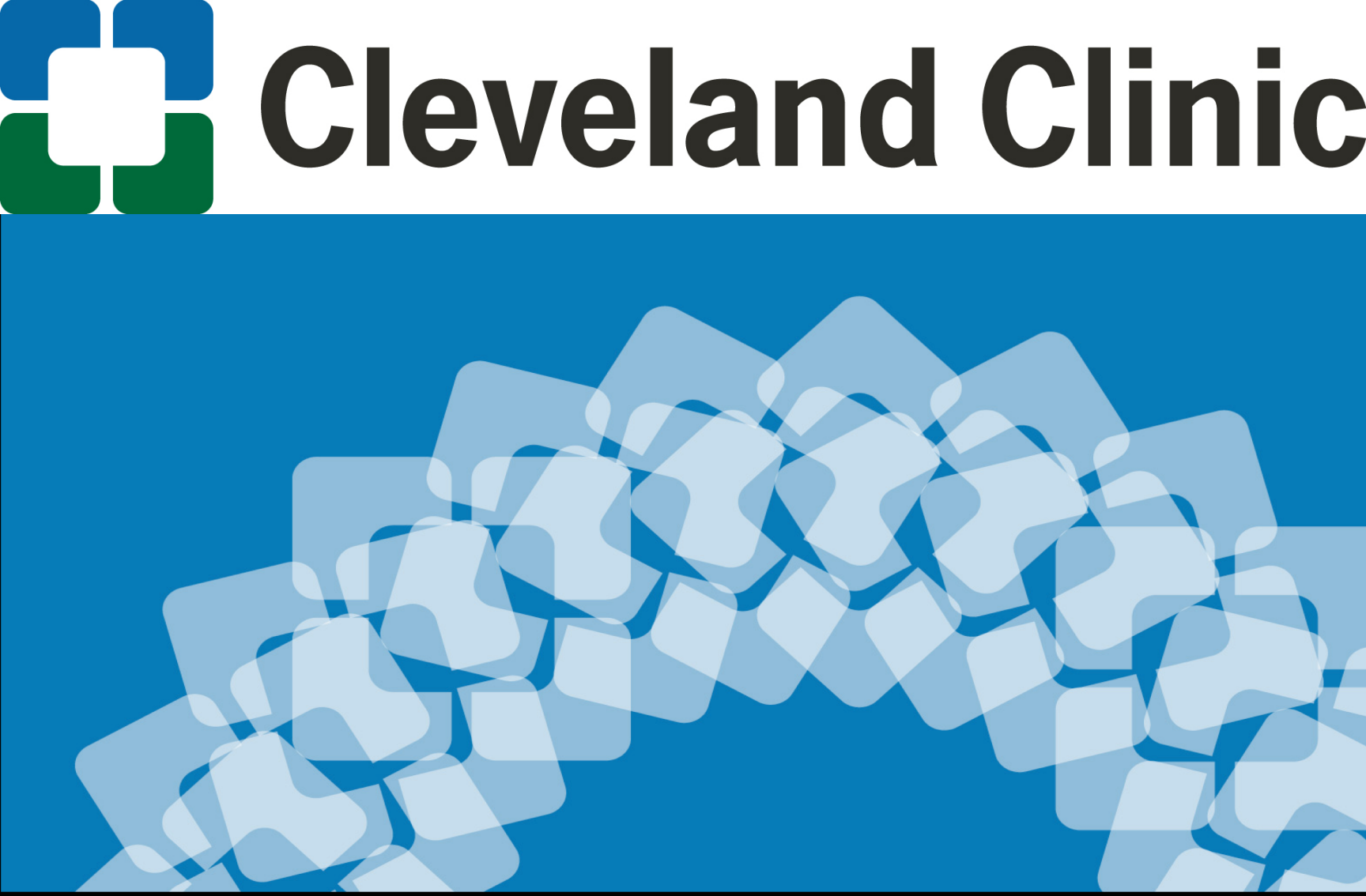
Cleveland Clinic
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# ICU Sedation Trials

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# Major Trends in Trials

Large size
- Robust results that guide clinical care

Composite outcomes
- Can reduce sample size
- Better characterize systemic treatment effect

