

Testing the Non-Inferiority of A Single Dosage of Curosurf for the Treatment of Neonatal Respiratory Distress Syndrome

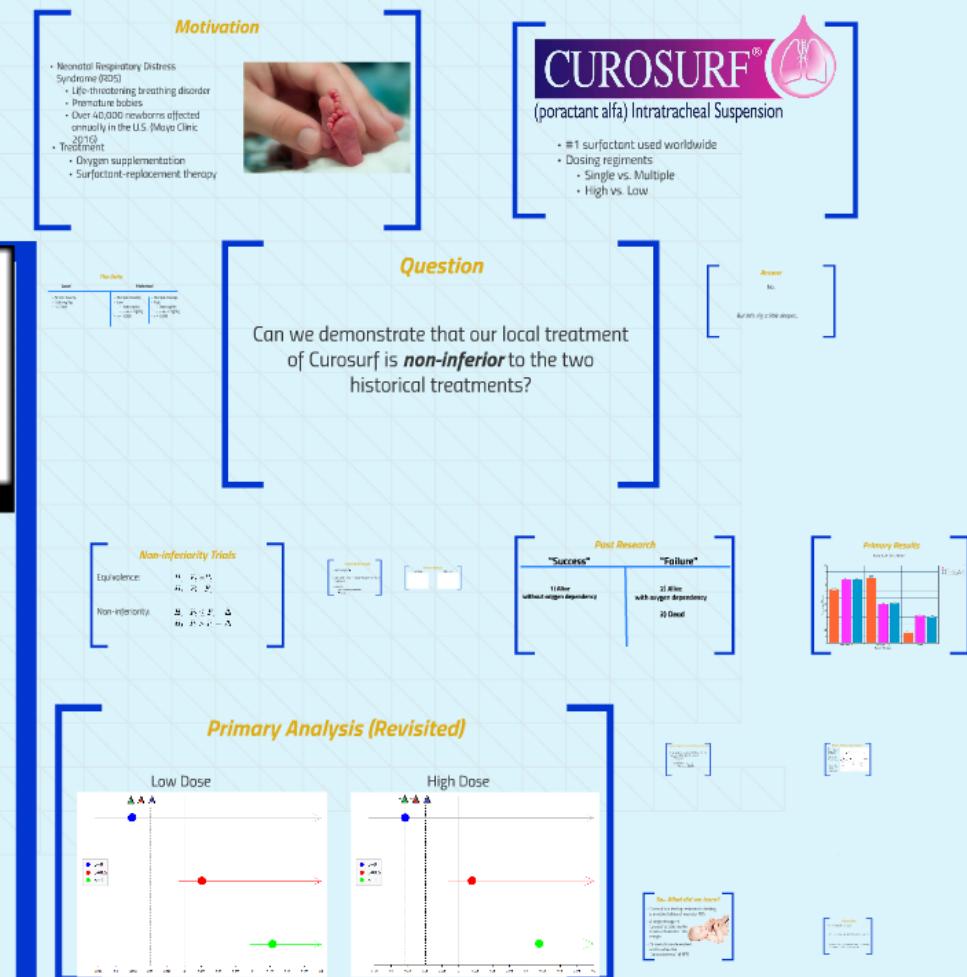
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PICMath

PIC Math is a program of the Mathematical Association of America (SIAM). Support is provided by the National Science Foundation(NSF grant DMS-1345499) and the Department of Mathematics at California State University-Fresno

