Hierarchical Models in the Analysis of Master Protocols for Rare Diseases

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Disclaimer

- This speech reflects the views of the author and should not be construed to represent FDA's views or policies.

Basket Trials

- In some situations, we may want to answer questions on efficacy for multiple related diseases under a single protocol.
- Typically, studies with such a design are referred to as basket trials.
- Goal is to increase efficiency and quality.

Woodcock, J., & LaVange, L. M. (2017). Master protocols to study multiple therapies, multiple diseases, or both. *New England Journal of Medicine*, *377*(1), 62-70.

Hierarchical Models and Basket Trials

- In cases where we believe that there is a relationship between diseases or disease subtypes, we may want to consider methods of borrowing information between the groups in the trial to improve efficiency.
- Hierarchical Bayesian models have been proposed in this context.

Thall, P. F., Wathen, J. K., Bekele, B. N., Champlin, R. E., Baker, L. H., & Benjamin, R. S. (2003). Hierarchical Bayesian approaches to phase II trials in diseases with multiple subtypes. Statistics in medicine, 22(5), 763-780.

Hierarchical Models

- We assume if patient i is a member of group, h, then their outcome results from the following distribution:

$$y_i|\theta_h \sim N\left(\theta_h, \sigma_h^2\right),$$

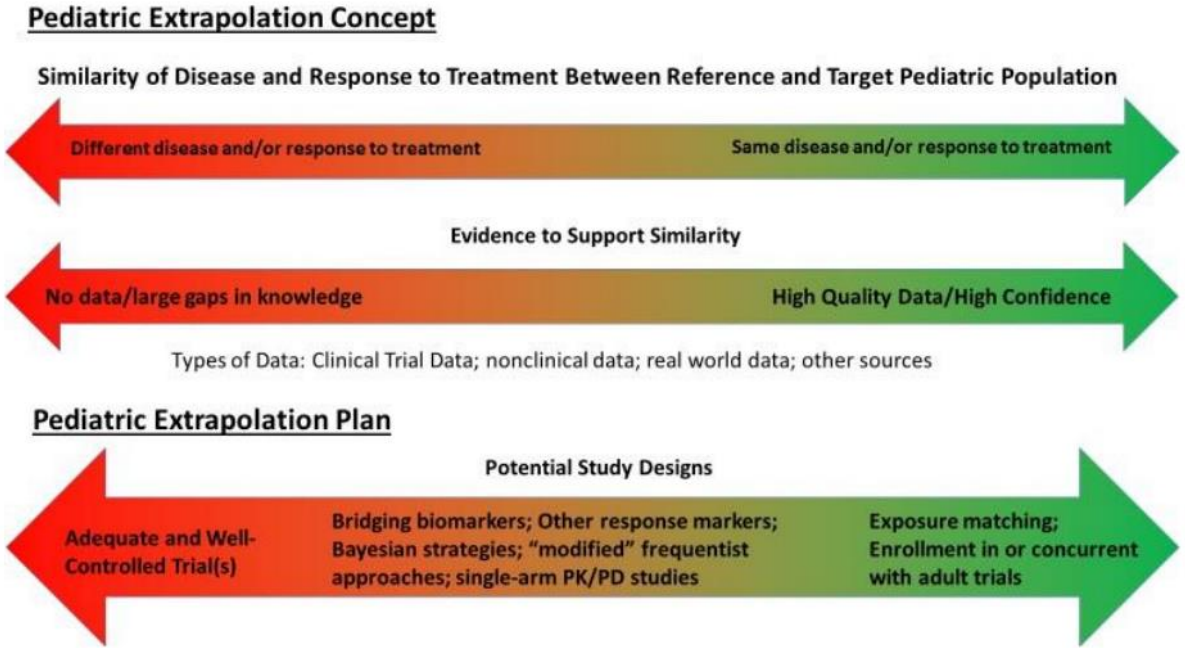
- We then assume the parameters for each group come from some common distribution characterized by the hyperparameters μ, τ:

$$\theta_1, \ldots, \theta_H, \theta^*|\mu, \tau^2 \sim N(\mu, \tau^2)$$

Hierarchical Model Hyperpriors

- For μ, the typical approach is to use a weak, locally noninformative prior distribution.
- Then τ controls the degree of borrowing
  - Small $\tau \Rightarrow$ more borrowing
  - Large $\tau \Rightarrow$ less borrowing
  - $\tau = 0 \Longrightarrow \text{pooling}$
  - $\tau = \infty \Longrightarrow \text{seperate analyses}$
- How do we calibrate τ for intermediate degrees of borrowing?

