HARVARD
MEDICAL SCHOOL

Ethical Conflicts in Randomized Controlled Trials

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Disclosure:
I serve as a paid member of several data safety monitoring boards for Sanofi and Covance

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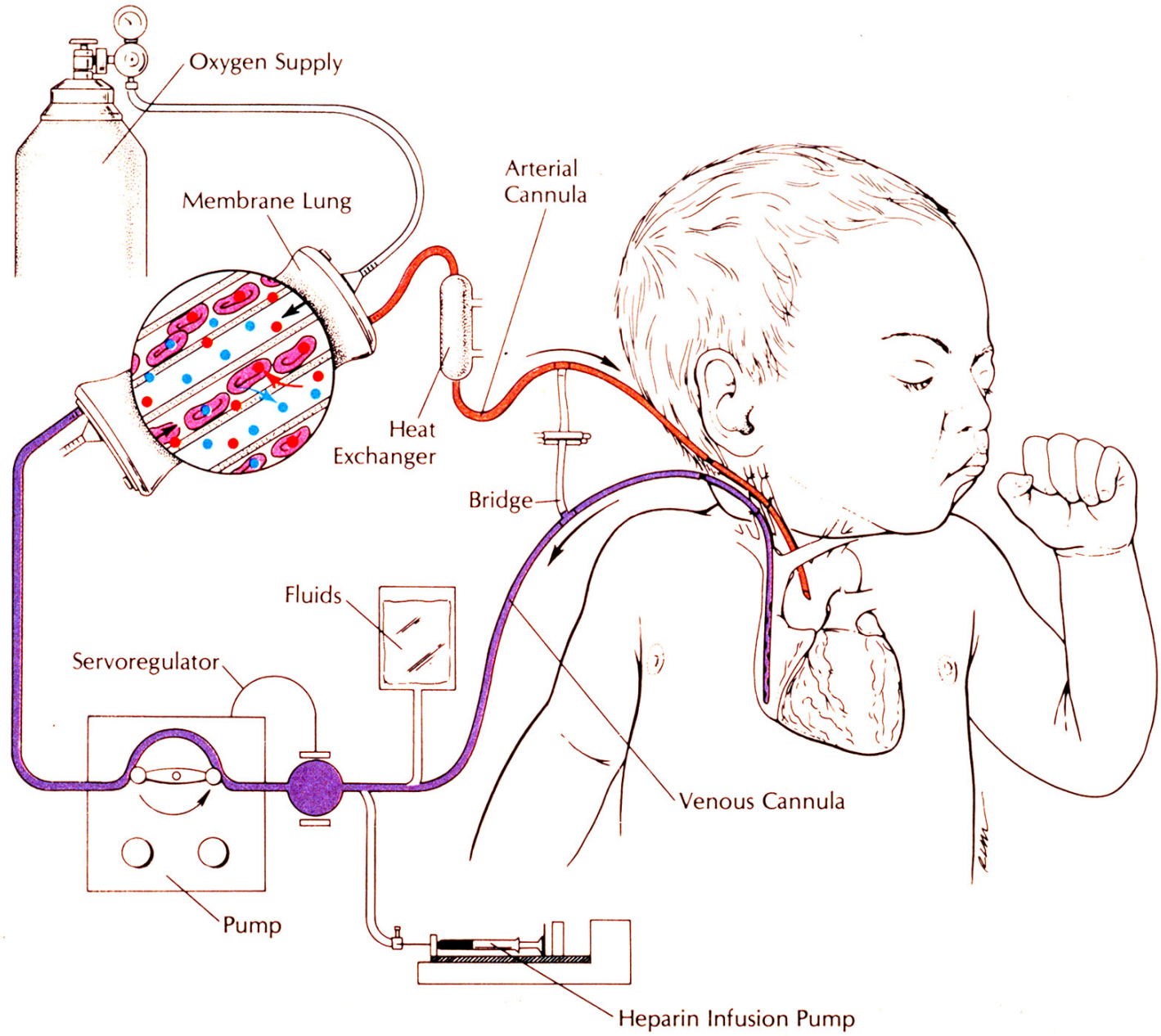
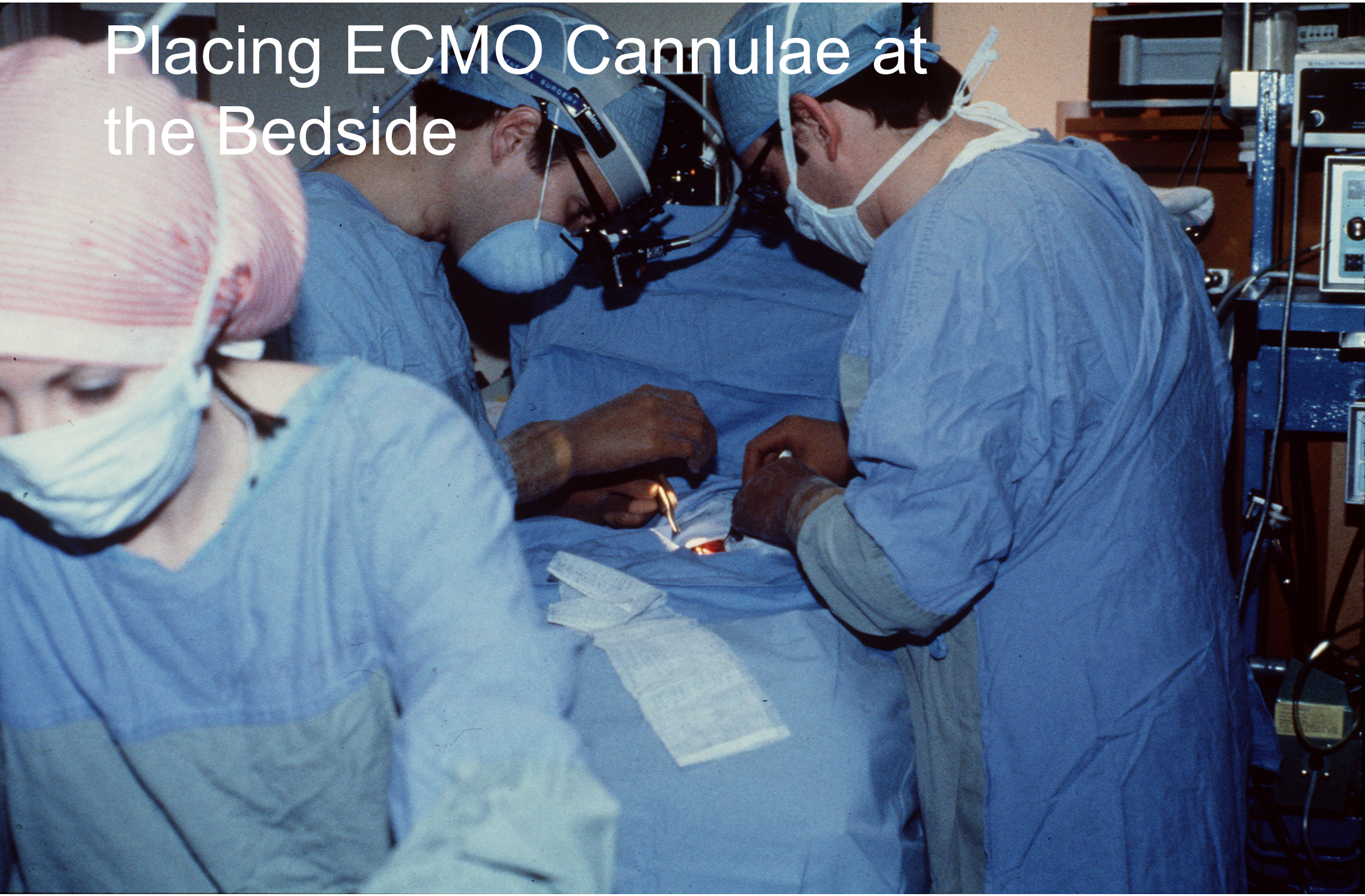
Extracorporeal Membrane Oxygenation and Conventional Medical Therapy in Neonates With Persistent Pulmonary Hypertension of the Newborn: A Prospective Randomized Study

