

# Understanding randomized controlled trials in neonatal-perinatal medicine

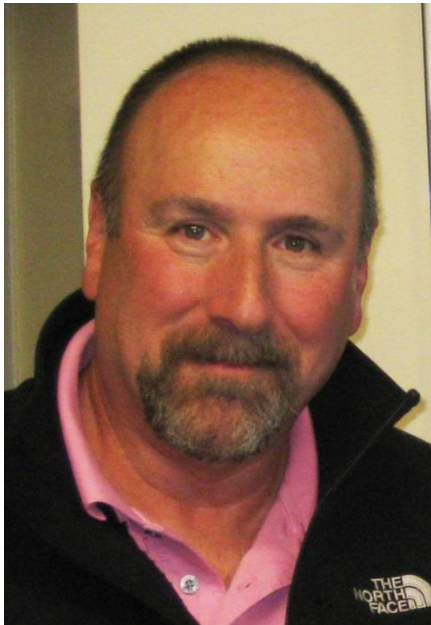
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Coordinating Editor, Cochrane Neonatal  
President, Vermont Oxford Network

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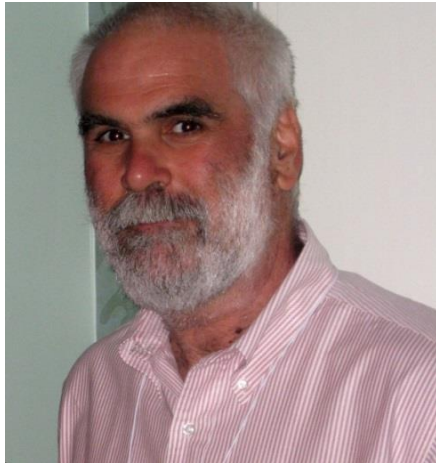


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Section on Neonatal-Perinatal Medicine

# **Understanding randomized controlled trials in neonatal-perinatal medicine**

Roger F. Soll, M.D. is the President  
of the Vermont Oxford Network  
and the Coordinating Editor  
of Cochrane Neonatal

No other relevant financial issues to disclose

## **Understanding randomized controlled trials in neonatal-perinatal medicine**

To develop an understanding of the strengths and weaknesses of evidence provided by randomized controlled trials to inform our practice of neonatal-perinatal medicine.



# Evidence Based Medicine



# The Evidence Hierarchy

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Systematic reviews

Meta analyses

RCT's

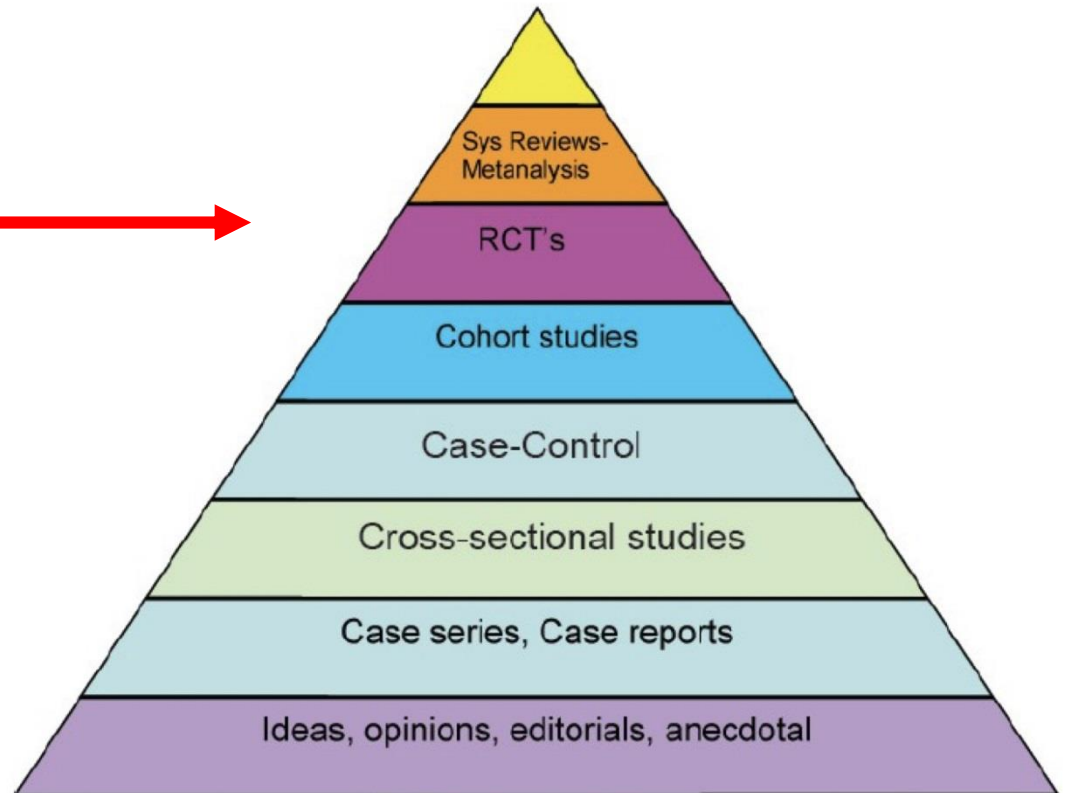


Non-controlled trials

Basic science trials

Observation studies

Case studies



What evidence should I use to inform my practice?

# Studies With Formal Controls

- Historical controls
- Case controls
- Non-randomized concurrent controls
- Randomized controls

# Historical Controls

Randomized (RCT) vs Historical (HCT) Controlled Trials

Six Therapies: 50 RCT's, 56 HCT's

- 79% Historical Controlled Trials supported intervention
- 20% Randomized Controlled Trials supported intervention

Sacks 1982

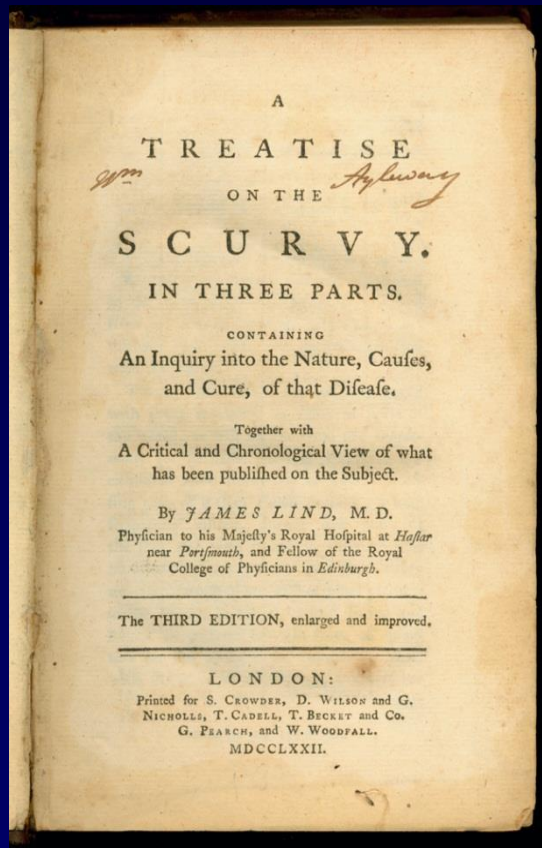
# The Problem with Historical Controls

- When substantial differences in outcome are noted between two different time frames, this may only reflect changes in other undocumented factors that have modified outcome
- Inferences based solely on studies that use historical controls tend to lead to conclusions that new forms of care are effective, when less biased comparisons suggest that they are not, or that the estimate is exaggerated



