

Ethical Conflicts in Randomized Controlled Trials

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I have no disclosures
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this presentation

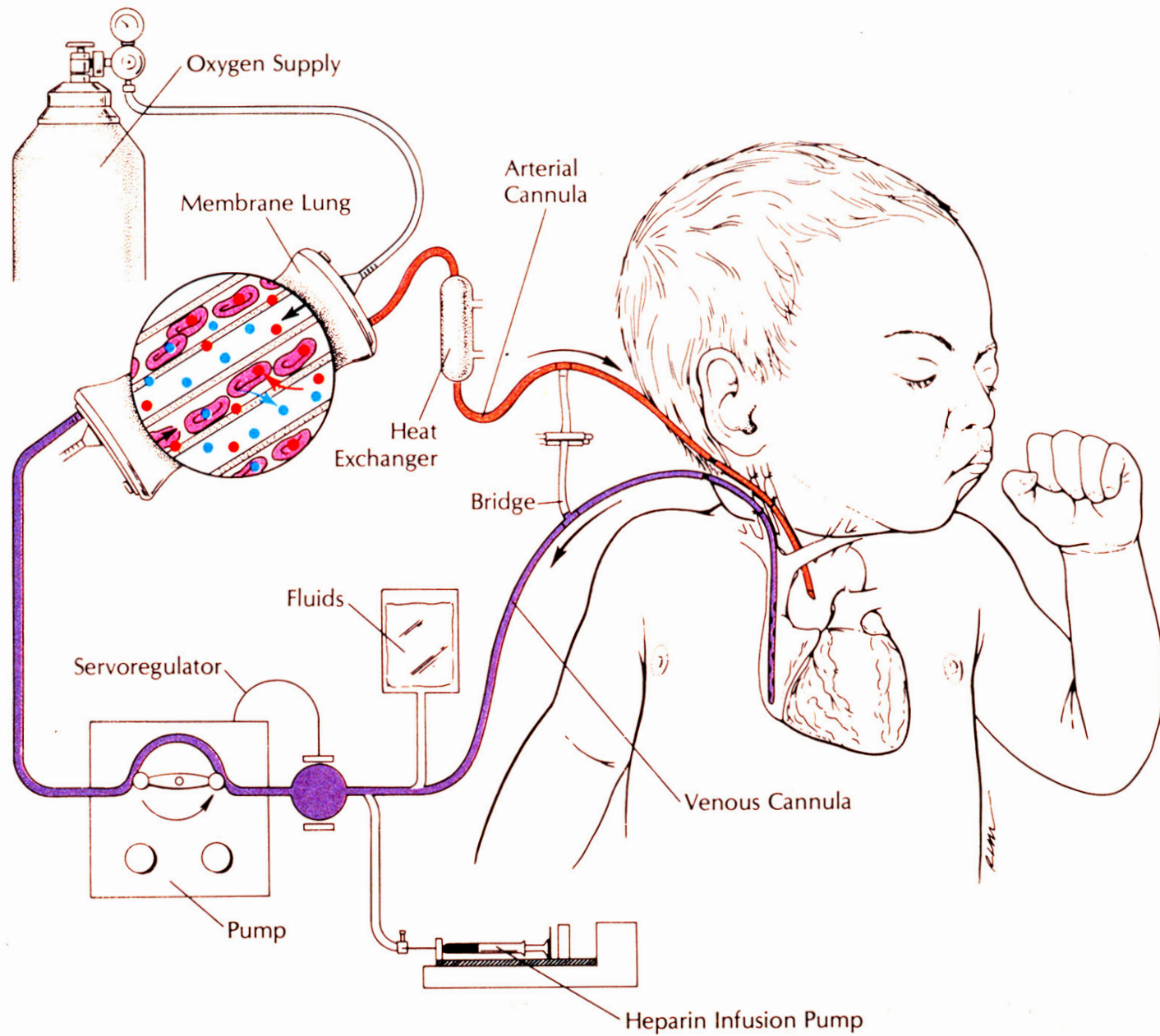
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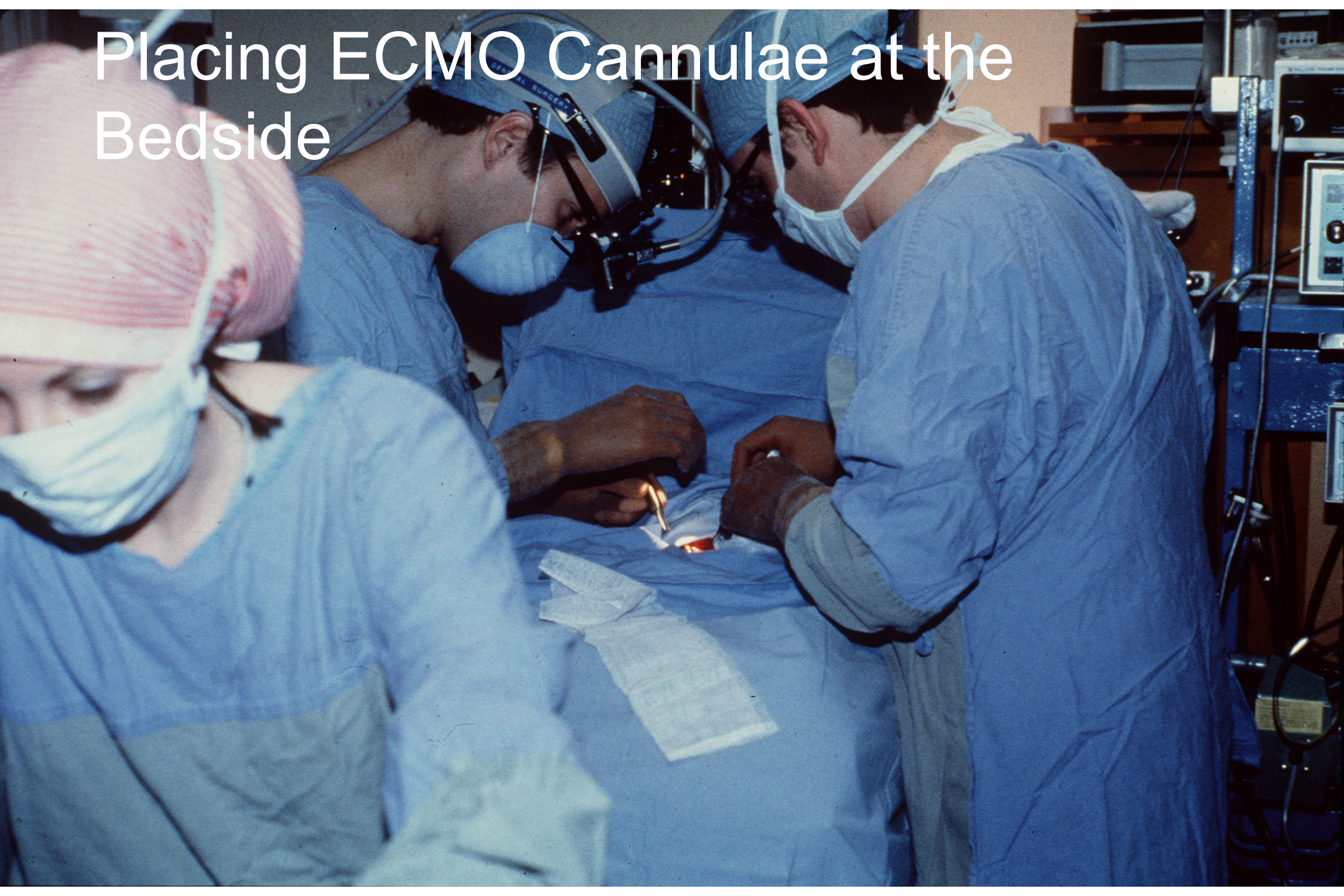
Extracorporeal Membrane Oxygenation and Conventional Medical Therapy in Neonates With Persistent Pulmonary Hypertension of the Newborn: A Prospective Randomized Study

