Between-endpoint predictive model to support phase III clinical design

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Objective and Agenda

Objective:

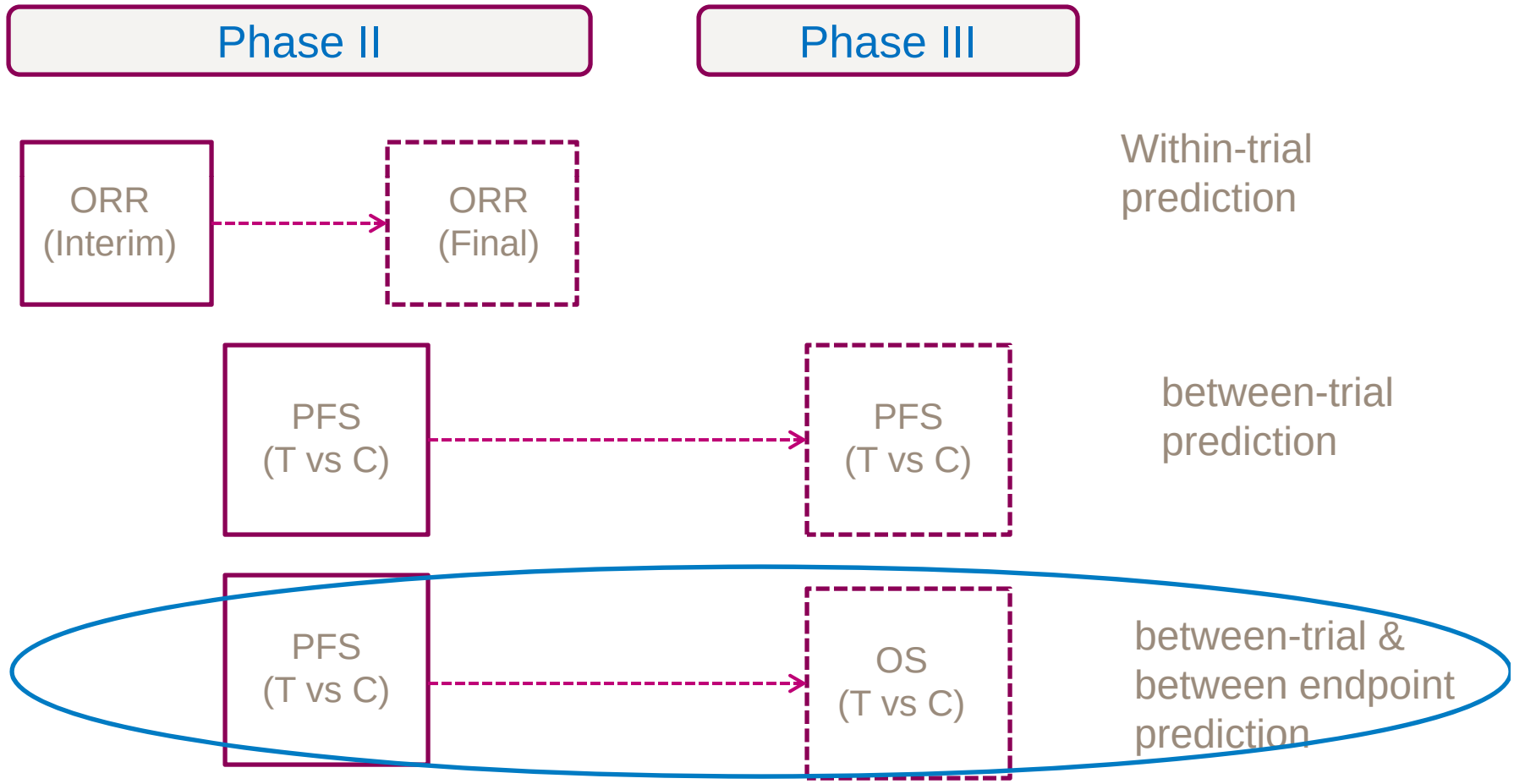
- To share how a simulation model is being used to predicate phase 3 endpoint and design phase III clinical trial.

Agenda

- Introduction to between-endpoint and between-trial prediction.
- Generate step for between-endpoint prediction
- A pre-term labor example with continuous endpoint to binary endpoint
- Adaptive design to mitigate the risk of design

Different type of Predictions (Oncology)

T:treatment C: Control
ORR: Objective response rate; PFS: Progression-free-survival; OS:Overall-survival



Source: Beat Neuenschwander FDA Industry Stat Workshop 2012

Why between-endpoint prediction?

- Different phase studies have different primary endpoints
  - Different objectives and/or populations
  - Registration endpoints vs surrogate biomarkers
  - Endpoints may be measured earlier and more conveniently than the final endpoint of interest.

- Prediction between endpoints can be more complex…
  - Phase 2 PoC based on surrogate, phase 3 on registration endpoint:
    - Is the phase 2 biomarker a good predictor of the phase 3 endpoint?
    - What is the relationship between these endpoints?
  - Varies by therapeutical area: should be assessed case by case

Between-Endpoint Prediction: General Considerations

Previous evidence / data / knowledge is a crucial component in Between-Endpoint Prediction…

- "Historical data" is important to understand the relationship between the two endpoints:
  - The shape of the relationship needs to be determined
  - A change in indication may impact this relationship
  - Understand the source of variability

Between-Endpoint Prediction: General Considerations

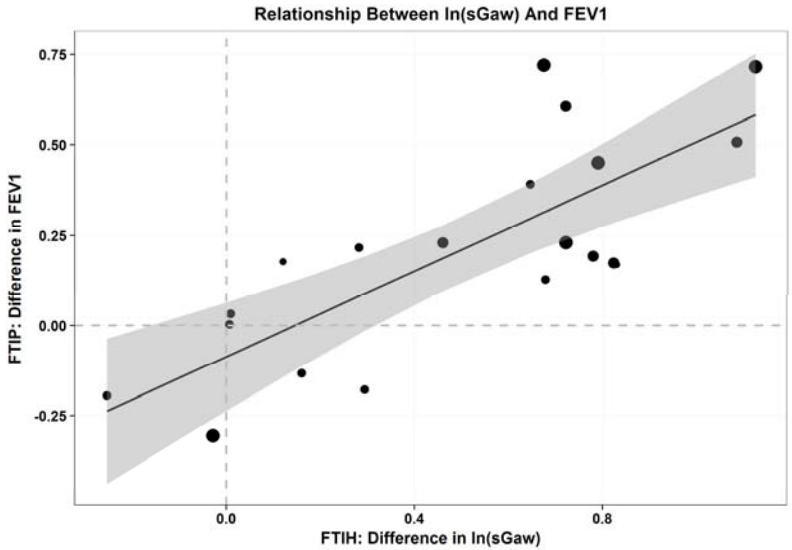
- Ideally one should construct a model to include all sources of variability

- Sensitivity analysis should be performed on any assumptions made!
  - There will be no 'correct answer' here and the prediction is only as good as the assumptions you put into the model. Therefore sensitivity analyses are crucial!