# Randomized Controlled Trials

## A bit of history.....



# Randomized Controlled Trials

## Scurvy

### Patient Population:

- “On the 20th of May 1747, I took twelve patients in the scurvy, on board the *Salisbury* at sea.
- Their cases were as similar as I could have them.
- They all in general had putrid gums, the spots and lassitude, with weakness of their knees.
- They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all...”

# Randomized Controlled Trials

## Intervention(s):



- cider
- elixir vitriol
- vinegar
- sea water
- oranges/lemons
- nutmeg

# Randomized Controlled Trials

Results:

“The consequence was that the most sudden and visible good effects were perceived from the use of the oranges and lemons; one of those who had taken them, being at the end of six days, fit for duty.”

James Lind 1753

# The Real World Results

Lind's therapeutic findings made little impact on medical opinion in Britain.

The year after publication of the treatise, the Navy's 'Sick and Hurt Board' rejected a proposal to provide sailors with supplies of fruit juice.

It was not used for 30 years...



# THE LANCET

The first “modern” randomized controlled trial...

## Streptomycin Treatment of Tuberculous Meningitis

Streptomycin in Tuberculosis Trials Committee, Medical  
Research Council

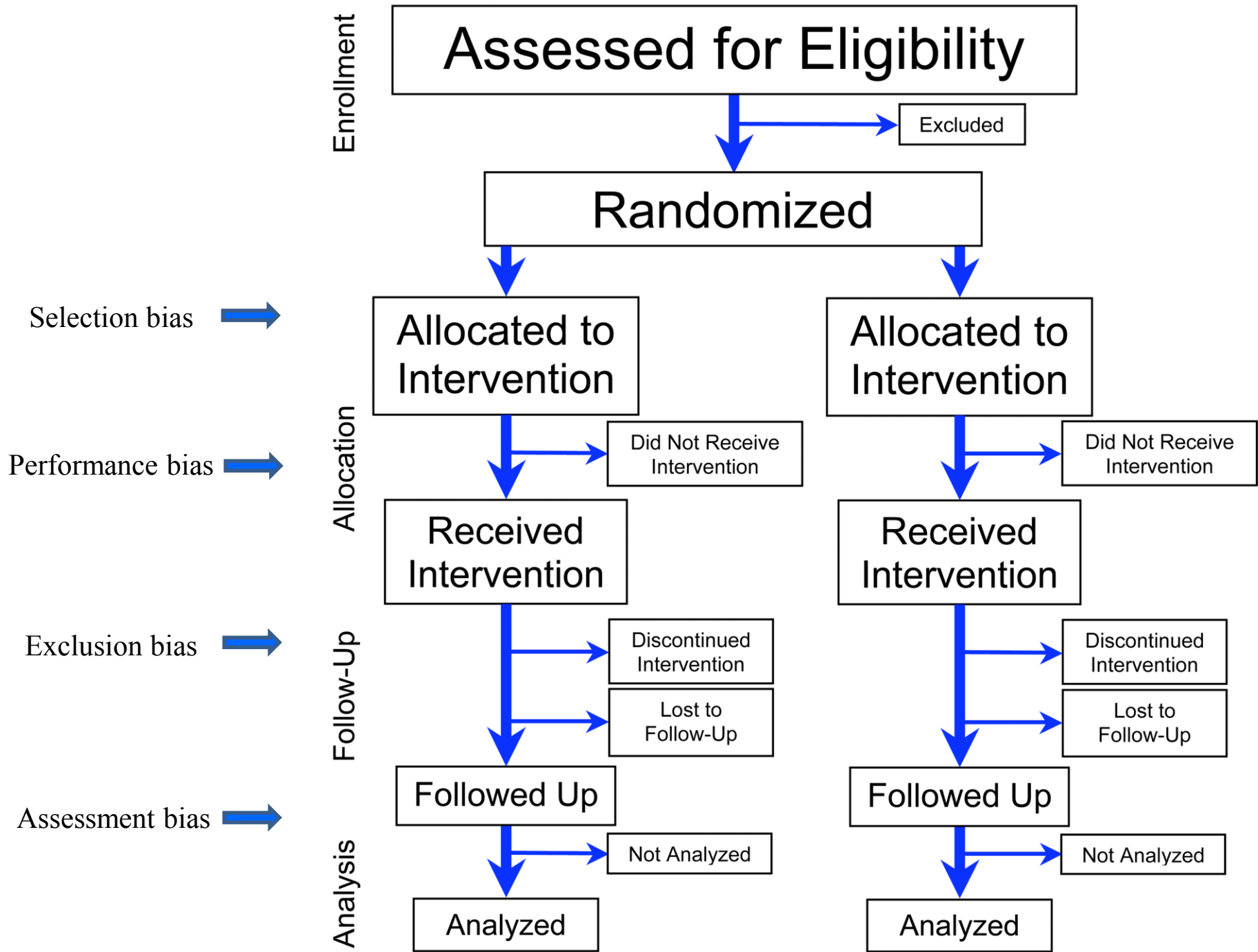
Lancet Volume 251, Issue 6503, P582-596, April 17, 1948

DOI:[https://doi.org/10.1016/S0140-6736\(48\)92003-0](https://doi.org/10.1016/S0140-6736(48)92003-0)

# Randomized Controlled Trials

## Need for randomization:

- likely to provide equivalent groups at study entry
- provides theoretical basis for statistical comparisons
- minimizes selection bias in treatment assignment



# Randomized Controlled Trials



Randomization...

# Randomized Controlled Trials: Randomization

Two critical processes involved in randomization of subjects:

1. A randomization procedure that generates an *unpredictable sequence of allocations*
2. Adequate "*allocation concealment*" (precautions taken to ensure that the group assignment of subjects are not revealed prior to allocating subjects to their respective groups).