P. Pearl O'Rourke, MD, Robert K. Crone, MD, Joseph P. Vacanti, MD, James H. Ware, PhD, Craig W. Lillehei, MD, Richard B. Parad, MD, and Michael F. Epstein, MD

Pediatrics 1989;84:957-63.



Placing ECMO Cannulae at the Bedside



Nurse and ECMO Specialist at Bedside 24x7



Baby on ECMO



Background to the Harvard Trial

- An RCT in the 1970s had shown ECMO not effective for ARDS in adults
- In the 1980s, Robert Bartlett used ECMO to treat newborns with PPHN
- Results were very impressive
- But, pediatricians were reluctant to adopt ECMO without convincing data from an RCT



Questions

- Imagine you were Bob Bartlett
- Would you have sought to perform an RCT to demonstrate the superiority of ECMO to Conventional Medical Therapy (CMT)?
- Why or why not?



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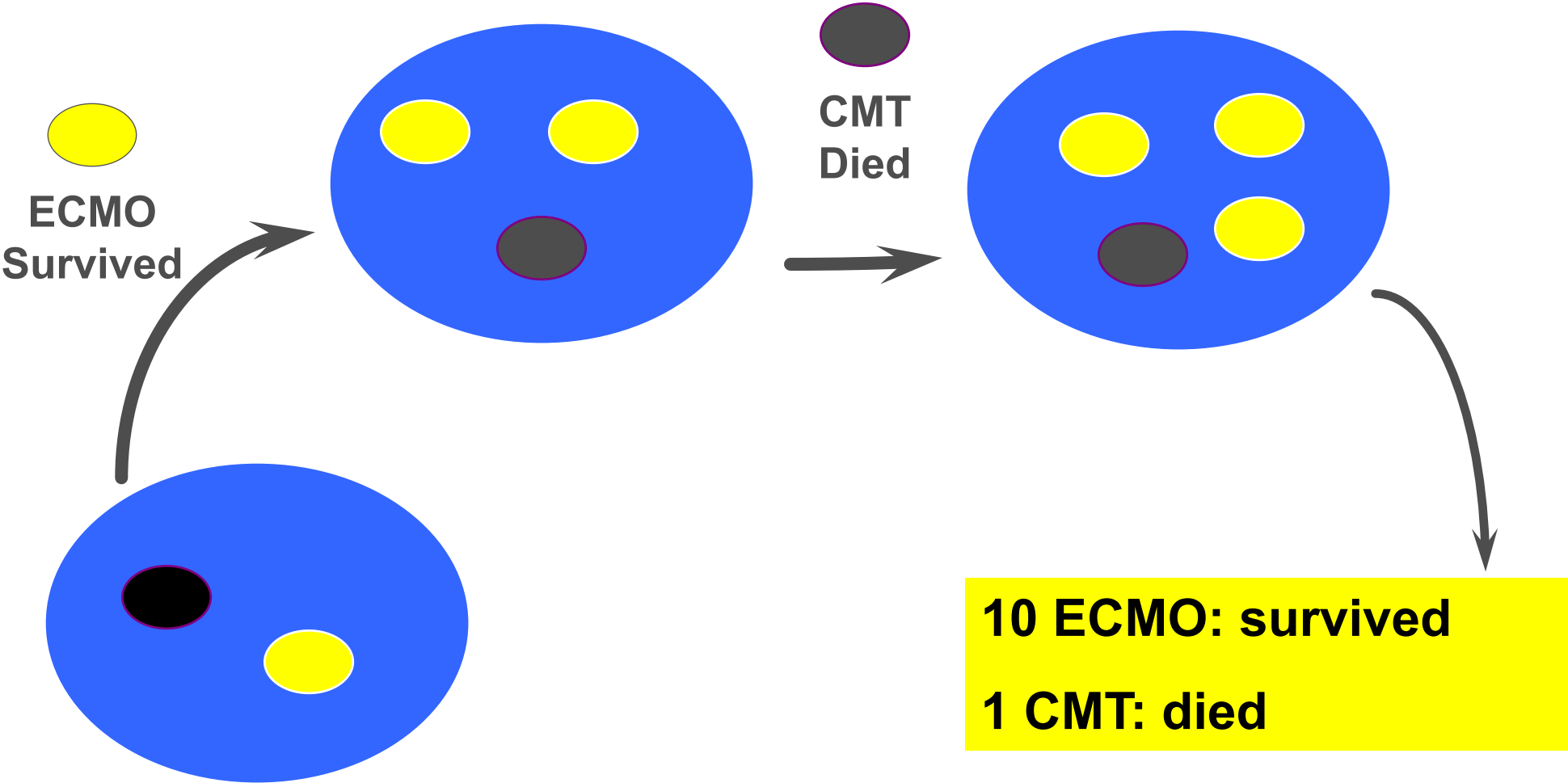
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Extracorporeal Circulation in Neonatal Respiratory Failure: A Prospective Randomized Study

**Robert H. Bartlett, MD, Dietrich W. Roloff, MD, Richard G. Cornell,
PhD, Alice French Andrews, MD, Peter W. Dillon, MD, and
Joseph B. Zwischenberger, MD**

Pediatrics 1985;76:479-87.

Bartlett: Play-the-Winner Design



Questions

- Imagine you were a neonatologist in Boston
- When you read this article, would you have told your hospital administrator that you needed to start an ECMO program?
- Why or why not?



**Extracorporeal Circulation in Neonatal Respiratory Failure: A Prospective
Randomized Study**

JAMES H. WARE and MICHAEL F. EPSTEIN
Pediatrics 1985;76:849-851

“The clinical indications for this new and complex treatment remain undefined. Further randomized controlled trials... will be difficult but remain necessary.”

