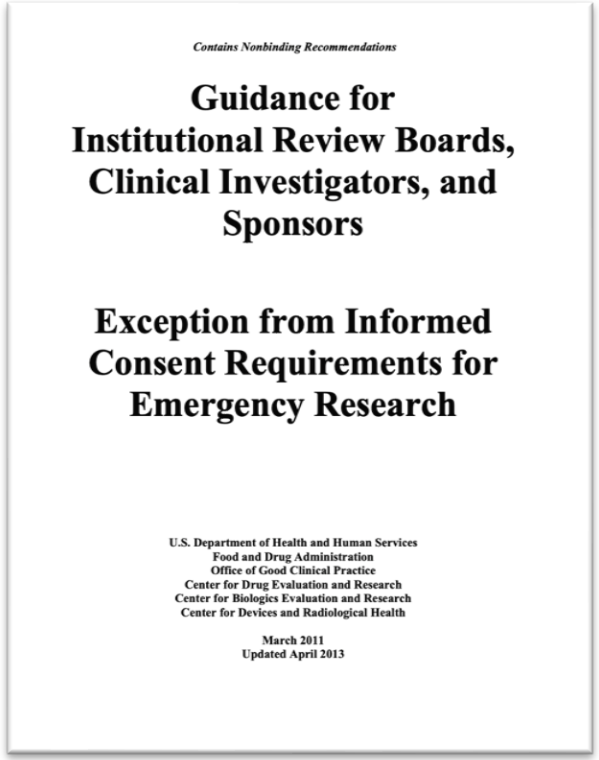
U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health

March 2011
Updated April 2013

https://www.fda.gov/media/80554/download

FDA EFIC Guidance

- Additional protections for participants required
  - Community consultation prior to study initiation
  - Public disclosure to communities after study completion
  - Independent DMC appointed to exercise oversight
- If subject to FDA regulations, IRB must find study meets EFIC requirements (21 CFR 50.24)
  - Requires separate IND or IDE
- If not subject to FDA regulations, then determine if subject to HHS waiver for emergency research studies and report to OHRP



Contains Nonbinding Recommendations

Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors

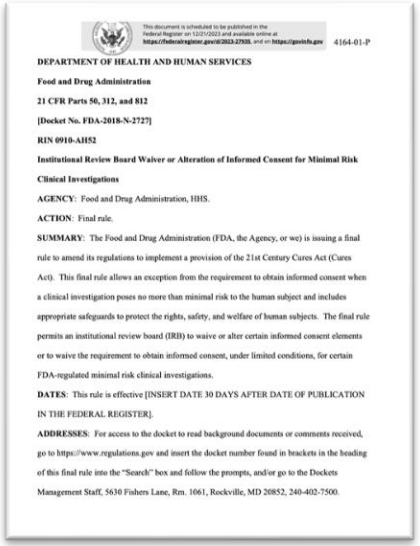
Exception from Informed Consent Requirements for Emergency Research

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health

March 2011
Updated April 2013

https://www.fda.gov/media/80554/download

FDA Waiver of Informed Consent (effective January 22, 2024)



This document is scheduled to be published in the Federal Register on 12/27/2023 and available online at https://federalregister.gov/d/2023-27935, and on https://govinfo.gov

4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 50, 312, and 812

[Docket No. FDA-2018-N-2727]

RIN 0910-AH52

Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is issuing a final rule to amend its regulations to implement a provision of the 21st Century Cures Act (Cures Act). This final rule allows an exception from the requirement to obtain informed consent when a clinical investigation poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of human subjects. The final rule permits an institutional review board (IRB) to waive or alter certain informed consent elements or to waive the requirement to obtain informed consent, under limited conditions, for certain FDA-regulated minimal risk clinical investigations.

DATES: This rule is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: For access to the docket to read background documents or comments received, go to https://www.regulations.gov and insert the docket number found in brackets in the heading of this final rule into the "Search" box and follow the prompts, and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

- Consistent with 21st Century Cures Act, section 3024
- Waives or alters certain elements of informed consent or waives the requirement to obtain informed consent if 5 criteria are met:
  - The clinical investigation involves "no more than minimal risk" to research subjects.
  - Waiving or altering informed consent will not adversely impact the rights and welfare of participants.
  - The investigation could not be practicably carried out without the waiver or alteration of informed consent.
  - When appropriate, participants are provided with additional relevant information after participation in the investigation.
  - For research involving identifiable private information or identifiable biospecimens, the research could not be practicably carried out without using the information or biospecimens in an identifiable format.
- Parallels the Common Rule at 45 CFR 46

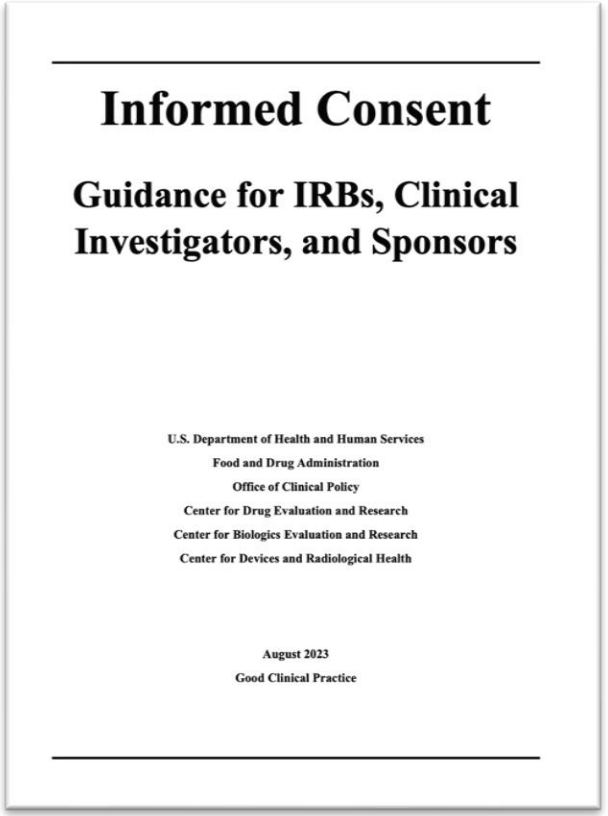
Note: No limitation to the authority of a physician to provide emergency medical care.

Updated FDA Guidance on Informed Consent (August 2023)

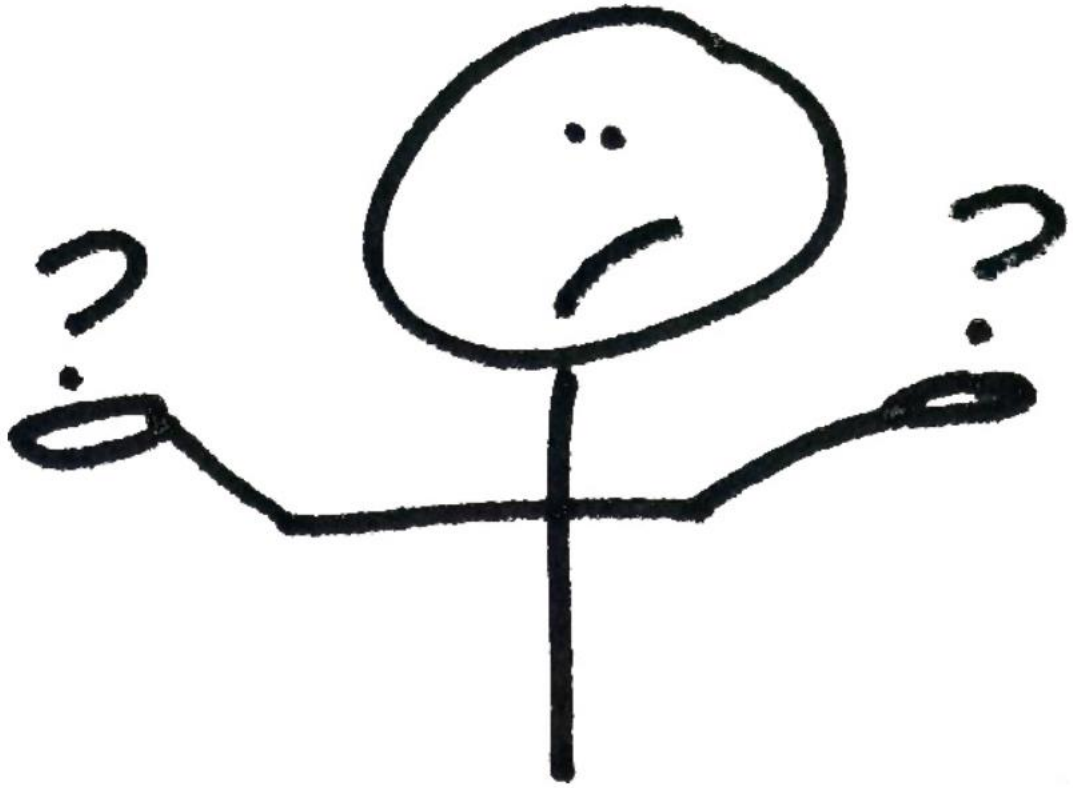
- Informed consent is required except under limited circumstances (21 CFR 50.23 and 50.24)
  - Certain life-threatening situations
  - Military operations
  - Public health emergencies
  - Emergency research

- And here, we make the assumption that clinical research is necessary

So, what regulatory pathway exists to review and approve the study?



https://www.fda.gov/media/88915/download



https://www.alifeofoptions.com/dont-know

Regs and Requirements

- Amendment (or enforcement discretion) if other conditions are met:
  - Limited to urgent clinical settings in which immediate intervention or treatment is indicated.
  - No FDA-approved intervention or treatment is available, or the approved intervention or treatment is unsatisfactory
  - The therapeutic window for intervention is too narrow for prospective informed consent.
  - Additional protections include consultation with the community ("representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn") are included
  - Independent DMC empaneled with responsibility for the oversight of the trial
  - IRB review and approval has been obtained
    - If FDA-regulated, then IND or IDE has been obtained
    - If not FDA-regulated, OHRP notified, and HHS Secretarial waiver pursued
  - Participant informed when and as soon as possible
  - Community informed at the conclusion of the trial

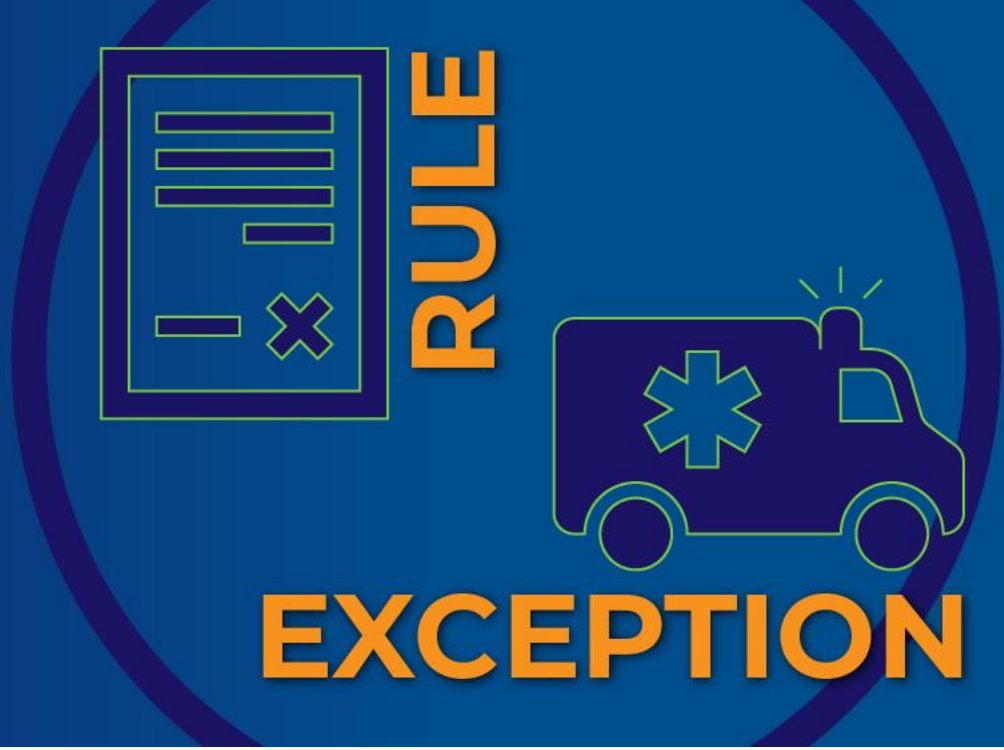
Thank you

Barbara E. Bierer, MD
bbierer@bwh.harvard.edu
(617) 827-7413

Office of Emergency Care Research

Regulatory Determinations related to Consent, EFIC and Waiver of Consent in Emergency Clinical Trials Workshop

An NIH hosted workshop for FDA, OHRP, IRBs, and Investigators



BREAK

We will resume at 10:10 AM ET

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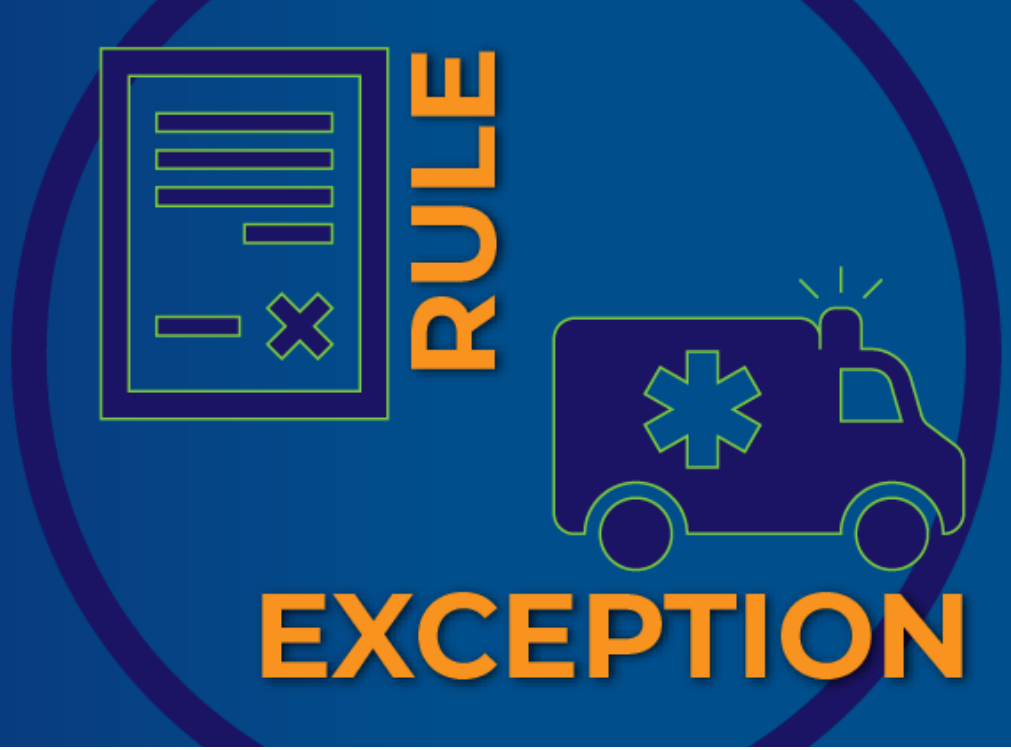


Cardiogenic Shock and Partial Capacity/Availability

Exception from Informed Consent (EFIC) in the Context of Cardiogenic Shock

Neal Dickert, MD, PhD, FACC
Thomas R. Williams Associate Professor of Medicine
Department of Medicine, Division of Cardiology
Emory Health Services Research Center
Emory University School of Medicine

EMORY UNIVERSITY SCHOOL OF MEDICINE | Department of Medicine

Disclosures and Acknowledgments

- Research funding
  - NIH
  - AHRQ
  - PCORI
  - Merck
- Abiomed- Member of Emergency Care Core (ECC) and Consulting Activity for Recover IV Trial (NCT05506449)

- Presentation reflects work within RECOVER IV and discussions at Cardiac Safety Research Consortium