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.


Oxygen Supply
Membrane Lung
Arterial Cannula
Heat Exchanger
Bridge
Fluids
Servoregulator
Venous Cannula
Pump
Heparin Infusion Pump

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

Question #1

- 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?

Poll #1

- YES:
  I would do an RCT to prove the superiority of ECMO over conventional medical therapy (CMT)

- NO:
  It would not be ethical for me to randomize patients to a control group, given my experience with ECMO

- Yes, I would do the RCT, because
  - Without a control group, we can never be sure if the new therapy is better
  - RCTs are the gold standard for convincing physicians to change their practice
  - By proving the superiority of ECMO, I can save the lives of many more babies – I have an ethical obligation to do the study
- No, I would not do an RCT
  - It would be unethical for me to randomize patients when I am convinced that one therapy is superior
  - It would be unethical for doctors and nurses to let a patient die when they think the patient could be saved

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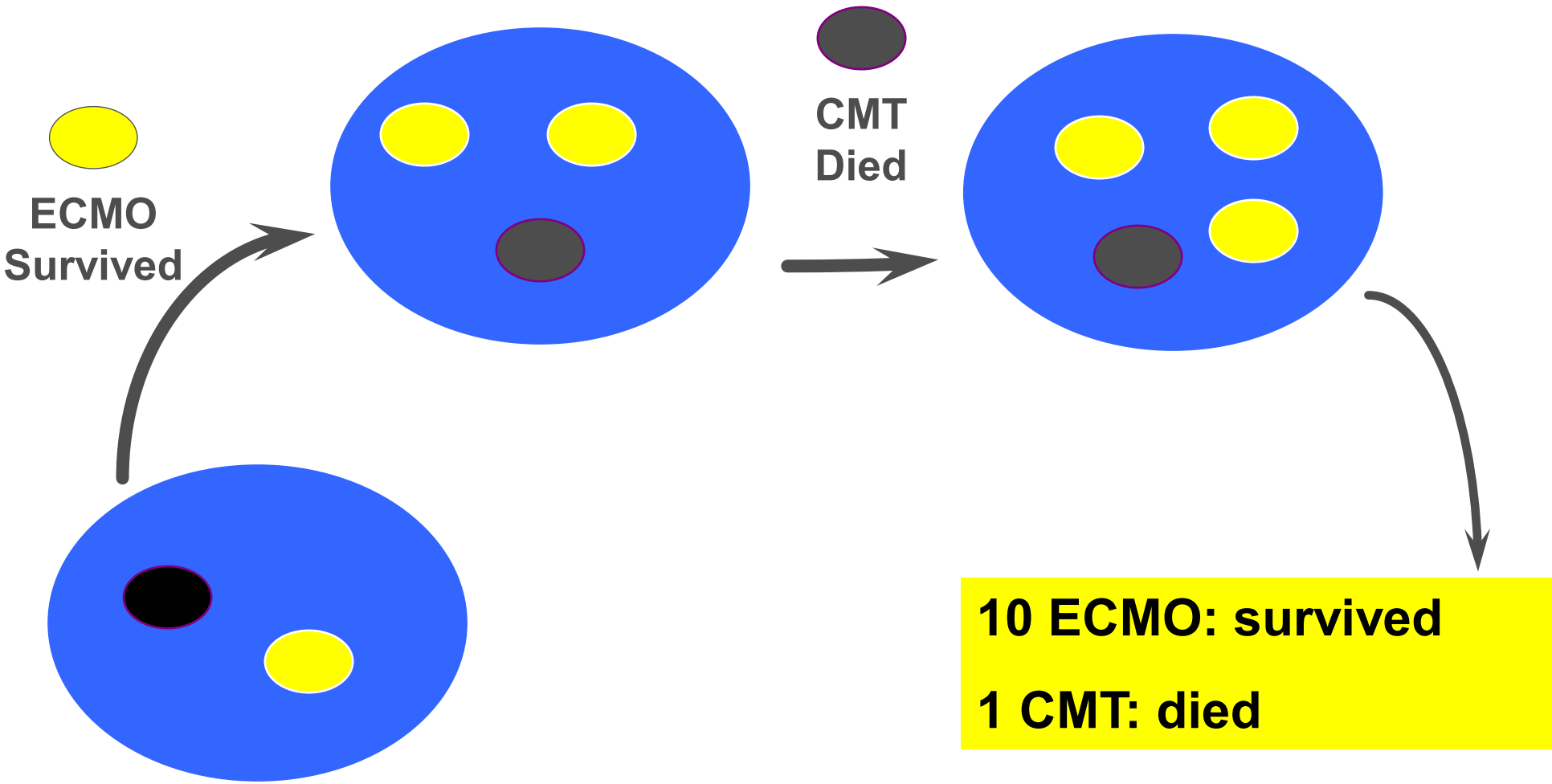
Extracorporeal Circulation in Neonatal Respiratory Failure: A Prospective Randomized Study

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?

Poll #2

- YES:
  This is a statistically significant trial – I should change my practice and create an ECMO program at my hospital

- NO:
  Regardless of the statistics, this trial does not convinced me that ECMO is a superior therapy.

- Yes, I would change my practice, because
  - We need to trust statistics – if this trial result is statistically significant, we should change our practice

- No, I would not change my practice, because
  - The result is contingent upon the outcome of only one patient – if that patient had survived the trial might have gone differently
  - RCTs must have balanced (50/50) randomization or they are not valid
  - The trial should have been done at another center with unbiased physicians

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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Pediatrics 1989;84:957-63.

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

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

and, similarly

$$F_2 = \frac{\Gamma(a+15)\Gamma(b+4)}{\Gamma(a+b+19)},$$

$$F_3 = \frac{1}{10}\left[\frac{\Gamma(a+6)\Gamma(b+3)}{\Gamma(a+b+9)} - \frac{\Gamma(a+16)\Gamma(b+3)}{\Gamma(a+b+19)}\right].$$