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Extracorporeal Membrane Oxygenation and Conventional Medical Therapy in Neonates With Persistent Pulmonary Hypertension of the Newborn: A Prospective Randomized Study

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The Harvard Neonatal ECMO Trial

Randomized newborns with PPHN to
conventional therapy versus ECMO

Conventional Therapy

NICU: 7th Floor

Neonatologists

**No patients had ever
been offered ECMO**

Anti-ECMO

ECMO

PICU: 5th Floor

**Anesthesiologists &
Surgeons**

**Already had experience
with ECMO for newborns
with CDH**

Pro-ECMO

The Harvard Neonatal ECMO Trial: Study Design

- Eligible newborns had PPHN and a predicted mortality of 85% based on retrospective data
- Phase I: 50/50 randomization until there were 4 deaths in one arm
- Phase II: Assign all patients to the more successful therapy, until there are 4 deaths in that arm or until statistical significance is achieved
- Seek consent only from those randomized to the experimental therapy



$$P(p_1 > p_2) = \frac{F_1}{F_1 + F_2 + F_3},$$

$$P(p_1 = p_2) = \frac{F_2}{F_1 + F_2 + F_3},$$

$$P(p_1 < p_2) = \frac{F_3}{F_1 + F_2 + F_3},$$

where

$$\begin{aligned} F_1 &= \int_0^1 \int_0^{p_1} p_1^{\alpha-2} (1-p_1)^{b-1} p_1^6 (1-p_1)^4 p_2^9 dp_1 dp_2 \\ &= \int_0^1 p_1^{\alpha+4} (1-p_1)^{b+3} \int_0^{p_1} p_2^9 dp_2 dp_1 \\ &= \frac{1}{10} \int_0^1 p_1^{\alpha+14} (1-p_1)^{b+3} dp_1 \\ &= \frac{1}{10} \frac{\Gamma(\alpha+15)\Gamma(b+4)}{\Gamma(\alpha+b+19)} \end{aligned}$$

and, similarly

$$\begin{aligned} F_2 &= \frac{\Gamma(\alpha+15)\Gamma(b+4)}{\Gamma(\alpha+b+19)}, \\ F_3 &= \frac{1}{10} \left[\frac{\Gamma(\alpha+6)\Gamma(b+3)}{\Gamma(\alpha+b+9)} - \frac{\Gamma(\alpha+16)\Gamma(b+3)}{\Gamma(\alpha+b+19)} \right]. \end{aligned}$$

