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Presentation #1: An application of the Bayesian robust meta-analytic approach in the group sequential design MDD pediatric trial, a case study



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Yevgen joined Johnson & Johnson in 2011. He has broad expertise in statistical methods and trial design successfully applied in numerous projects while supporting early and late stages drug development and submissions.

Prior to joining Johnson & Johnson, Yevgen worked for six years at Merck Research Laboratories. He has a Ph.D. in Statistics from the University of Maryland, Baltimore County. He is actively involved in scientific collaborations in the field of randomization, adaptive design methodology and software which led to an extensive list of publications and presentations. Yevgen also served as an associate editor for the Journal of Statistics in Biopharmaceutical Research.

An application of the Bayesian robust meta-analytic approach in the group sequential design MDD pediatric trial, a case study

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Outline

- Background and Literature
 - Methods available
 - Type I and power consideration
 - Measure of information
- Case Study in MDD
- Concluding Discussion

Bayesian Approaches to Incorporate Adult Data into Pediatric Trials

- Limited populations => poor accrual opportunities =>
 - Innovative approach to design and analysis
- Partial extrapolation “when disease and intervention are believed to behave similarly” (FDA Guidance for Pediatric Studies)
 - Uncertainty as for what extent adult data are relevant to pediatric settings
- Bayesian Methods for including historical data:

Method	Parameter
Power Prior (modified)	weight (power) param
Commensurate prior	between study heterogeneity
Meta-analytic-predictive (MAP)	between study heterogeneity
Robust version of MAP	weight and variance of the robust component

Key Statistical Considerations

- Ideally, approaches should provide automatic adjustment as for what amount of information will be “borrowed” from historical data
- Operating characteristics
 - Bias and precision of estimates
 - Frequentist characteristics: Type I, Power
 - Control of Type I
 - Kopp-Schneider et al (2018) “Power gains by using external information in clinical trials are typically not possible when requiring strict type I error control”
- Measure of information
 - Borrowed information (similarity assessment)
 - Effective sample size