# Randomized Controlled Trials: Selection Bias

Failure of allocation  
concealment



# Randomized Controlled Trials: Allocation Concealment

Some standard methods of ensuring allocation concealment include:

- sequentially numbered, opaque, sealed envelopes;
- sequentially numbered containers;
- pharmacy controlled randomization;
- central randomization.

# Conclusions Regarding Treatment Effect Based on Treatment Assignment

<u>Characteristic</u>	[-----Randomized-----]		Not <u>Randomized</u>
	<u>Cheating Difficult</u>	<u>Cheating Easy</u>	
Population Imbalance	14%	27%	58%
Significant Difference	9%	24%	58%
Favors Experimental Rx	30%	31%	56%

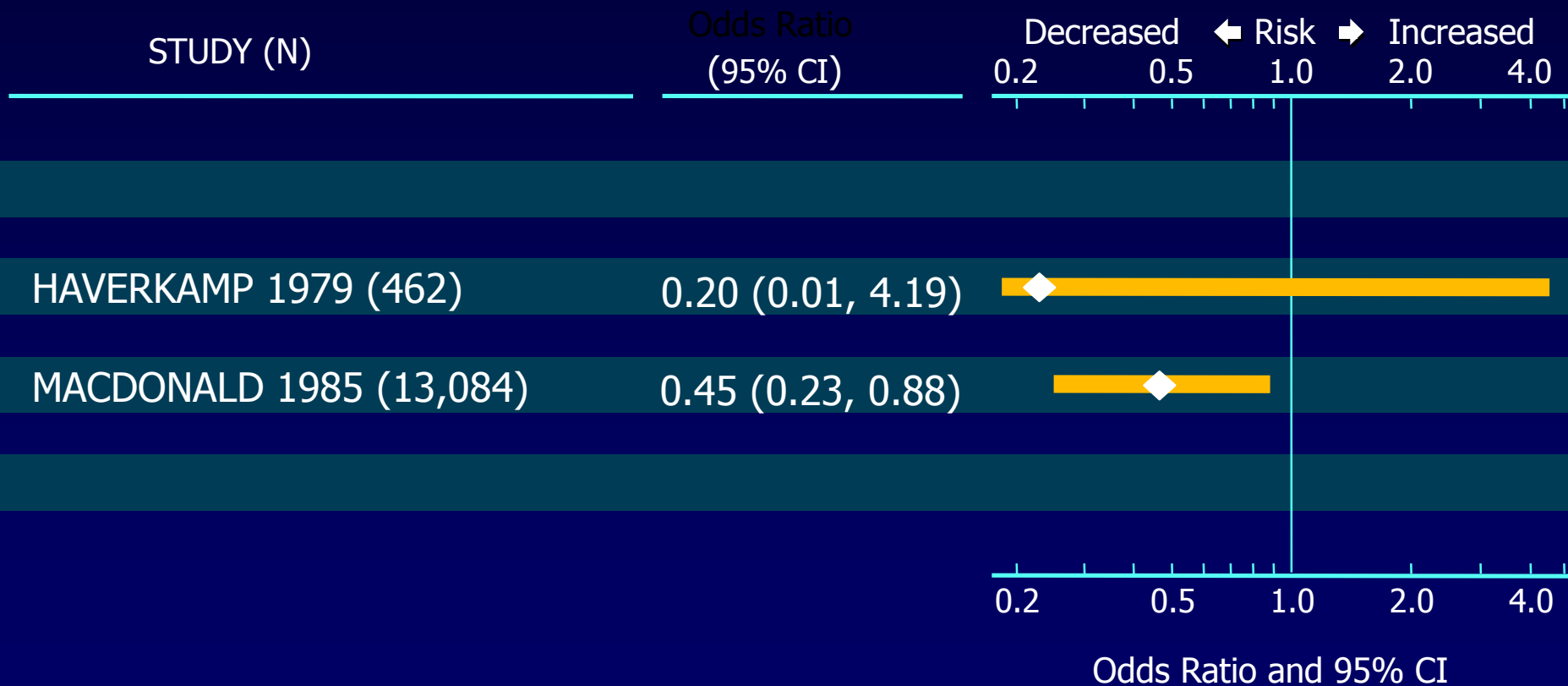
# Randomized Controlled Trials: Sample Size

The number of subjects assigned to control and treatment groups affects the “precision” of a randomized controlled trial.

If the true effect of the treatment is meaningful but small, enrolling a small number of subjects in either group may be insufficient for rejecting the null hypothesis.

# Small vs. Large Randomized Controlled Trials

## EFFECT OF INTENSIVE FETAL MONITORING ON NEONATAL SEIZURES





# Randomized Controlled Trials: Sample Size

The need for collaborative research: sample size requirements

<u>Effect size</u>	<u>Change in rate</u>	<u>Sample size</u>
10%	25% to 22.5%	9254
15%	25% to 21.25%	3574
20%	25% to 20%	2268
30%	25% to 17.5%	986

# Randomized Controlled Trials: Blinding

A randomized controlled trial may be “blinded” or “masked” by utilizing procedures that prevent study participants, caregivers, or outcome assessors from knowing which intervention was received.

Unlike allocation concealment, blinding is sometimes inappropriate or impossible to perform in a randomized controlled trial...

for example, if an RCT involves a treatment in which active participation of the subject is necessary (for example “skin to skin” care), participants cannot be blinded to the intervention.

# Randomized Controlled Trials: Analysis

The types of statistical methods used in RCTs depend on the characteristics of the data and include:

For dichotomous (binary) outcome data, logistic regression and other methods can be used.

For continuous outcome data, analysis of covariance tests the effects of predictor variables.

For time-to-event outcome data that may be censored, survival analysis (e.g., Kaplan–Meier estimators and Cox proportional hazards models) is appropriate.

# Randomized Controlled Trials: Analysis

Other considerations in the analysis of RCT data include:

- Whether an RCT should be stopped early due to interim results.
- The extent to which the groups can be analyzed exactly as they existed upon randomization ("intention-to-treat analysis").
- Whether subgroup analysis should be performed.

# Effect of Beta Blockers in the Treatment of Acute Myocardial Infarction

<u>Astrological Sign</u>	<u>Reduction in Odds of Death</u>	
Scorpio	- 48%	P < 0.04
All Other Astrological Signs	- 12%	NS
Overall	- 15%	P < 0.05

*Collins 1987*

# Randomized Controlled Trials

What's in a name...



# Randomized Controlled Trials: Study Design

The major categories of RCT study designs are:

- Classic Randomized Controlled Trials
- Crossover Randomized Controlled Trials
- Cluster Randomized Controlled Trials
- Factorial Randomized Controlled Trials



# Randomized Controlled Trials: Study Design

## Classic Randomized Controlled Trial

Each participant is randomly assigned to a group and all the participants in the group receive (or do not receive) the assigned intervention.