The Harvard Neonatal ECMO Trial: Results

	ECMO	CMT
Phase I	9 s, 0 d	6 s, 4 d
Phase II	19 s, 1 d	



Healer versus Investigator

The Fundamental Conflict

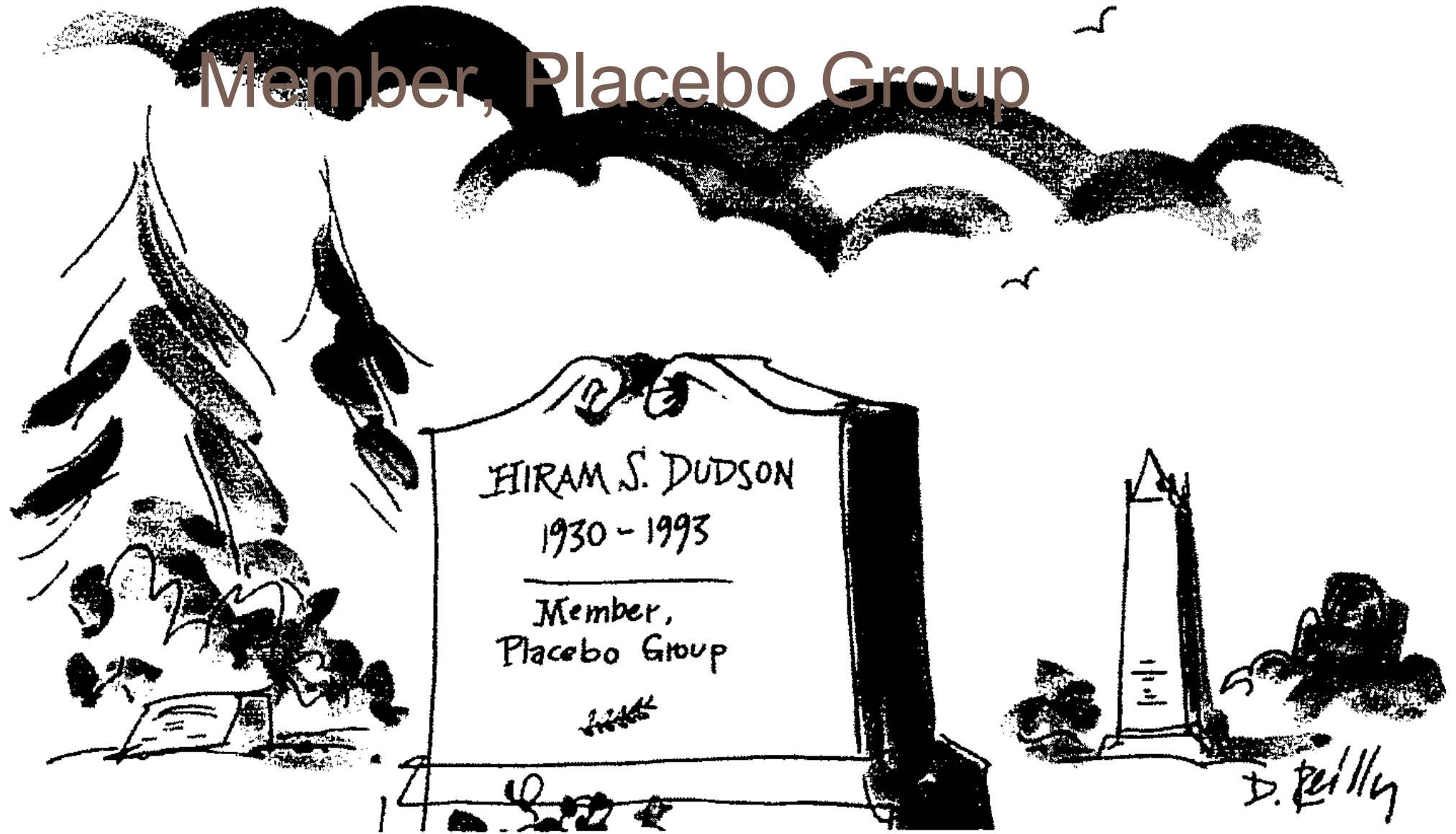
The Fundamental Dilemma

- A dilemma confronts physician-investigators...
- As physicians they are dedicated to caring for their patients...
- As investigators they are dedicated to caring for their research...
- These two commitments conflict whenever an individual physician/investigator comes face to face with an individual patient/subject.

Jay Katz, 1993



Member, Placebo Group



Possible Solution #1: Full Separation of Roles

- “Researchers must give patients stark, bold, and dramatic signs that research is different from clinical care... instead of the white coats associated with medical care, investigators could wear red ones...”