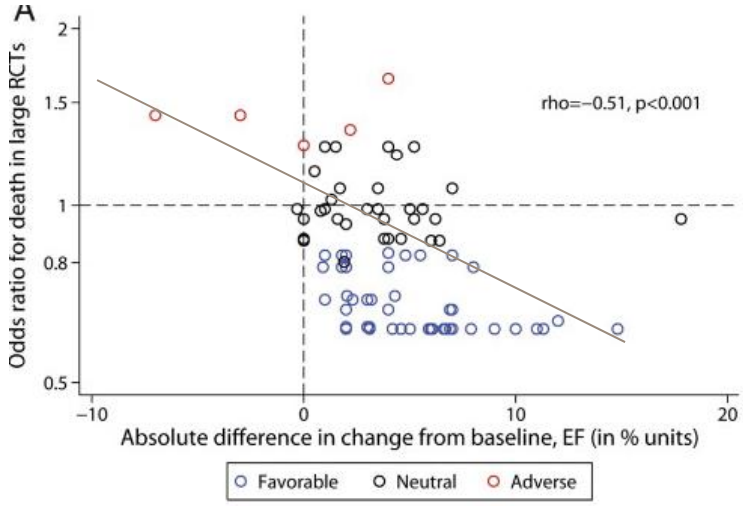
- Simulations can help to understand the relationship and to design the next study

To Start……

- The prediction is usually straightforward if the relationship is known
  - i.e. Linear relationship surrogate and clinical endpoints
  - Other source of variability can be addressed in the model



Simulated data



Reviewed historic data (Kramer 2010)

More complex when unknown relationship

- Motivations:
  - –Preterm birth is leading cause of neonatal mortality and morbidity globally
  - –Objective of tocolytic therapy to treat pre-term labor (PTL) is to prolong pregnancy resulting in improved neonatal health.
  - –ACOG/RCOG: No tocolytic has been shown to improve neonatal outcomes
- GSK has asset in development to treat PTL.
  - –Phase 2 demonstrated a significant prolongation of pregnancy as measure by days to delivery
  - –Phase 3 studies designed to demonstrate both prolongation of pregnancy and improved neonatal health

Motivation for building simulation model

- Determine appropriate measure of neonatal benefit
  - Development of neonatal composite endpoint
- Determine relationship between prolongation of pregnancy and neonatal benefit
- Determine sample size of Phase 3 trials
- Determine operating characteristics of adaptive design

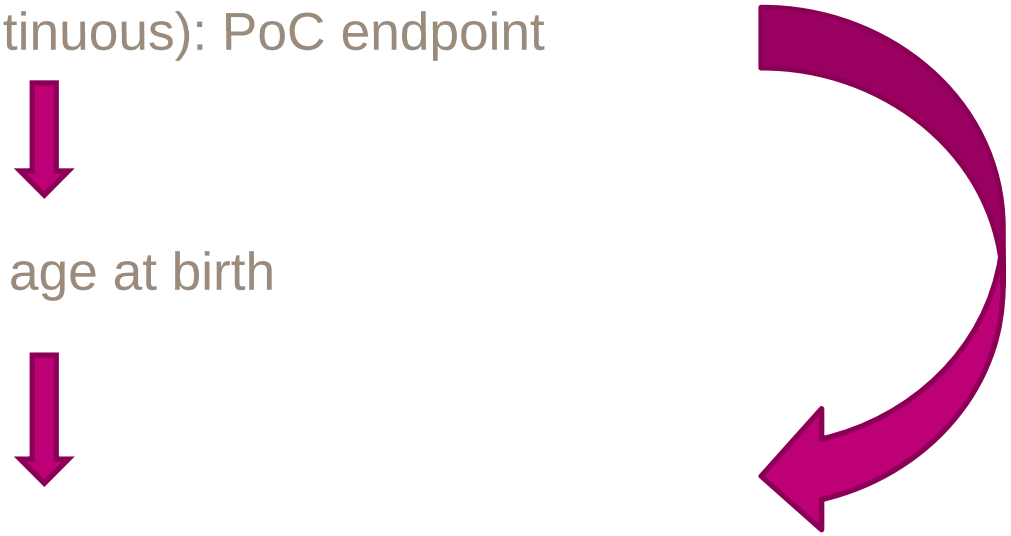
Ultimately, impact clinical development and registration strategies

Step 1:

: Literature review from historical data (placebo or control data)

Endpoint relationships based on what we knew…

- Three endpoints
  - Days to delivery (D2D, the time between GA at randomization and GA at birth, continuous): PoC endpoint
  - Gestational age at birth
  - Neonatal outcome (binary) : Phase III Registration endpoint (US)