Factorial randomization
- Two for one! Characterize interactions

Adoptive designs
- Incorporate new information

Novel designs with altered or waived consent

# Trial Size Matters

Consider two identical trials of treatment for infarction

- N=200 *versus n=8,000*

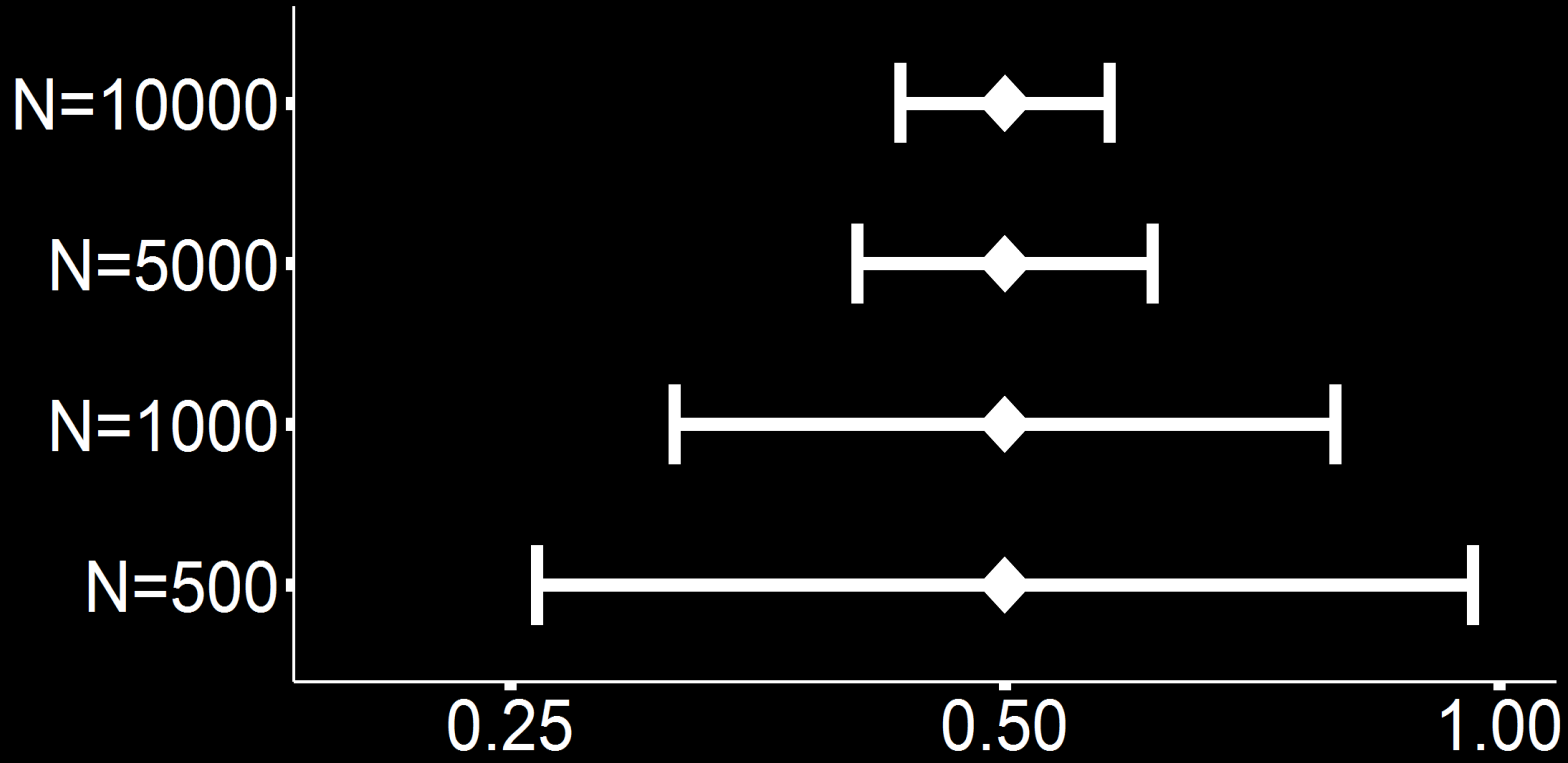
| Trial | N | Treatment Infarctions | Placebo Infarctions | RR | P |
|---|---|---|---|---|---|
| A | 200 | 1 | 9 | 0.11 | 0.02 |
| B | 4,000 | 200 | 250 | 0.80 | 0.02 |

Which result do you believe? Which is biologically plausible?

What happens if you add two events to each Rx group?