Objectives

Use cardiogenic shock and the RECOVER IV Trial as a case study to explore application of the EFIC framework in contexts characterized by two important challenges that can arise in multiple conditions:

- The population of interest has variable ability to engage in consent for research enrollment

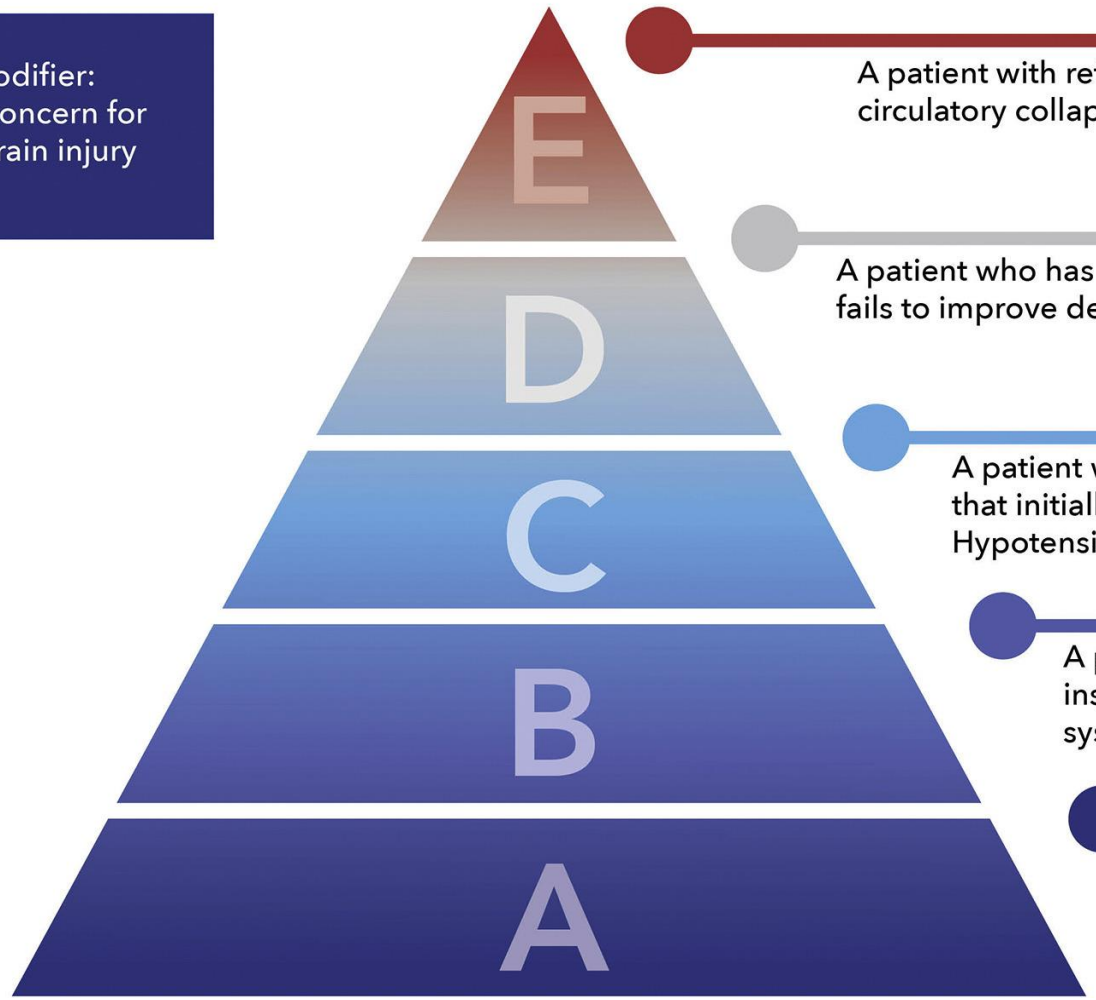
- The therapeutic window provides an opportunity for engagement but is often insufficient for consent

Background- Cardiogenic Shock

- Cardiogenic shock (CS) is defined by end-organ hypoperfusion due to reduced cardiac output.
- CS is a serious complication of acute myocardial infarction, particularly ST-elevation myocardial infarction (STEMI).
- CS in the context of STEMI is associated with high mortality (40-50%) and downstream morbidity.
- Early percutaneous coronary intervention (PCI) is the only RCT-supported intervention to improve mortality/morbidity
- Increasing use of mechanical circulatory support, but there is a need for RCT evidence to guide use of MCS

Background-Cardiogenic Shock Population

(A) Modifier:
CA with concern for anoxic brain injury



EXTREMIS

A patient with refractory shock or actual/impending circulatory collapse.

DETERIORATING

A patient who has clinical evidence of shock that worsens or fails to improve despite escalation of therapy.

CLASSIC

A patient who has clinical evidence of hypoperfusion that initially requires pharmacologic or mechanical support. Hypotension is usually present.

BEGINNING

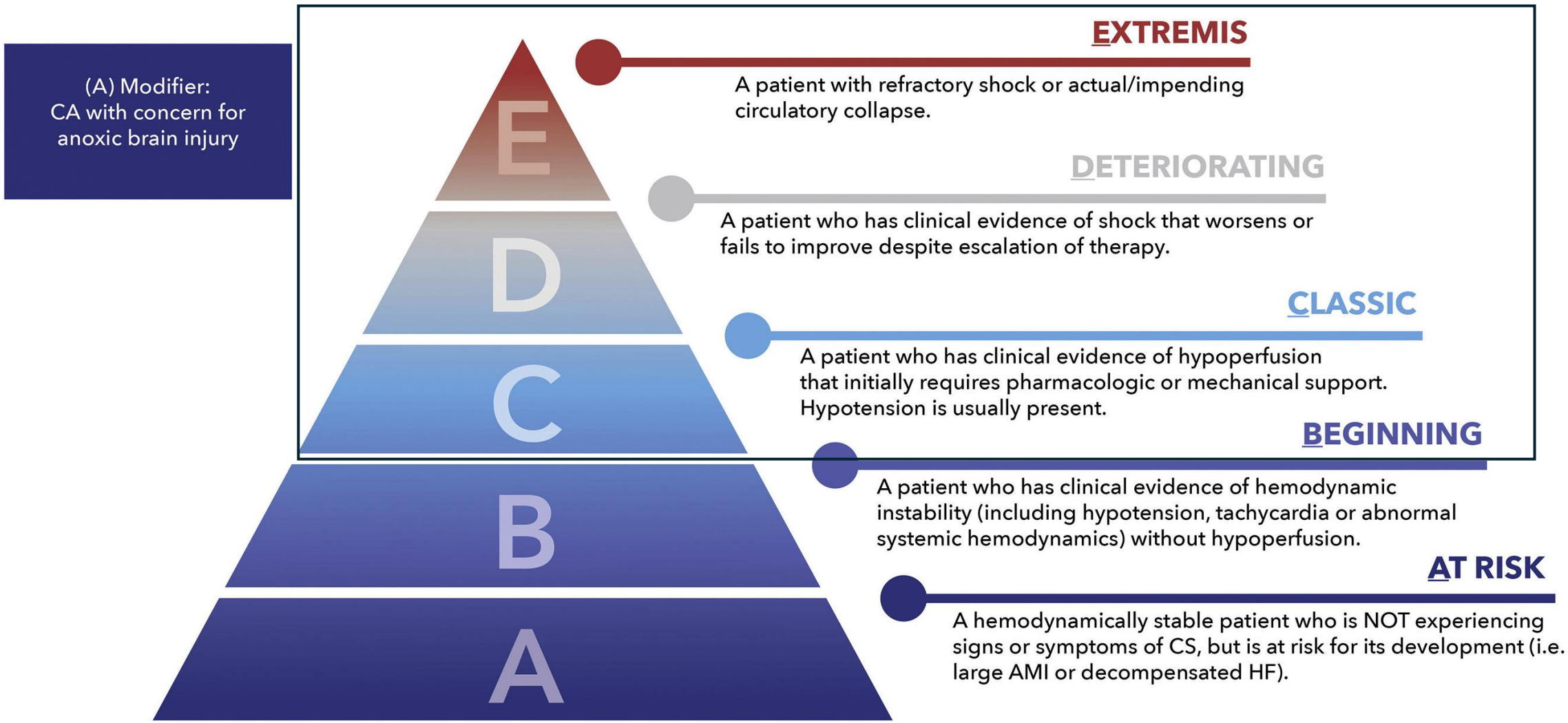
A patient who has clinical evidence of hemodynamic instability (including hypotension, tachycardia or abnormal systemic hemodynamics) without hypoperfusion.

AT RISK

A hemodynamically stable patient who is NOT experiencing signs or symptoms of CS, but is at risk for its development (i.e. large AMI or decompensated HF).

Naidu SS et al. SCAI SHOCK Stage Classification Expert Consensus Update: A Review and Incorporation of Validation Studies. *Journal of the Society for Cardiovascular Angiography & Interventions.* 2022.

Background-Cardiogenic Shock Population



Naidu SS et al. SCAI SHOCK Stage Classification Expert Consensus Update: A Review and Incorporation of Validation Studies. *Journal of the Society for Cardiovascular Angiography & Interventions.* 2022.

Background- Cardiogenic Shock Treatment

- Cornerstone= Prompt PCI
  - Guidelines support PCI within 90 minutes of first medical contact
  - Median ”Door to ballon time” currently 64 minutes
- Vasoactive drugs
  - Inotropes and vasopressors
- Mechanical circulatory support (MCS)
  - Intraaortic balloon pump
  - Axial flow devices
  - Extracoporeal Membrane Oxygenation (ECMO)

RECOVER IV Trial (NCT05506449)

- Design- Prospective, multicenter, randomized, controlled, open-label, two-arm trial with an adaptive design
  - Planned up to 50 sites (US and EU), planned sample size (n= 548, up to 800)
  - Primary outcome- 30-day all-cause mortality
- Population- Acute STEMI with cardiogenic shock
  - Eligible for Impella placement based on femoral angiogram
- Intervention Arm- Standard Treatment with early Impella support
  - Treatment according to guidelines *with* Impella CP® device placed prior to PCI and subsequent treatment according to a prescribed Impella-based treatment algorithm.
- Control Arm- Standard Treatment without Impella support
  - Treatment according to guidelines *without* prescribed upfront mechanical support. MCS with IABP and other non-Impella support at operator discretion

Straightforward elements of EFIC Justification

- Life-threatening condition
- Existing treatments unsatisfactory or unproven
- Potential for direct benefit
- Risks are reasonable in relation to standard therapy
- Subjects cannot be identified in advance
- Narrow therapeutic window
  - Enrollment within 30 minutes from presentation
  - Consistent w guidelines regarding first medical contact to PCI time (90 minutes), typical door to balloon time, and steps to institute Impella support pre-PCI
  - First 15 minutes to be used to engage the patient or identify LAR/decision-maker who is present and seek consent from that person

Obtaining Consent is Often not Feasible

- Prior shock trials and registries suggest that most patients in SCAI shock stages C-E (population of interest) are unable to provide consent
- Availability of appropriate LAR in the appropriate timeframe will be highly variable
- Lengthy attempts at identification of an LAR and conduct of consent would jeopardize appropriate treatment within the therapeutic window

Impracticable to Conduct Study with Only Patients for whom Consent is Possible

- *Scientific*- Patients capable of providing consent will be less ill. Restricting enrollment would likely skew population toward SCAI shock stage C and limit generalizability across the appropriate patient population.
  - Sicker patients more likely to be intubated, to have suffered cardiac arrest, and to have severe hypoperfusion driving altered mental status
  - Availability of surrogate decision-makers will be highly variable

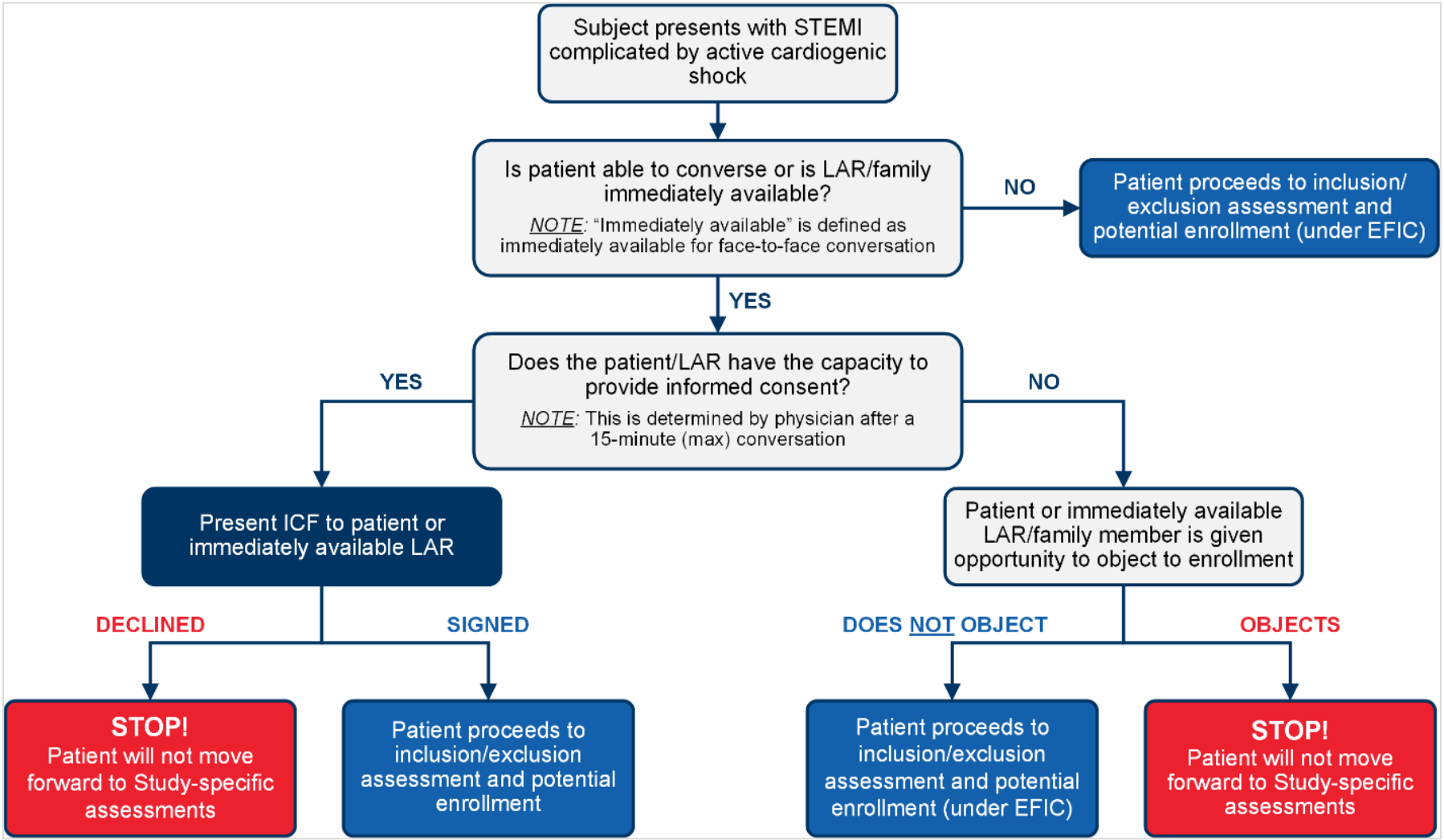
- *Practical*- Enrolling only capacitated individuals or those with an available surrogate capable of engaging in a consent process in this narrow therapeutic window would jeopardize the ability to conduct this trial in an appropriate timeframe for the population of interest.

- *EFIC guidance does not require a specific percentage to be incapable of consent or designate a specific time threshold for practicability.*

Trial Will Enroll 3 “Types” of Patients

- Patients who can provide consent or who have a surrogate immediately available who can provide consent.
  - EFIC regulations/guidance require a consent process
- Patients who are not capable of engaging in a consent process at all and who do not have a surrogate available.
  - EFIC regulations/guidance permit enrollment without prospective consent
- Patients (or surrogate) who is able to engage in minimal discussion about the study but not full consent.
  - EFIC regulations/guidance specify a need to provide an opportunity to object to enrollment, but there has been little attention to how this is operationalized.