Dresser R. Soc Philos Policy 2002; 19:271



Possible Solution #2: Personal Equipoise

- Requires that the investigator be personally unbiased between the treatment arms, “perfectly balanced on the edge of the sword”
- But, researchers usually “believe in” the treatments they study
- Requiring personal equipoise leaves investigators feeling either “guilty” or “cynical”



Possible solution #3: Clinical Equipoise

- Requires uncertainty within the medical community as a whole
 - “I believe that “A” is better, but if your appointment had been with my colleague down the hall, she would have recommended “B”
 - “So... would you agree to have your treatment determined by a coin flip, so that we can learn from this experience?”
- Harvard ECMO Trial
 - Likely that no single investigator was in personal equipoise
 - Freedman: the collective uncertainty represented clinical equipoise

Freedman B. N Engl J Med 1987;317:141





Adaptive Randomization

**Balancing Conflicting
Obligations**

Adaptive Randomization

- Definition: Deviating from “balanced” or 50/50 randomization, with more patients assigned to the therapy that is “leading” during the trial
- Betting on the horse who is out in front, before we know how the race will end



Adaptive Randomization

- Attempts to minimize number of patients assigned to the less-successful therapy
- Attempts to mitigate the conflict of healer versus investigator
 - In the Bartlett trial, 50/50 randomization was guaranteed only for the first patient
 - In the Harvard trial, 50/50 randomization was guaranteed until the 4th death in one arm



Adaptive Randomization

- In the literature, the trial was criticized from both directions
 - No patients should have been assigned to CMT
 - Not enough patients were assigned to CMT
- Perhaps this approach was a good balance



Adaptive Clinical Trials

A Partial Remedy for the Therapeutic Misconception?

William J. Meurer, MD, MS

Roger J. Lewis, MD, PhD

Donald A. Berry, PhD

Adaptive Trials in Clinical Research

Scientific and Ethical Issues to Consider

Rieke van der Graaf, PhD

Kit C. B. Roes, PhD

Johannes J. M. van Delden, MD, PhD

[van der Graaf et al. JAMA 2012;307:2379](#)

[Meurer et al. JAMA 2012;307:2377](#)



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at
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I-SPY 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy

AD Barker¹, CC Sigman², GJ Kelloff¹, NM Hylton³, DA Berry⁴ and LJ Esserman³

I-SPY 2 (investigation of serial studies to predict your therapeutic response with imaging and molecular analysis 2) is a process targeting the rapid, focused clinical development of paired oncologic therapies and biomarkers. The framework is an adaptive phase II clinical trial design in the neoadjuvant setting for women with locally advanced breast cancer. I-SPY 2 is a collaborative effort among academic investigators, the National Cancer Institute, the US Food and Drug Administration, and the pharmaceutical and biotechnology industries under the auspices of the Foundation for the National Institutes of Health Biomarkers Consortium.

treatment options remain limited. These patients continue to represent a disproportionately large fraction of those who die of their disease. Given that the standard of care for these women increasingly includes neoadjuvant therapy prior to surgical resection, this combination of group and setting represents a unique opportunity to learn how to tailor the treatment to patients with high-risk breast cancers.

Cancer research from the past decade has shown that breast cancer is a number of heterogeneous diseases; this finding suggests that directing drugs to molecular pathways that characterize the disease in subsets of patients will improve treatment efficacy. Currently, however, most phase II and III trials of new