Type I Error Inflation

K. Viele *et al.*

Pharmaceutical Statistics

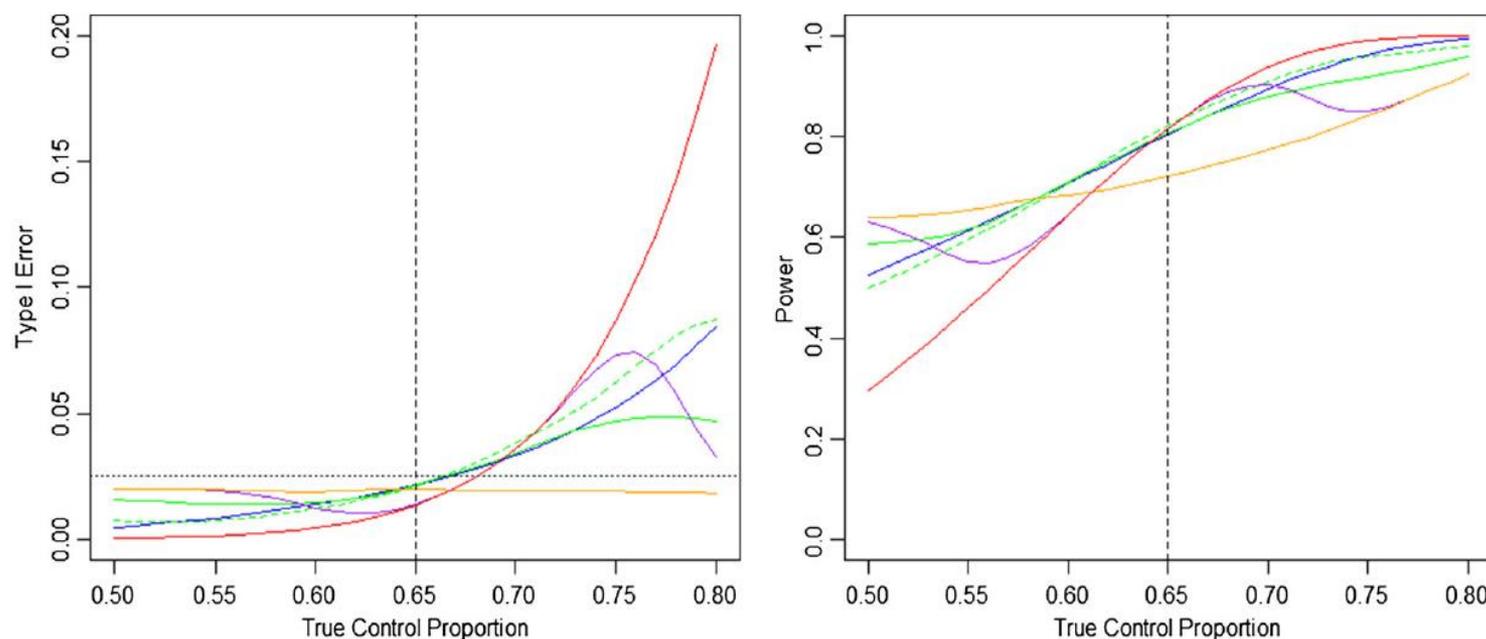
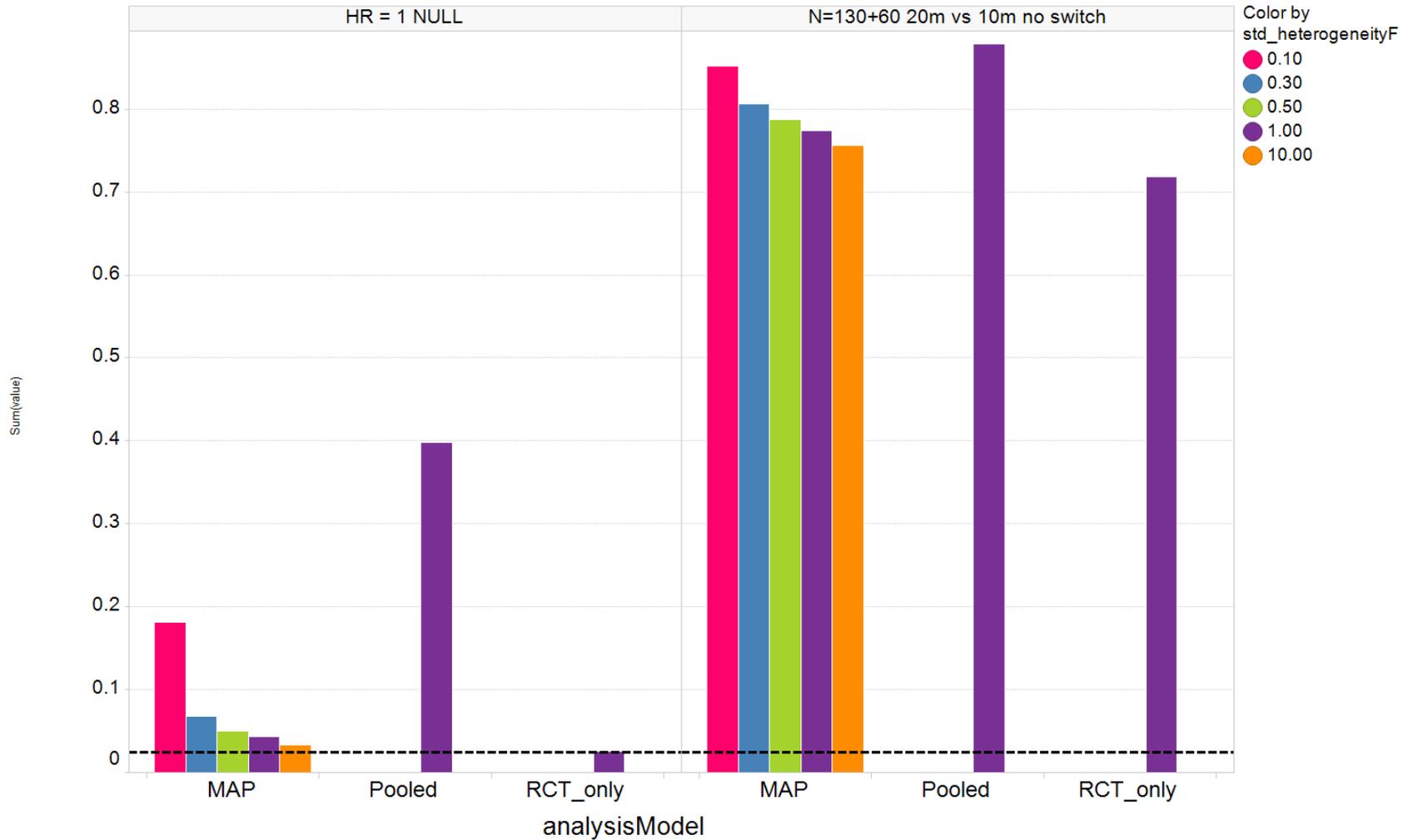


Figure 9. Type I error and power comparison for separate (orange), pooling (red), selected test-then-pool (size 0.10, purple), downweighted power prior (40% weight, blue), and hierarchical model (IGamma(1, 0.01) in dashed green, and IGamma(0.001, 0.001) in solid green). Generally, the test-then-pool approach has lower type I error and also lower power near a control rate of 0.65, but has reduced power compared to power priors and hierarchical models outside that range. For control rates near 0.65, all methods achieve similar power gains as pooling (red) with much less type I error inflation.