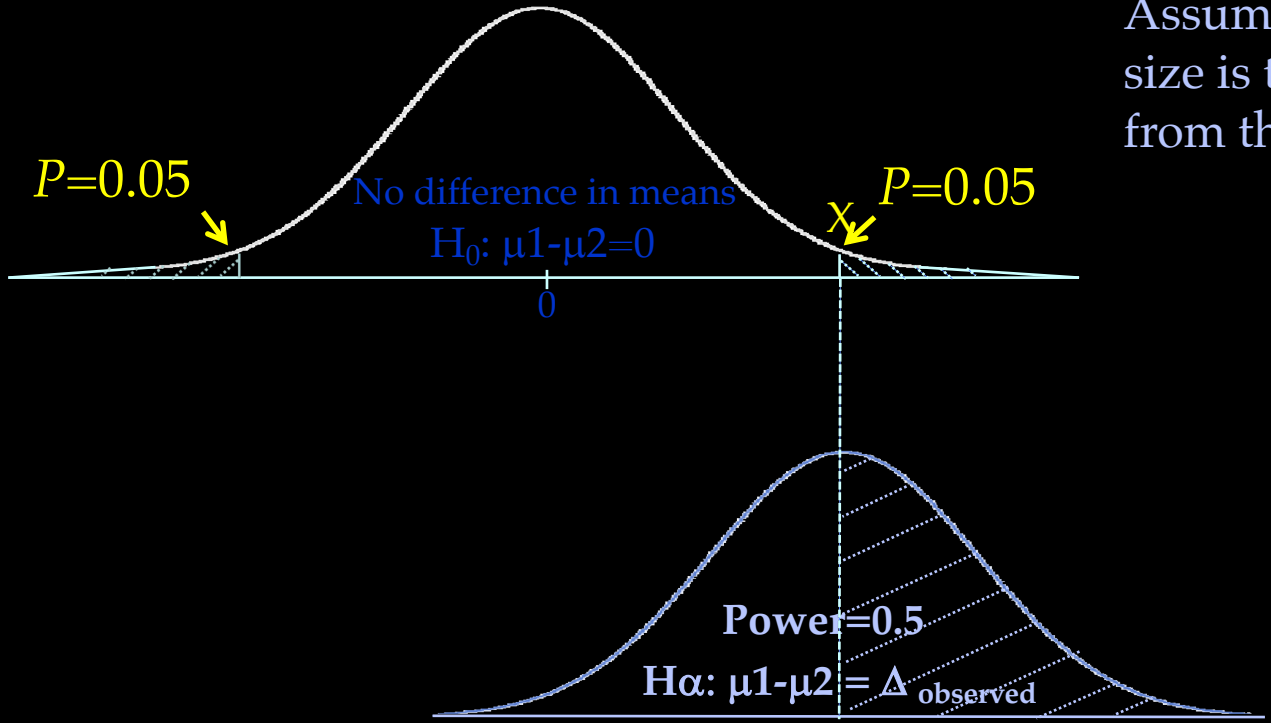
- Study A p=0.13
- Study B p=0.02

# Sample Size and 95% Confidence Intervals



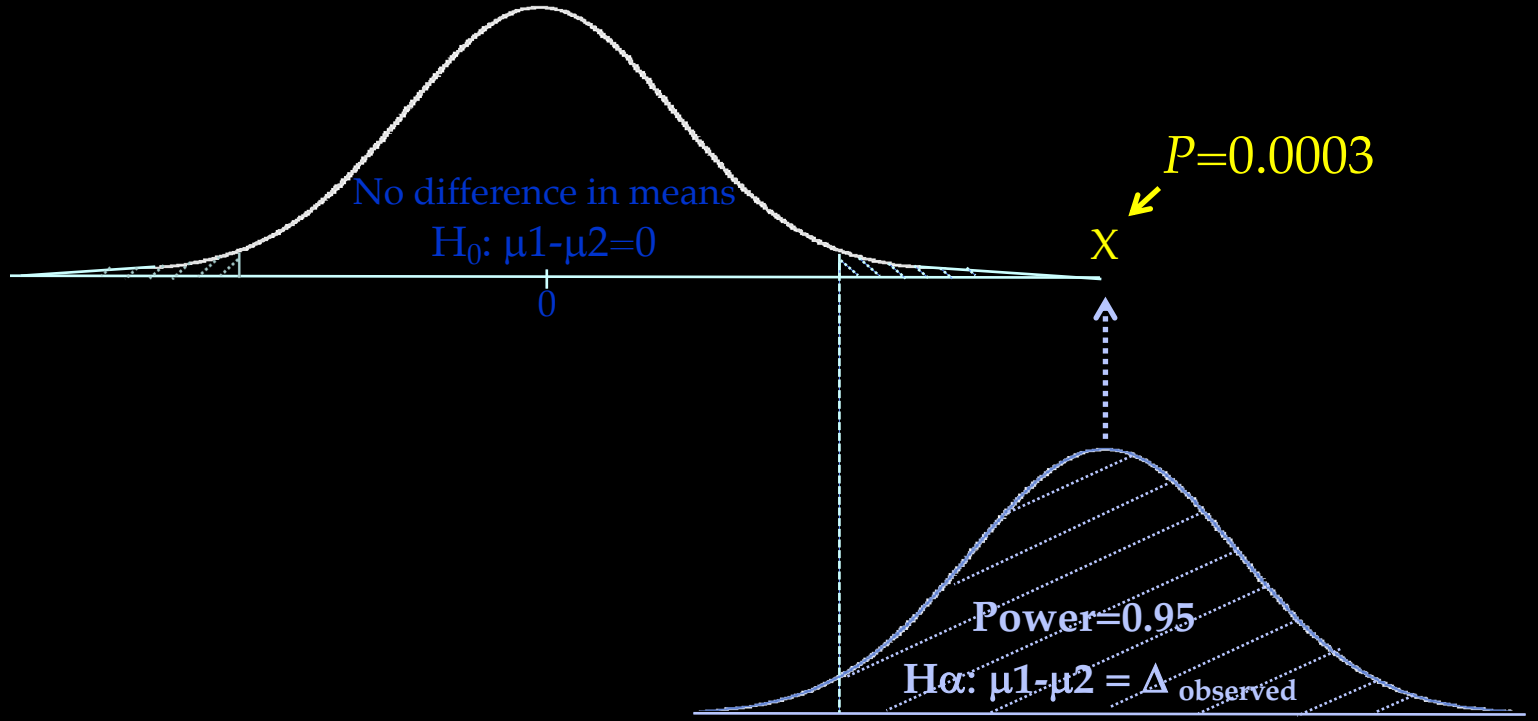

Intervention reduces risk from 10% to 5%

# Replication of Studies




Assume the true effect size is the estimate from the first study.

# Replication of Studies



# Composite Outcomes

Any of ≥2 component outcomes, for example:

- Cardiac death, myocardial infarction, or non-fatal arrest
- Wound infection, anastomotic leak, abscess, or sepsis

Usually used for uncommon dichotomous outcomes

Usually permits a smaller sample size

- Power *reduced* by including uninfluenced components

May better characterize wide-ranging effects

- Diabetic control and amputation, blindness, ESRD, and MI

Beware of heterogeneous results

# Composite Considerations

"Collapsed composite" (one or more) most common

Incidence of each should be comparable

- Otherwise common outcome(s) dominate composite

Severity of each should be comparable

- Unreasonable to lump minor and major events
- Death often included to prevent survivor bias

Alternatives without these restrictions include

- Number of positive components
- Average relative effect
- Weighted components

# Factorial Randomization

## Advantages

- More efficient than separate trials
- Can test for interactions

## Disadvantages

- Complexity, potential for reduced compliance
- Reduces fraction of eligible subjects and enrollment
- Rarely powered for interactions
  - But interactions influence sample size requirements