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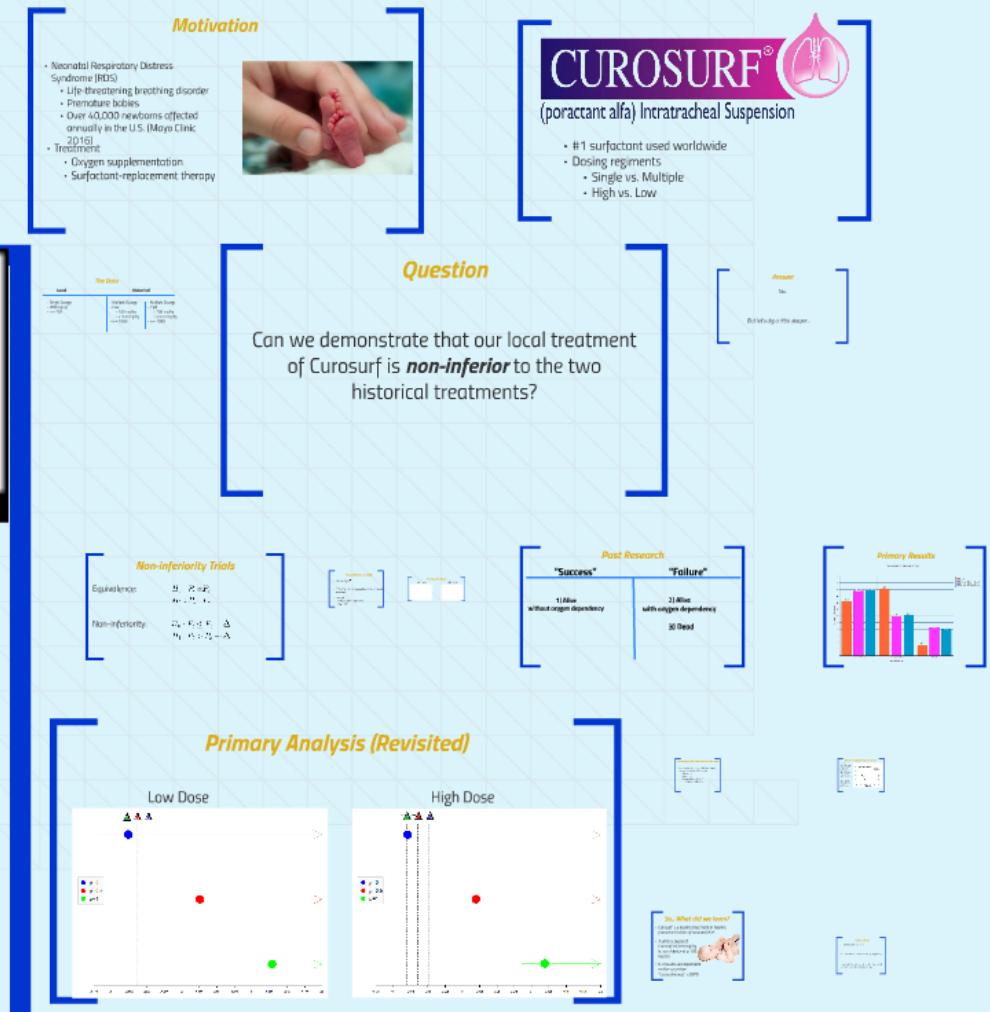
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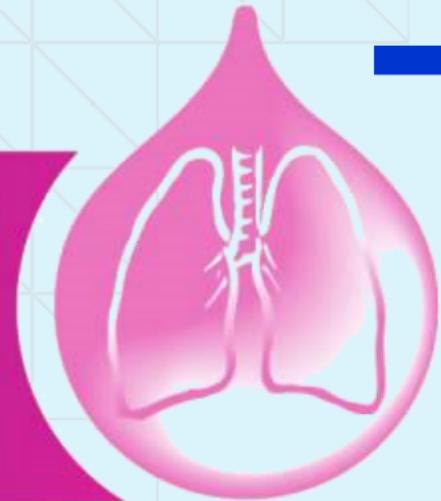


Motivation

- Neonatal Respiratory Distress Syndrome (RDS)
 - Life-threatening breathing disorder
 - Premature babies
 - Over 40,000 newborns affected annually in the U.S. (Mayo Clinic 2016)
- Treatment
 - Oxygen supplementation
 - Surfactant-replacement therapy



CUROSURF®



(poractant alfa) Intratracheal Suspension

- #1 surfactant used worldwide
- Dosing regimens
 - Single vs. Multiple
 - High vs. Low

The Data

Local

- Single Dosage
- 200 mg/kg
- n = 281

Historical

- Multiple Dosage
- Low
 - 100 mg/kg
 - < 300 mg/kg
- n = 1069

- Multiple Dosage
- High
 - 200 mg/kg
 - < 600 mg/kg
- n = 1099

Question

Can we demonstrate that our local treatment
of Curosurf is *non-inferior* to the two
historical treatments?