Method Comparisons in Literature

- Rosmalen et al (2018) SMMR “Including historical data in the analysis of clinical trials: Is it worth the effort ?”
 - Comprehensive comparison using TTE endpoint setting
 - Evaluated heterogeneity in datasets, in a presence of time trend
 - R code available
 - MAP appears to provide some modest increase in power (2-10% depending on scenario) compared to the “current data” analysis while controlling Type I close the nominal level

Example of Type I and Power Dependence on a Specification of Prior for the Heterogeneity parameter



Filter Settings : HR = 1 NULL, N=130+60 (alternative)



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Adaptive Sizing of a Pediatric Study

- Early stopping for efficacy in pediatric trials
 - Discord with obtaining “maximum possible information”
 - Many options as for implementation using frequentist or Bayesian methods
 - E.g., Ye et al (2020) “A Bayesian approach in design and analysis of pediatric cancer clinical trials” - proposed sequential monitoring for efficacy and futility
- Let’s consider a case study where sizing is done using a group sequential framework by “borrowing data” from adult studies using the MAP approach

Pediatric Program in MDD, a Case Study

- Major Depressive Disorder (MDD) indication:
 - Deferral for the start of the adolescent studies until data from MDD Phase 3 studies in adults is available
 - Two Ph3 are planned in adults

Objective:

- To evaluate incorporation of data from the adult program into the pediatric program
 - Using placebo-adjusted response from Ph3 in adults to the pediatric study

Pocock Criteria for “Pooling”

1. Same standard treatment
2. Eligibility criteria
3. Methods of treatment evaluation
4. Distributions of important patient characteristics
5. Investigators expected to be largely similar
6. No other indications expected to lead to systematic differences

Pocock SJ. The combination of randomized and historical controls in clinical trials. *J Chron Dis* 1976; 29: 175–188.

“Proving” that Data can be Pooled

- Establishing similarity formally requires high sample size
 - If controlling the “false positive” probability of pooling when the true effects are substantially different

Significance level, α	Margin (standardized effect)	N	Power
5%	0.45	90	15%
10%	0.45	90	37%
10%	0.30	180	30%

Effects are the same in adults and adolescents;
Target effect size of interest relative to placebo 0.45

Considered Bayesian Methods

- Hierarchical model with hyper-parameters that describe how “similar” historical and observed data
 - Too few studies – 2 in adults and the trial in adolescents itself
- Test-then-Pool approach:
 - Just two options: “pool” / “No pool”
- Recommended framework:
 - Robust Meta-Analytic-Predictive Priors approach**
Schmidli et. al. (2014, Biometrics)