The Harvard Neonatal ECMO Trial: Results

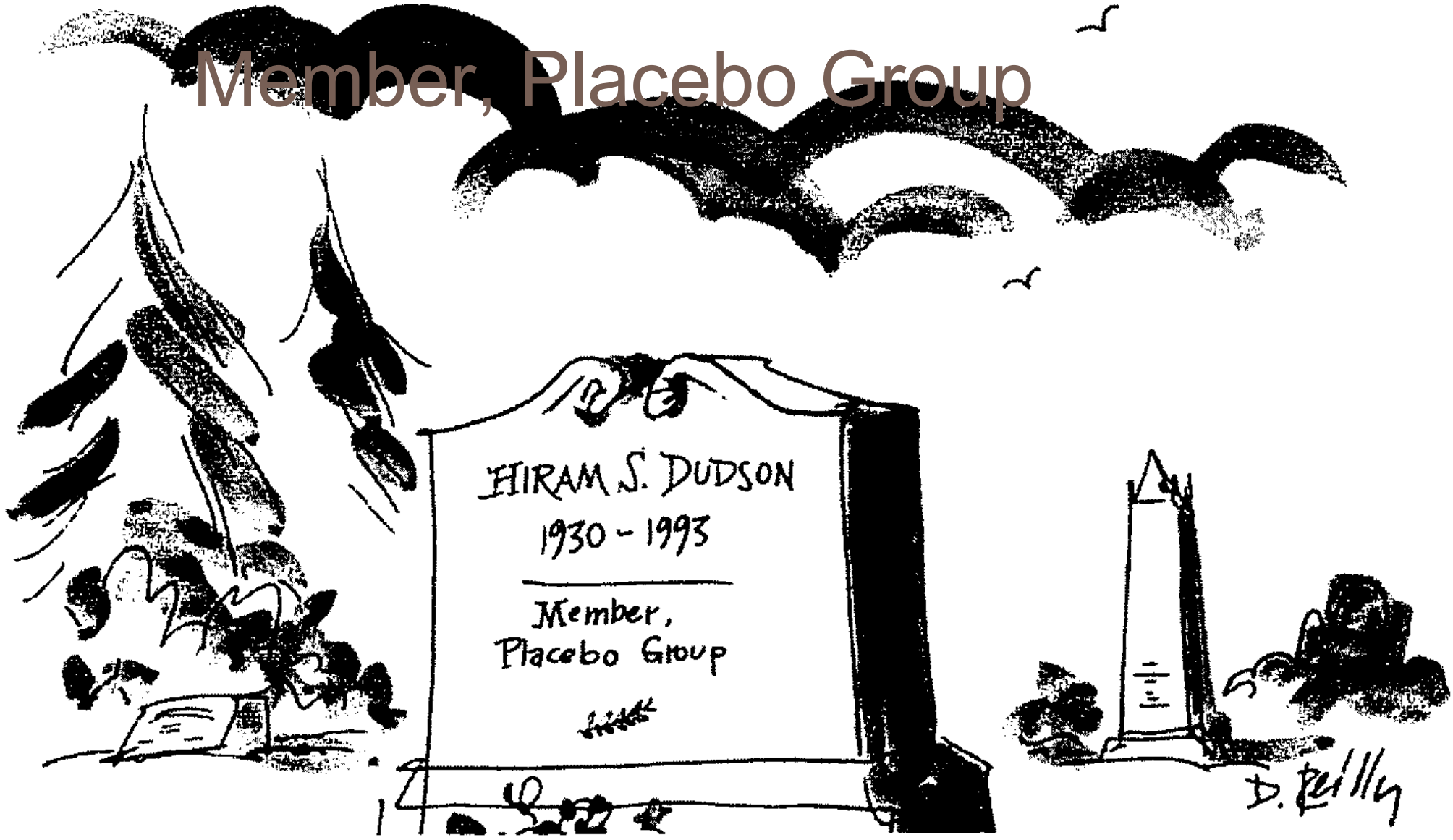
	ECMO	CMT
Phase I	**9 s, 0 d**	**6 s, 4 d**
Phase II	**19 s, 1 d**	

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
HIRAM S. DUDSON
1930 - 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 equipose

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: Disadvantages

- There must be only one primary outcome of interest
- The outcome must be apparent within a short period of time
- May suffer from accrual bias: volunteers may want to be recruited into the trial later

The trial was was criticized from both directions

- No patients should have been assigned to CMT

  "The clear expectation was that more patients would die on conventional therapy. Was having an excess number of deaths balanced by the worth of the information gained? My answer is a resounding no."

  Don Berry, U of Minnesota

- Not enough patients were assigned to CMT

  The researchers were so preoccupied with ethical problems that they stopped the conventional therapy too soon.

  Colin Begg, Memorial Sloan Kettering

  "There is a slightly hysterical view that we need to stop a study as soon as we have an idea which treatment might be better.

  Paul Meyer, U of Chicago

- Perhaps this approach was a good balance

Adaptive Clinical Trials

A Partial Remedy for the Therapeutic Misconception?

