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Fit for Purpose: Improving the Ethical Oversight of Comparative Effectiveness Research

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NIH Pragmatic Trials Collaboratory Grand Rounds

June 13, 2025

Two Key Problems

1. Insufficient evidence to guide key clinical decisions
2. Challenges with ethics oversight for trials aimed at #1

Roadmap

- Brief overview of the two problems & prior work
- **Main focus:** proposed **new** model to improve the *"fit for purpose"* of research ethics oversight that might be feasible for current regulatory structures
- Especially eager for **feedback** on proposed oversight consideration: "available and meaningful patient decision"

Problem 1: Insufficient Evidence

- Vast majority of clinical decisions still made in the absence of high-quality evidence
  - Ex: fewer than 10% of current recommendations in cardiology based on the highest quality evidence. Over 40% based solely on expert opinion.

Original Investigation

FREE

March 19, 2019

Levels of Evidence Supporting American College of Cardiology/American Heart Association and European Society of Cardiology Guidelines, 2008-2018

Alexander C. Fanaroff, MD, MHS[1]; Robert M. Califf, MD[2,3,4]; Stephan Windecker, MD[5]; et al

» Author Affiliations | Article Information

JAMA. 2019;321(11):1069-1080. doi:10.1001/jama.2019.1122

Problem 1: Insufficient Evidence

- What's the best oxygen saturation target during mechanical ventilation?
- Which is the best sedative to use before emergency intubation?
- What is better for dialysis patients—treatment sessions of 4 hours, or 4.25?
- Should adults aged 50-64 get a high-dose flu shot?
- How humid should the incubator be when treating NICU babies?

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ORIGINAL ARTICLE

Video versus Direct Laryngoscopy for Tracheal Intubation of Critically Ill Adults

Authors: Matthew E. Prekker, M.D., M.P.H., Brian E. Driver, M.D., Stacy A. Trent, M.D., M.P.H., Daniel Resnick-Ault, M.D., Kevin P. Seitz, M.D., Derek W. Russell, M.D., John P. Gaillard, M.D., +37, for the DEVICE Investigators and the Pragmatic Critical Care Research Group* Author Info & Affiliations

Published June 16, 2023 | N Engl J Med 2023;389:418-429 | DOI: 10.1056/NEJMoa2301601 | VOL. 389 NO. 5

Targeted versus Universal Decolonization to Prevent ICU Infection

Susan S. Huang, M.D., M.P.H., Edward Septimus, M.D., Ken Kleinman, Sc.D., Julia Moody, M.S., Jason Hickok, M.B.A., R.N., Taliser R. Avery, M.S., Julie Lankiewicz, M.P.H., Adrijana Gombosev, B.S., Leah Terpstra, B.A., Fallon Hartford, M.S., Mary K. Hayden, M.D., John A. Jernigan, M.D., Robert A. Weinstein, M.D., Victoria J. Fraser, M.D., Katherine Haffenreffer, B.S., Eric Cui, B.S., Rebecca E. Kaganov, B.A., Karen Lolans, B.S., Jonathan B. Perlin, M.D., Ph.D., and Richard Platt, M.D., for the CDC Prevention Epicenters Program and the AHRQ DECIDE Network and Healthcare-Associated Infections Program*

ORIGINAL ARTICLE

A Pragmatic, Randomized Clinical Trial of Gestational Diabetes Screening

Authors: Teresa A. Hillier, M.D., Kathryn L. Pedula, M.S., Keith K. Ogasawara, M.D., Kimberly K. Vesco, M.D., M.P.H., Caryn E.S. Oshiro, Ph.D., Suzanne L. Lubarsky, M.D., and Jan Van Marter, M.P.A., R.N. Author Info & Affiliations

Published March 10, 2021 | N Engl J Med 2021;384:895-904 | DOI: 10.1056/NEJMoa2026028

Problem 2: Ethics Oversight

What are the appropriate protections for research subjects when comparing therapies widely used in clinical care?