Answer

No.

But let's dig a little deeper...

Non-inferiority Trials

Equivalence:

$$H_0 : P_t = P_c$$

$$H_1 : P_t \neq P_c$$

Non-inferiority:

$$H_0 : P_t \leq P_c - \Delta$$

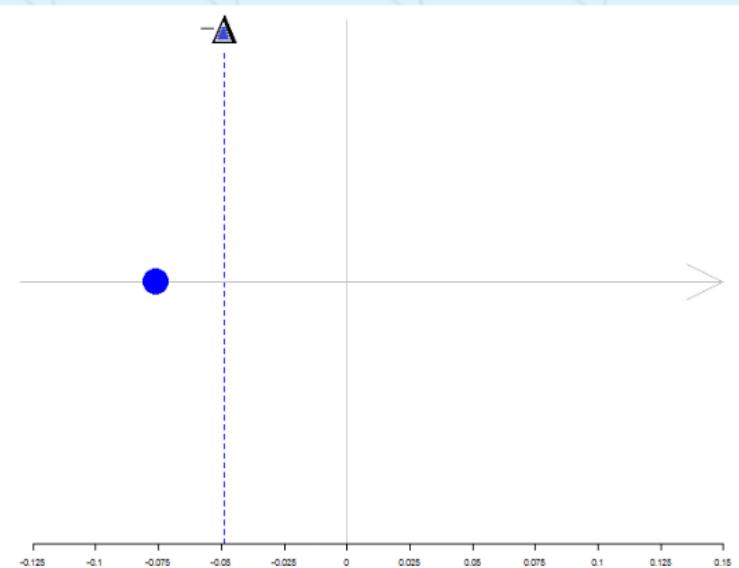
$$H_1 : P_t > P_c - \Delta$$

Choosing the margin

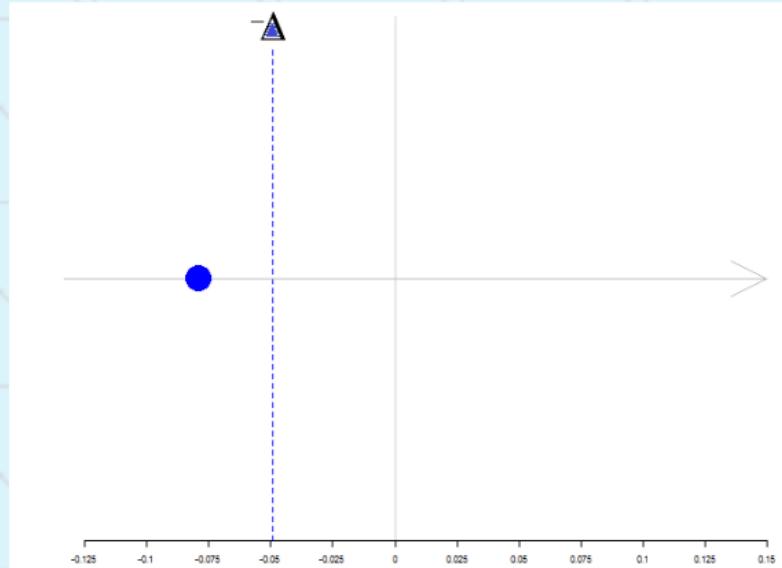
- Fixed margin Δ
- 10% of the success proportion of the historical treatment
- Example:
 - 50% success proportion
 - Δ is .05

Primary Analysis

Low Dose



High Dose



Past Research

"Success"