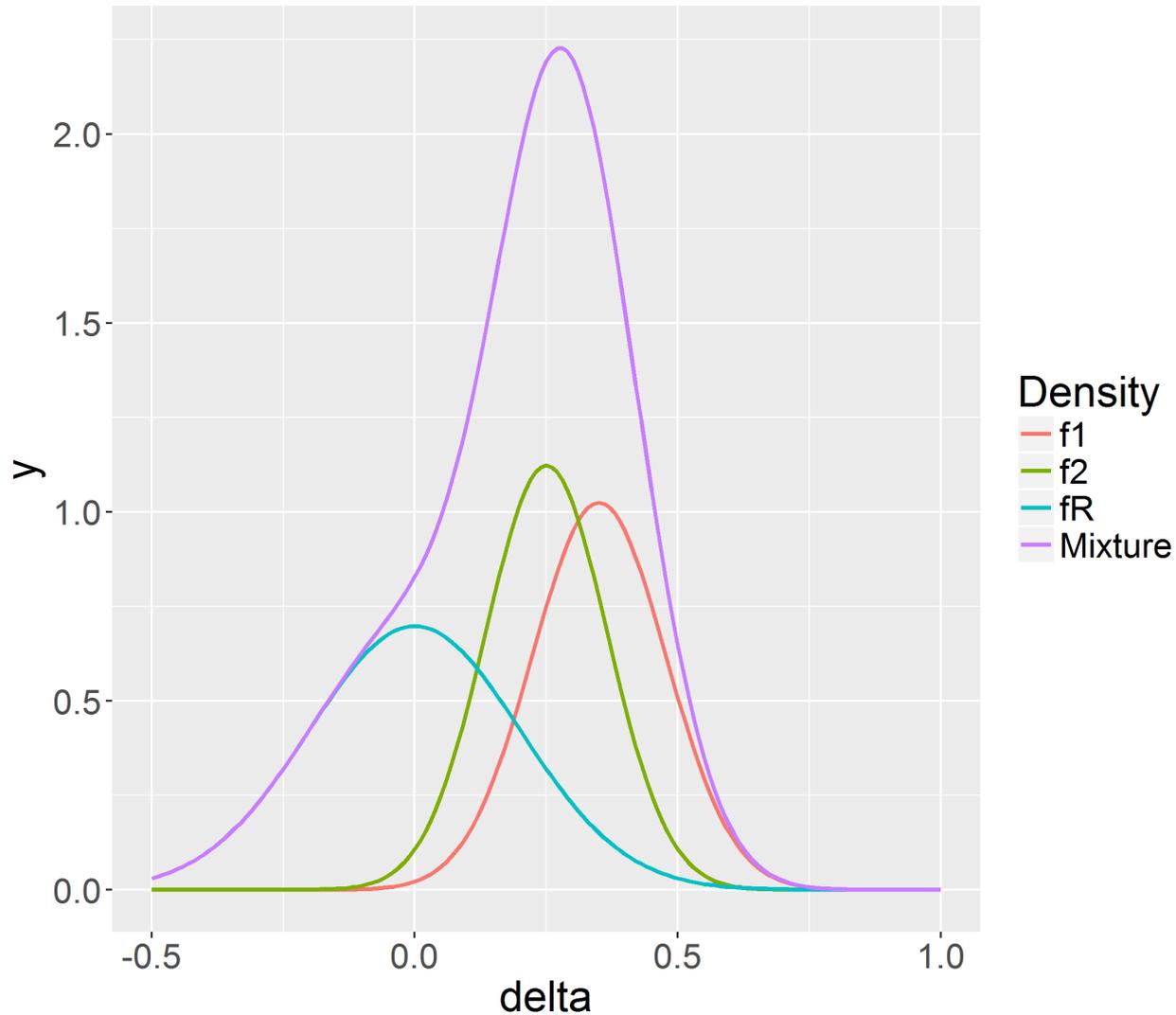
Prior Mixture Distribution

- Prior distribution is a mixture:

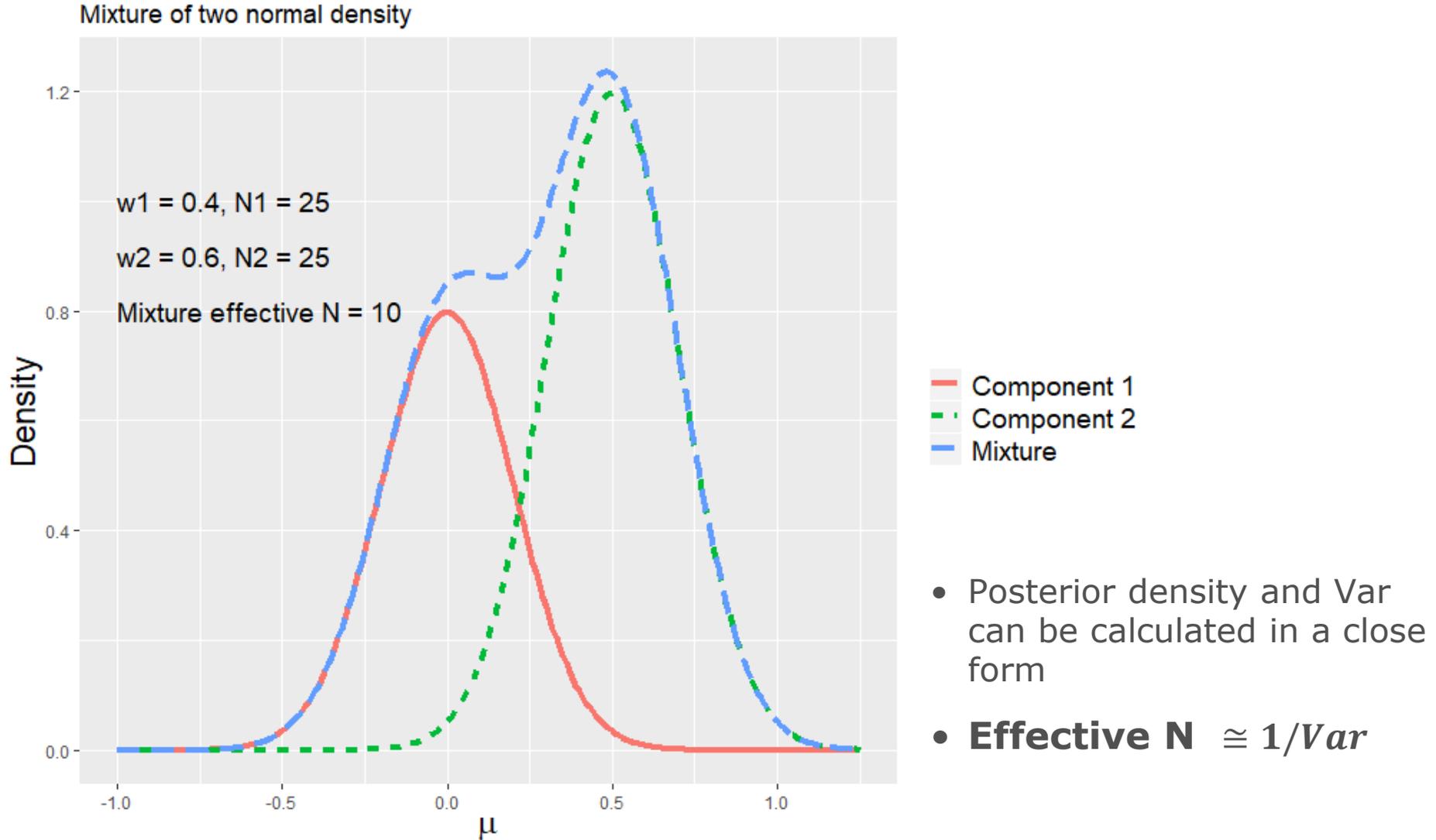
$$w_R f_R + \frac{1}{2}(1 - w_R)f_1 + \frac{1}{2}(1 - w_R)f_2$$