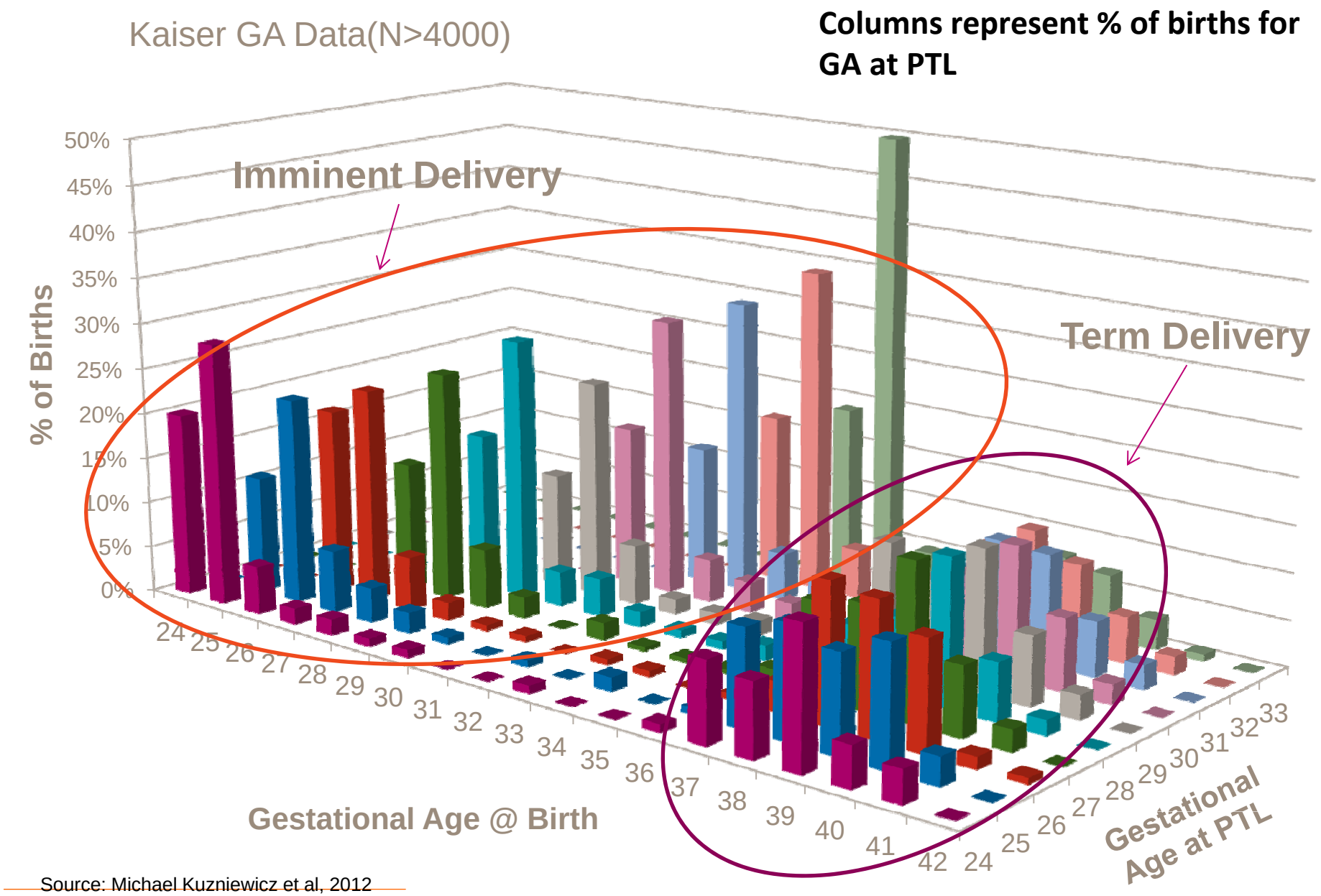


The relationship between changes in days to delivery (D2D), GA at birth, and neonatal outcome is not known

Model Assumptions

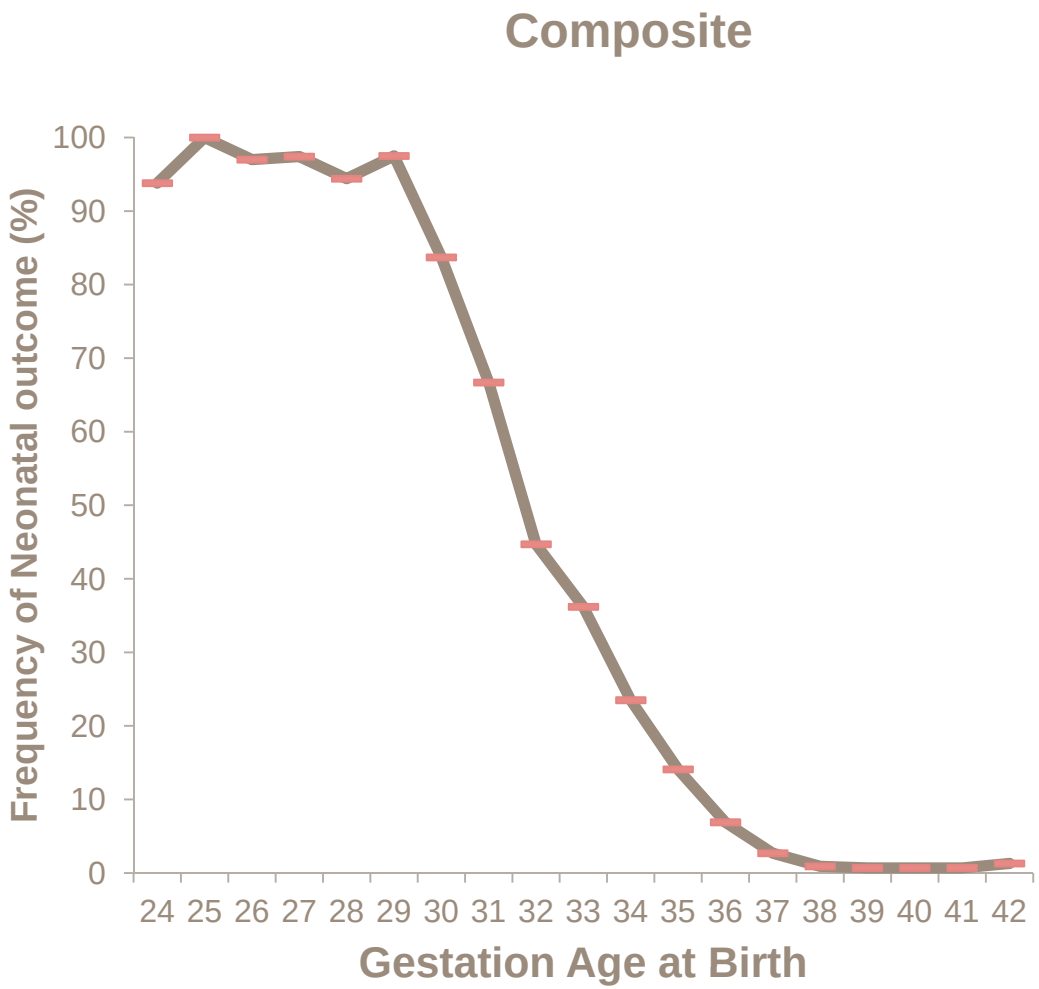
- Gestational Ages to be recruited (Less in early GA)
- Different population
- Placebo response
- Treatment response
- Relationship between GA at birth and neonatal mortality and morbidity