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# Caffeine Therapy for Apnea of Prematurity

Barbara Schmidt, M.D., Robin S. Roberts, M.Sc., Peter Davis, M.D.,  
Lex W. Doyle, M.D., Keith J. Barrington, M.D., Arne Ohlsson, M.D.,  
Alfonso Solimano, M.D., and Win Tin, M.D. for the Caffeine for Apnea of  
Prematurity Trial Group

N Engl J Med 2006; 354:2112-2121 May 18, 2006 DOI:  
10.1056/NEJMoa054065

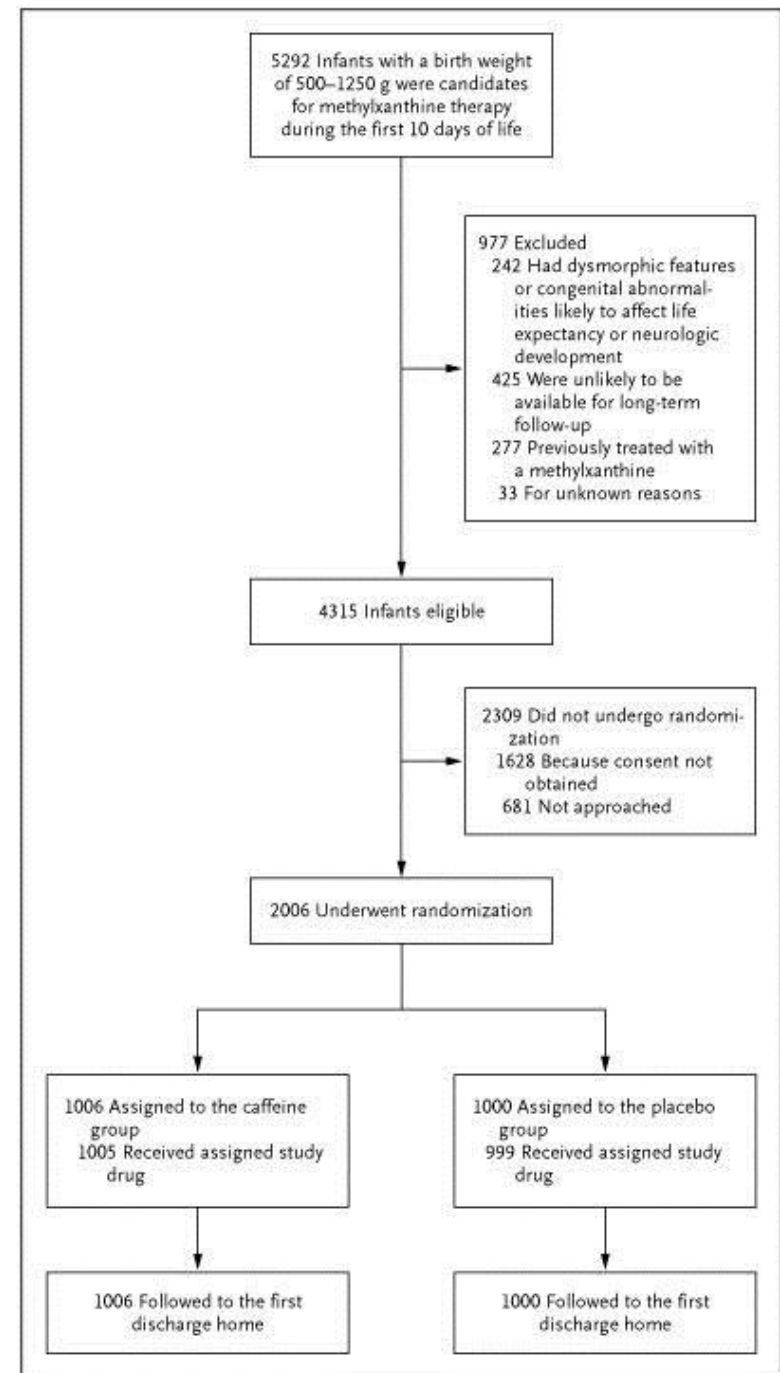


## Caffeine Therapy for Apnea of Prematurity

Infants with a birth weight of 500 to 1250 grams were eligible for enrollment if their clinicians considered them to be candidates for methylxanthine therapy during the first 10 days of life.

We documented the following reasons why clinicians intended to use methylxanthines: to prevent apnea, to treat apnea, or to facilitate the removal of an endotracheal tube.

Barbara Schmidt and colleagues.  
N Engl J Med 2006; 354:2112-2121 May 18, 2006





# Caffeine Therapy for Apnea of Prematurity

## Randomization

A computer-generated randomization scheme was used to assign the infants to treatment groups in a 1:1 ratio.

Randomization was stratified according to the study center and balanced in random blocks of two or four patients.

A designated pharmacist at each center received a binder containing the prespecified sequence of treatment-group assignments from a statistician at the coordinating center who was not otherwise involved in the trial. Access to the binder was restricted to selected pharmacy personnel.

The pharmacy study logs were retrieved after the completion of recruitment to ensure that all randomly assigned infants were included in the analysis.



# Caffeine

## The CAP Trial: Schmidt and coworkers

Outcome	Caffeine	Control	Adjusted OR (95% CI)
Initial Report			
BPD	36.3%	46.9%	0.64 (0.52 to 0.78)
Death	5.2%	5.5%	0.96 (0.64 to 1.44)
2 Year Report			
CP	4.4%	7.3%	0.59 (0.39 to 0.89)
Death or Disability	40.2%	46.2%	0.79 (0.65 to 0.92)
5 Year Report			
Death or Disability	21.1%	24.8%	0.86 (0.67 to 1.09)

# Randomized Controlled Trials: Study Design

## Crossover Randomized Controlled Trial

Subjects are randomly allocated to study arms where each arm consists of a sequence of two or more treatments given consecutively.

The simplest model is the AB/BA study. Subjects allocated to the AB study arm receive treatment A first, followed by treatment B, and vice versa in the BA arm.

Crossover trials allow the response of a subject to treatment A to be contrasted with the same subject's response to treatment B.

Cross-over trial of treatment for bradycardia attributed to gastroesophageal reflux in preterm infants.

A randomized, controlled, masked cross-over study was performed. Each infant was randomly assigned to 1 of 2 study groups.

Study group assignment (order of medication and placebo administration) was determined by blocked random number generation.

A research pharmacist assigned the study group for each patient at the time of enrollment. Investigators, clinicians, and parents were all blinded to the group assignment during the study period.



Cross-over trial of treatment for bradycardia attributed to gastroesophageal reflux in preterm infants.