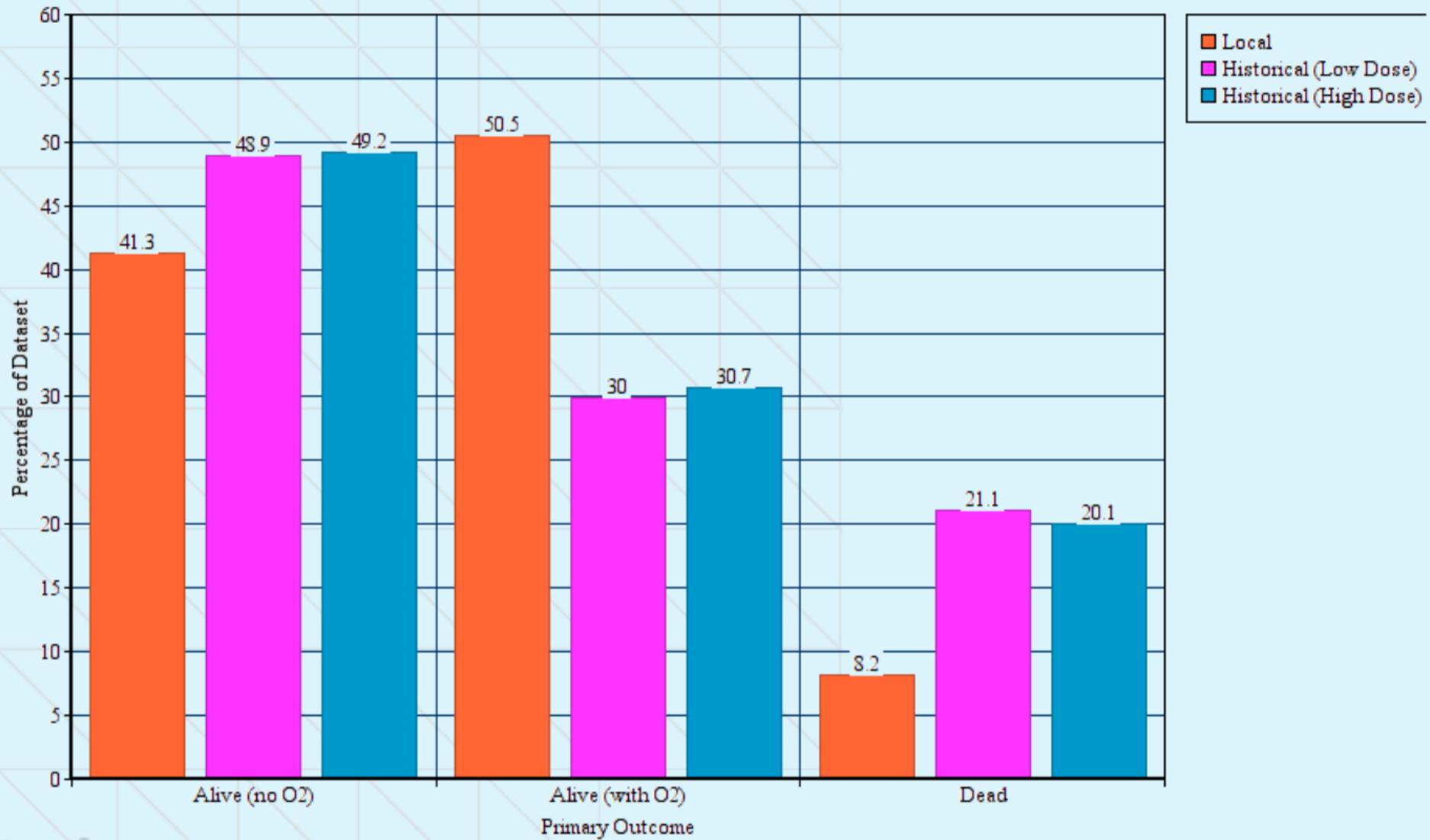
**1) Alive
without oxygen dependency**

"Failure"