- Data sources to consider
  - Phase 2a data
  - Medical University of Southern Caroline (MUSC) Perinatal Information System Database (PINS)
  - Kaiser Permanente Division of Research, Perinatal Research Unit
  - Literature



Source: Michael Kuzniewicz et al, 2012

GA at Birth and Neonatal Outcomes (MUSC)

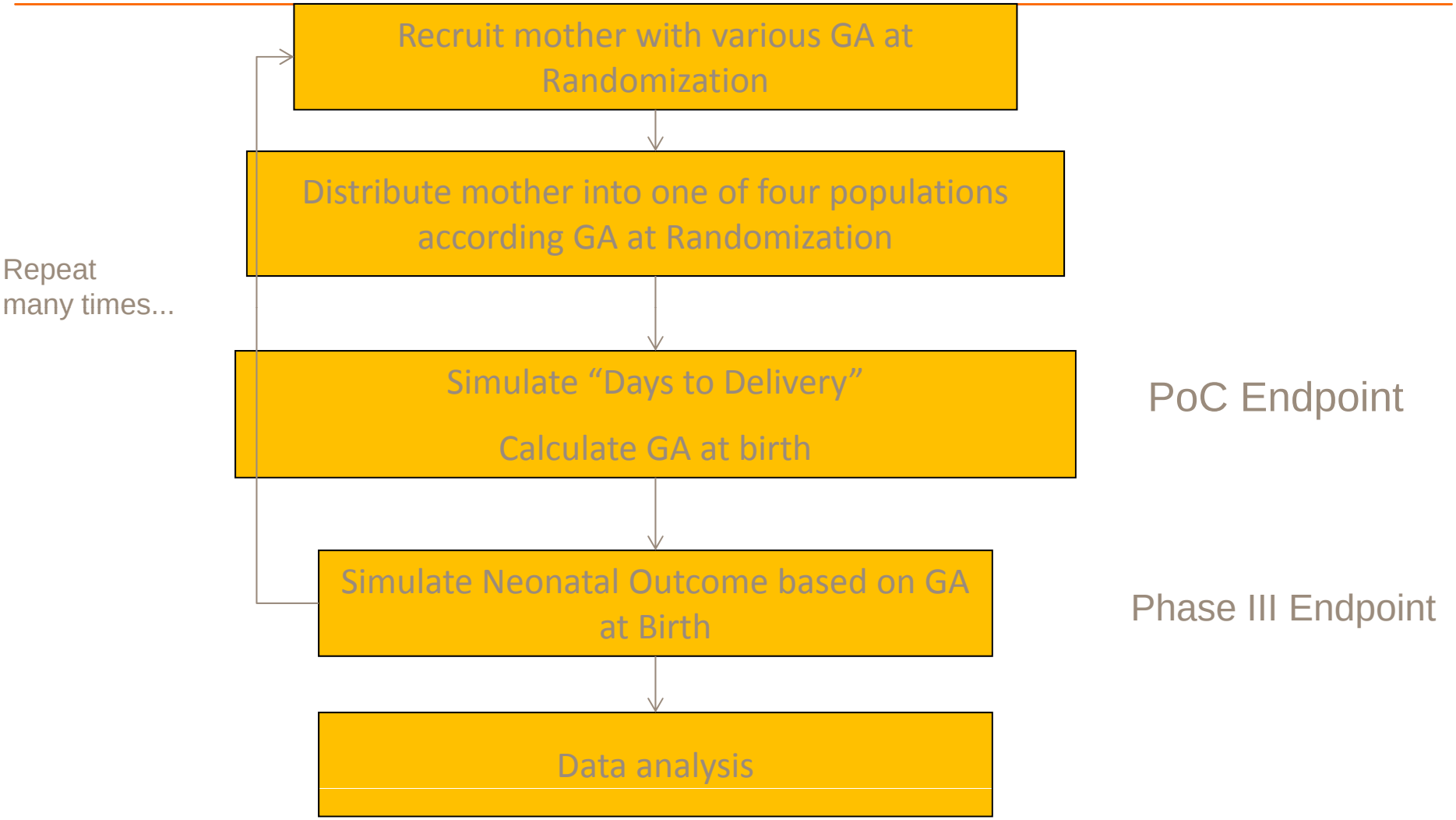


Source: Medical University of Southern Caroline (MUSC) Perinatal Information System Database (PINS) 2000-2009

Step 2:

Build model to simulate placebo/control and treatment responses

Prediction model: Simulation Procedure



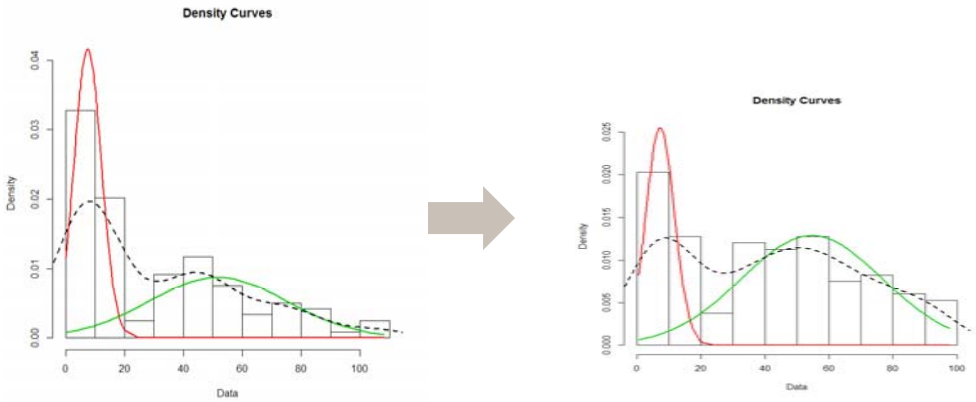
Assumptions regarding efficacy of Treatment: women who will deliver within 2 weeks