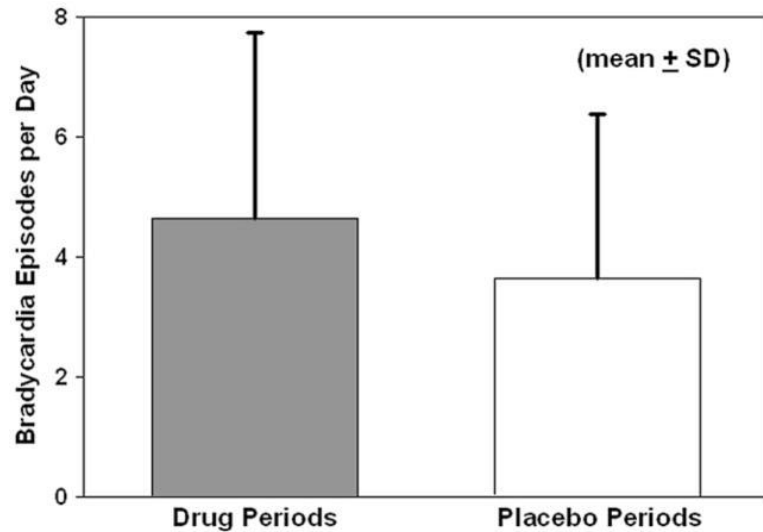
The “drug first” group received a 3-day course of anti-reflux medications followed by a 7-day course of placebo and then a 4-day course of anti-reflux medications.

The “placebo first” group received a 3-day course of placebo followed by a 7-day course of anti-reflux medications and then a 4-day course of placebo.

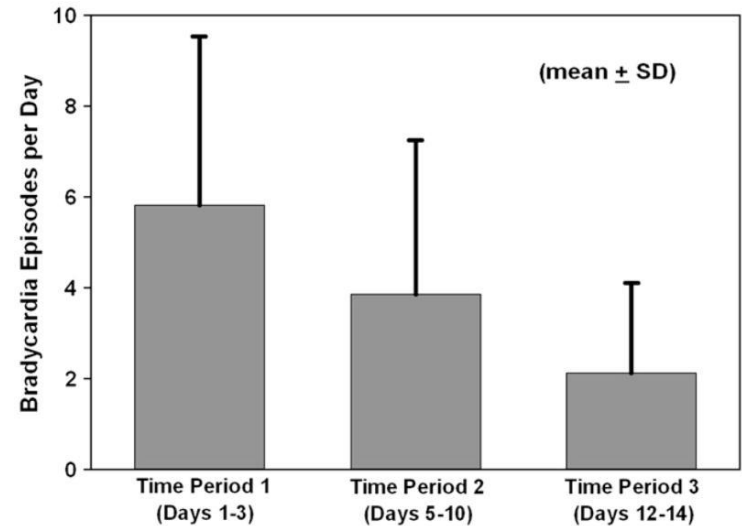
To allow for a period of washout between the drug regimens, outcomes were not assessed for the initial 24 hours of the second and third time periods.

Wheatley E, Kennedy KA. J Pediatr. 2009 Oct;155(4):516-21.  
doi: 10.1016/j.jpeds.2009.03.044. Epub 2009 Jun 21.

Cross-over trial of treatment for bradycardia attributed to gastroesophageal reflux in preterm infants.



Bradycardia episodes per day for all study participants by treatment period.



Bradycardia episodes per day for all study participants by time period.

# Randomized Controlled Trials: Study Design

## Cluster Randomized Controlled Trials

Pre-existing groups of participants are randomly selected to receive (or not receive) an intervention.

Unit of randomization:

- Clinics
- Hospitals
- Worksites
- Entire communities

# Randomized Controlled Trials: Study Design

## Cluster Randomized Controlled Trials

### Advantages:

- Increased administrative efficiency
- Decreased risk of experimental contamination
- Improved study subject compliance
- Allows for study of interventions that effect processes or entire group/institution

### Disadvantages:

- Substantially reduces statistical efficiency  
variance inflation due to clustering or “design effect”

# Randomized Controlled Trials: Study Design

## Cluster Randomized Controlled Trials

### Sample size

Members of clusters cannot be treated as independent, and the effect of this on outcomes leads to a need to increase the sample size

This problem can also be described as follows:

“For any given sample size, the correlation between cluster members will reduce the overall power of the study”

# Randomized Controlled Trials: Study Design

## Cluster Randomized Controlled Trials

### Concerns:

Ethical issues regarding trial participation

### Consent:

- Need for institutional review board approval
- Need for patient information
- Opportunity to withdraw



# Collaborative quality improvement to promote evidence based surfactant for preterm infants: a cluster randomised trial

Jeffrey D Horbar, Joseph H Carpenter, Jeffrey Buzas, Roger F Soll, Gautham Suresh, Michael B Bracken, Laura C Leviton, Paul E Plsek, John C Sinclair.

BMJ 2004;329:1004 (30 October), doi:10.1136/bmj.329.7473.1004



Assessed for eligibility (300 neonatal intensive care units)

Excluded:

Already participating in quality improvement collaboratives (n=78)

More than half of very low birthweight infants born outside hospital and transferred after birth (n=6)

Already treating more than half of infants with surfactant within 15 minutes of birth (n=29)

Randomised (n=114)

Intervention (n=57)  
(1 unit did not attend  
intervention workshop)