Operationalizing EFIC in STEMI-CS for RECOVER IV



Opportunity to Object

- Provided to any patient/family member who is capable of engaging (de minimus threshold for engagement)
- Executed using a brief script
- Does not equate to consent for participation; patient/LAR asked for consent as soon as feasible, just as with “full” EFIC
- Any objection/refusal is honored

Keys to Success in This Case

- Collaborative process involving numerous stakeholders (sponsor, investigators, CSRC, FDA, and IRB)
- Careful consideration of evidence from prior studies
- Commitment to developing and protocolizing context-appropriate enrollment across the spectrum of eligible patients

Key Topics for Discussion

- *What are key points to operationalizing the "impracticability" of consent from both scientific and practical perspectives?*
  - Unlike cardiac arrest and traumatic brain injury, many conditions/trials are characterized by enrollment of patients with varying ability to engage and provide consent and variable availability of LARs.
  - Not necessarily a majority.

- *What are key elements to operationalizing the "opportunity to object?"*
  - Threshold for consent vs opportunity to object may not always be clear (consent in acute settings is always challenging).

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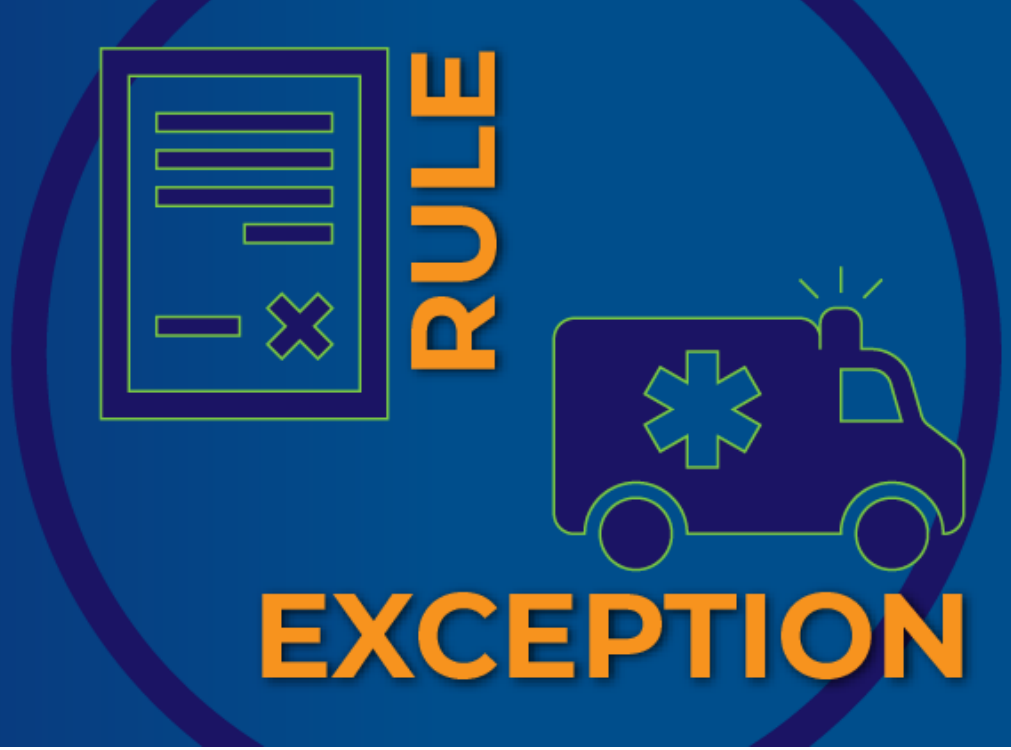


Drug Choices for Rapid Sequence Intubation and Comparative Effectiveness

PRAGMATIC CRITICAL CARE RESEARCH GROUP

Comparative Effectiveness Research in Emergency Tracheal Intubation

Jonathan D. Casey, MD, MSc
Director of the Coordinating Center
Pragmatic Critical Care Research Group

Disclosures

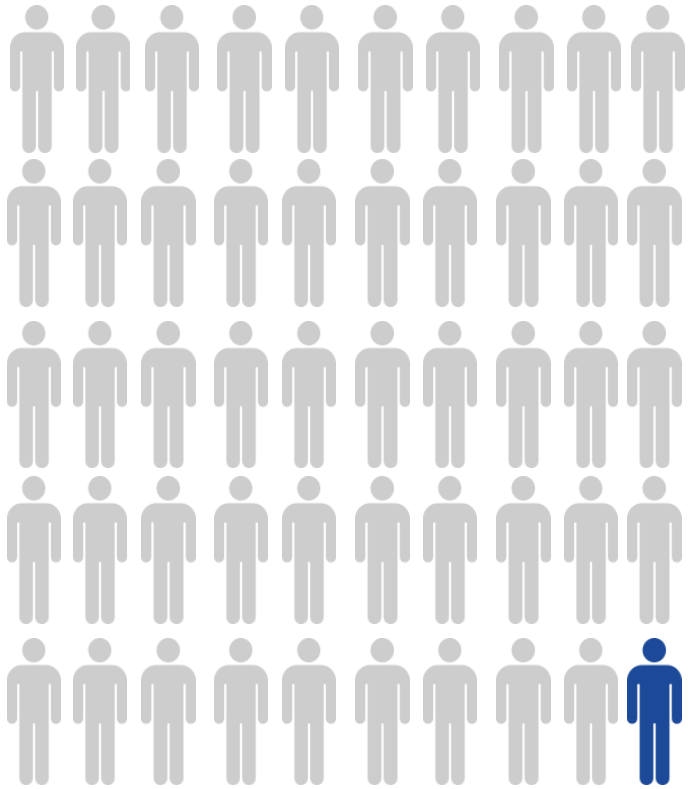
- Funding:
  - NIH
  - U.S. Department of Defense
  - PCORI
- Conflicts of interest:
  - None

Emergency Tracheal Intubation

- 5 million adults each year in United States
- Pre-hospital or within minutes of ED presentation
- ~70% of patients are unconscious or delirious

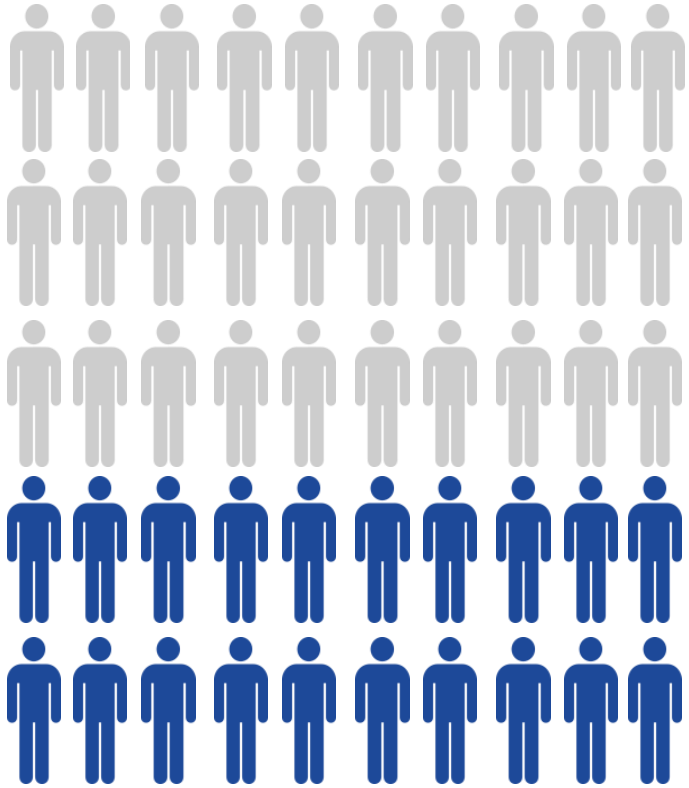
During emergency tracheal intubation, life-threatening complications are common

Operating Room



2%

Intensive Care Unit



Hypoxemia (10-40%)
Hypotension (20-40%)
Cardiac arrest (1-3%)

40%

Russotto et al. JAMA 2021

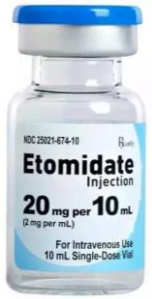
Decisions a clinician must make during every emergency tracheal intubation

30%

or

70%

70%



or

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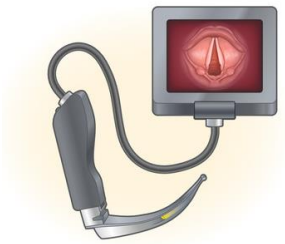
40%

or

60%

30%



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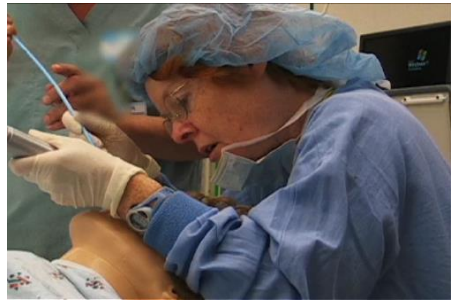
70%

25%



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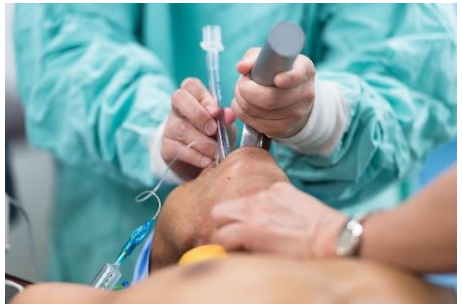

75%

1960 to 2010

- No RCTs to inform which treatments produced the best outcomes for patients
- Variation in clinical care exposes patients to ineffective or harmful treatments

- Clinical trial network, founded in 2014
- EDs and ICUs at 20 centers across the U.S.
- Multidisciplinary investigators
  - Emergency medicine, anesthesiology, and critical care
- **Aim: Improve outcomes for critically ill patients via pragmatic trials comparing effectiveness of emergency interventions already in clinical care**

IOWA · CU · UAB · Wake Forest Baptist Health · Beth Israel Deaconess Medical Center · BaylorScott&White HEALTH · Hennepin Healthcare · VANDERBILT UNIVERSITY MEDICAL CENTER · UW · W · LSUHealth · Lahey Hospital & Medical Center · Montefiore · Ochsner · DENVER HEALTH · The Ohio State University College of Medicine · Our Lady of the Lake Health · OHSU · DukeHealth

Decisions a clinician must make during every emergency tracheal intubation

or

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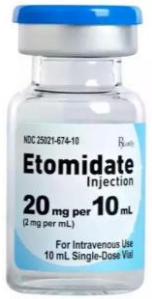

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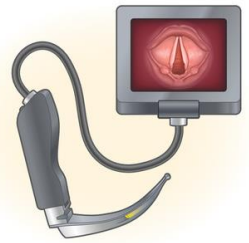

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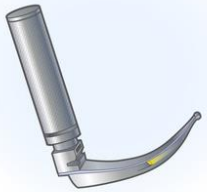

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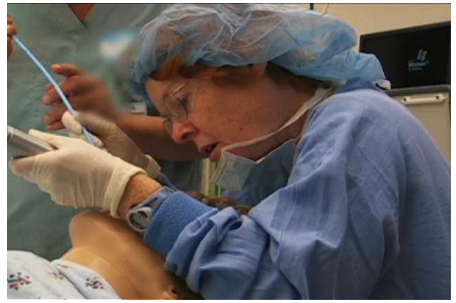

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Decisions a clinician must make during every emergency tracheal intubation

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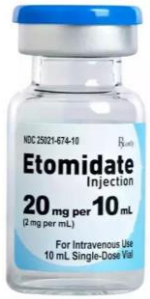

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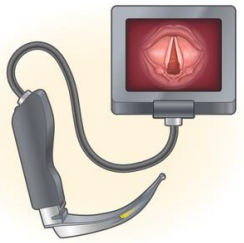

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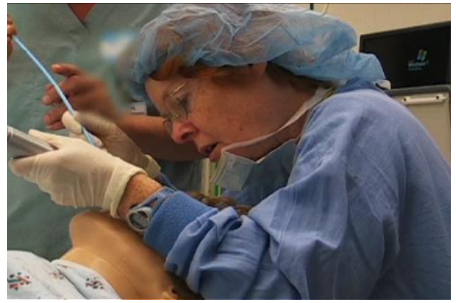
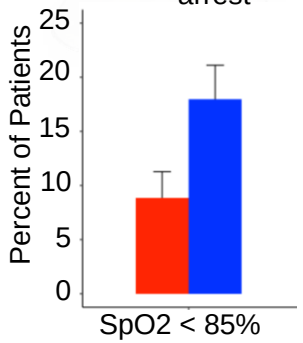


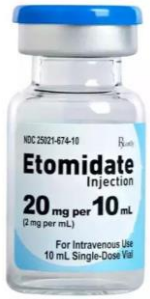
PREOXI trial

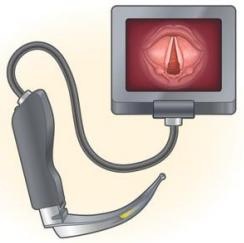
Noninvasive ventilation

prevents hypoxemia & cardiac arrest



Decisions a clinician must make during every emergency tracheal intubation





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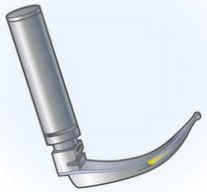
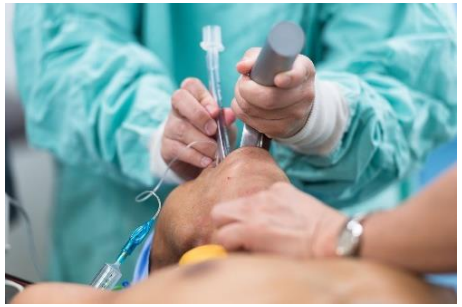
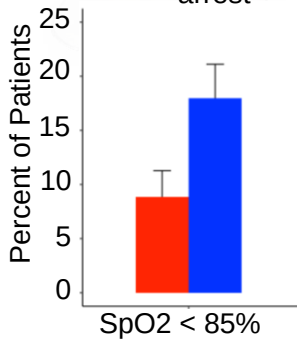




PREOXI trial

Noninvasive ventilation

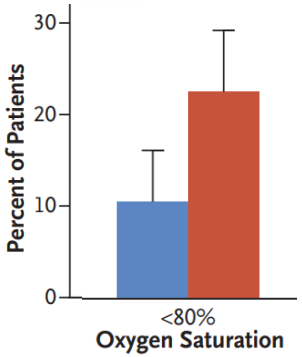
prevents hypoxemia & cardiac arrest



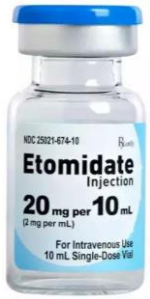
PreVent trial (NEJM 2019)

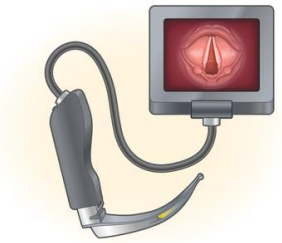
Bag-mask ventilation

prevents severe hypoxemia



Decisions a clinician must make during every emergency tracheal intubation





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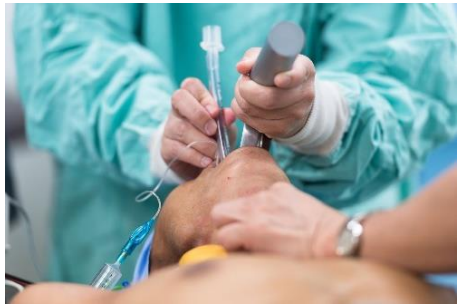
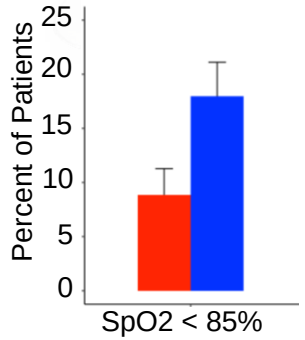
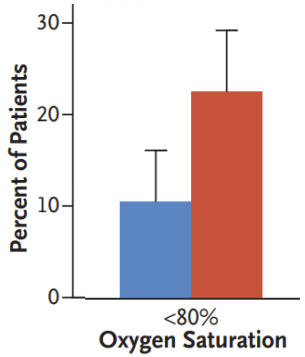