Problem 2: Ethics Oversight

- Should informed consent for these trials be more similar to *research* informed consent or *clinical* informed consent?
- When can informed consent ethically be waived or altered?
- How to determine what constitutes "minimal risk"?
- Which risks are appropriately considered "research" risks?

Background: Traditional approach to research ethics

- Research is conceptually different from care
  - "Systematic investigation" to produce "generalizable knowledge"
  - Undertaken for sake of future patients vs. care for current patient
  - Risks and uncertainties expected for the sake of science

"Medical care is characterized by a convergence of the doctor's interests and the patient's interests. The patient desires to regain or maintain health; the physician is dedicated to providing the medical help that the patient needs.

"By contrast, in clinical trials, the principal interests of the investigator and the participating patient may diverge. Patient-subjects typically seek therapeutic benefit from research participation… Investigators are primarily interested in answering scientific questions about groups of patients…"

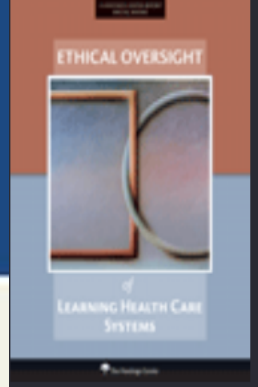
--Miller & Rosenstein, NEJM

Background: Traditional approach to research ethics

- **Oversight system (1970s) thus required to ensure:**
  - Risk/benefit is acceptable
  - People **know they're in research, know it's NOT care**
  - People can voluntarily agree (or refuse) to take part

Prior Work: Maybe it's not so neat and clean

- A clinical trial **really might be** someone's best "treatment option"
- Quality improvement work **should be done rigorously**, with systematic data collection, and **of course is intended to be generalized** to future patients
- **Comparative effectiveness studies are on the rise, and were desperately needed.** They further studied ongoing care, were typically randomized. But interventions had passed FDA safety/efficacy standards.
- And by the way, clinical care wasted **billions of dollars** delivering care that was unproven, unnecessary, or in error. More ongoing learning in the context of care is good.



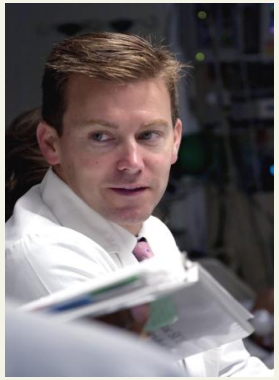
Hastings Center Report
Volume 43, Issue s1
Jan 2013
Pages S2-inside_back_cover

The Research-Treatment Distinction: *A Problematic Approach for Determining Which Activities Should Have Ethical Oversight*

BY NANCY E. KASS, RUTH R. FADEN, STEVEN N. GOODMAN, PETER PRONOVOST, SEAN TUNIS, AND TOM L. BEAUCHAMP

An Ethics Framework for a Learning Health Care System: *A Departure from Traditional Research Ethics and Clinical Ethics*

BY RUTH R. FADEN, NANCY E. KASS, STEVEN N. GOODMAN, PETER PRONOVOST, SEAN TUNIS, AND TOM L. BEAUCHAMP



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Central Argument: Ongoing learning in healthcare settings is essential but must have sound ethical oversight

- Learning from ongoing care should be the norm
  - Learning what does and doesn't work in healthcare is ethically required
- This learning should proceed in ethically appropriate ways
- Propose framework with 7 specific obligations/principles for an ethically acceptable learning health system

Two big challenges over the years, in response

- That's nice, but learning health care doesn't exist (many reasons)
- That's nice, but we have to abide by U.S. regulations. Too risky to deviate without further regulatory guidance.