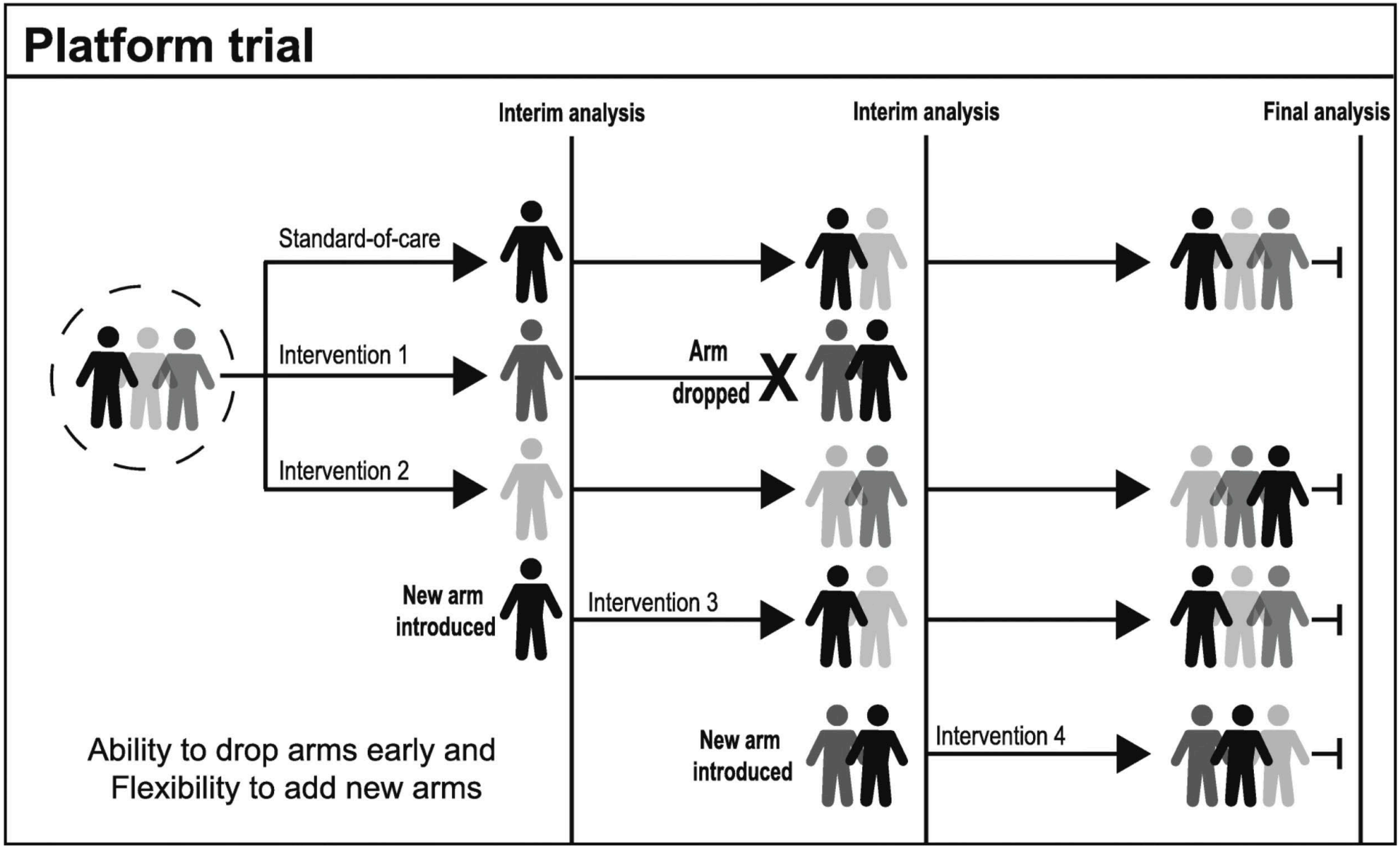
William J. Meurer, MD, MS
Roger J. Lewis, MD, PhD
Donald A. Berry, PhD

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



Park JJH, et al. *Trials.* 2019;20(1):572.

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

AD Barker[1], CC Sigman[2], GJ Kelloff[1], NM Hylton[3], DA Berry[4] and LJ Esserman[3]

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.