- The normal zero-mean, component, f_R
 - refer to as (“null” or “robust” or “skeptical”)
 - reflects a potential absence of a positive treatment effect in the pediatric population
 - Need to pre-specify the weight, w_R , and the variance for f_R
 - $(1 - w_R)$ is termed [the relevance factor](#), Pr(applicability of adult results) in Ye et. al. (2020)
- The normal densities f_1 and f_2 , will reflect data observed in the two short-term Phase 3 studies in adults
 - Effect sizes and the corresponding precisions will be known and fixed (“historical” data)

Example of Prior Mixture Density



Effective Sample Size Example



Posterior Computation for Mixture of Normal Densities

- Posterior distribution is also a mixture of normal densities

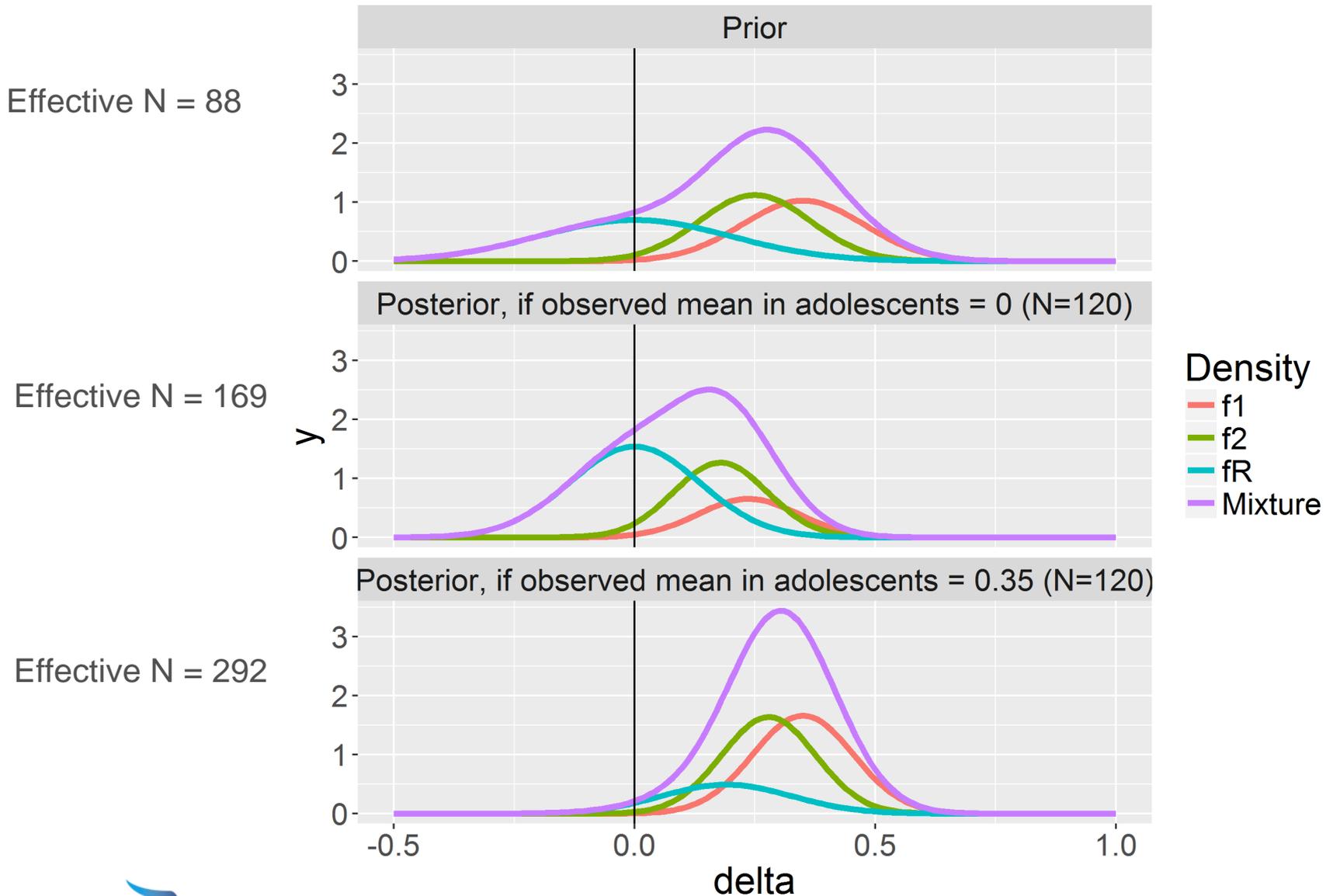
$$w_R^U f_R^U + w_1^U f_1^U + w_2^U f_2^U$$

- Data: Each individual component \mathbf{f} 's is updated as usual:
 - If prior: $Normal(m_0, 1/n_0)$
 - Then posterior: $Normal((n_0 m_0 + nM) / (n_0 + n), 1/(n_0 + n))$, where \mathbf{M} – the observed mean based on n pediatric study subjects