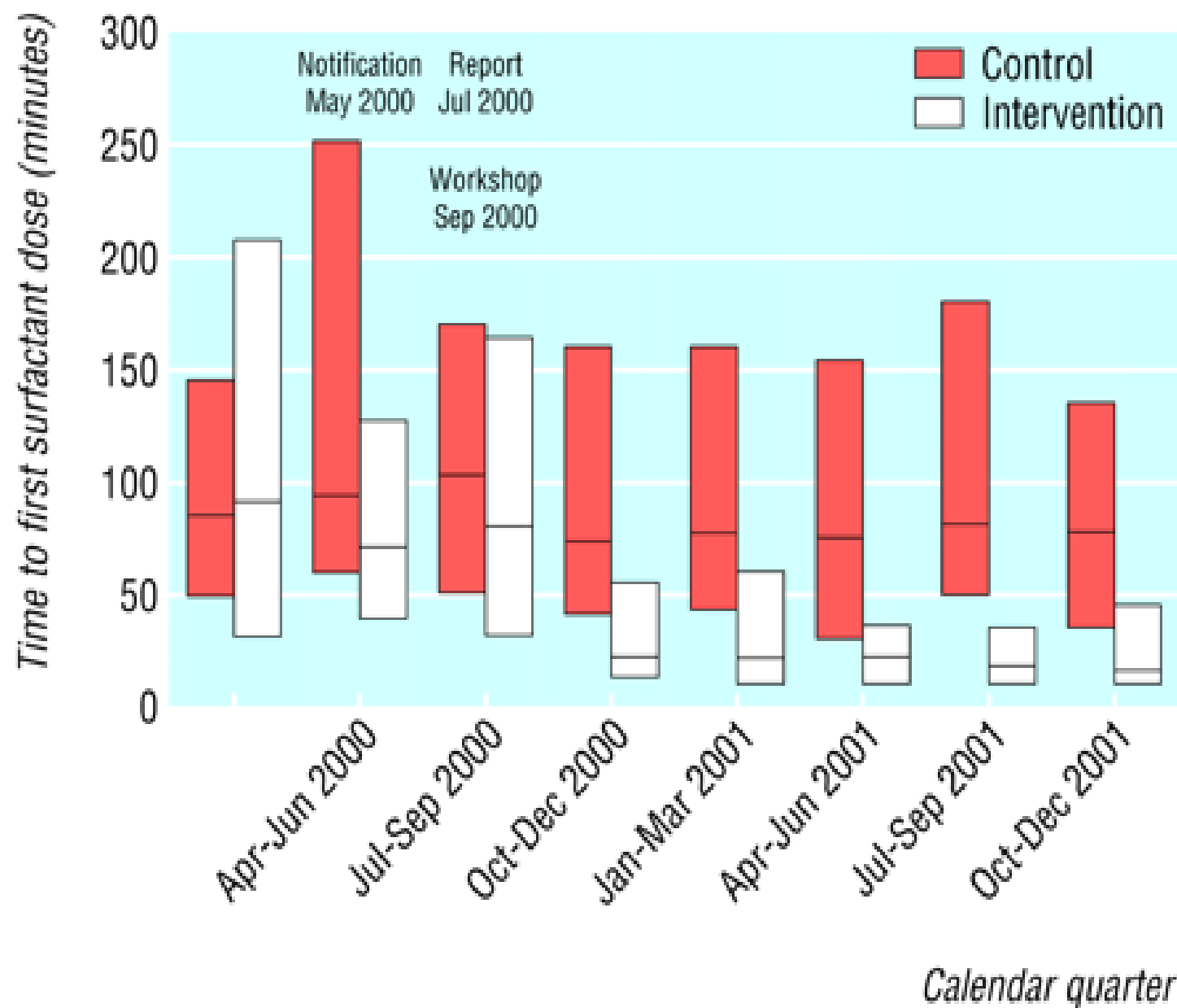
Control (n=57)

Baseline assessment  
Median No of eligible infants/  
unit = 47 (interquartile range  
33-72)  
Total No of infants = 3332

Baseline assessment  
Median No of eligible infants/  
unit = 48 (interquartile range  
26-64)  
Total No of infants = 2850

Follow up analysis (n=57)  
Median No of eligible infants/  
unit = 40 (interquartile range  
33-64)  
Total No of infants = 3313

Follow up analysis (n=57)  
Median No of eligible infants/  
unit = 36 (interquartile range  
22-56)  
Total No of infants = 2726



# Randomized Controlled Trials: Study Design

## Factorial Randomized Controlled Trials

Each participant is randomly assigned to a group that receives a particular *combination* of interventions or non-interventions

(e.g., group 1 receives vitamin X and vitamin Y, group 2 receives vitamin X and placebo Y, group 3 receives placebo X and vitamin Y, and group 4 receives placebo X and placebo Y).



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

- Early CPAP versus Surfactant in Extremely Preterm Infants. N Engl J Med 2010; 362:1970-1979. DOI: 10.1056/NEJMoa0911783
- Target Ranges of Oxygen Saturation in Extremely Preterm Infants. N Engl J Med 2010; 362:1959-1969. DOI: 10.1056/NEJMoa0911781

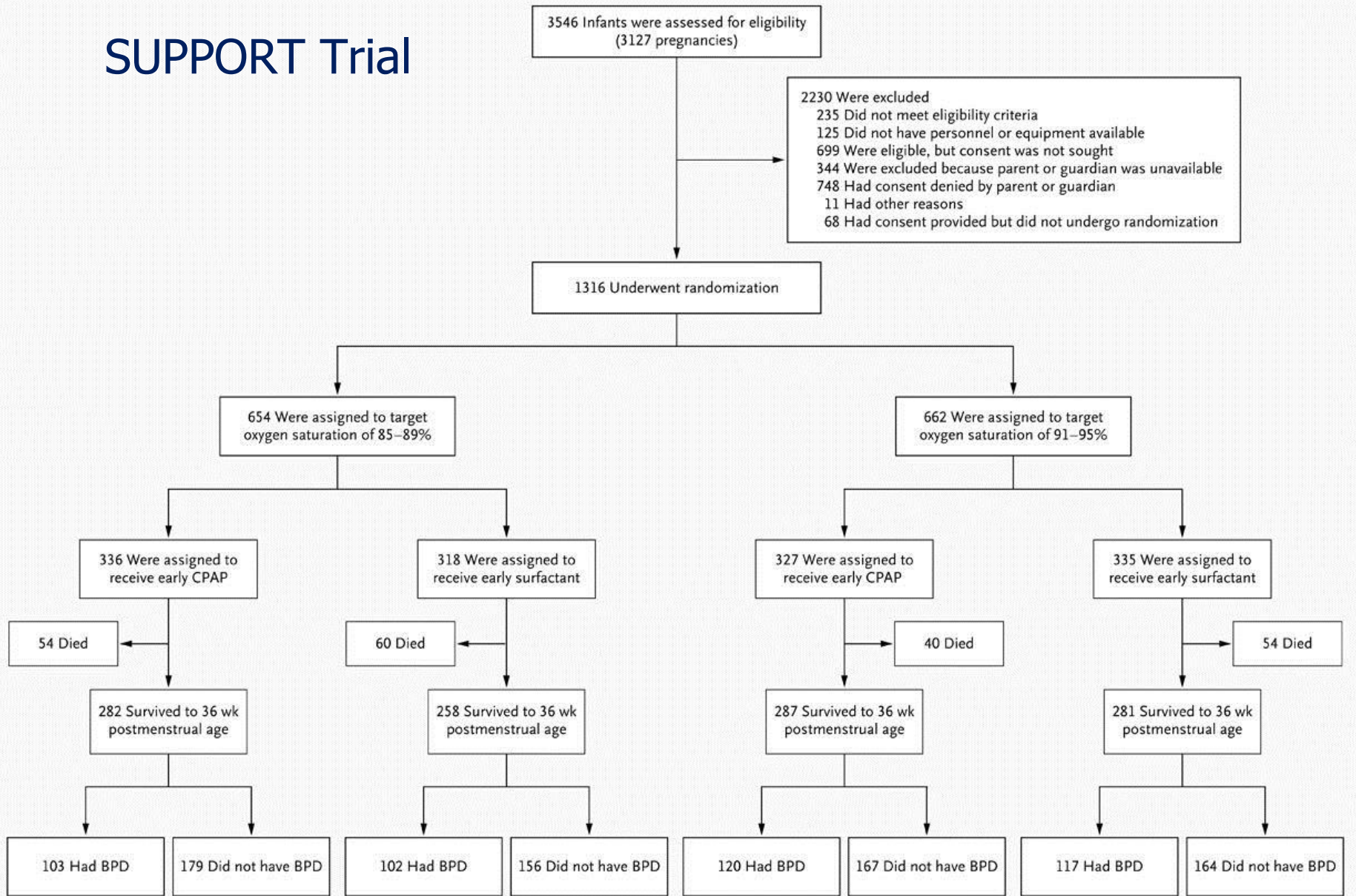
# The SUPPORT Trial(s)