- 2) Alive
with oxygen dependency**
- 3) Dead**

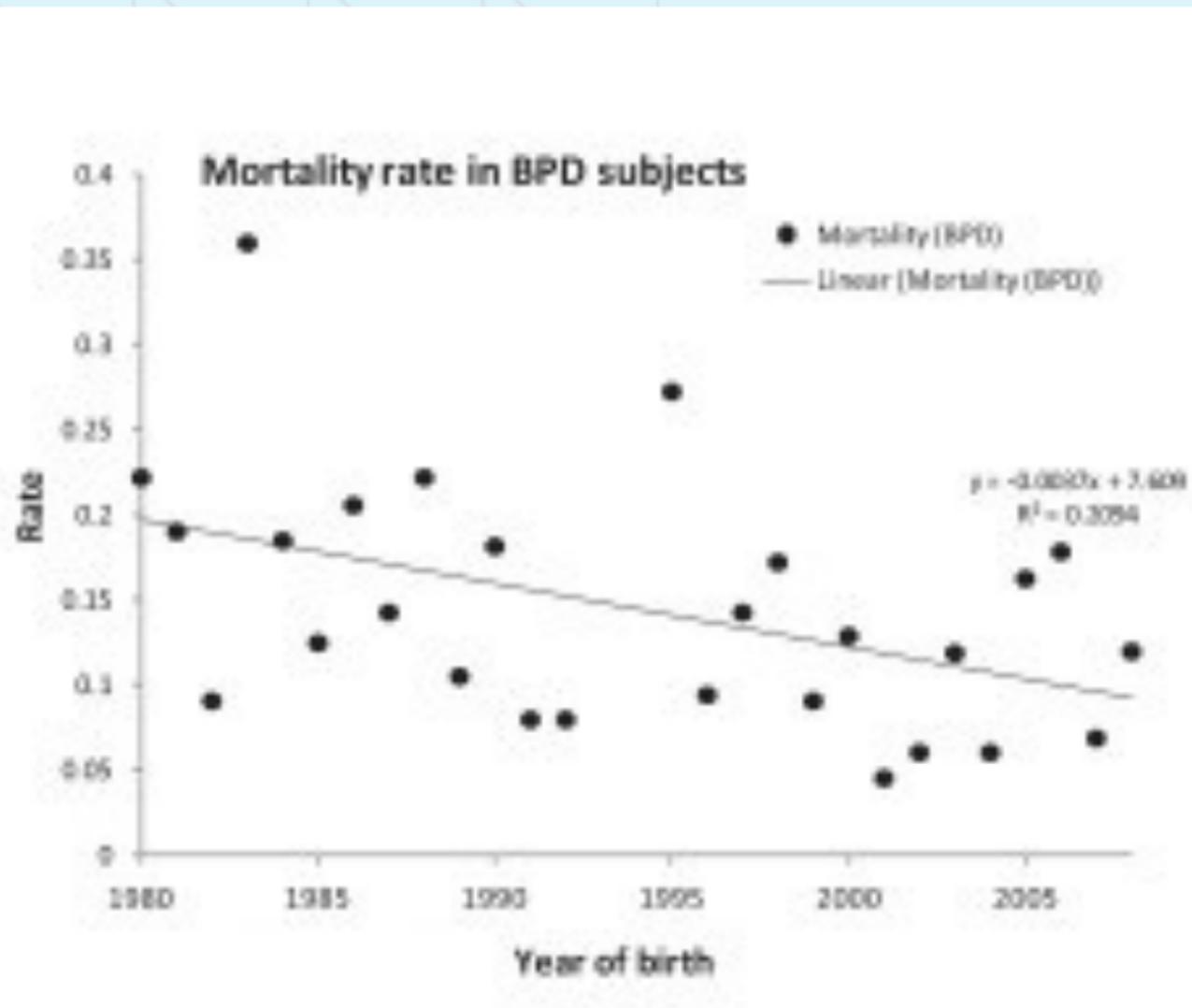
Primary Results

Primary Results - Status at 28 Days



What is "Oxygen Dependency?"

- Defined as Bronchopulmonary Dysplasia (BPD) (Collaborative European Multicenter Study Group, 1988; Speer et al., 1992)
- Infants with BPD tend to get better with age (lung.org, 2016)