Scenario 1: Conversion PBO Treatment

%of women **delivering imminently**

To

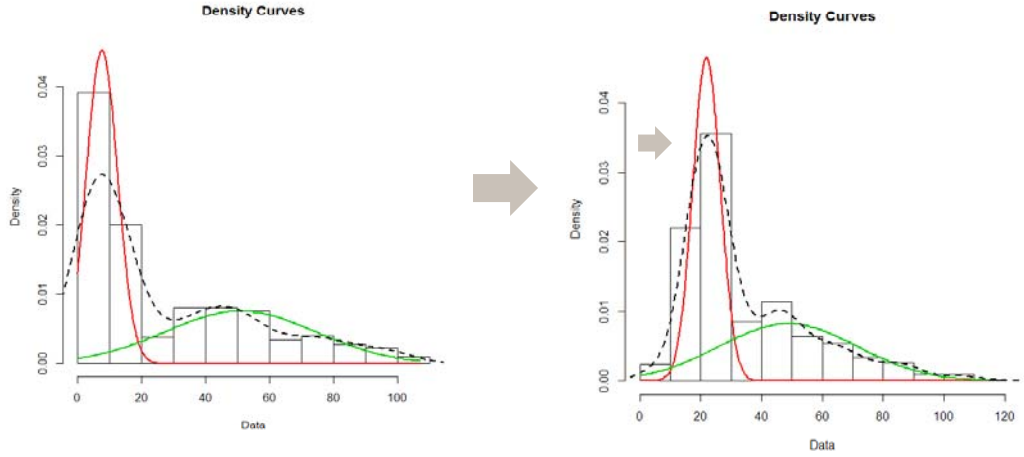
Delivering at term



Scenario 2: Prolongation

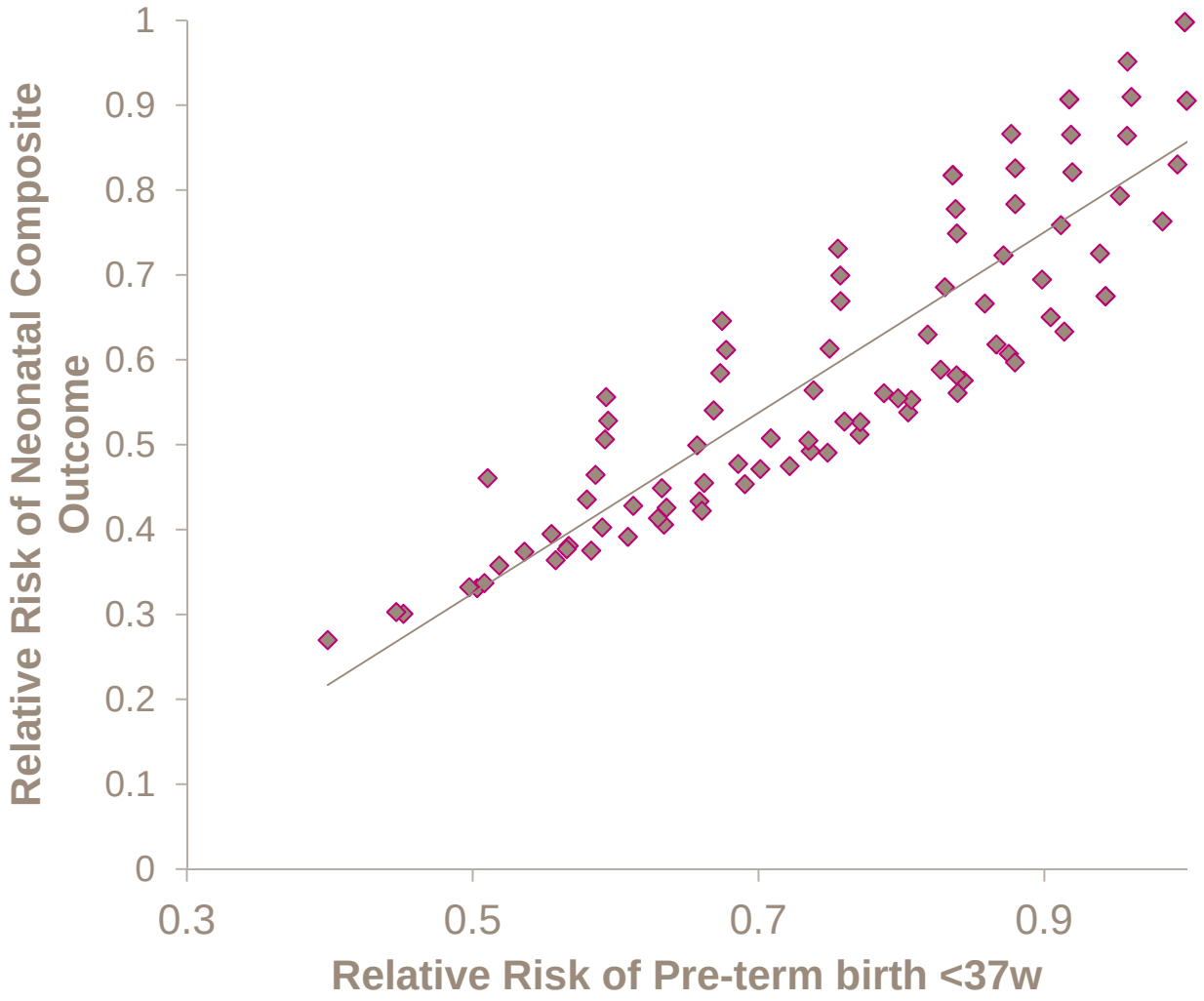
Shift %of women **delivering**

imminently X days to the right



Scenario 3: Mixture of the above two

Relationship of Neonatal Outcome and Pre-term Birth



each point is the result from mean of simulations for each treatment scenario

Relationship of Neonatal Outcome and D2D

each point is the result from mean of simulations for each treatment scenario

Step 3:

Sample size and Sensitivity Analysis

What can I do with this model?