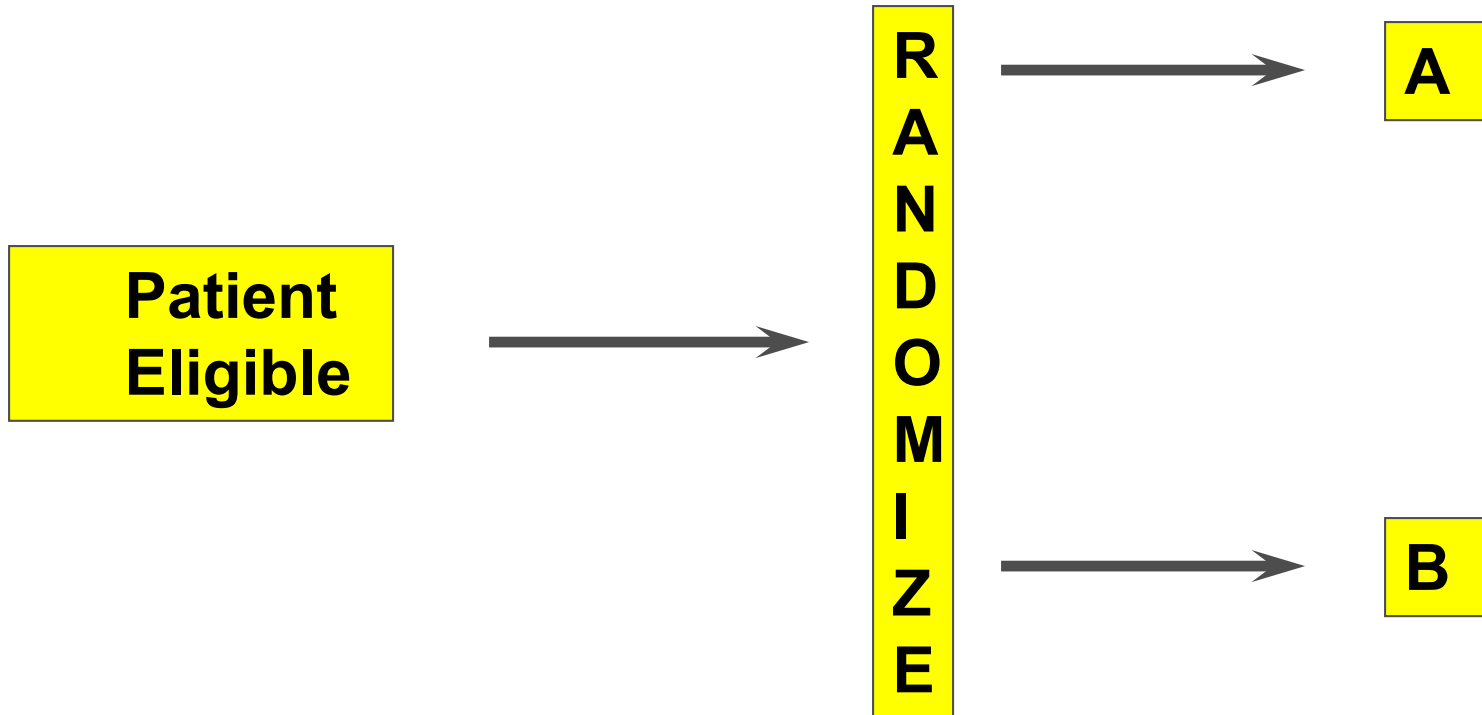


Randomized Consent

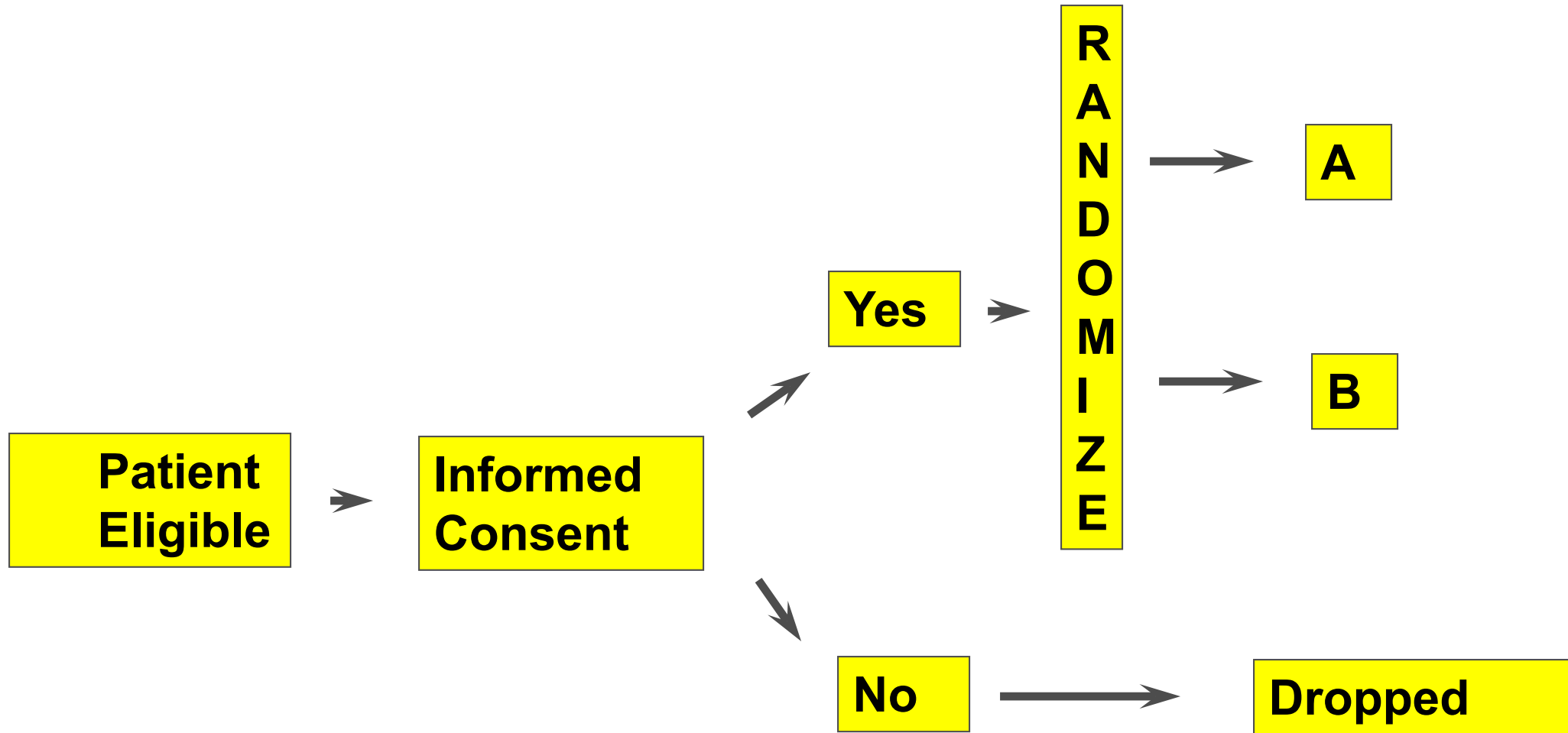
(Zelen Randomization)

**Easing the Psychological
Burdens**

Conventional RCT, Without Informed Consent



Conventional RCT, With Informed Consent



Zelen M. A new design for randomized clinical trials. *New England Journal of Medicine* 1979;300:1242-5.