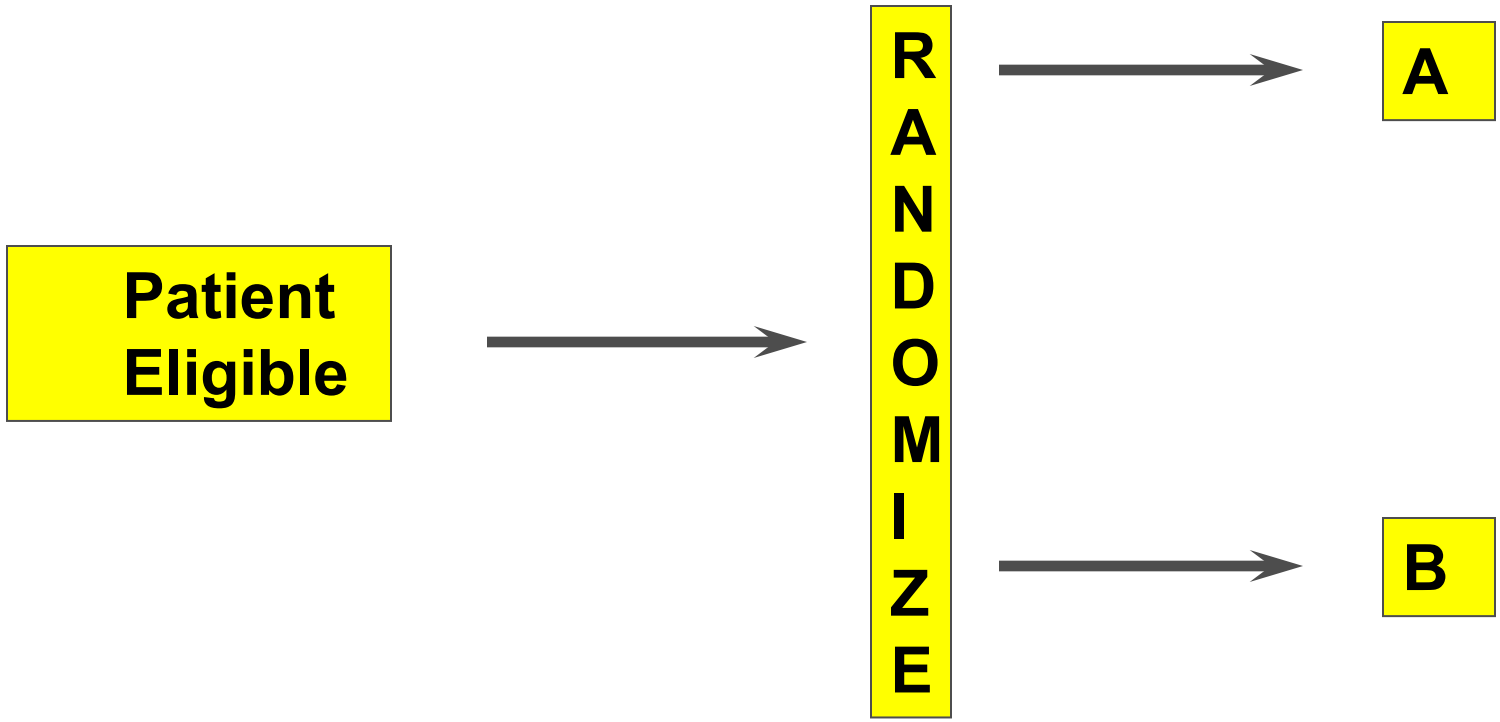
Cancer research from the past decade has shown that breast cancer is a number of heterogeneous diseases; this finding suggests that directing drugs to molecular pathways that characterize the disease in subsets of patients will improve treatment efficacy. Currently, however, most phase II and III trials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

Randomized Consent

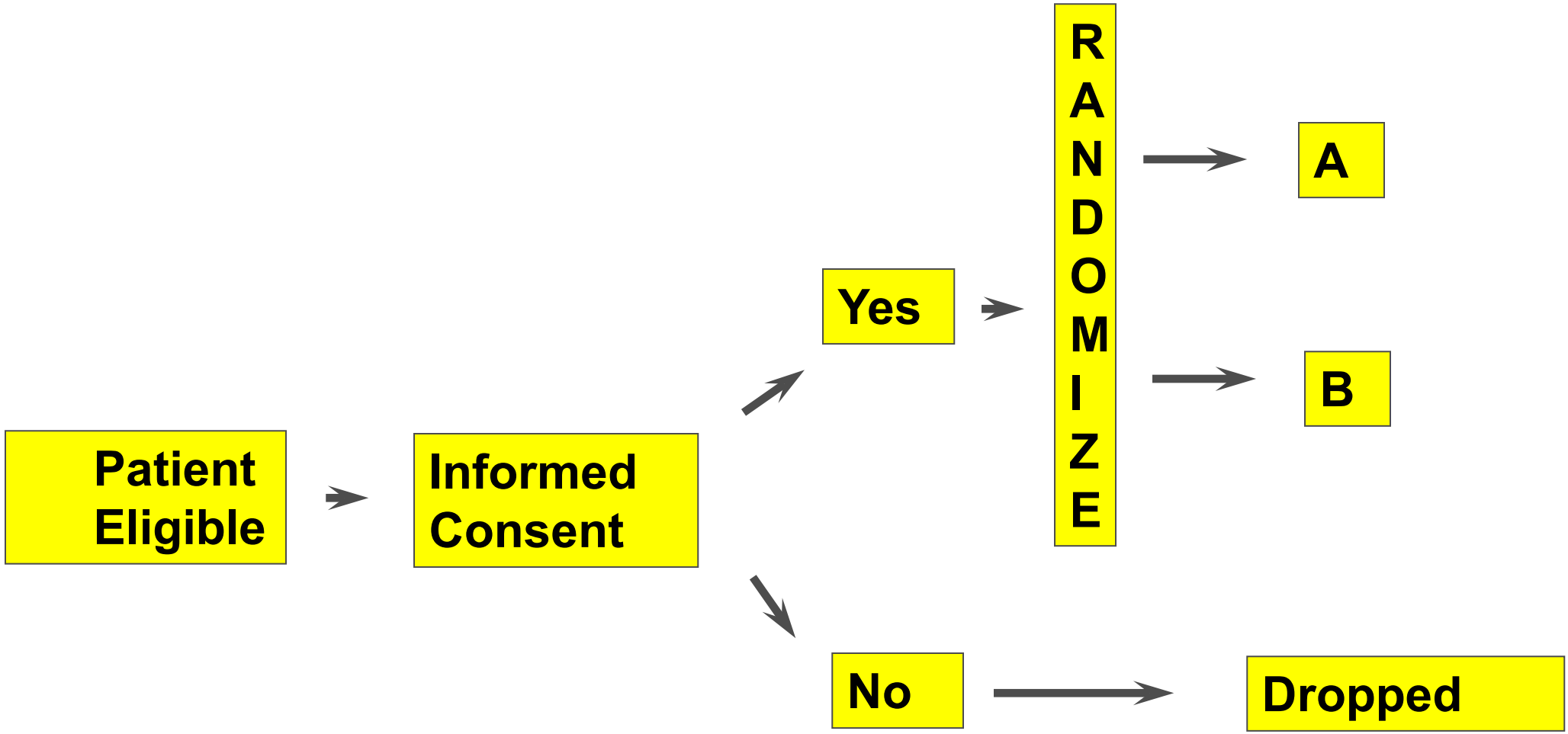
(Zelen Randomization)