- Posterior weights in the mixture are updated by data in a way that reflects concordance of each component with the observed data

$$\simeq \exp\left(-\frac{(M - m_0)^2}{2(1/n_0 + 1/n)}\right)$$

Example Prior-to-Posterior Update



Outline of Design and Analysis

- Consider a conventional study design
 - Delta=0.45 (standardized), power=85%, N=180 (“completers”)
- Group sequential design: analyses at N=120, 150 and 180 (final).
- Bayesian MAP approach at interim and final analysis
- At interim analyses:
 - First, check precision (in terms of reaching the target effective N)
 - If the precision target is met, then run an efficacy analysis
 - Stop for efficacy, if
 - Posterior probability of a positive drug effect > X%
- If no early stopping for efficacy,
 - Perform final efficacy analysis regardless of meeting the precision target

Outline of Simulation Scenarios

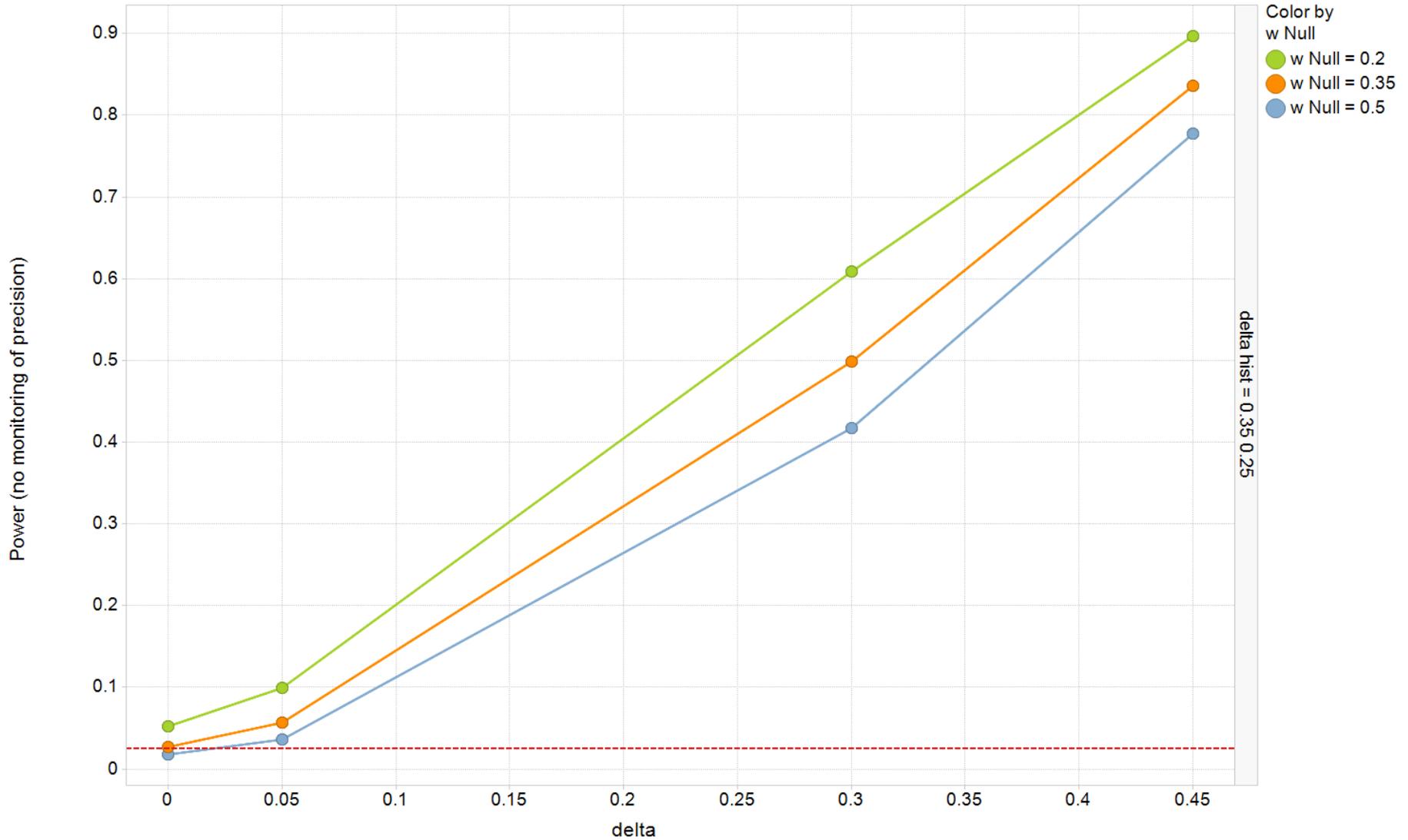
- Phase 3 program in the adult population:
 - Sample size 550 (combined for two studies)
 - Effect sizes 0.25 and 0.35 (will be known before trial)
- Grid of specifications for all design parameters:
 1. Prior mixture distribution (both weight and variability)
 2. Cut-off of the posterior probability to a positive treatment effect, e.g. 98%, 99%,..
 3. Also, Target precision at IA

Task: to select parameters that control Type I

- Also, evaluated power, the effective sample size (precision),...
- Under different schemes as for number and timing of IA