## STUDY DESIGN

In this randomized, multicenter trial, we compared a strategy of treatment with CPAP and protocol-driven limited ventilation begun in the delivery room and continued in the neonatal intensive care unit (NICU) with a strategy of early intratracheal administration of surfactant (within 1 hour after birth) followed by a conventional ventilation strategy.

In a 2-by-2 factorial design, infants were also randomly assigned to one of two target ranges of oxygen saturation (85 to 89% or 91 to 95%) until the infant was 36 weeks of age or no longer received ventilatory support or supplemental oxygen.

# SUPPORT Trial



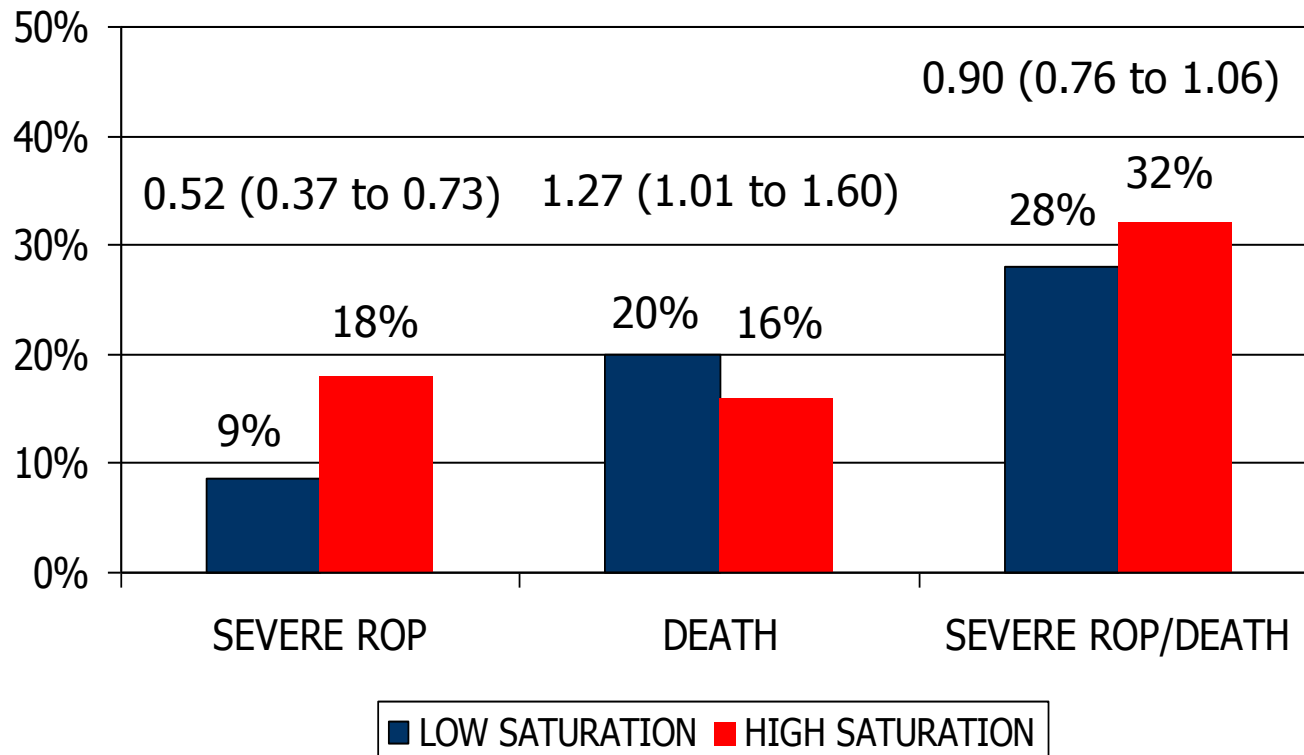
# Early CPAP vs. Surfactant in Extremely Preterm Infants

## BPD or death at 36 weeks' postmenstrual age

Outcome	CPAP (N=663)	Surfactant (N=653)	Relative Risk with CPAP (95% CI)	Difference in Means (95% CI)	Adjusted P Value
BPD or death by 36 wk of postmenstrual age — no. (%)					
Physiological definition of BPD†	317 (47.8)	333 (51.0)	0.95 (0.85 to 1.05)		0.30
BPD defined by need for supplemental oxygen	323 (48.7)	353 (54.1)	0.91 (0.83 to 1.01)		0.07
BPD by 36 wk of postmenstrual age — no./ total no. (%)					
Physiological definition of BPD†	223/569 (39.2)	219/539 (40.6)	0.99 (0.87 to 1.14)		0.92
BPD defined by need for supplemental oxygen	229/569 (40.2)	239/539 (44.3)	0.94 (0.82 to 1.06)		0.32
Death by 36 wk of postmenstrual age — no. (%)	94 (14.2)	114 (17.5)	0.81 (0.63 to 1.03)		0.09

# Oxygen Saturation Targets and Outcomes in Extremely Preterm Infants

## Outcome of Infants in the SUPPORT Trial



SUPPORT NEJM 2010



# Randomized Controlled Trials:

## Other “terminology” used to describe trial design

RCTs can be classified as "explanatory" or "pragmatic."

- **Explanatory RCTs** test the *efficacy* of an intervention in a research setting with highly selected participants and under highly controlled conditions.
- **Pragmatic RCTs** test the *effectiveness* of an intervention in everyday practice with relatively unselected participants and under flexible conditions.