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.

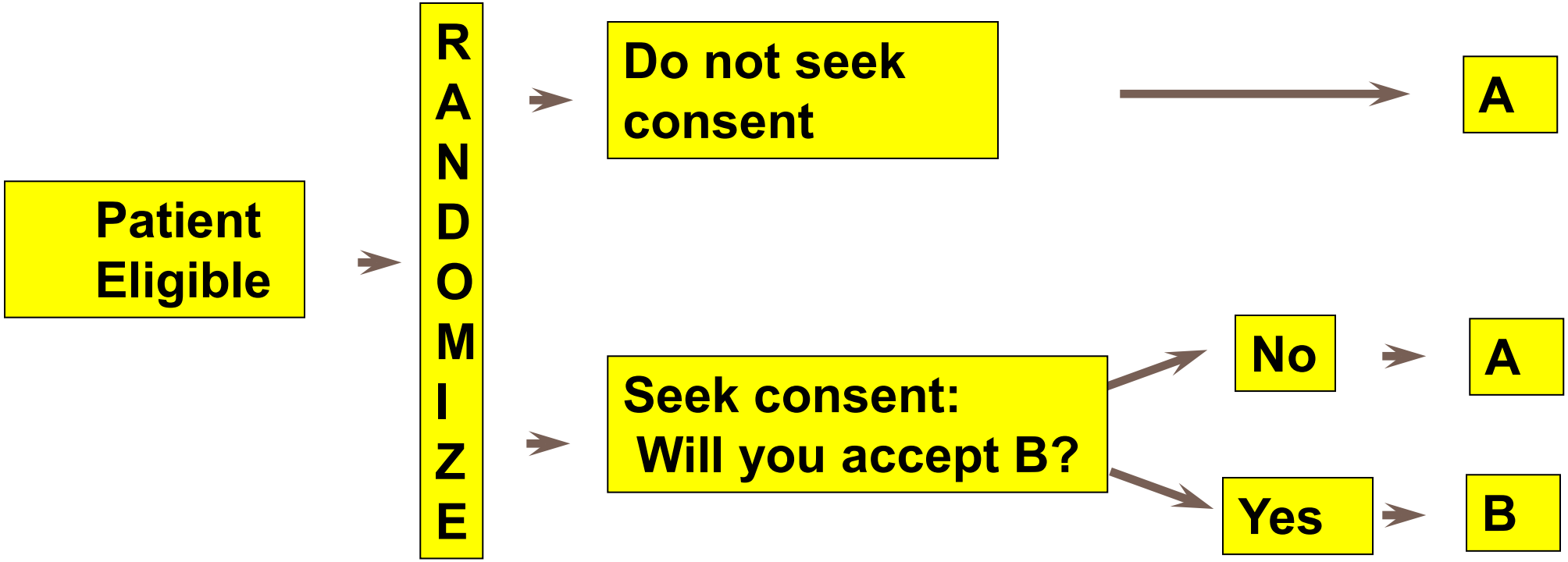
Marvin Zelen

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

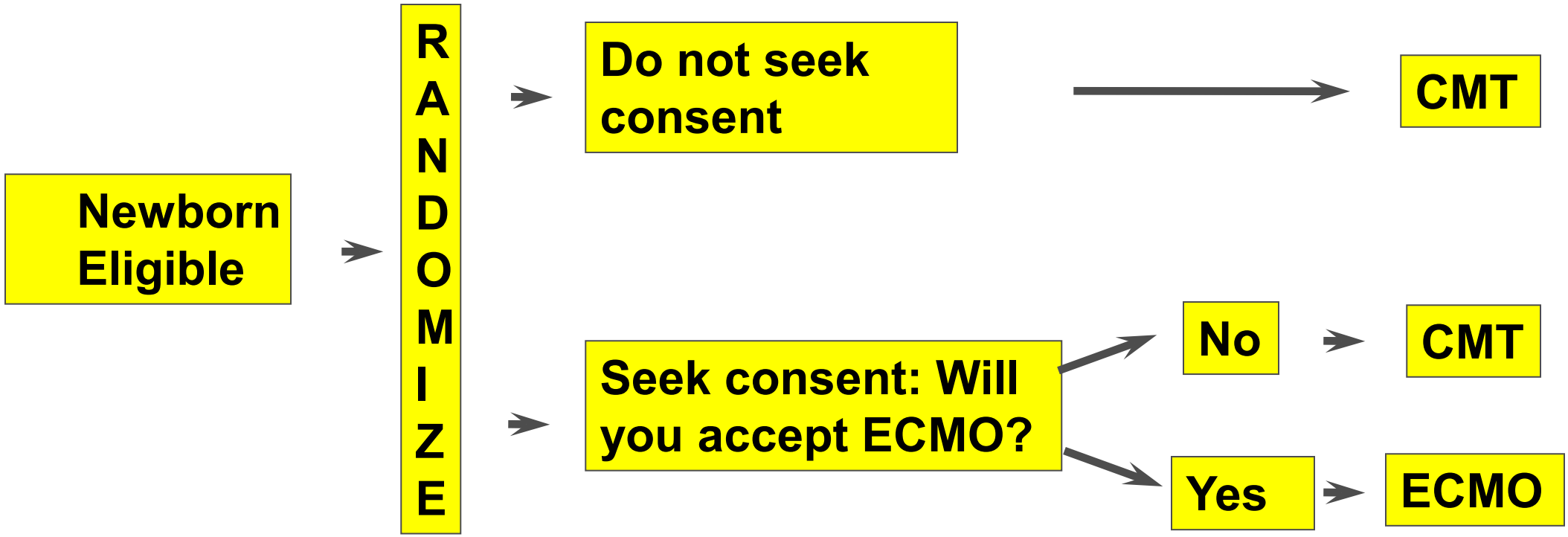
Department of Biostatistics

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?

Poll #3

- YES: I would have voted to approve the Zelen randomization scheme

- NO: I would not have voted to approve the Zelen randomization scheme

- Yes, I would have voted to approve the scheme, because:
  - The control babies were not really research subjects – their care was unchanged from what it would have been if the study had never been performed
  - It would have been cruel to tell parents that a treatment that might have saved their baby's life was available, but they couldn't have it.
- No, I would not have voted to approve the scheme, because:
  - It is always unethical to use data from patients without their informed consent
  - It is wrong to use data without the patient's knowledge
  - Intentionally withholding information from patients is deceptive, and deception is always wrong

ETHICS

A Harvard study on newborns draws fire

Doctors faulted for limiting life-saving treatment

By Richard A. Knox
Globe Staff

A Harvard University study involving mortally ill newborns is being challenged as unethical in a debate that raises important questions about how to do research on promising new therapies.

Critics around the country are raising two kinds of objections to the still-unpublished Harvard study.

The study was unethical in the first place, some charge, because it involved withholding from some infants with lung damage potentially life-saving therapy that earlier, less scientifically rigorous data had indicated was probably superior to conventional treatment.

Four infants with potentially reversible lung damage died on conventional respirator therapy before the researchers stopped assigning babies to that alternative.

Second, critics say it was improper for the researchers not to seek consent from parents of the infants assigned to conventional therapy. Parents of 10 conventionally treated infants were not told their children were part of a randomized trial in which some babies would get the promising but possibly risky new treatment.

Parents of nine babies randomly assigned to the new treatment, called extracorporeal membrane oxygenation, or ECMO, were asked for their consent. All ECMO-treated babies survived.