- The phase 3 study has 2 co-primary endpoints:
  - Days to delivery (D2D)
  - Neonatal composite outcome

Base case: treatment effect as of % conversion so it matches with PoC data

Based on all the assumptions made so far, a sample size and power can be calculated:

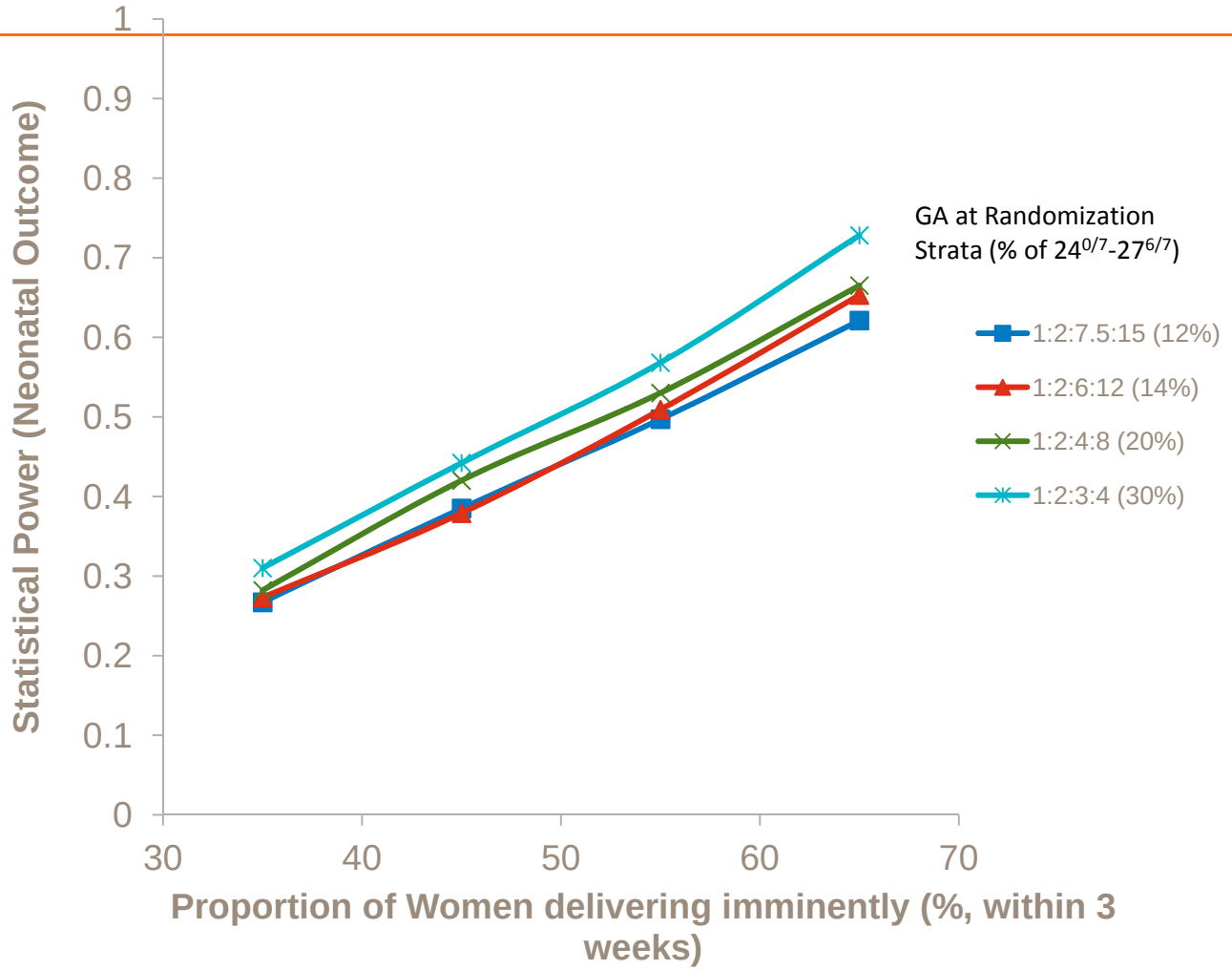
- Neonatal outcome relative risk reduction is expected to be 32% given PoC effect. With the sample size, the probably of success is expected to be 90%.

Sensitivity Analysis

	Base Case	Scenarios
GA at randomization % of women in early GA strata (24 $^{0/7}$ to 27 $^{6/7}$) (4 GA strata)	20% **(1:2:4:8)**	10%, 14% (1:2:6:12) 12% (1:2:7.5:15) 30% (1:2:3:4)
% of women delivering imminently (within 23 weeks)	55%	35%,45%, and 65%
Distribution of women delivering imminently (within 3 weeks)	Uniform distribution	Normal distribution

Assumptions to be explored

- GA at Randomization
- Placebo/Comparator response
- Treatment response
- Neonatal outcomes (based on historical database)


Statistical Power (Neonatal Outcome)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
30
40
50
60
70
Proportion of Women delivering imminently (%, within 3 weeks)
GA at Randomization Strata (% of 24^0/7-27^6/7)
1:2:7.5:15 (12%)
1:2:6:12 (14%)
1:2:4:8 (20%)
1:2:3:4 (30%)