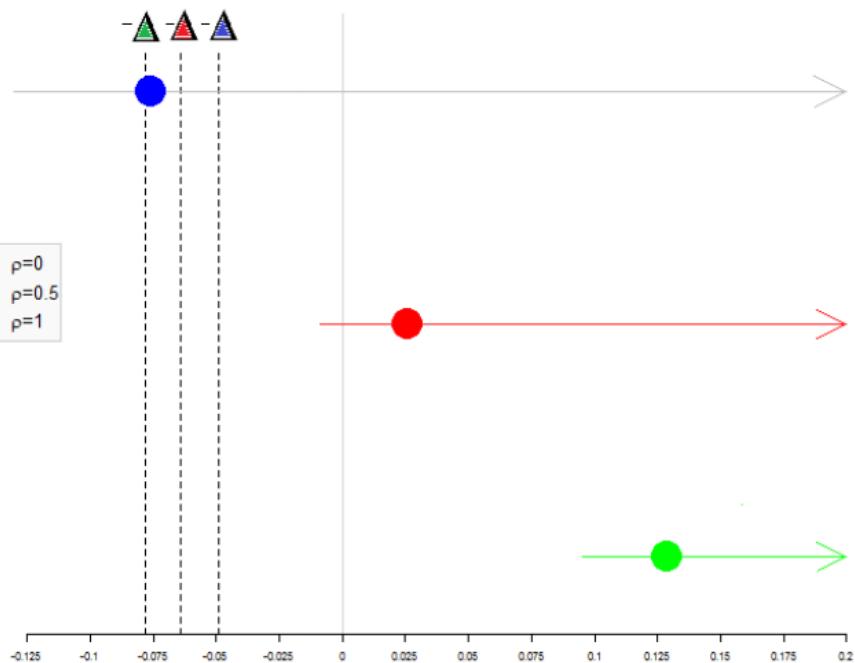


Interpreting the Intermediate Outcome

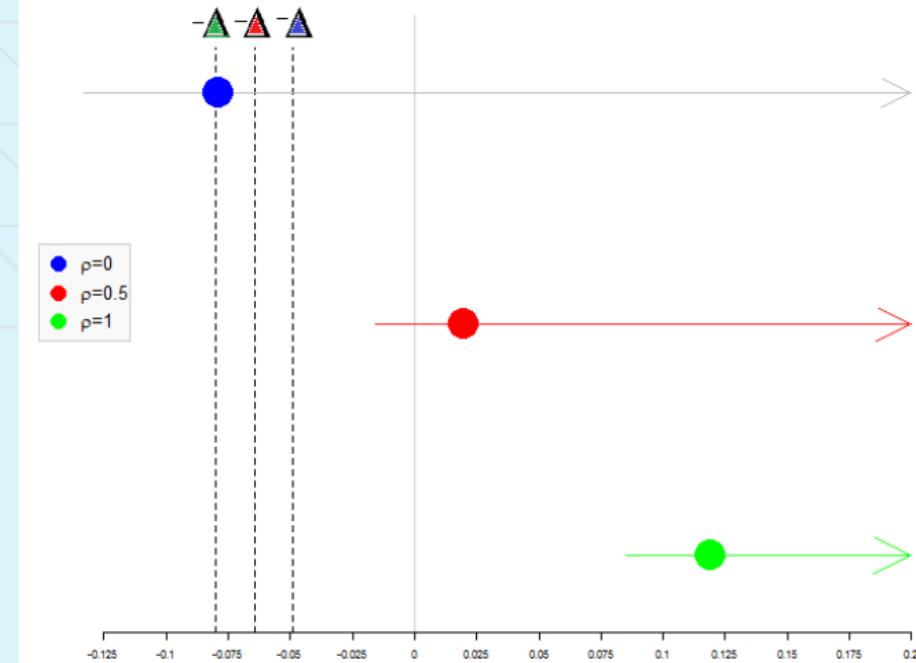
- Non-inferiority testing with three primary outcomes (Brittain & Hu, 2009)
 - Failure = 0
 - Success = 1
 - Intermediate = $0 < \rho < 1$
 - ρ value is subjective

Primary Analysis (Revisited)

Low Dose



High Dose



So... What did we learn?

- Curosurf is a leading treatment in healing premature babies of neonatal RDS
- A single dosage of Curosurf at 200 mg/kg is *non-inferior* at a 10% margin
- Our results are dependent on the subjective "successiveness" of BPD



Future Work

- Fine-tuning the value for ρ
- Choose the non-inferiority margin differently
- Re-evaluate past research within the context of Brittain and Hu's (2009) study

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