# Caffeine: Who should I treat?

## Effect on Bronchopulmonary Dysplasia

Indication	Caffeine	Control	Odds Ratio (95% CI)
Apnea treatment	107/413	141/392	0.62 [0.46, 0.84]
Apnea prophylaxis	84/226	94/211	0.74 [0.50, 1.08]
Pre-extubation	158/322	212/350	0.63 [0.46, 0.85]
OVERALL			0.65 [0.54, 0.78]

Peter G. Davis and colleagues. Caffeine for Apnea of Prematurity Trial: Benefits May Vary in Subgroups. The Journal of Pediatrics , Volume 156 , Issue 3 , 382 - 387.e3

# Randomized Controlled Trials: Study Design

## Superiority vs. noninferiority vs. equivalence

- Most RCTs are superiority trials, in which one intervention is hypothesized to be superior to another in a statistically significant way.
- Some RCTs are noninferiority trials “to determine whether a new treatment is no worse than a reference treatment.”
- Other RCTs are equivalence trials in which the hypothesis is that two interventions are indistinguishable from each other.



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## Noninferiority Trials

# Nasal High-Flow Therapy for Primary Respiratory Support in Preterm Infants

Calum T. Roberts, M.B., Ch.B., Louise S. Owen, M.D., Brett J. Manley, Ph.D., Dag H. Frøisland, Ph.D., Susan M. Donath, M.A., Kim M. Dalziel, Ph.D., Margo A. Pritchard, Ph.D.,  
David W. Cartwright, M.B., B.S., Clare L. Collins, M.D.,  
Atul Malhotra, M.D., and Peter G. Davis, M.D. for the HIPSTER Trial  
Investigators

N Engl J Med 2016; 375:1142-1151 DOI: 10.1056/NEJMoa1603694



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## Nasal High-Flow Therapy for Primary Respiratory Support in Preterm Infants

### METHODS

International, multicenter, randomized, noninferiority trial

564 preterm infants (gestational age,  $\geq 28$  weeks 0 days) with early respiratory distress who had not received surfactant replacement were assigned to treatment with either nasal high-flow therapy or nasal CPAP.

The primary outcome was treatment failure within 72 hours after randomization

Noninferiority was determined by calculating the absolute difference in the risk of the primary outcome; the chosen margin of noninferiority was 10 percentage points. Infants in whom high-flow therapy failed could receive rescue CPAP; infants in whom CPAP failed were intubated and mechanically ventilated.

Roberts and colleagues. N Engl J Med 2016; 375:1142-1151 DOI: 10.1056/NEJMoa1603694



## Nasal High-Flow Therapy for Primary Respiratory Support in Preterm Infants

### Treatment Failure within 72 hours

Outcome	High-Flow Group (N = 278) <i>no./total no. (%)</i>	CPAP Group (N = 286) <i>no./total no. (%)</i>	Risk Difference (95% CI)* <i>percentage points</i>	P Value
<b>Primary intention-to-treat analysis</b>				
Treatment failure within 72 hr	71/278 (25.5)	38/286 (13.3)	12.3 (5.8 to 18.7)	<0.001
Gestational age <32 wk	46/140 (32.9)	27/149 (18.1)	14.7 (4.8 to 24.7)	0.004
Gestational age ≥32 wk	25/138 (18.1)	11/137 (8.0)	10.1 (2.2 to 18.0)	0.01
Intubation within 72 hr	43/278 (15.5)	33/286 (11.5)	3.9 (−1.7 to 9.6)	0.17
Gestational age <32 wk	30/140 (21.4)	24/149 (16.1)	5.3 (−3.7 to 14.3)	0.25
Gestational age ≥32 wk	13/138 (9.4)	9/137 (6.6)	2.9 (−3.5 to 9.3)	0.38

# Randomized Controlled Trials: Ethics

The ethics of clinical research requires equipoise--a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial.

The current understanding of this requirement, which entails that the investigator have “no treatment preference” throughout the course of the trial can represent a nearly insurmountable obstacle to trial conduct, particularly when conducting trials of available therapies.

One interpretation of “clinical equipoise” is that the requirement is satisfied if there is genuine uncertainty within the expert medical community--not necessarily on the part of the individual investigator--about the preferred treatment.

Freedman B (1987). "Equipoise and the ethics of clinical research". N Engl J Med. 317 (3): 141–5. doi:10.1056/NEJM198707163170304. PMID 3600702.

# Randomized Controlled Trials: Ethics

Individual patient consent is the cornerstone of ethics in clinical trials.

Although subjects almost always provide informed consent for their participation in a randomized controlled trial, many studies have documented that RCT subjects may believe that they are certain to receive treatment that is best for them personally; that is, they do not understand the difference between research and routine clinical treatment.

Further research is necessary to determine the prevalence of and ways to address this "therapeutic misconception".

Henderson GE, Churchill LR, Davis AM, Easter MM, Grady C, Joffe S, Kass N, King NM, Lidz CW, Miller FG, Nelson DK, Peppercorn J, Rothschild BB, Sankar P, Wilfond BS, Zimmer CR (2007). "Clinical trials and medical care: defining the therapeutic misconception". PLoS Med. 4 (11): e324.



# Randomized Controlled Trials: Trial Registration

## Trials Registration

In 2004, the International Committee of Medical Journal Editors (ICMJE) announced that all trials starting enrolment after July 1, 2005 must be registered prior to consideration for publication in one of the 12 member journals of the committee.

De Angelis C, Drazen JM, Frizelle FA, et al. (September 2004). "Clinical trial registration: a statement from the International Committee of Medical Journal Editors". *The New England Journal of Medicine*. 351 (12): 1250–1. doi:10.1056/NEJMe048225. PMID 15356289.

# Randomized Controlled Trials: Data and Safety Monitoring

The Data and Safety Monitoring Board (DSMB) regularly reviews accumulating data from the clinical trial to ensure the continuing safety of current participants and those yet to be enrolled.

The DSMB may review efficacy data at pre-defined interim points to assess whether there's overwhelming evidence of efficacy or the lack thereof, such that the clinical equipoise at the beginning of the trial is no longer justified.

DSMB has the additional responsibilities to advise the sponsor regarding the continuing validity and scientific merit of the trial.

Members of the DSMB typically include clinical trial experts, including physicians with the appropriate specialty, at least one biostatistician and possibly person(s) from other disciplines, such as biomedical ethics, basic science/pharmacology or law.

# Limitations of Randomized Controlled Trials

- Evaluation of preventive therapy
- Multiple therapeutic candidates
- Minor changes in therapeutic agents
- “Instability” of available therapy
- Long-term adverse effects of therapy
- Evaluation of etiologic agents
- Evaluation of diagnostic technology
- Evaluation of process or structure



## Hazardous Journeys

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Smith Gordon C S, Pell Jill P. BMJ 2003; 327  
doi: <https://doi.org/10.1136/bmj.327.7429.1459>





# Guest Discussants



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Get your facts first,  
then you can distort them as you please

Mark Twain