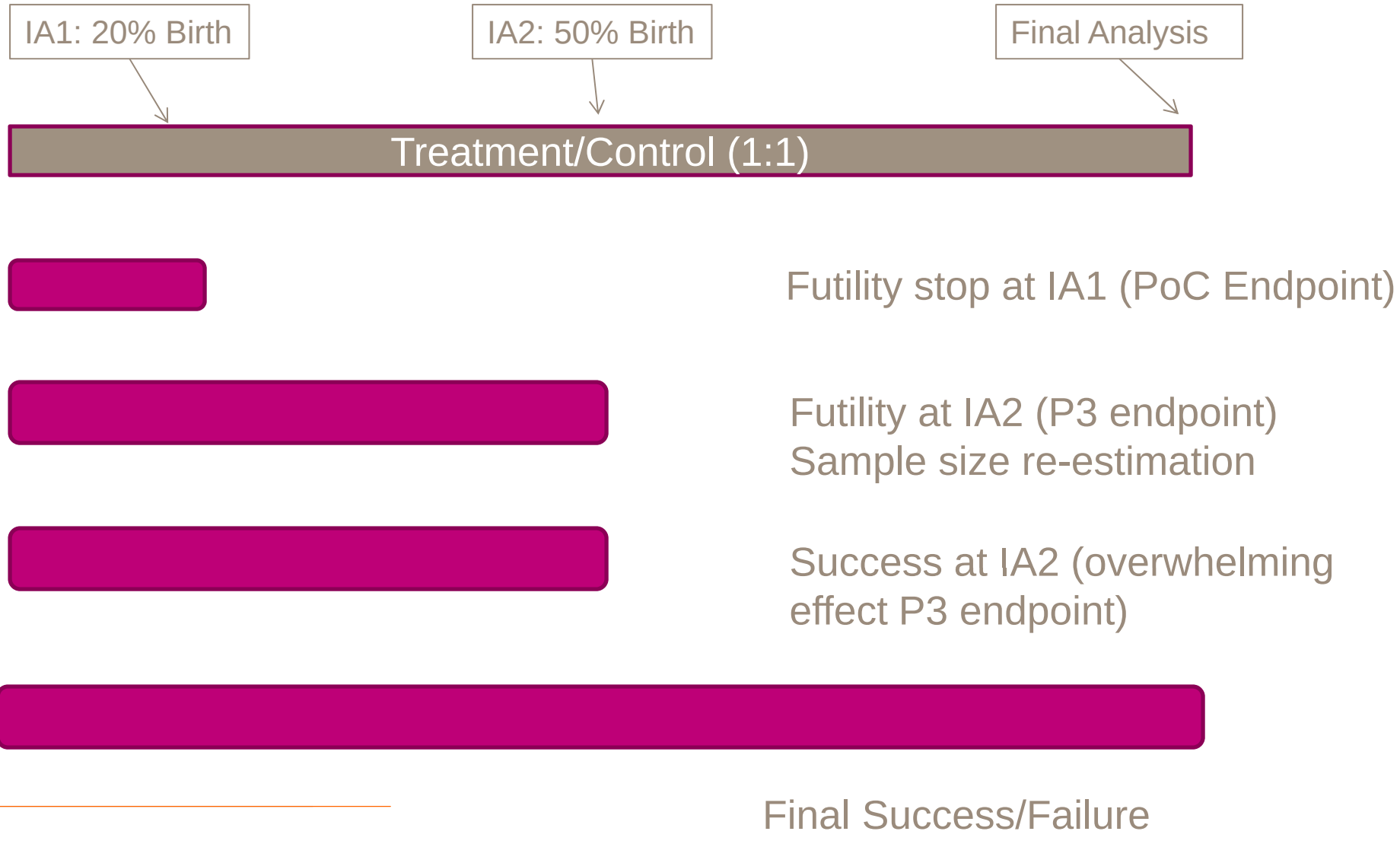
Step 3:

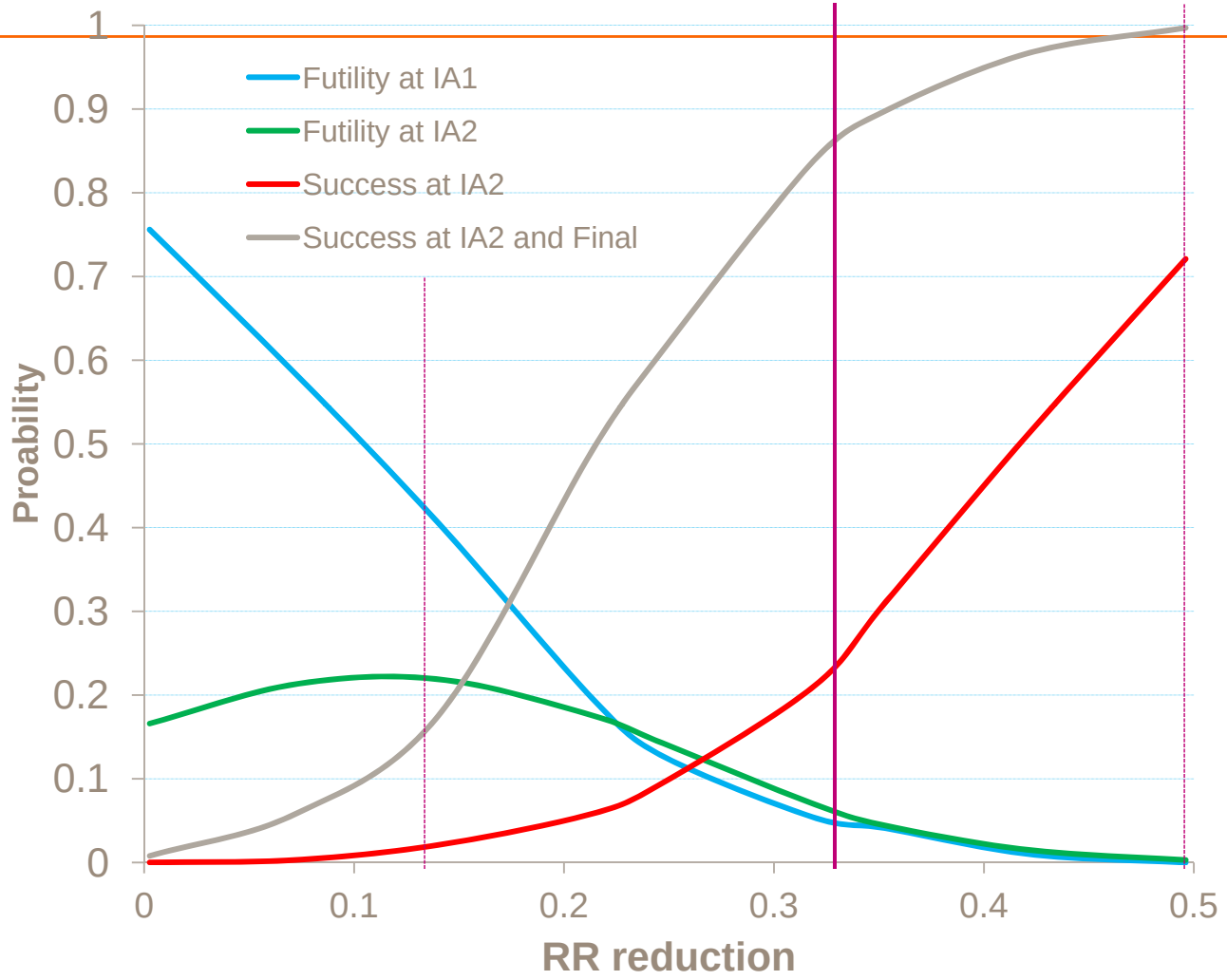
Implementation of between endpoints prediction in adaptive design to mitigate the risk and examine assumptions

Why adaptive design?