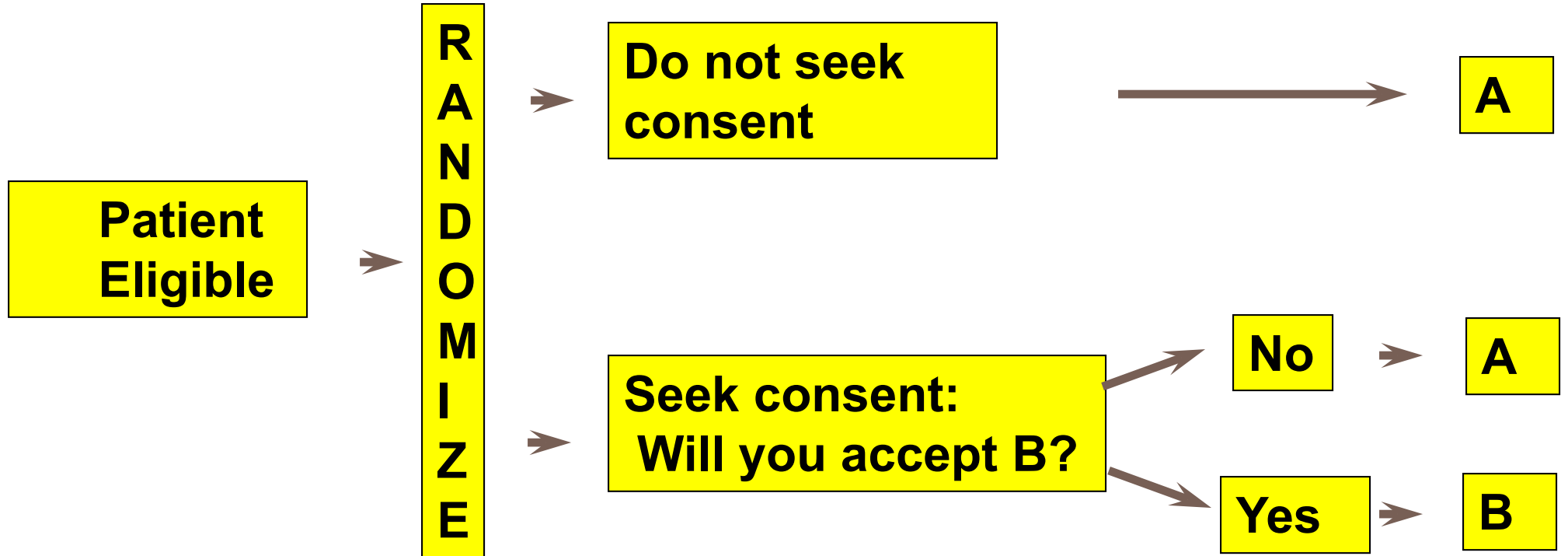
Marvin Zelen

Lemuel Shattuck Research Professor of Statistical Science and Member of the Faculty of Arts and Sciences