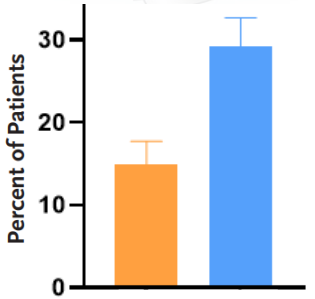
PREOXI trial
Noninvasive ventilation prevents hypoxemia & cardiac arrest



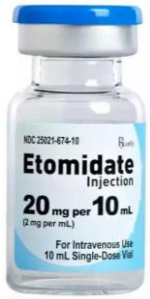
PreVent trial (NEJM 2019)
Bag-mask ventilation
prevents severe hypoxemia



DEVICE trial (NEJM 2023)
Video laryngoscopy
increases successful intubation



Decisions a clinician must make during every emergency tracheal intubation



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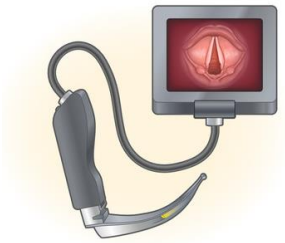

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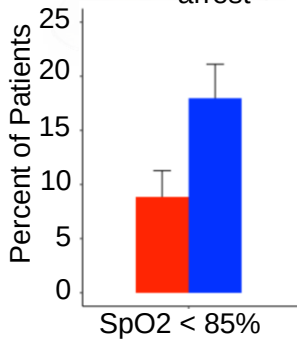

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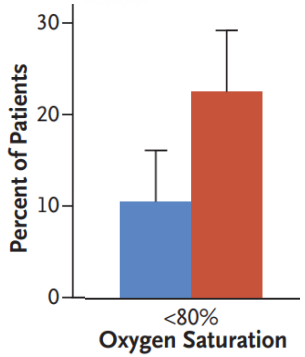

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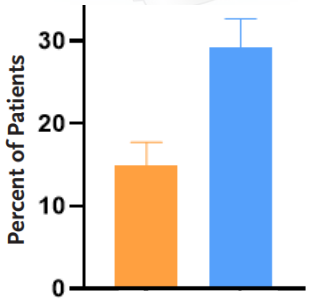
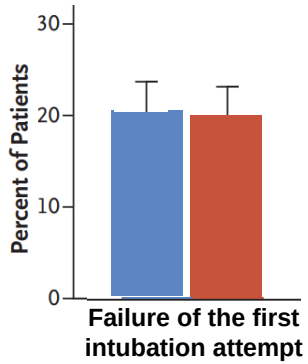
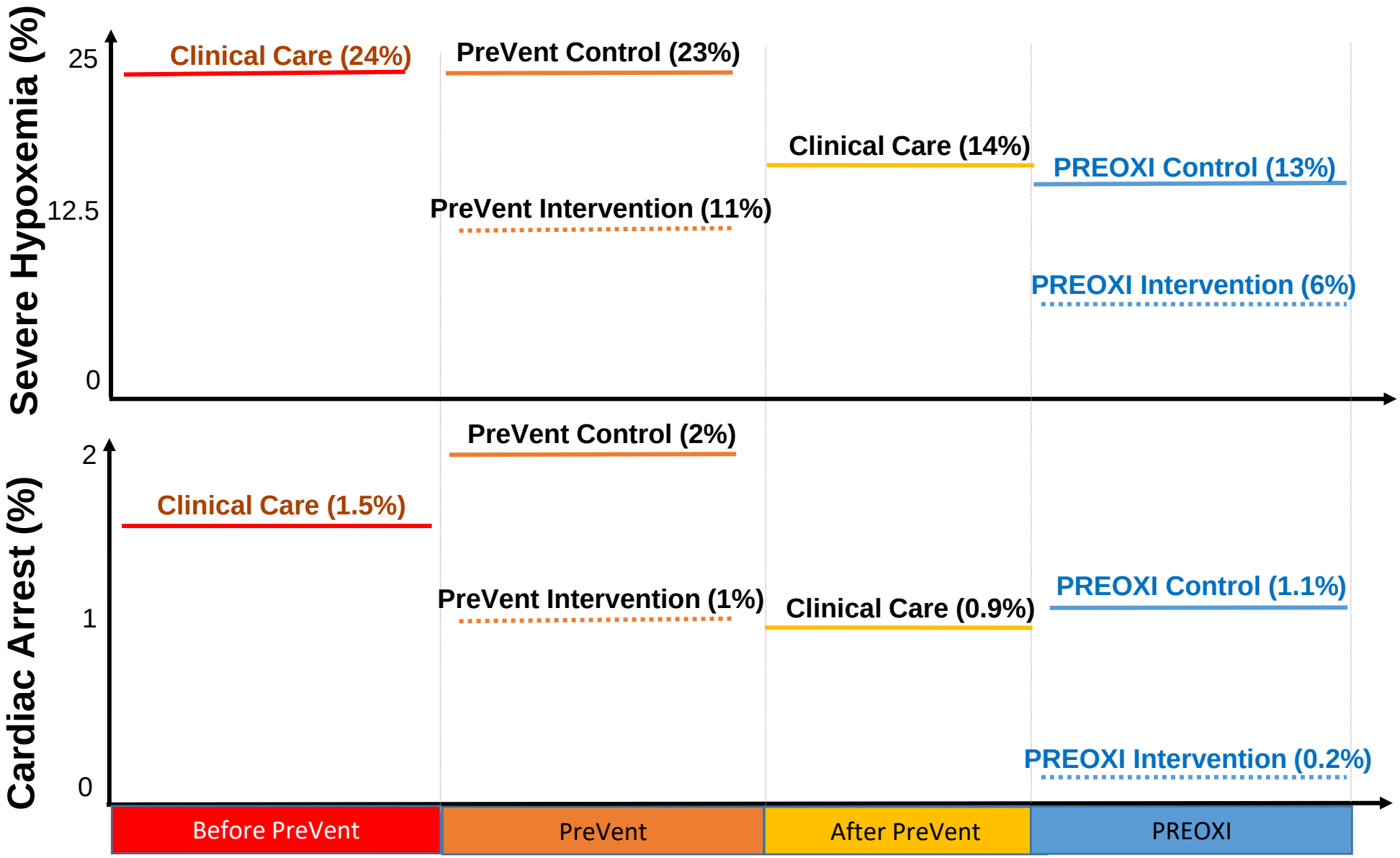


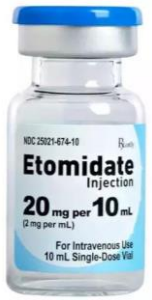
BOUGIE trial (JAMA 2021)
Bougie or **stylet** equally effective for intubation



This comparative effectiveness research has decreased patients' risk of hypoxemia and cardiac arrest in our own ICU



What's different about the choice of induction drug?

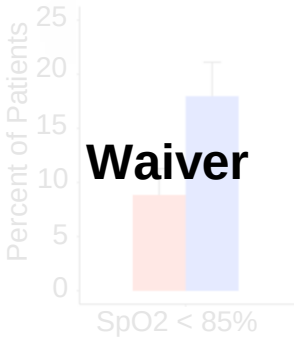


or

EFIC

or

PREOXI trial
Noninvasive ventilation prevents hypoxemia & cardiac arrest



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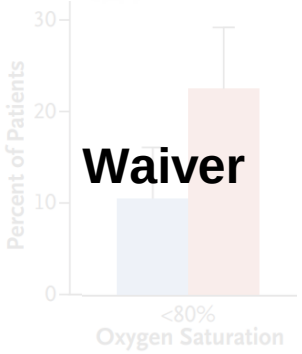

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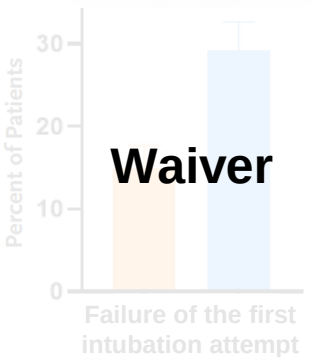

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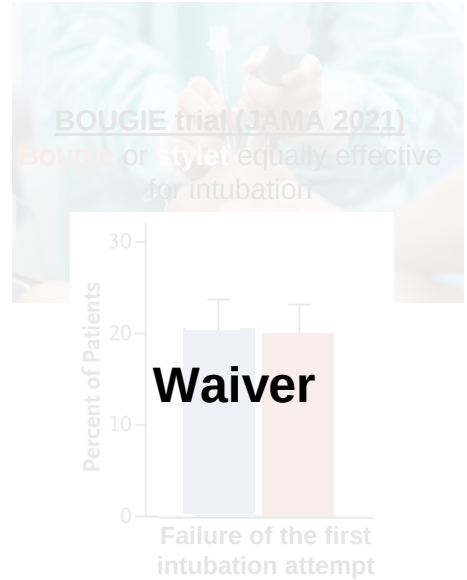
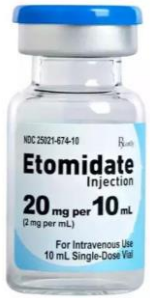


EFIC for Comparative Effectiveness Research in Emergency Tracheal Intubation: A Tale of Two Trials