# Marginal Effects

Simultaneously test 2 or more interventions

- POISE-2: Devereaux NEJM 2014

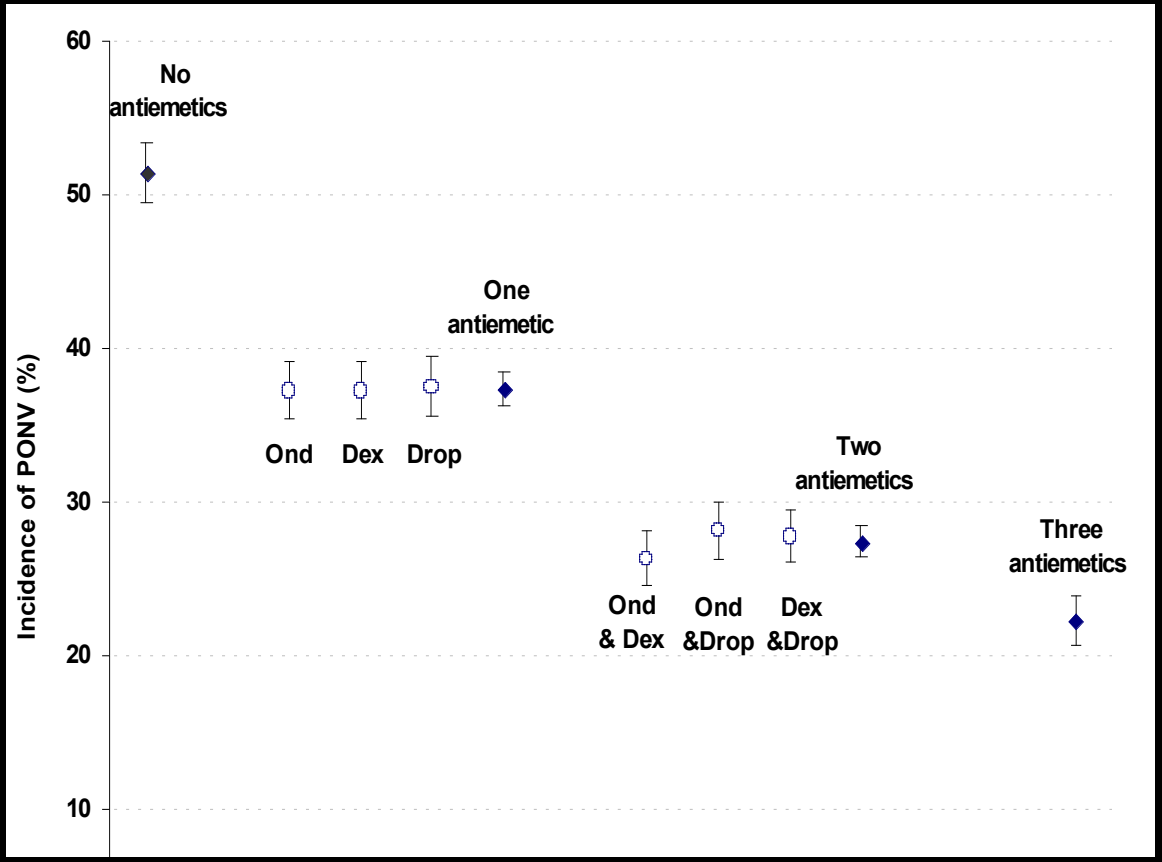
Clonidine *vs*. Placebo

| | |
|---|---|
| Clonidine +ASA | Placebo + ASA |
| Clonidine + Placebo | Placebo + Placebo |

ASA *vs*. Placebo

| | |
|---|---|
| Clonidine +ASA | Placebo + ASA |
| Clonidine + Placebo | Placebo + Placebo |

# Interactions




Apfel, et al. NEJM 2004

# Adoptive Designs

Altering study population

- Based on new external or internal information
- Focusing on population that apparently most benefits

Adoptive randomization

- Changing treatment group assignment ratios
- "Play the winner" based on accruing results
  - For example, Dixon up-and-down determination of MAC

Changing sample size

- Group sequential (interim analyses & stopping rules)
- Re-estimate sample-size at some point before completion

Changing drug or dose based on initial responses

# Novel Designs

## Cluster randomization or randomized step-wedge

- All or no patients at various sites exposed to intervention
- Avoids learning and Hawthorne effect
- Requires many sites, making them difficult, expensive, and rare

## Opt-out only in routine care arm

- Consent obtained only in experimental arm
- Requires a clear local definition of "routine care"
- Potential for bias because patients randomized before consent
  - Some eligible patients will decline consent after randomization
  - If they decline non-randomly, results might be biased

## Alternating cohort controlled trials

- Like a cluster trial, distributed in time rather than space

# Waived or Altered Consent (US)

No more than minimal risk

- Does not include experimental drugs
- Best for comparative effectiveness trials

Impracticable without altered or waiver of consent

High social value

Alteration or waiver will not adversely affect rights and welfare, and where appropriate:

- Consent model developed or ratified with public involvement
- Information about trial will be broadcast to allow autonomy
- Participants given pertinent information after participation

# Definition of “Impractical”

Scientific validity would be compromised by consent if it introduced bias to the sample selection

Subjects’ behaviors or responses would be altered, such that study conclusions would be biased

The consent procedure would create threats to privacy

Risk of significant psychological, social or other harm by contacting individuals or families

Thereafter, the IRB can consider logistical issues

- Cost, convenience, and speed

# Summary

Trials need to be well powered

- Avoid fragile and spurious results
- Provides useful guidance to clinicians

Composite outcomes can reduce sample size

- Select components for value and avoid heterogeneity
- Collapsed composites require components that:
  - Are of similar severity and frequency

Factorial designs are efficient and can test interactions

Adoptive designs incorporate new information

Novel trial designs are efficient

- Many require modified or waived consent

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