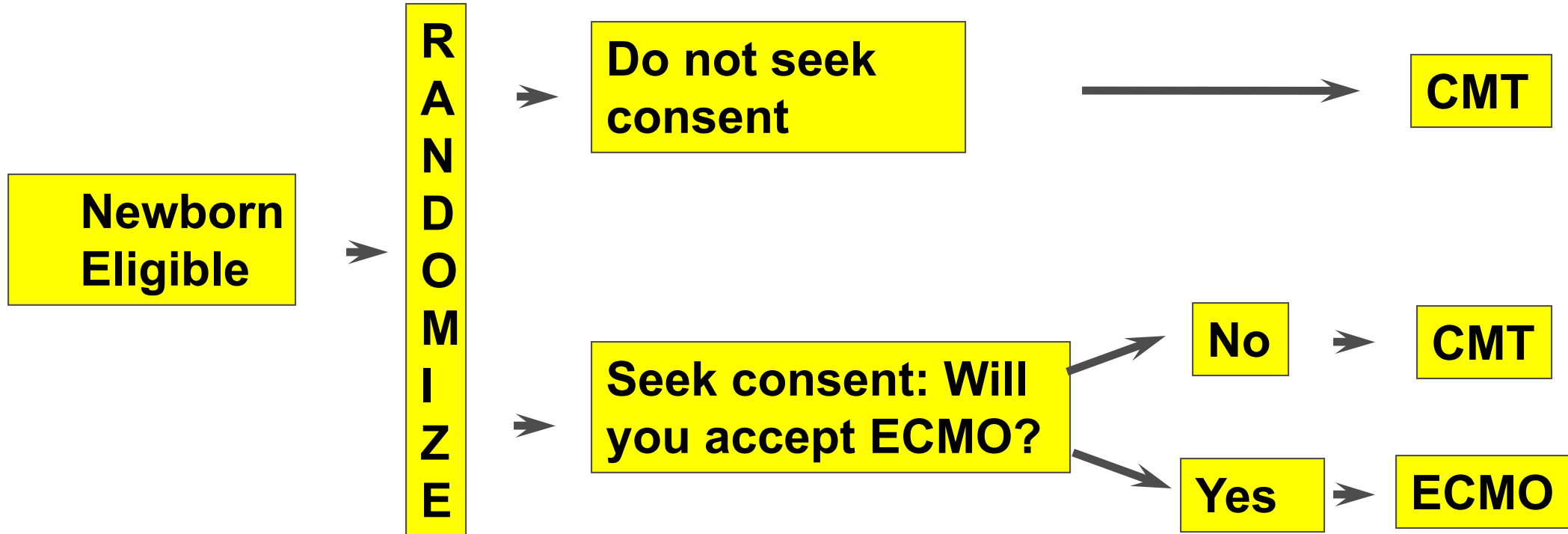
Department of Biostatistics

Harvard School of Public Health

Randomized Consent



Randomized Consent



Question

- Imagine you were on the IRB at Boston Children's Hospital when this study was proposed
- Would you have approved the Zelen randomization scheme?
- Why or why not?



ETHICS

Aug 7 89
p 25
Boston Globe

A Harvard study on newborns draws fire

Doctors faulted for limiting life-saving treatment

By Richard A. Knox
Globe Staff

ECMO, were asked for their consent. All
ECMO-treated babies survived.

The ECMO Trial:

Justifications for Randomized Consent

- Control patients were not really research subjects
- Parents of control patients were not really being offered a choice, so why subject them to stress?
- Pressure to cross-over from CMT to ECMO would have been unbearable



The Response to the ECMO Trial

- The NIH Office for Protection from Research Risks (OPRR) reprimanded the hospital
 - The hospital IRB “made decisions that rightfully belonged to the parents. They really blew it.” [Charles McCarthy, Director of OPRR](#)
 - The doctors “were doing exactly what physicians did before we had a doctrine of informed consent - making decisions for parents.” [George Annas, Boston University](#)





Are RCTs the only way to learn?

Approaches to Learning: Ascending Order of Confidence

- Meta-analyses
- Randomized Controlled Trials
- Case / Control Observational Studies
- Databases
- Case Series with Historical Controls
- Case Series with Literature Controls
- Case Series without Controls
- Anecdotal Case Reports



Are RCTs the only way to learn?

- “The brilliant success of the RCT has now become a form of intellectual tyranny”
Freireich
- “We should not proceed on the fallacious assumption that where there is no randomization, there is no truth.” *Royall*



Special Articles

A COMPARISON OF OBSERVATIONAL STUDIES AND RANDOMIZED,
CONTROLLED TRIALS

KJELL BENSON, B.A., AND ARTHUR J. HARTZ, M.D., PH.D.

Conclusions

We found little evidence that estimates of treatment effects in observational studies reported after 1984 are either consistently larger than or qualitatively different from those obtained in randomized, controlled trials. (N Engl J Med 2000;342:1878-86.)

We should abandon randomized controlled trials in the intensive care unit

Jean-Louis Vincent, MD, PhD, FCCM

The randomized controlled trial is seen by many as the summit of evidence-based medicine, yet, in the intensive care unit, randomized controlled trials can be challenging to conduct, and results are often difficult to interpret and apply. Many randomized controlled trials in intensive care patients have not demonstrated beneficial effects of the intervention under investigation often despite good preclinical and even previous randomized controlled

trial evidence. There are many reasons for these negative results including problems with timing, end point selection, and heterogeneous populations. In this article, we will discuss the limitations of randomized controlled trials in the intensive care unit population and highlight the importance of considering other study designs in the challenging intensive care unit environment. (Crit Care Med 2010; 38[Suppl.]:S534–S538)

“I will argue that in many situations with the ICU context, the RCT as we know it should be abandoned, at least temporarily, and much greater emphasis be placed on gathering information from well-designed observational studies.”

Data published in 1988

- ECMO database of 715 newborns treated with ECMO (no controls)
- These patients had an 81% survival
- ECMO statistically superior to any other treatment with a survival rate less than 78.4%



Question

- Given all you've seen, are you now convinced that ECMO is superior to conventional therapy?



The UK Neonatal ECMO Trial

THE LANCET

Articles

UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation

- The existing “RCTs of neonatal ECMO... suggested reductions in mortality but were not conclusive.”
- Because they “used adaptive designs, which may have introduced bias...”

Field et al. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. Lancet 1996;348:75-82

The UK Neonatal ECMO Trial

- 1993-1995: 185 neonates randomized to ECMO vs CMT
- Trial stopped early by DSMB,
 - ECMO survival 60/93 = 65%
 - CMT survival 38/92 = 41%, $p < 0.0005$
- Were 22 babies unnecessarily “sacrificed”?



Conclusions

- RCTs are usually the best approach for evaluating new therapies, but...
- The conflict between clinician and investigator is profound and can never be entirely eliminated
- Adaptive randomization is one way to balance the competing obligations
- Zelen randomization reduces the psychological burdens of the investigators, but is probably unacceptable



Conclusions

- “The use of statistics in medical research has been compared to a religion: it has its high priests (statisticians), supplicants (journal editors and researchers), and orthodoxy (for example, $p < .05$ is “significant”)”

Benjamin Freedman





“Never, ever, think outside the box”