Example: Type I dependence on prior specification

Power (no monitoring of precision) vs. delta



Filter Settings

- delta: (0.00, 0.05, 0.30, 0.45)

- Number of Analysis in the Study: (4)

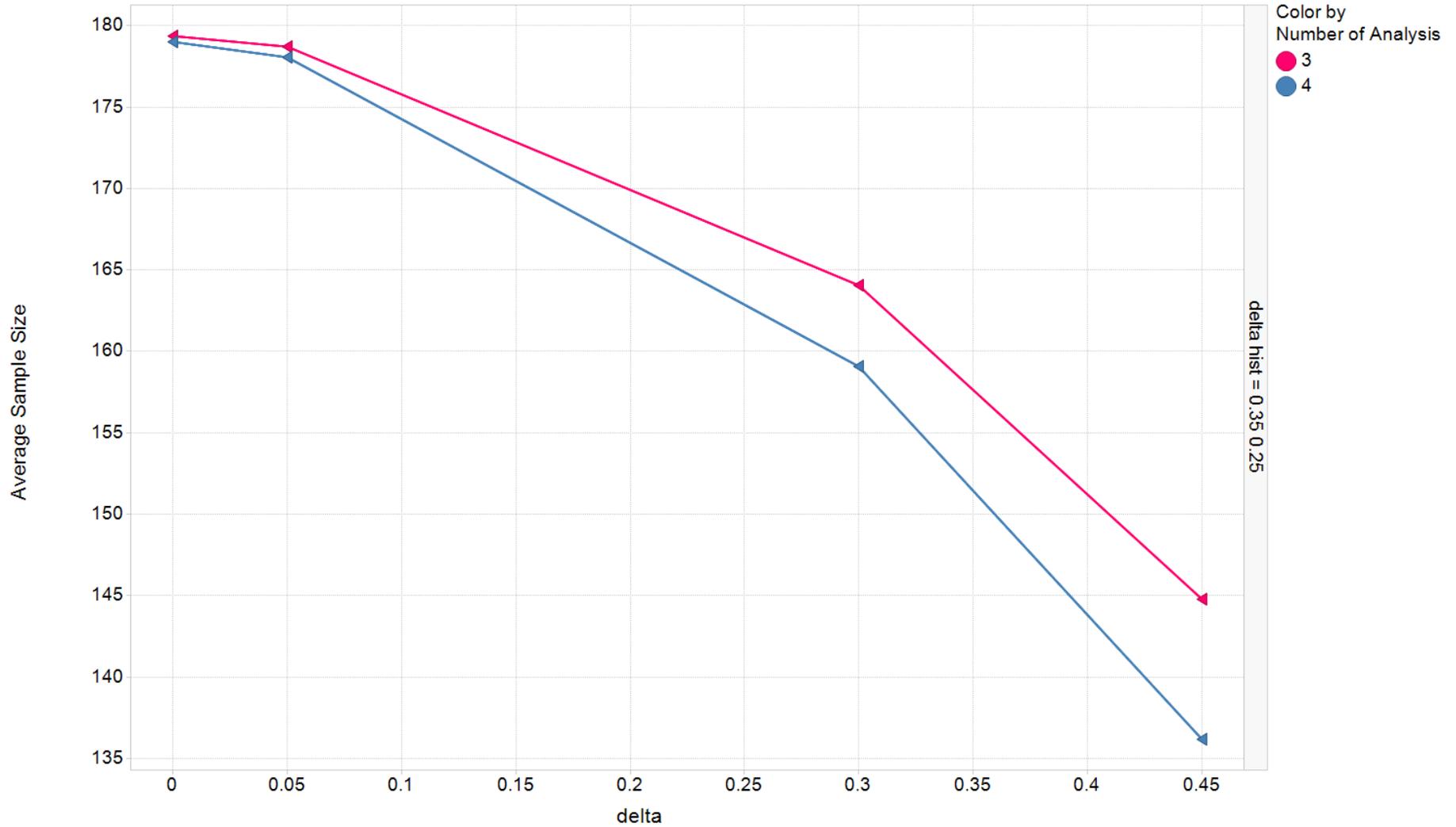
- N.target: (280)

- cutoffPr: (0.9925)

- w Null: (w Null = 0.2, w Null = 0.35, w Null = 0.5)