JAMA October 19, 2024

Special Communication | Integrating Clinical Trials and Practice

FREE

October 19, 2024

Making the Ethical Oversight of All Clinical Trials Fit for Purpose

Nancy E. Kass, ScD[1,2]; Ruth R. Faden, PhD, MPH[1]; Derek C. Angus, MD, MPH[3,4]; et al

Editorial

FREE

October 19, 2024

Facilitating Efficient and Ethical Trials at the Intersection of Research and Clinical Care

Holly Fernandez Lynch, JD, MBE[1]; Daniel B. Kramer, MD, MPH[2]

» Author Affiliations | Article Information

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Ethics oversight for clinical research must be "Fit for Purpose"

- Clinical research is not all the same. Oversight must be matched ("fit") to the specifics of the study.
- **Sometimes it does fit:** e.g., for studies of experimental, pre-market products, with high uncertainty
- But one-size-fits-all oversight = problematic for some clinical research (e.g. CER on approved products)
- Excessive oversight results in greater-than-appropriate burdens for researchers and collaborating clinicians
  - Hinders conduct of valuable research
  - May mislead patients about how risky participation is

Two key considerations for "fit for purpose" oversight

- **Oversight** should be **based on the ethically relevant features** and concerns of a specific project
  - **Not on an activity's label** ("clinical trial" vs. "quality improvement" vs. "implementation science")
- Two key considerations:
  - **Impact on Welfare:** To what extent does participation increase risks and burdens *compared to usual care?*
  - **Impact on Autonomy:** To what extent does participation restrict or remove a care decision that would have been both *available* to patients and *meaningful* to them?

Consideration #1 -- Impact on welfare: Assessing Risk and Burden

- Oversight bodies should consider how much ***additional* risk and burden** is introduced with participation, **compared to that of usual or recommended care** for that patient/indication

  - **Current minimal risk definition focuses on absolute risk (or, at least, is ambiguous**), which can inflate the perceived risk of research participation, especially in high stakes clinical contexts

More work to do on Consideration #1:

- **How to define "additional study risk" in highest stakes clinical contexts?**
  - E.g., where death might be an outcome? (NICU, cancer)

- **How much moral relevance (requiring more oversight or disclosure) to attach to randomization itself** when background context is of widespread "arbitrary" variation in clinical practice.

Consideration #2 -- Impact of Participation on "Available and Meaningful Patient Decisions"

- **Does the study restrict a decision that would have been *available* to patients and *meaningful* for them?**
  - **Available**: Is it (or should it be) typically a "*patient* decision" or one where patient input is usually sought? [rather than an operational one?]
  - **Meaningful**: Is it a *meaningful* choice or decision for patients? Does the research limit or remove a decision where patients likely would have had important preferences, based on values, logistics, priorities, etc.

Consideration #2 -- Impact of Participation on "Available and Meaningful Patient Decisions"

- Grounded in general ethical duty to respect patient autonomy
- But the obligation to respect autonomy does not imply unfettered choice in every aspect of people's lives, nor that all choices are equally worthy of respect
- Respecting patients and their autonomy **requires discerning which aspects of care/research ethically require patient involvement** and decision-making and which do not

Respect for autonomy (like other ethics commitments) is not absolute

- The obligation to respect autonomy is not absolute;
  - it is instead bounded by other morally important duties, such as promoting welfare and seeking justice.
- In the clinical context, it is also bounded by tradeoffs where patients have other interests
  - Institutions need to function efficiently for large populations of individuals who cannot realistically be personally consulted on every practice or policy.
  - Most operational decisions, appropriately, are neither disclosed to patients nor discussed with them and certainly are not decided by them

So what would “fit for purpose” oversight require?

- Observational studies will require minimal oversight due to minimal increased risk compared to usual care, and no restriction of meaningful choice
- Randomized trials require case-by-case evaluation
  - Nurse staffing ratios: patients are not usually involved in decision making (despite welfare impact!)
  - Surgery vs. physical therapy: significant patient involvement and likely important preference sensitivity.
  - Comparing statins: potentially less preference-sensitive.

We'd love feedback on…

- "Available and meaningful choice"
  - Is it useful?
  - Better language?
  - Concerns?

- "Additional study risk" compared to that of usual or recommended patient care
  - Is it useful?
  - Better language?
  - Concerns?