RSI trial

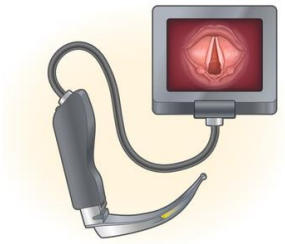


or

EFIC

vs

DEVICE trial

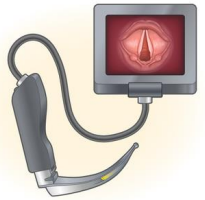


or

Waiver

RSI trial

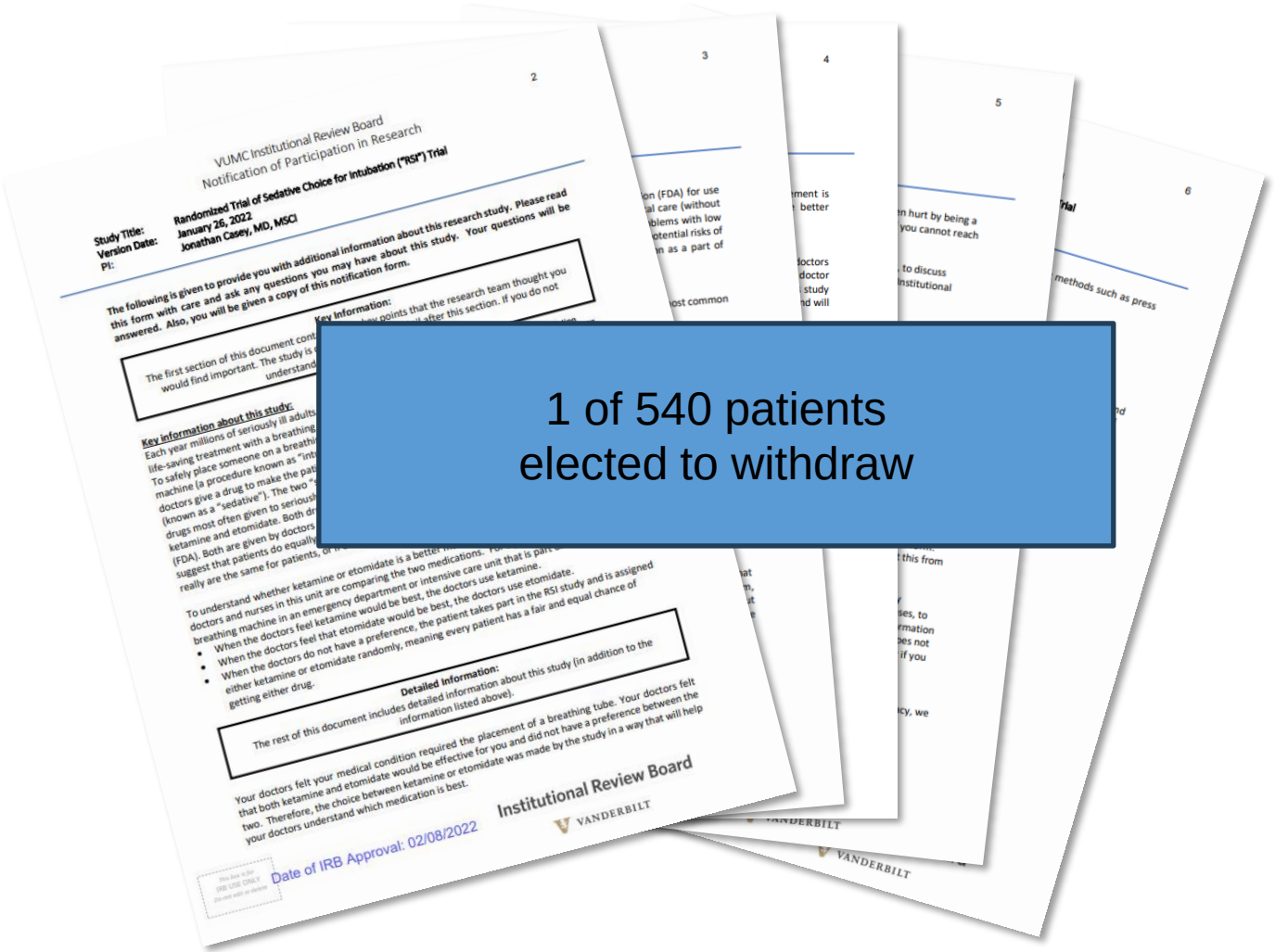
DEVICE trial



Consent	EFIC	Waiver
Cost	$9 million	$1.5 million

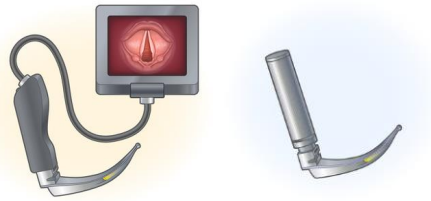
Patient Notification

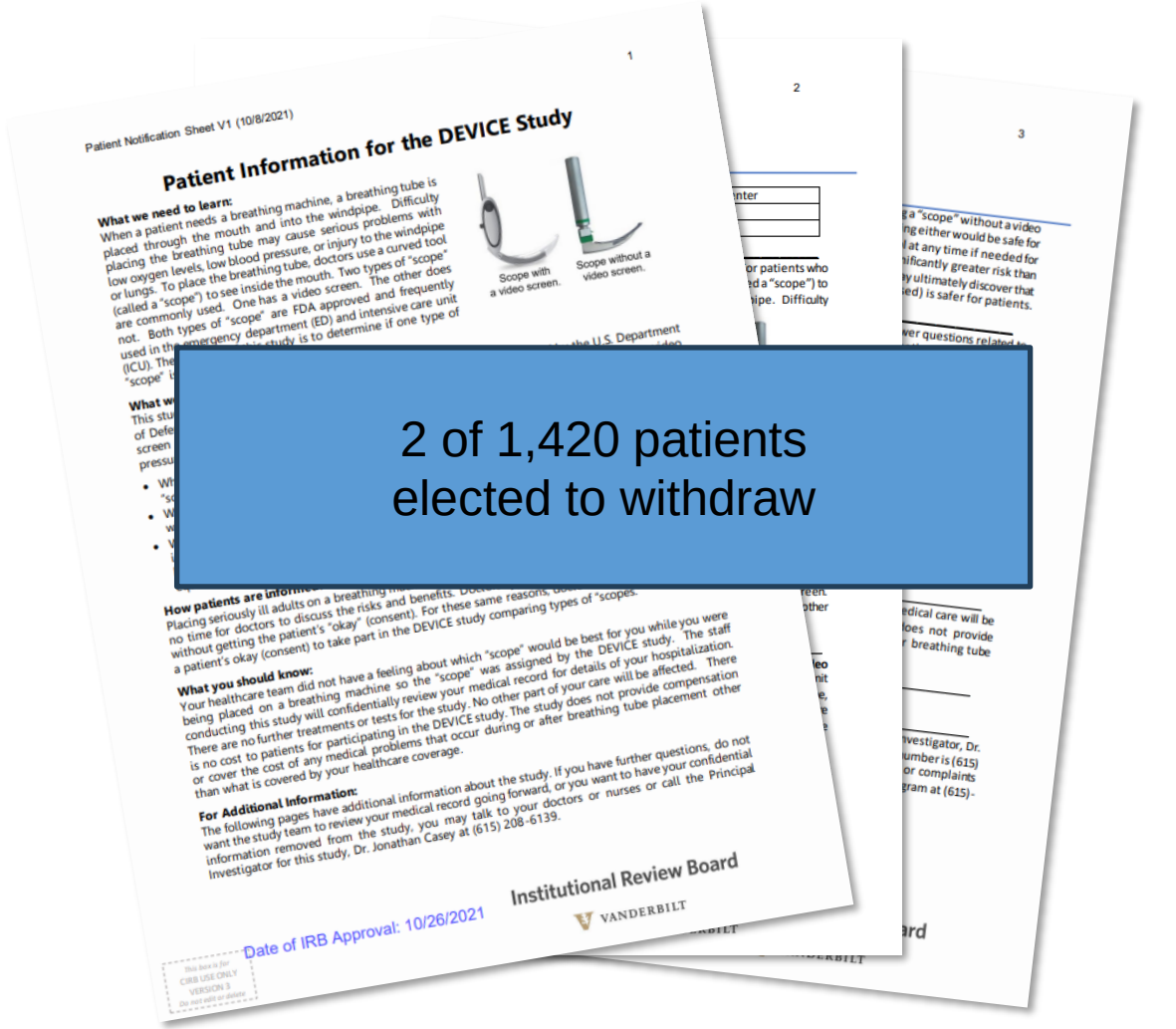
RSI trial



1 of 540 patients
elected to withdraw

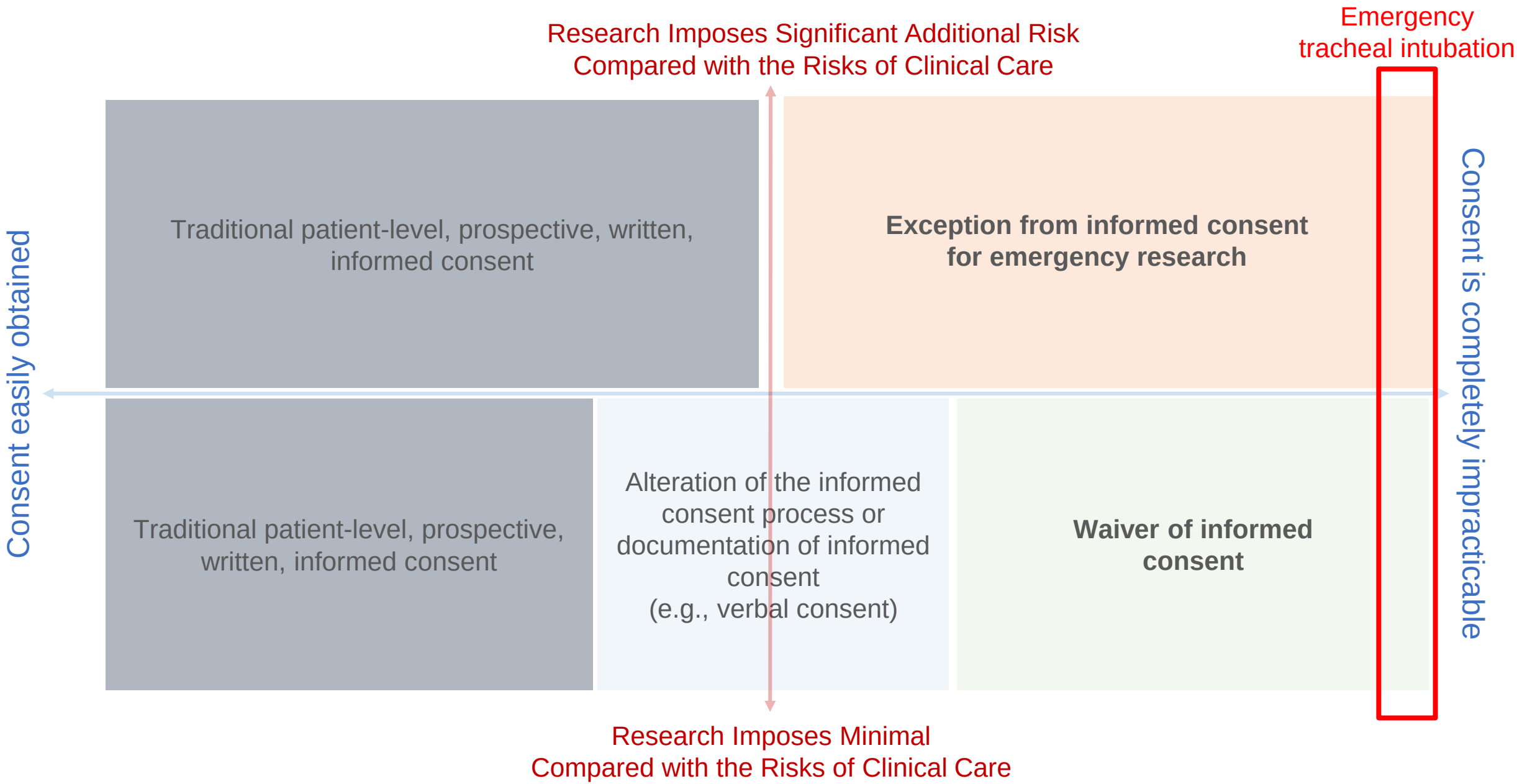
DEVICE trial





2 of 1,420 patients
elected to withdraw

Current Regulations for Informed Consent



EFIC

Exception from Informed Consent (EFIC)

- Implemented by the FDA in 1996 to standardize the approach to research in emergency settings and procedures

- Regulates research in which therapeutic window is too short to allow prospective informed consent and:
  - The condition being studied is **life-threatening**
  - Existing treatments are **unproven or unsatisfactory**

- Do trials comparing the effectiveness of approved therapies being used in clinical careevaluate "treatments that are unproven or unsatisfactory"?

Exception from Informed Consent (EFIC)

Pre-Trial:

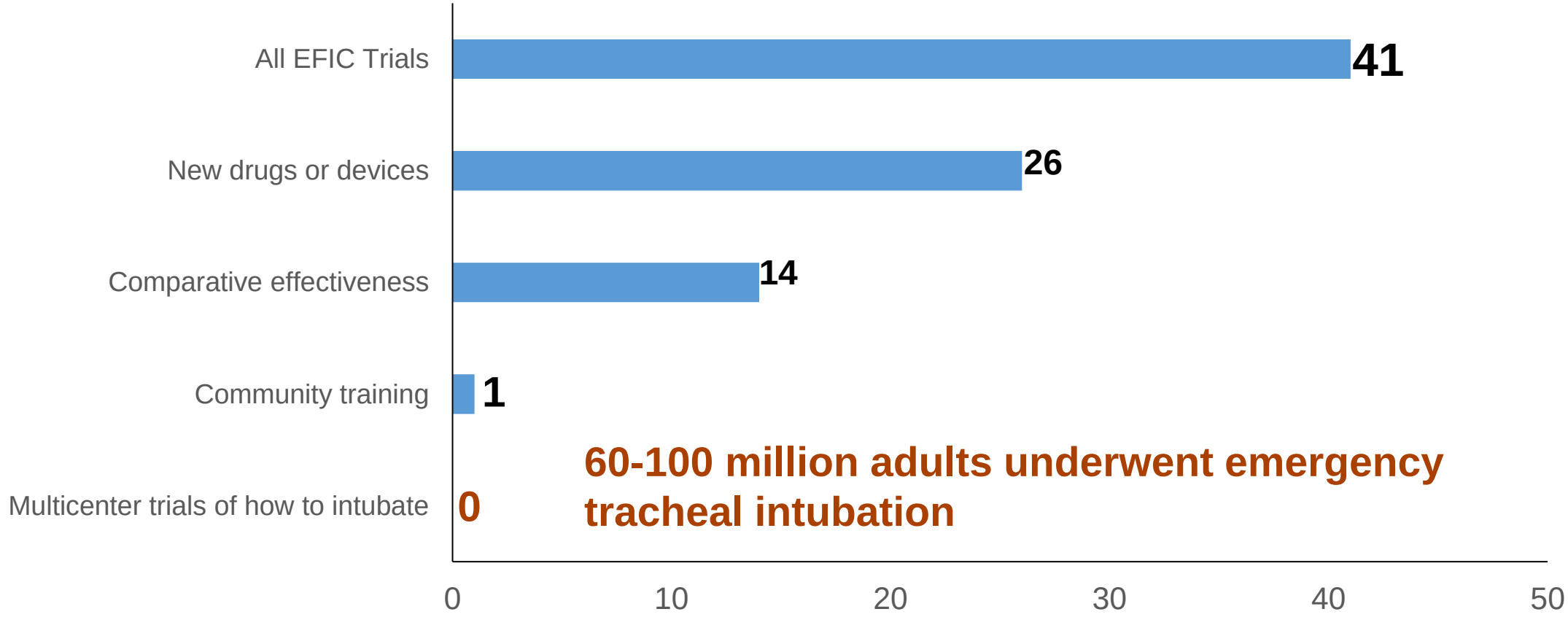
1. Community consultation
   - Opportunity for affected communities to provide meaningful input to investigators and the IRB
   - Two-way communication: town hall meetings, focus groups, one-on-one meetings
2. Public disclosure
   - Maximize transparency
   - One-way communication: press releases, radio/newspaper/social media advertisements
3. FDA oversight (IND/IDE)

Cost and duration: 1-3 years and $50,000 per site

Silbergleit R, et al. Acad Emerg Med. 2012

First 20 Years of EFIC Trials:

Zero multicenter trials comparing available approaches during emergency tracheal intubation



Feldman WB, et al. Health Aff. 2018

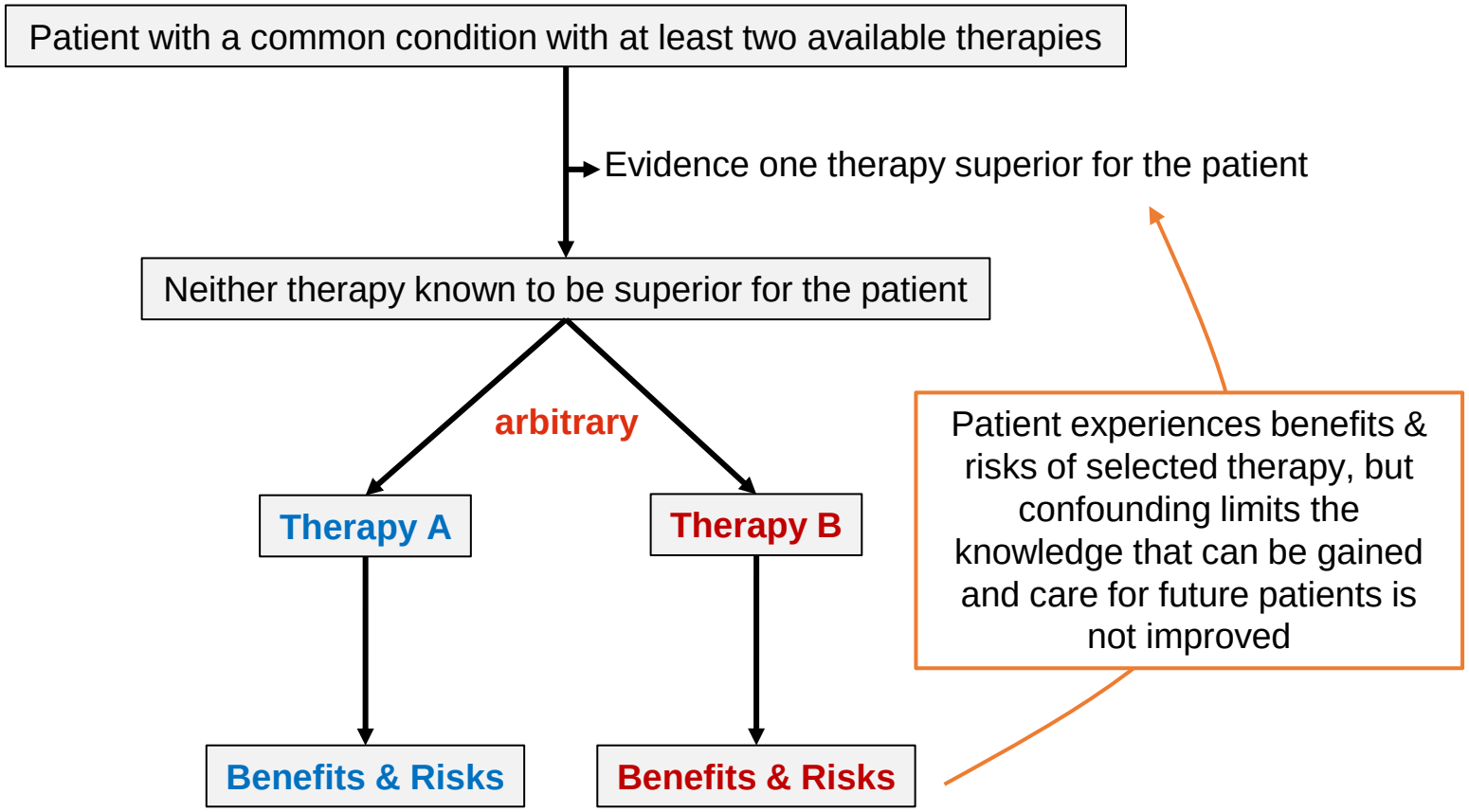
Waiver of informed consent

Waiver of Informed Consent

Criteria for waiver of informed consent (45 CFR 46.116(f))

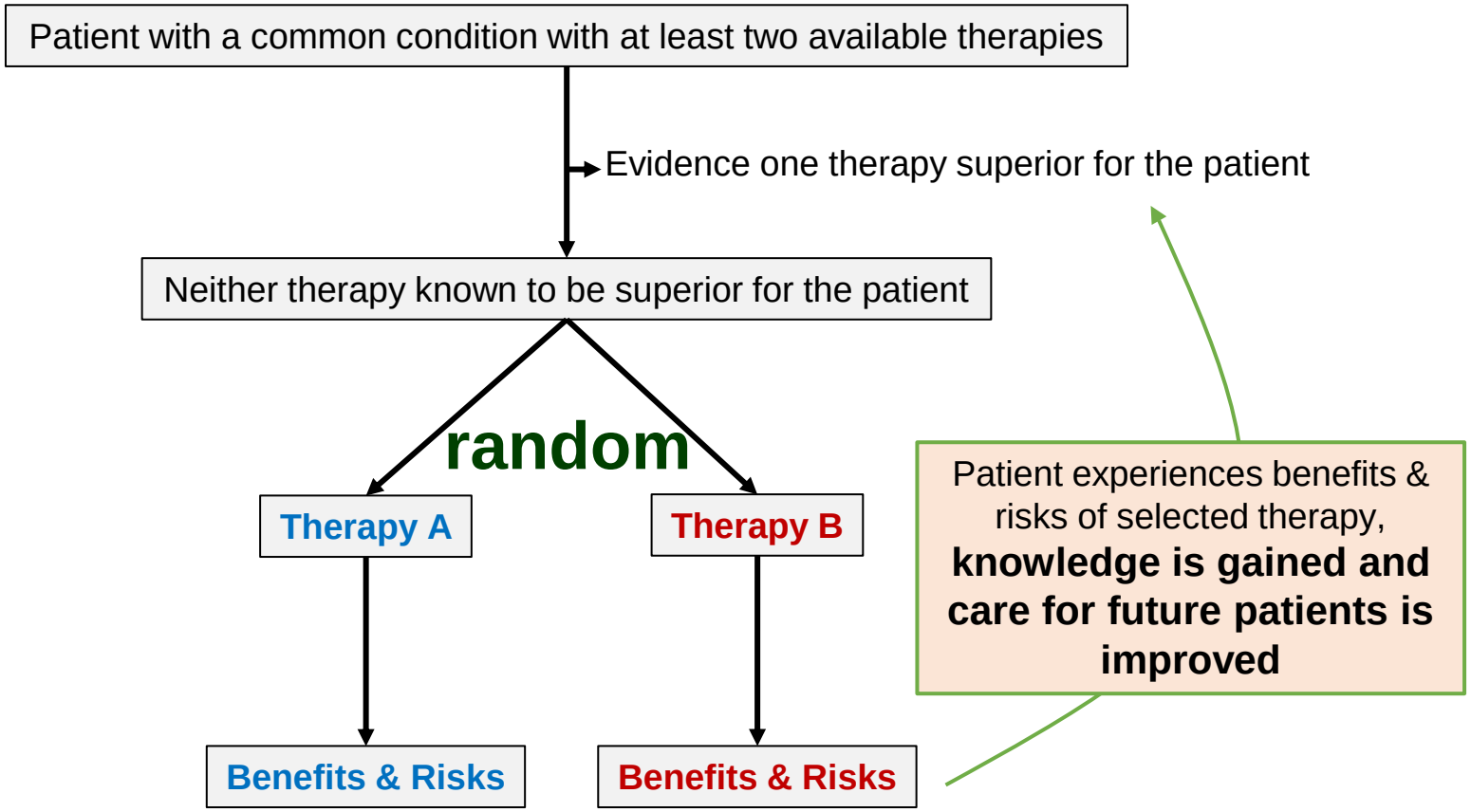
1. **No more than minimal risk to patients**
2. Could not be carried out without the waiver;
3. Only uses identifiable private health information if such information is required to conduct the study
4. Does not adversely affect patients' rights or welfare
5. Whenever appropriate, additional pertinent information is provided after participation.