Average Sample Size

Average Sample Size vs. delta



Filter Settings

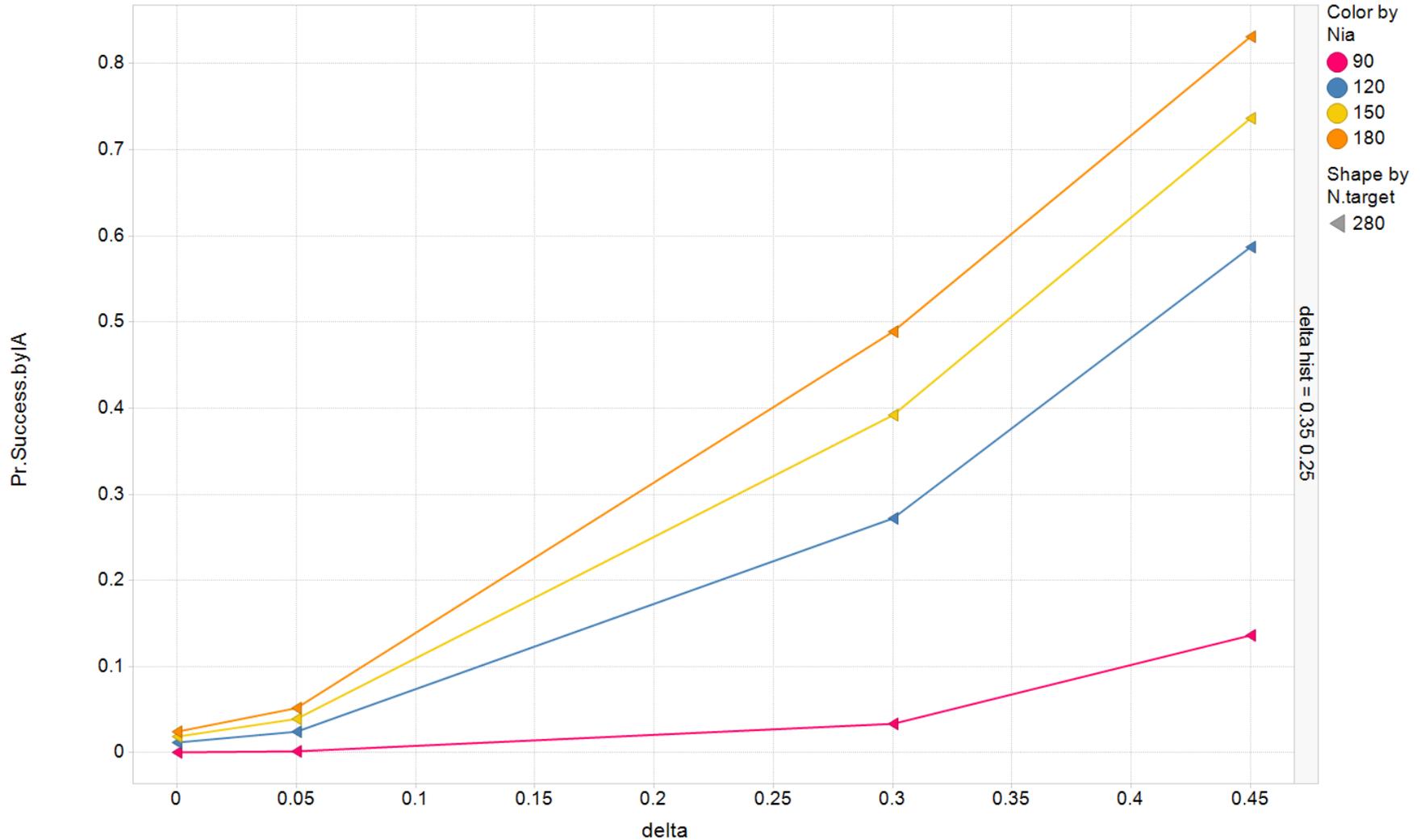
- delta: (0.00, 0.05, 0.30, 0.45)
- N.target: (280)
- cutoffPr: (0.9925)
- multipleVisits: (0.35)



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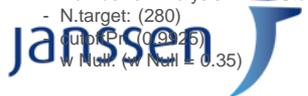
Probability of Success by IA

Pr.Success.byIA vs. delta



Filter Settings

- delta: (0.00, 0.05, 0.30, 0.45)
- Number of Analysis in the Study: (4)
- N.target: (280)
- W.Null: (W.Null = 0.35)



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Summary regarding Study Design and Analysis

- Robust MAP approach is recommended as the primary analysis
 - Combines historic data and observed data accounting on a potential prior-data conflict
- Control the Type I error
 - **Simulation based**
 - **Pre-specification** of
 - the prior distribution
 - number and timing of IA
 - rules applied at analyses
 - Actual specification will need to wait until results from Ph3 in adults will become available. Needed to be agreed with regulatory agencies
- **The proposed design and analysis maintain power and provided a substantial reduction in average sample size**

Clarification on Applying the Robust Meta-Analytic approach

- The similarity of placebo-adjusted effects in the adult and pediatric populations is not required for the validity of inferences
 - Regardless of the similarity level, the overall Type I error control will be preserved
- Potential similarity of the placebo-adjusted treatment effect in the paediatric and adult populations provides a possibility to minimize the unnecessary exposure of patients and gain efficiency

List of the Key Challenges

1. A concern regarding a simulation-based control of Type I
 - How to mitigate? Extensive simulation studies. Software and tools availability
2. Estimation (and control?) of a degree to which historical data will be brought into a pediatric study
 - Especially when a very few historical trials are available
3. A concern regarding early stopping for efficacy in pediatric studies in general
4. Measure of statistical information
 - Several definitions of an effective sample size are available
 - Amount of borrowed information is a random variable
5. Selection of “the best” method
 - Simplicity and interpretability seems to play an important role

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