Thank You!!!

Reactions?

Criticism?

Regulatory Criteria

In order for an IRB to waive or alter consent … the IRB must find and document that:

(i) The research involves **no more than minimal risk** to the subjects;

(ii) The research **could not practicably** be carried out without the requested waiver or alteration;

(iii) If the research involves identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;

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

(v) Whenever appropriate, the subjects or legally authorized representatives will be **provided with additional pertinent information** after participation.

Table. Ethical Concerns With How Certain Areas of Oversight Are Interpreted and Possible Solutions

Area of oversight	Current approaches	Ethical concerns with current approach	Possible solution
Projects requiring ethics oversight	Labels such as "research" and "quality improvement" often determine which projects receive ethics oversight.	The degree of oversight required for a given project should fit how ethically concerning the project is. Relying on labels as surrogates for what needs ethics review may result in underprotection of participants in ethically complex projects labeled quality improvement and overprotection of participants in projects of low ethical concern labeled clinical research.	Oversight (IRB review, disclosure, consent) should be based on ethically relevant project features: (1) the additional risks and burdens posed by adding the research compared with reasonably expected usual care; and (2) the degree to which participation restricts patients' ability to make decisions about their care that are meaningful to them and that would and should have been available to them to make in clinical care.
Risk assessment in clinical studies	Risk assessment for clinical research often takes account of study risks but also the risks of usual care and of the underlying disease.	Including baseline risks of the underlying disease and its usual tests or treatments into risk assessment can exaggerate the assessment of risks of study participation.	Oversight should focus on the additional risks and burdens posed by participation compared with those of reasonably expected usual care.
Randomization	Oversight bodies often assume that randomized clinical studies pose greater than minimal risk.	While some randomized studies remove important choices from patients and thus must allow full patient consent, other studies do not remove important patient-level choices: some low-risk randomized studies compare operational decisions never raised with patients or compare practice variations with interventions that are not preference-sensitive.	Investigators and IRBs should determine the degree to which either group and being randomized (1) poses greater or importantly different risks or uncertainties than those of reasonably expected usual care; and (2) alters the patient experience of care in meaningful ways (eg, mode of administration, frequency of treatment or visits, likelihood of having important preferences of one vs the other).
Alterations and waivers of traditional informed consent requirements	Oversight bodies often consider traditional informed consent vs a waiver for clinical studies but less typical may be recommending consent alterations, which may be optimal ethically.	In some clinical and comparative effectiveness studies, it might be ethically preferable to let participants know that research is ongoing, why, and how it works, but not require full, traditional consent. Full consent may prevent many clinical sites from participating and may paradoxically result in potential participants believing studies are more consequential than they actually are.	Alterations of consent (eg, transparency, short discussions, opt-out options, videos) should be considered for some lower-risk clinical studies, including some comparative effectiveness studies. Alterations may be a better ethical fit than either complete consent waivers or full, traditional consent procedures.
Respecting autonomy in research	Oversight bodies often assume that research involvement must involve patient discussions, regardless of type of clinical study.	Respect for autonomy must remain centrally important. Yet medical care and research regularly and appropriately triage which types of decisions should be discussed with patients and which should not. Most operational decisions are never discussed with patients, and many straightforward aspects of care, where meaningful decisions are not at stake, typically are never discussed. This is not simply for efficiency—it also focuses clinicians' and patients' attention on areas where autonomy is important—where relevant and differing values, preferences, and priorities can be heard and respected.	Most clinical trials will likely invoke meaningful patient decisions and will appropriately require full informed consent. But some comparative effectiveness and other studies of postmarket and widely used approaches may involve approaches not typically controlled by or discussed with patients (eg, system-level or operational decisions) or may not involve decisions or approaches likely to be sensitive to patient values or preferences. Identifying how studies alter care and whether this alteration involves meaningfully important patient-level considerations is essential for good ethical fit of oversight.

Abbreviation: IRB, institutional review board.