Treatment decisions in **Clinical Care**



Arbitrary variation (different clinicians choosing different treatments for the same patient) = Clinical Equipoise

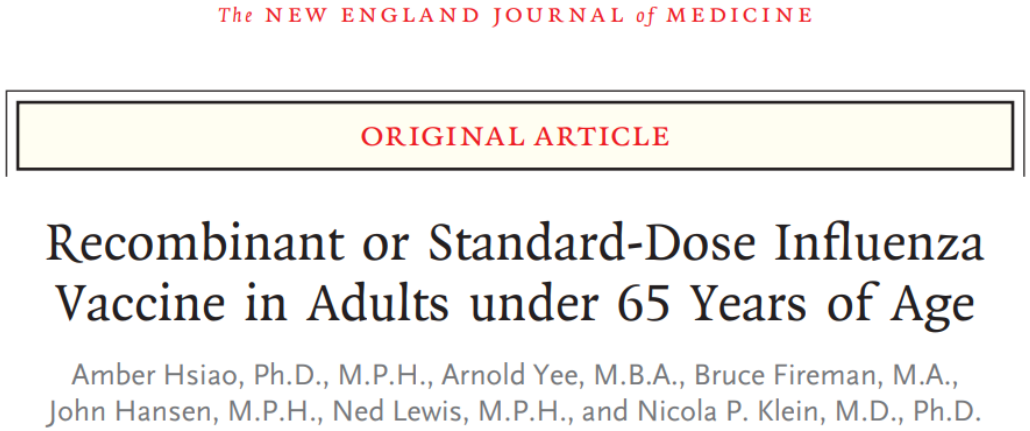
Treatment decisions in a **Comparative Effectiveness Trial**



When two interventions are commonly used in clinical care and neither is known to be superior, having the choice between the two made randomly rather than based on arbitrary factors unrelated to knowledge of which therapy is best for a given patient may represent **no more than minimal incremental risk**, compared to the risk of routine clinical care

Trials conducted with waiver outside of emergency care

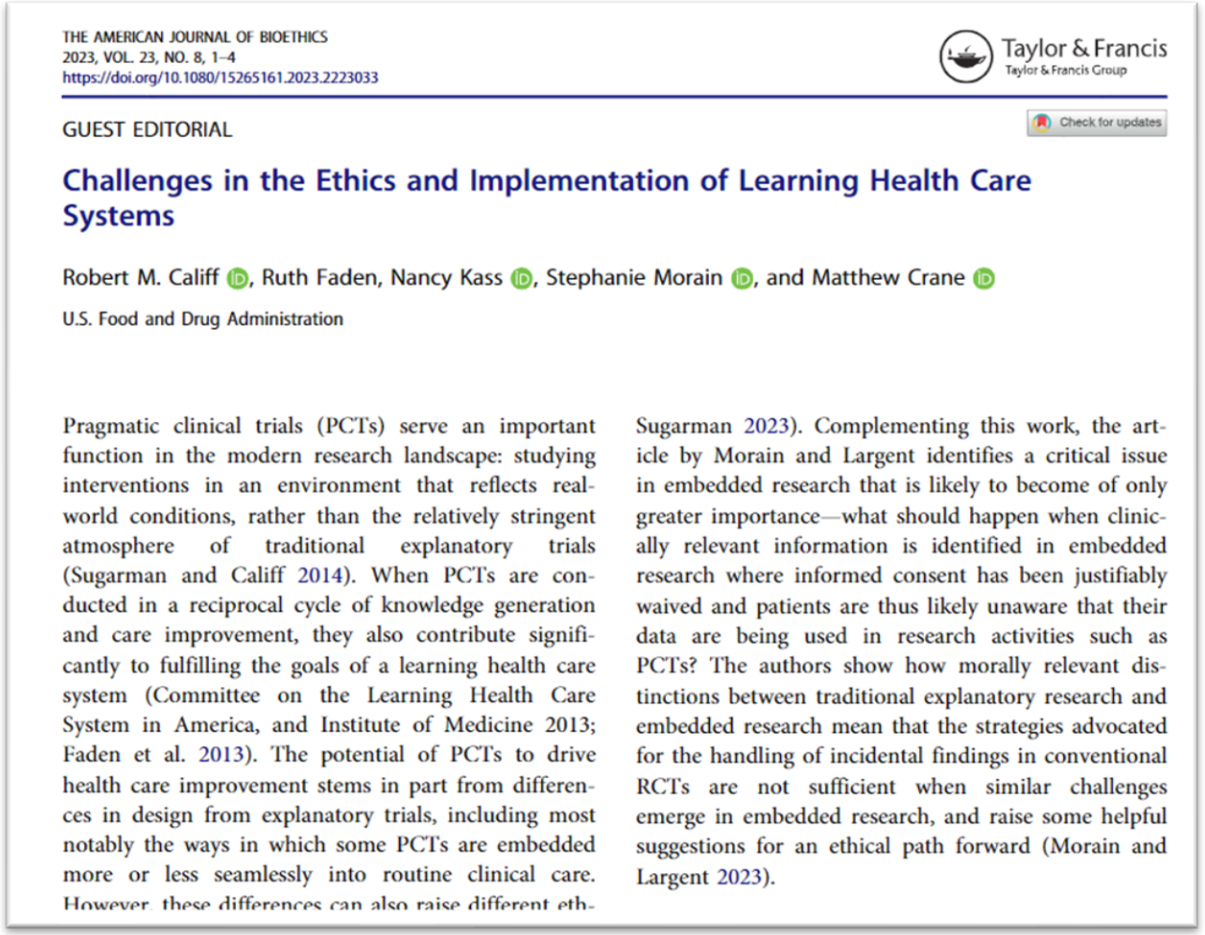
- 23,792 pregnant women randomized under waiver of informed consent to one of two approaches of screening for gestational diabetes



- 1,630,328 patients randomized to quadrivalent vs standard influenza vaccines.

Why is there controversy on the role of EFIC and waiver in comparative effectiveness research?

- FDA Commissioner:
- ***"Neither HHS nor FDA regulations currently have guidance on whether or when [pragmatic trials] might be categorized as minimal risk . . . These issues need the joint attention of federal agencies, the research community, the health care delivery ecosystem, and patient advocates"***



THE AMERICAN JOURNAL OF BIOETHICS
2023, VOL. 23, NO. 8, 1–4
https://doi.org/10.1080/15265161.2023.2223033

GUEST EDITORIAL

Challenges in the Ethics and Implementation of Learning Health Care Systems

Robert M. Califf, Ruth Faden, Nancy Kass, Stephanie Morain, and Matthew Crane

U.S. Food and Drug Administration

Pragmatic clinical trials (PCTs) serve an important function in the modern research landscape: studying interventions in an environment that reflects real-world conditions, rather than the relatively stringent atmosphere of traditional explanatory trials (Sugarman and Califf 2014). When PCTs are conducted in a reciprocal cycle of knowledge generation and care improvement, they also contribute significantly to fulfilling the goals of a learning health care system (Committee on the Learning Health Care System in America, and Institute of Medicine 2013; Faden et al. 2013). The potential of PCTs to drive health care improvement stems in part from differences in design from explanatory trials, including most notably the ways in which some PCTs are embedded more or less seamlessly into routine clinical care. However, these differences can also raise different eth-

Sugarman 2023). Complementing this work, the article by Morain and Largent identifies a critical issue in embedded research that is likely to become of only greater importance—what should happen when clinically relevant information is identified in embedded research where informed consent has been justifiably waived and patients are thus likely unaware that their data are being used in research activities such as PCTs? The authors show how morally relevant distinctions between traditional explanatory research and embedded research mean that the strategies advocated for the handling of incidental findings in conventional RCTs are not sufficient when similar challenges emerge in embedded research, and raise some helpful suggestions for an ethical path forward (Morain and Largent 2023).

What would be required to facilitate the emergency care trials needed to examine treatments patients are receiving in clinical care?

My suggested short term solutions

- On January 22, 2024, the FDA implemented the final rule for waiver or alteration using the same 5 requirements as the OHRP. The final rule did not define “minimal risk” but noted that:
  - “*FDA plans to publish guidance to assist IRBs in applying the criteria for waiver or alteration . . . . In that guidance, we intend to include additional information on the types of research activities that may involve no more than minimal risk to the subjects and therefore might qualify for a waiver or alteration of informed consent*”

- **Upcoming FDA guidance for IRBs should explicitly state that trials comparing the effectiveness of approved therapies being used in clinical care may represent minimal risk and may be conducted with waiver of informed consent.**

My suggested long term solutions

- For minimal risk comparative effectiveness trials conducted under waiver or alteration of consent, additional work should define :
  - The process that investigators and IRBs should use to determine that the research is minimal risk
  - How patients and community members should be involved in the design, approval, or conduct of studies
  - How patients should be notified of their participation
  - How results should be shared with patients who may have participated
  - What additional obligations institutions have to disseminate and implement the results of research

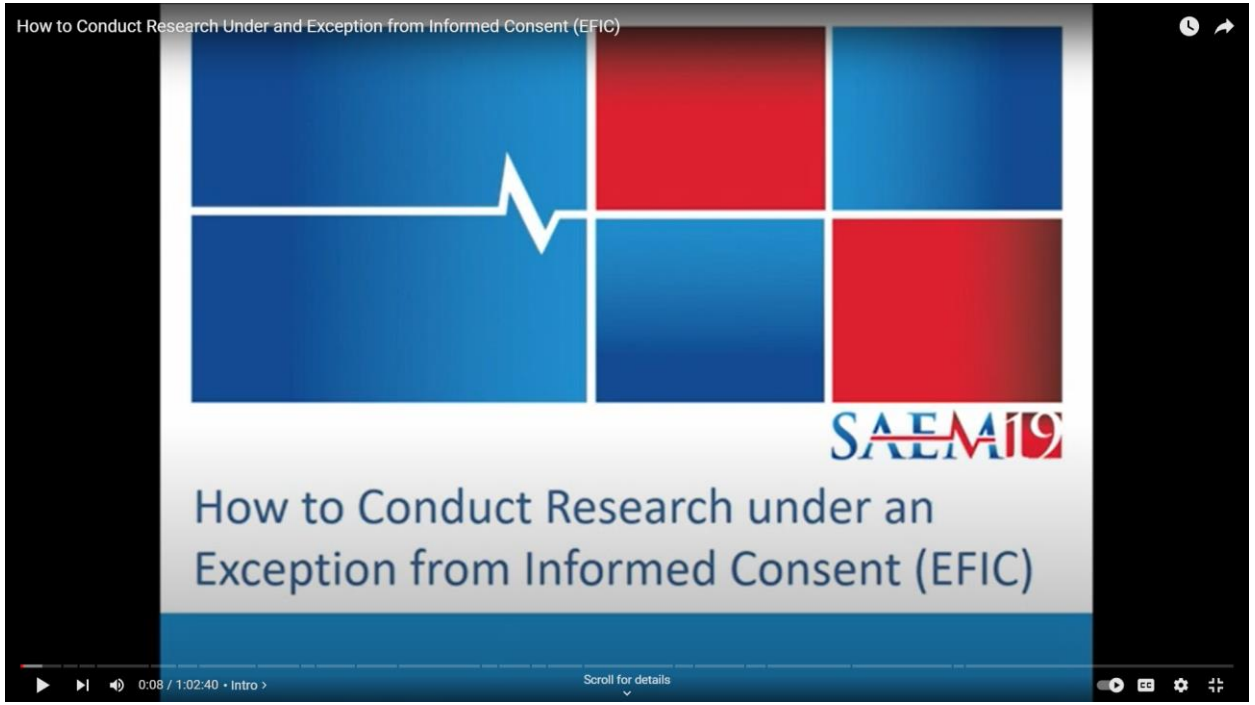
Conclusion

1. In current clinical care, patients with the same problem routinely receive different treatments, which systematically exposes patients to interventions that may be suboptimal or even harmful.

2. Many experts and bioethicist have advocated for comparative effectiveness trials of standard-of-care interventions with waiver or alteration of consent.

3. Current regulations do not provide a clear framework for trials comparing approved and commonly used therapies, and the lack of a clear framework is preventing research that would help patients.