- Ideally, stop the trial early if the drug is futile or stop early for success or confirm the effect if the drug is effective
  - Minimize the false negative and false positive rates
  - Traditional fixed design takes too long to draw the right decision
  - Mitigate development risk with early futility decisions based on days to delivery and between-endpoint prediction.
- Substantial uncertainty regarding target population, placebo and treatment response
  - Important in different study populations, high between-study heterogeneity
  - Sample size re-estimation based on nuisance parameters
- FDA's adaptive design guidance

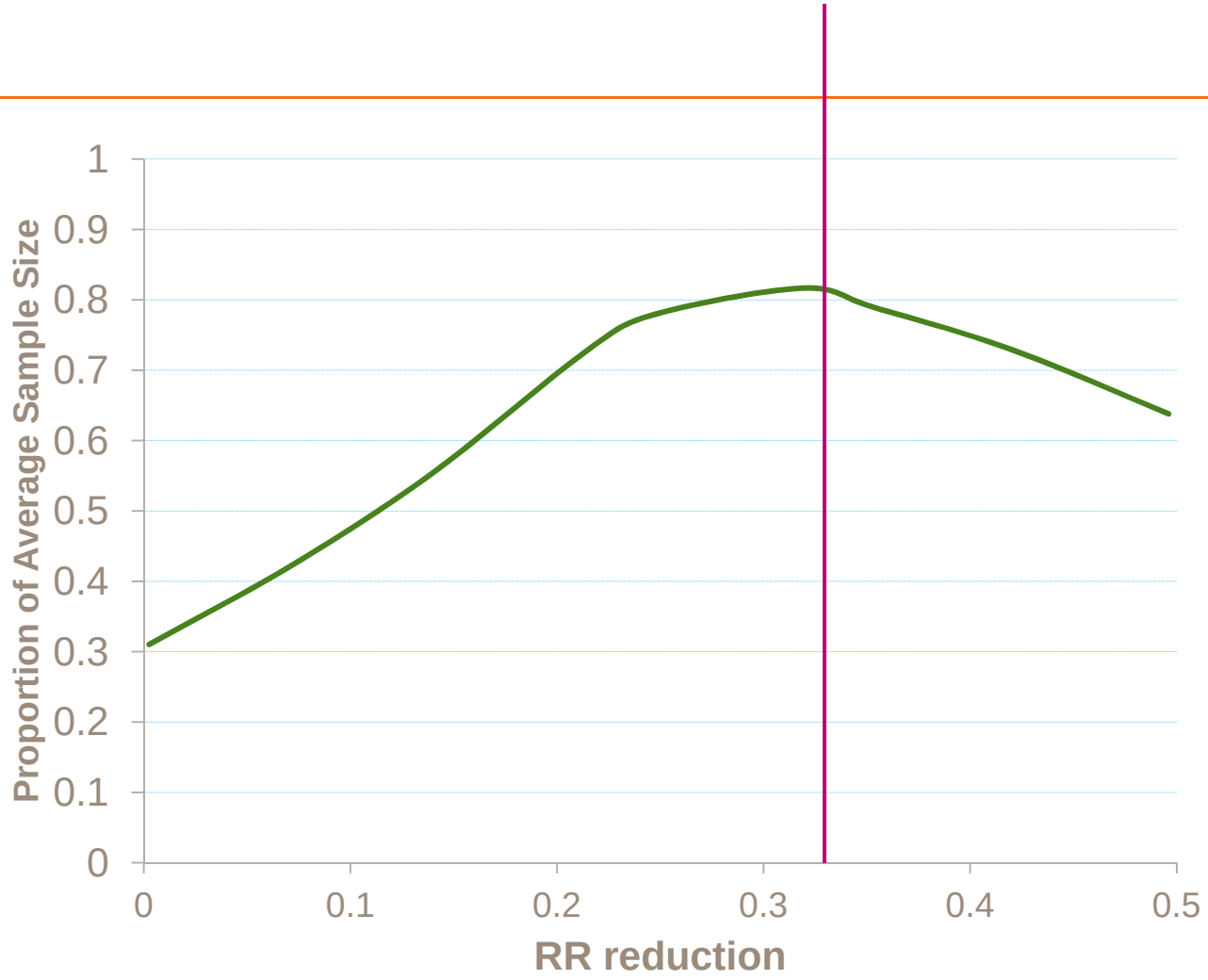
Phase 3 study with predictive inference model





D2D (R-C)

0 2 4 7 9 14


Proportion of Average Sample Size
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.1
0.2
0.3
0.4
0.5
RR reduction

Pros and Cons of predictive model

- **Pros**
  - Provides estimate of the potential neonatal benefit
  - Provides ability to evaluate potential study designs and decision rules.
  - Flexibility to evaluate multiple assumptions.
  - The predictive seems robust with various assumed treatment effect
  - Mitigate development risk by stopping early
- **Cons**
  - Computation intensive
  - Complexity
  - Dependency on multiple assumptions

Discussion / General Considerations

- Use of historical data, previous in-house studies, etc is crucial to understand the relationship between the endpoints of interest!
  - Involve project team members in the selection of studies to be included in the historical data set
  - Try to build a robust set of historical studies that does not include reporting bias
- It is helpful to specify the model in term of sufficient statistics since subject level historical data are often inaccessible
- Ideally we would take into account all sources of uncertainty in an hierarchical model framework
- Real life can be much more complex, however predictions can still be derived! But think carefully about any assumptions made.

Between-Endpoint Prediction: Summary

- It is possible to quantify probability of success in one study using evidence from an earlier study on a different (but related!) endpoint
- Careful literature review necessary to fully characterize relationship between endpoints
- Sensitivity analysis is crucial to assess impact of assumptions on final results

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Thank you!