"The clear expectation was that more patients would die on conventional therapy," statistician Donald A. Berry of the University of Minnesota, one of the study's harshest critics, said in a telephone interview. "So the question is whether having an excess of deaths balances the worth of information gained. Since I believe such information is available without randomizing, my answer is a resounding no."

Prof. Richard M. Royall of the Johns Hopkins School of Public Health charged in an interview that once the Harvard researchers decided a randomized clinical trial was necessary, they had to "cut corners" on informed consent in order to proceed. "It's clear to me they did not ask consent because it would be hard to get a control group otherwise," Royall said. "Properly informed parents would say 'No thank you.' "

However, not all agree the study was unethical at the outset.

A second group, represented by Colin B. Begg of Memorial Sloan-Kettering Cancer Center in New York and Paul Meier of the University of Chicago, lambastes the Harvard researchers from the diametrically opposite side. They say the researchers were so preoccupied with ethical problems that they stopped assigning babies to conventional therapy too soon, before

NEWBORNS, Page 27

The ECMO Trial: Justifications for Randomized Consent

- Control patients were not really research subjects
- Families of control patients were really not be offered a choice
  - ”The decision was controversial among the team. We had several weeks of discussion over ‘autonomy’ versus ‘paternalism’” – Mike Epstein
  - “I’d prefer to call it ‘openness’ versus ‘compassion’ – Jim Ware
- 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/OHRP) reprimanded the hospital

  - The hospital IRB "made decisions that rightfully belonged to the parents. They really blew it."

    Charles McCarthy, Director of OPRR (OHRP)

  - 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

The New England Journal of Medicine

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.)

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?

Poll #4

- YES:
  Based on the data from the two trials and the ECMO database, I am convinced that ECMO is superior in the treatment of newborns with life-threatening PPHN

- NO:
  I am not convinved

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”