Supplemental Slides

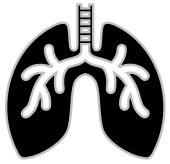


Experience from PECARN Study

"I would not recommend that anyone enter in an EFIC study thinking that it is going to be less than a 5-7 year turnaround time"

Common emer…pies for which the effec…nknown

Pragmatic Critical Care Research Group



The NEW ENGLAND JOURNAL of MEDICINE

Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H., Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H., Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D., Avinash B. Kumar, M.D., Christopher G. Hughes, M.D., Antonio Hernandez, M.D., Oscar D. Guillamondegui, M.D., M.P.H., Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SMART Investigators and the Pragmatic Critical Care Research Group*

The NEW ENGLAND JOURNAL of MEDICINE

Balanced Crystalloids versus Saline in Noncritically Ill Adults

Wesley H. Self, M.D., M.P.H., Matthew W. Semler, M.D., Jonathan P. Wanderer, M.D., Li Wang, M.S., Daniel W. Byrne, M.S., Sean P. Collins, M.D., Corey M. Slovis, M.D., Christopher J. Lindsell, Ph.D., Jesse M. Ehrenfeld, M.D., M.P.H., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SALT-ED Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

Oxygen-Saturation Targets for Critically Ill Adults Receiving Mechanical Ventilation

Matthew W. Semler, M.D., Jonathan D. Casey, M.D., Bradley D. Lloyd, R.R.T.-A.C.C.S., Pamela G. Hastings, R.R.T.-A.C.C.S., Margaret A. Hays, R.N., Joanna L. Stollings, Pharm.D., Kevin G. Buell, M.B., B.S., John H. Brems, M.D., Edward T. Qian, M.D., Kevin P. Seitz, M.D., Li Wang, M.S., Christopher J. Lindsell, Ph.D., Robert E. Freundlich, M.D., Jonathan P. Wanderer, M.D., Jin H. Han, M.D., Gordon R. Bernard, M.D., Wesley H. Self, M.D., M.P.H., and Todd W. Rice, M.D., for the PILOT Investigators and the Pragmatic Critical Care Research Group*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 28, 2019 VOL. 380 NO. 9

Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults

Jonathan D. Casey, M.D., David R. Janz, M.D., Derek W. Russell, M.D., Derek J. Vonderhaar, M.D., Aaron M. Joffe, D.O., Kevin M. Dischert, M.D., Ryan M. Brown, M.D., Aline N. Zouk, M.D., Swati Gulati, M.B., B.S., Brent E. Heideman, M.D., Michael G. Lester, M.D., Alexandra H. Toporek, M.D., Itay Bentov, M.D., Ph.D., Wesley H. Self, M.D., Todd W. Rice, M.D., and Matthew W. Semler, M.D., for the PreVent Investigators and the Pragmatic Critical Care Research Group*

Research

JAMA | Original Investigation

Effect of Fluid Bolus Administration on Cardiovascular Collapse Among Critically Ill Patients Undergoing Tracheal Intubation

A Randomized Clinical Trial

Derek W. Russell, MD; Jonathan D. Casey, MD, MSc; Kevin W. Gibbs, MD; Shekhar Ghamande, MD; James M. Dargin, MD; Derek J. Vonderhaar, MD; Aaron M. Joffe, DO; Akram Khan, MD; Matthew E. Prekker, MD, MPH; Joseph M. Brewer, DO; Simanta Dutta, MD; Janna S. Landsperger, MS, ACNP-BC; Heath D. White, DO, MS; Sarah W. Robison, MD; Joanne M. Wozniak, MS, PA-C; Susan Stempek, MMSc, PA-C; Christopher R. Barnes, MD; Olivia F. Krol, BS; Alejandro C. Arroliga, MD, MS; Tasnim Lat, DO; Sheetal Gandotra, MD; Swati Gulati, MBBS, MS; Itay Bentov, MD, PhD; Andrew M. Walters, MD; Kevin M. Dischert, MD; Stephanie Nonas, MD; Brian E. Driver, MD; Li Wang, MS; Christopher J. Lindsell, PhD; Wesley H. Self, MD, MPH; Todd W. Rice, MD, MSc; David R. Janz, MD, MSc; Matthew W. Semler, MD, MSc; for the PREPARE II Investigators and the Pragmatic Critical Care Research Group

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Use of a Bougie vs Endotracheal Tube With Stylet on Successful Intubation on the First Attempt Among Critically Ill Patients Undergoing Tracheal Intubation

A Randomized Clinical Trial

Brian E. Driver, MD; Matthew W. Semler, MD; Wesley H. Self, MD; Adit A. Ginde, MD; Stacy A. Trent, MD; Sheetal Gandotra, MD; Lane M. Smith, MD, PhD; David B. Page, MD; Derek J. Vonderhaar, MD; Jason R. West, MD; Aaron M. Joffe, DO; Steven H. Mitchell, MD; Kevin C. Doerschug, MD; Christopher G. Hughes, MD; Kevin High, RN; Janna S. Landsperger, PA-C; Karen E. Jackson, MD; Michelle P. Howell, RN; Sarah W. Robison, MD; John P. Gaillard, MD; Micah R. Whitson, MD; Christopher M. Barnes, MD; Andrew J. Latimer, MD; Vikas S. Koppurapu, MD; Bret D. Alvis, MD; Derek W. Russell, MD; Kevin W. Gibbs, MD; Li Wang, MS; Christopher J. Lindsell, PhD; David R. Janz, MD; Todd W. Rice, MD; Matthew E. Prekker, MD; Jonathan D. Casey, MD; for the BOUGIE Investigators and the Pragmatic Critical Care Research Group

The NEW ENGLAND JOURNAL of MEDICINE

Video versus Direct Laryngoscopy for Tracheal Intubation of Critically Ill Adults

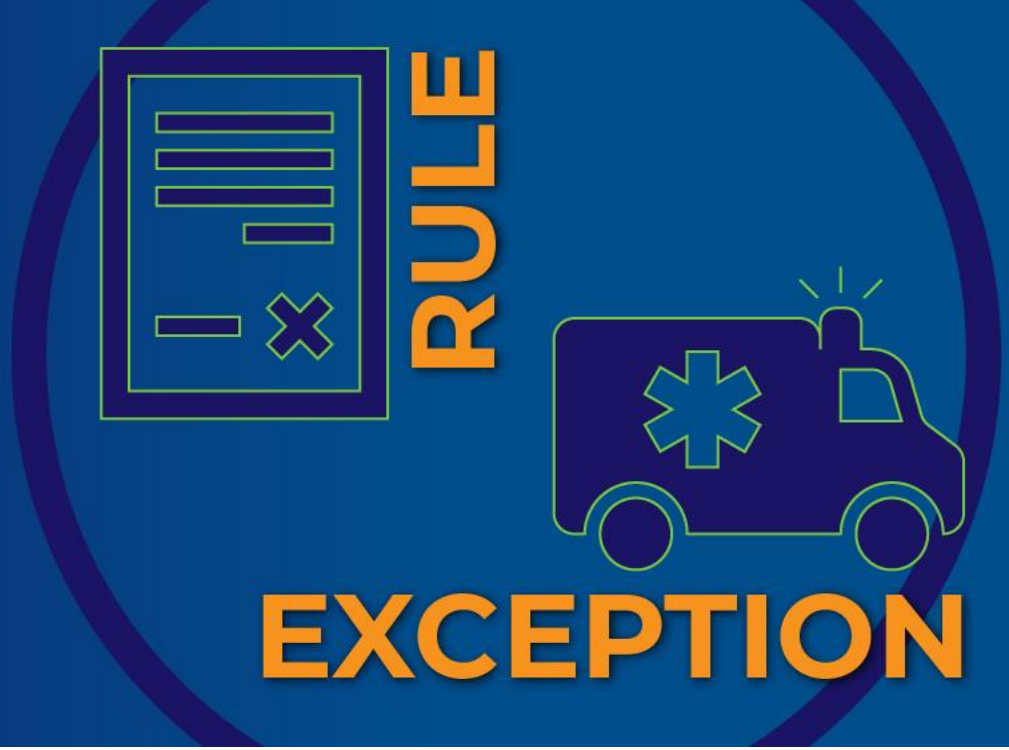
M.E. Prekker, B.E. Driver, S.A. Trent, D. Resnick-Ault, K.P. Seitz, D.W. Russell, J.P. Gaillard, A.J. Latimer, S.A. Ghamande, K.W. Gibbs, D.J. Vonderhaar, M.R. Whitson, C.R. Barnes, J.P. Walco, I.S. Douglas, V. Krishnamoorthy, A. Dagan, J.J. Bastman, B.D. Lloyd, S. Gandotra, J.K. Goranson, S.H. Mitchell, H.D. White, J.A. Palakshappa, A. Espinera, D.B. Page, A. Joffe, S.J. Hansen, C.G. Hughes, T. George, J.T. Herbert, N.I. Shapiro, S.G. Schauer, B.J. Long, B. Imhoff, L. Wang, J.P. Rhoads, K.N. Womack, D.R. Janz, W.H. Self, T.W. Rice, A.A. Ginde, J.D. Casey, and M.W. Semler, for the DEVICE Investigators and the Pragmatic Critical Care Research Group*

Trial	Topic	N	Status
Chlorhexidine	Infection Control	9,340	Published (JAMA)
SMART	IVF	15,802	Published (NEJM)
SALT-ED	IVF	13,347	Published (NEJM)
SALT	IVF	974	Published (AJRCCM)
FELLOW-AO	Intubation	150	Published (AJRCCM)
FELLOW-VL	Intubation	150	Published (CCM)
CHECK-UP checklist	Intubation	262	Published (Chest)
CHECK-UP ramped	Intubation	260	Published (Chest)
PREPARE	Intubation	337	Published (LRM)
PreVent	Intubation	401	Published (NEJM)
PROPER	Post-Extubation	751	Published (AJRCCM)
BASE	IVF	2,093	Complete
BOUGIE	Intubation	1,106	Published (JAMA)
PREPARE2	Intubation	1,065	Published (JAMA)
PILOT	Oxygen Targets	2,541	Published (NEJM)
DEVICE	Intubation	1,417	Published (NEJM)
ACORN	Antibiotic choice	2,050	Complete
RSI	Intubation	1,900	Enrolling
PREOXI	Intubation	1,300	Enrolling
MODE	Mechanical ventilation	606	Enrolling
TOTAL - 20 RCTs		**55,856**	

Office of Emergency Care Research

Regulatory Determinations related to Consent, EFIC and Waiver of Consent in Emergency Clinical Trials Workshop

An NIH hosted workshop for FDA, OHRP, IRBs, and Investigators



LUNCH

We will resume at 1:20 PM ET

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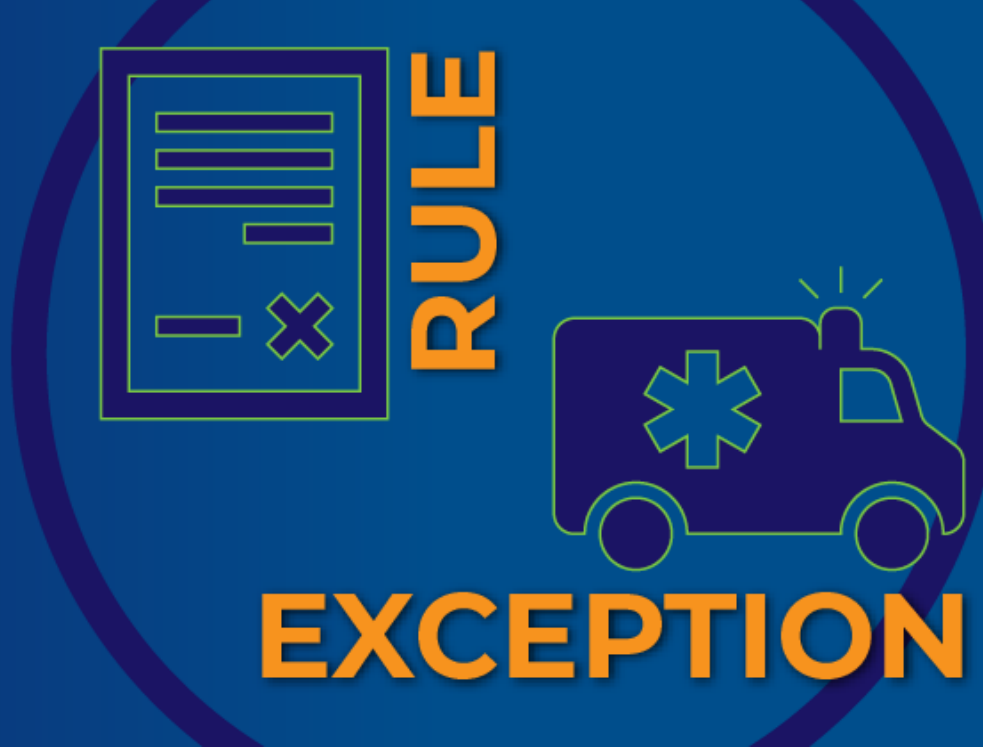

Acute Pain

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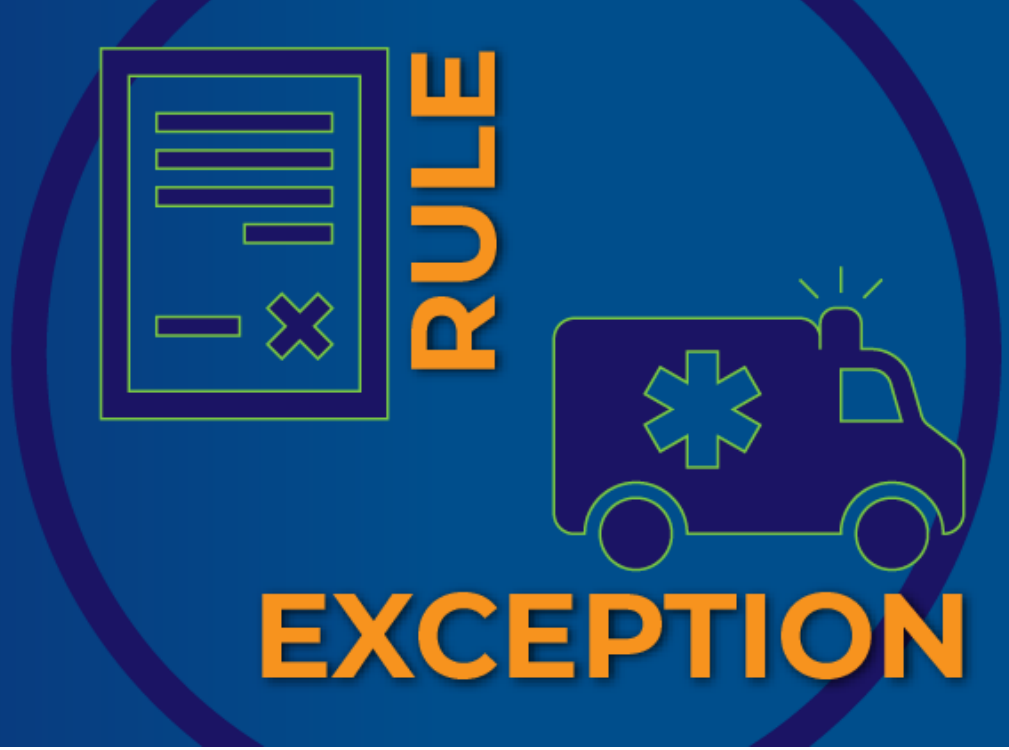


Social Justice and Equitable Inclusion

Exemption From Informed Consent (EFIC) Workshop:
Social Justice and Equitable Inclusion

National Institute of Neurological Disorders and Stroke

NINDS Health Equity Strategic Plan

March 12, 2024
2:30 pm – 3:30 pm

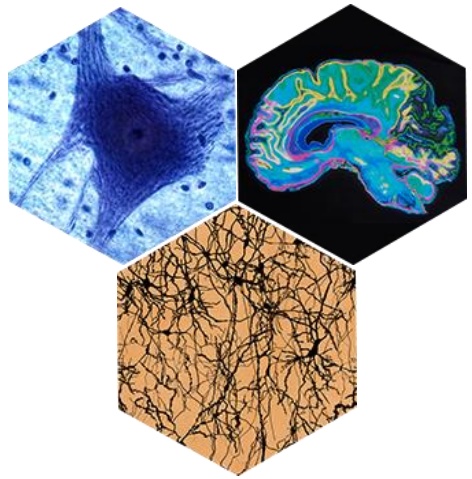
Presenter:
Richard T. Benson, MD, PhD

National Institute of Neurological Disorders and Stroke

The mission of NINDS is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease for all

Strategies:

- Invest in basic, translational and clinical research
- Identify gaps in research and public health needs
- Train a talented and diverse research workforce
- Support development of tools and resources to enable discoveries
- Communicate and collaborate with all stakeholders, including the public
- Evaluate and continuously improve all NINDS programs



NINDS' mission is to reduce the burden of neurological diseases *for all.* However, there is a disproportionate burden of disparities and inequities in neurological disorders and neurologic care borne by underserved groups of society.

National Institute of Neurological Disorders and Stroke

Populations that experience health disparities (HDPs)
*NIH-designated U.S. health disparity populations include:

- American Indians/Alaska Natives
- Asian Americans
- Blacks/African Americans
- Hispanics/Latinos
- Native Hawaiians and other Pacific Islanders
- Sexual and gender minorities
- Socioeconomically disadvantaged populations
- Underserved rural populations

*__Intersectionality__ - addresses the multiple dimensions of individuals' identity (e.g., race, ethnicity, gender, sexual orientation, gender identity) and social systems as they intersect with one another

*Persons with **limited English proficiency**

https://www.nimhd.nih.gov/about/overview/

NINDS Health Disparities Mission Statement

National Institute of Neurological Disorders and Stroke

Why is recruitment and inclusion of diverse populations (e.g. race, ethnic, gender, age) important for clinical trials :

1. Diversity of clinical trial participants is needed to help ensure that the trial population is representative of the patients who will use the medicine, medicinal product or intervention and ensure that the results are generalizable. (Rigor)
2. Participants in research should reflect the diversity of our culture and conditions, taking into account race, ethnicity, gender, age, etc.
3. The lack of diversity among research participants has serious ethical and research consequences.

Why is recruitment and inclusion of diverse populations (e.g. race, ethnic, gender, age) important for clinical trials :

IT'S THE LAW...!!!!

The NIH is mandated by the Public Health Service Act sec. 492B, 42 U.S.C. sec. 289a-2 to ensure the inclusion of women and minority groups in all NIH-funded clinical research in a manner that is appropriate to the scientific question under study. The primary goal of this law is to ensure that research findings can be generalizable to the entire population. Additionally, the statute requires clinical trials to be designed to provide information about differences by sex/gender, race and/or ethnicity.

AMERICAN ACADEMY OF NEUROLOGY 75 YEARS

Volume 101, Number 7, Supplement 1, August 15, 2023
Neurology.org/N

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SUPPLEMENT

The National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH) Health Equity Research Strategic Planning Process and Recommendations

Guest Editors: Karen C. Johnston, MD, MSc and Edwin Trevathan, MD, MPH

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Health Disparities Definition

National Institute of Neurological Disorders and Stroke

HEALTHY PEOPLE 2030

*"A particular type of health difference that is closely linked with **economic, social, or environmental disadvantage**. Health disparities adversely affect groups of people who have systematically experienced greater social or economic obstacles to health based on their racial or ethnic group, religion, socio-economic status, gender, age, or mental health; cognitive sensory or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion".**

*https://health.gov/healthypeople/priority-areas/health-equity-healthy-people-2030

NINDS Health Equity Definition

National Institute of Neurological Disorders and Stroke

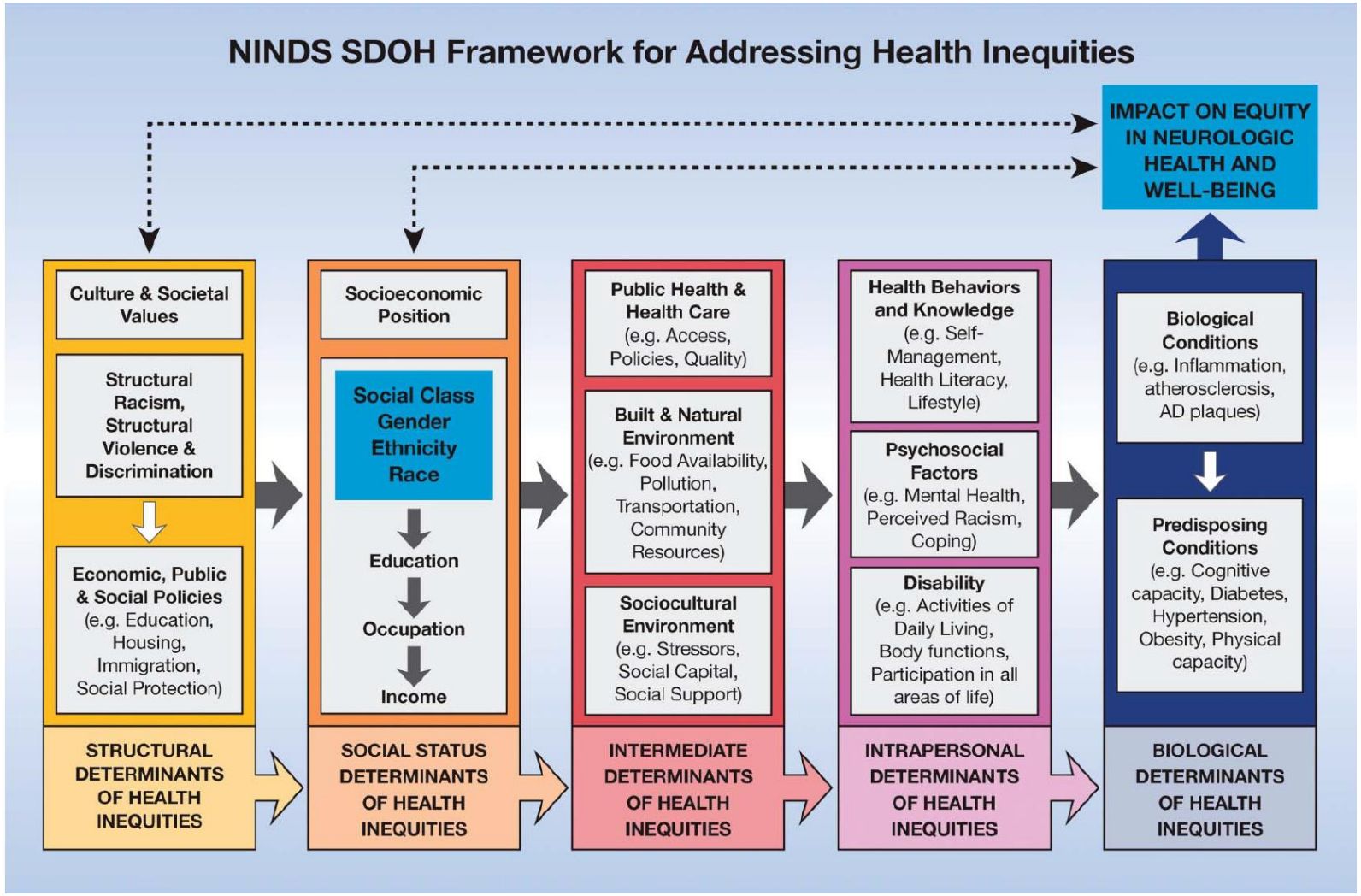
Health Equity

Healthy People 2030 defines *health equity* as the "attainment of the highest level of health for all people. Achieving health equity requires valuing everyone equally with focused and ongoing societal efforts to address avoidable inequalities, historical and contemporary injustices, and the elimination of health and health care disparities.

https://health.gov/healthypeople/priority-areas/health-equity-healthy-people-2030

NINDS SDOH Health Equity Research Framework

National Institute of Neurological Disorders and Stroke



Determinants of Inequities in Neurologic Disease, Health, and Well-being
The NINDS Social Determinants of Health Framework

Derek M. Griffith, Amytis Towfighi, Spero M. Manson, Erica L. Littlejohn, Lesli E. Skolarus. ***Neurology*** Aug 2023, 101 (7 Supplement 1) S75-S81.

Office of Global Health & Health Disparities (OGHHD) | Division of Clinical Research Staff

National Institute of Neurological Disorders and Stroke

OGHHD MISSION STATEMENT:

The NINDS Office of Global Health and Health Disparities (OGHHD) leads the coordination, development, and reporting on programs and initiatives related to national and international research on disparities and inequities in neurological disease.

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NINDS Office of Global Health & Health Disparities (OGHHD)

National Institute of Neurological Disorders and Stroke

Scan the following QR codes to browse our website for funding opportunities, contact information, and more!

Visit our OGHHD Website

Subscribe to the ***NINDS-OGHHD Listserv***

Thank You

Exemption From Informed Consent (EFIC) Workshop: Social Justice and Equitable Inclusion

Opeolu Adeoye, MD MS

March 12, 2024

Department of Emergency Medicine

Washington University in St. Louis
School of Medicine

Frequency of EFIC Trials

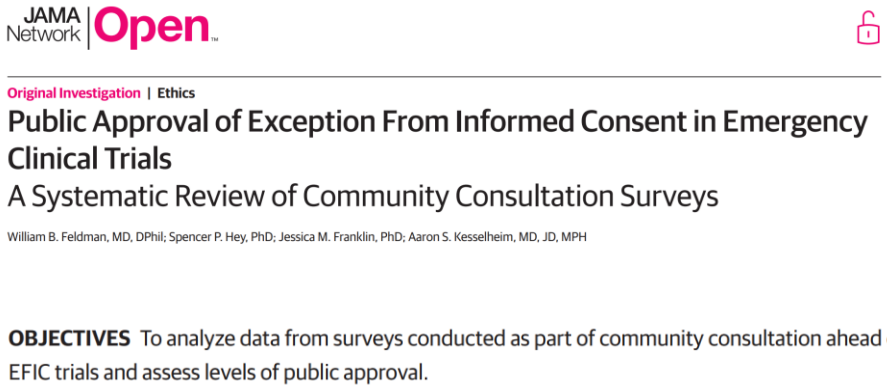
- 1996 – 2022
  - 110 total trials
  - 78 complete, 13 recruiting, remainder terminated before enrollment or planning
  - Approximately 18 new trials/five year period
  - About half of the trials are terminated early, more than half of those for futility
  - **Authors unsure of completeness of search

TABLE 1 Health condition/disease focus of trial

Condition	Adult trials	Trials
Cardiac arrest	30 (31.2)	2 (14.3)
TBI	13 (13.5)	1 (7.1)
Other trauma[a]	28 (29.2)	2 (14.3)
Respiratory failure	9 (9.4)	2 (14.3)
Stroke	8 (8.3)	0
Other[b]	8 (8.3)	7 (50.0)
Totals	96	14

Snyder and Merz
Acad Emerg Med. 2023 Feb;30(2):133-138.

Community Consultation



JAMA Network | Open

Original Investigation | Ethics

Public Approval of Exception From Informed Consent in Emergency Clinical Trials

A Systematic Review of Community Consultation Surveys

William B. Feldman, MD, DPhil; Spencer P. Hey, PhD; Jessica M. Franklin, PhD; Aaron S. Kesselheim, MD, JD, MPH

OBJECTIVES To analyze data from surveys conducted as part of community consultation ahead of EFIC trials and assess levels of public approval.

- 42,448 individuals, 27 trials
- 58.4% approved of EFIC
- 68.6% family-member enrollment
- 73.0% personal enrollment
- 86.5% community inclusion

Feldman et al. JAMA Network Open. 2019;2(7):e197591

Community Consultation

- African Americans
  - 29% of EFIC enrollees, 17% of those surveyed
- Men
  - 67% of enrollees, 43% of those surveyed
- Aggregates with higher African American and Male populations were less likely to approve EFIC
- "The demographic characteristics of those surveyed did not match the demographic characteristics of EFIC enrollees."

Feldman et al. JAMA Network Open. 2019;2(7):e197591

Discussion

- Importance of EFIC in answering key clinical questions and improving population outcomes
- Moral/ethical dilemma of "easier" enrollments once EFIC is approved
  - Less engagement of actual enrollee patients/surrogates
- Community consultation/public disclosure versus individual autonomy
- Trust versus Mis-trust
- Impact of surrogacy requirements on minoritized communities
- Moral – Ethical – Legal implications of EFIC for minoritized communities
- Autonomy – "self-rule"; the ability of competent individuals to make decisions over their own lives.

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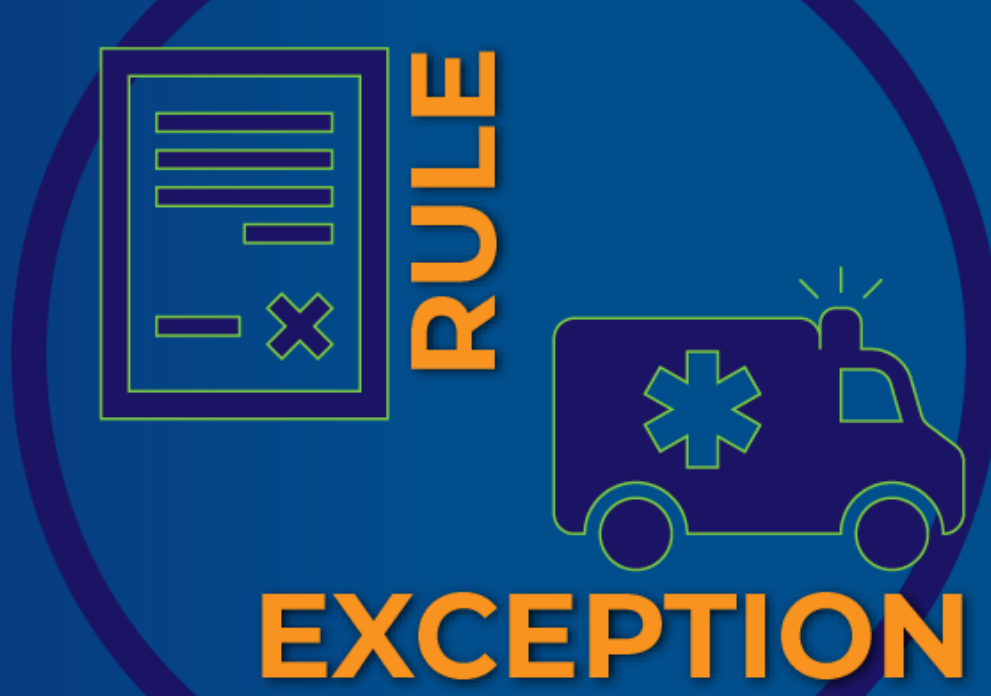

On what can we all agree?

Office of Emergency Care Research

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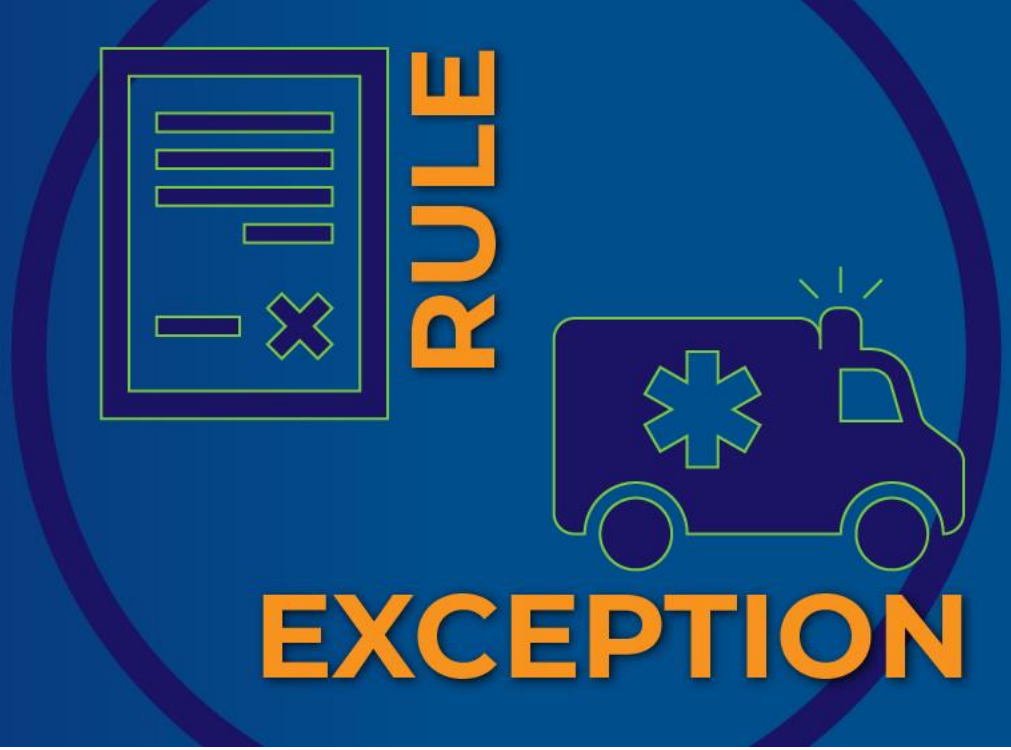

Thank you for attending!

Return Shuttle Available to the Embassy Suites