Pediatric Extrapolation



E11A Pediatric Extrapolation – https://www.fda.gov/media/161190/download

Hierarchical Model Calibration

- If we perform the analysis with and without utilizing the prior information, then we can compute the effective sample size contribution of the prior information using the following:

$$ESS = N_{Trial} \frac{Var(\theta^* | \text{prior information ignored})}{Var(\theta^* | \text{prior information utilized})}$$

Pennello, G., & Thompson, L. (2007). Experience with reviewing Bayesian medical device trials. *Journal of Biopharmaceutical Statistics*, *18*(1), 81-115.

ESS – Hierarchical Models (1/3)

- An alternative method of estimating the effective sample size, n^*, is:

$$n^* = \frac{V_0}{V_\tau} N_{Historical}$$

- $V_0 = Var(\theta^* | Y_1, \ldots, Y_H, \tau = 0) = \frac{1}{\sum \sigma_h^{-2}}$ (Pooling)
- $V_\tau = Var(\theta^* | Y_1, \ldots, Y_H, \tau)$

Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ. Summarizing historical information on controls in clinical trials. Clinical Trials. 2010;7(1):5-18. doi:10.1177/1740774509356002

ESS – Hierarchical Models (2/3)

- If we have approximately constant within-trial variance over all the trials, such that:

$$\sigma_h^2 = \frac{\sigma^2}{n_h}$$

- Then for a particular τ the ESS is as follows:

$$n^* = \frac{\sigma^2}{\frac{\sigma^2}{N} + \tau^2\left(1 + \left(\frac{1}{H}\right)\right)}$$

ESS – Hierarchical Models (3/3)

- If we solve for τ, then we can calculate the value of τ that corresponds to a particular effective sample size:

$$\tau = \sigma \sqrt{\frac{N - n^*}{N n^* \left(1 + \frac{1}{H}\right)}}$$

Calibration of τ and ESS

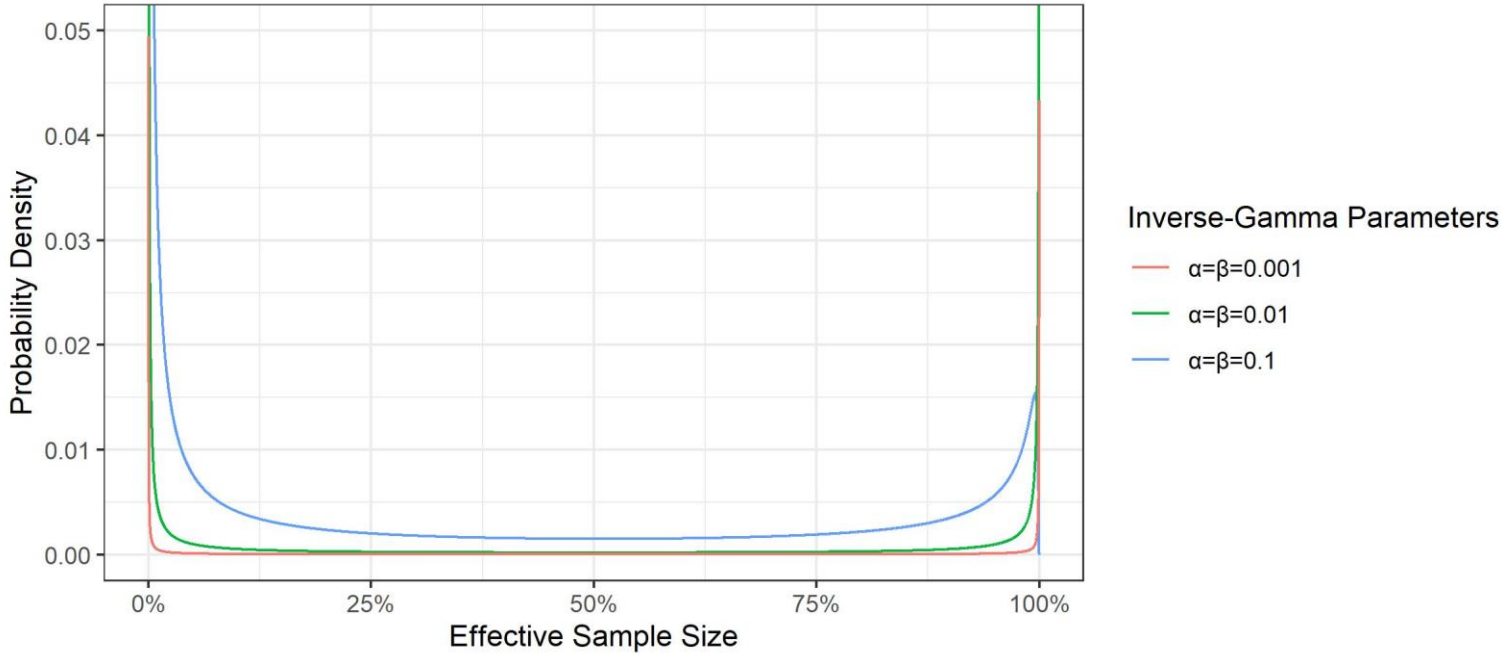
- The degree of borrowing is related to the asymptotic behavior of the prior for τ.
- To examine this, we can transform priors on τ to the ESS space. If f is the pdf of τ, then the pdf for n^* is:

$$\left|\frac{dg(n*)}{dn^*}\right| f\left(g(\mathrm{n}^*)\right)$$

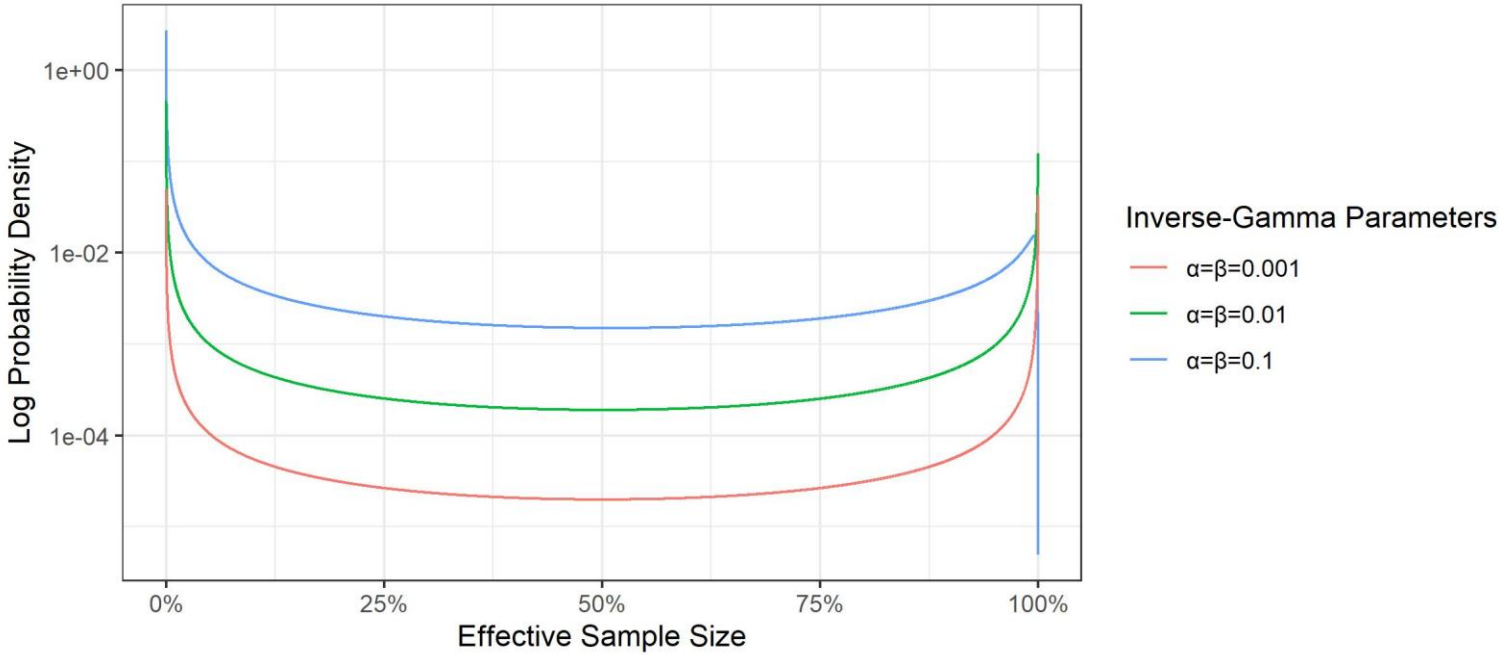
- Where:

$$\tau = g(\mathrm{n}^*) = \sigma\sqrt{\frac{N-n^*}{2Nn^*}}, \qquad \left|\frac{dg(n*)}{dn^*}\right| = \frac{\sigma}{2\sqrt{2}(n^*)^2\sqrt{\frac{1}{n^*}-\frac{1}{N}}}$$

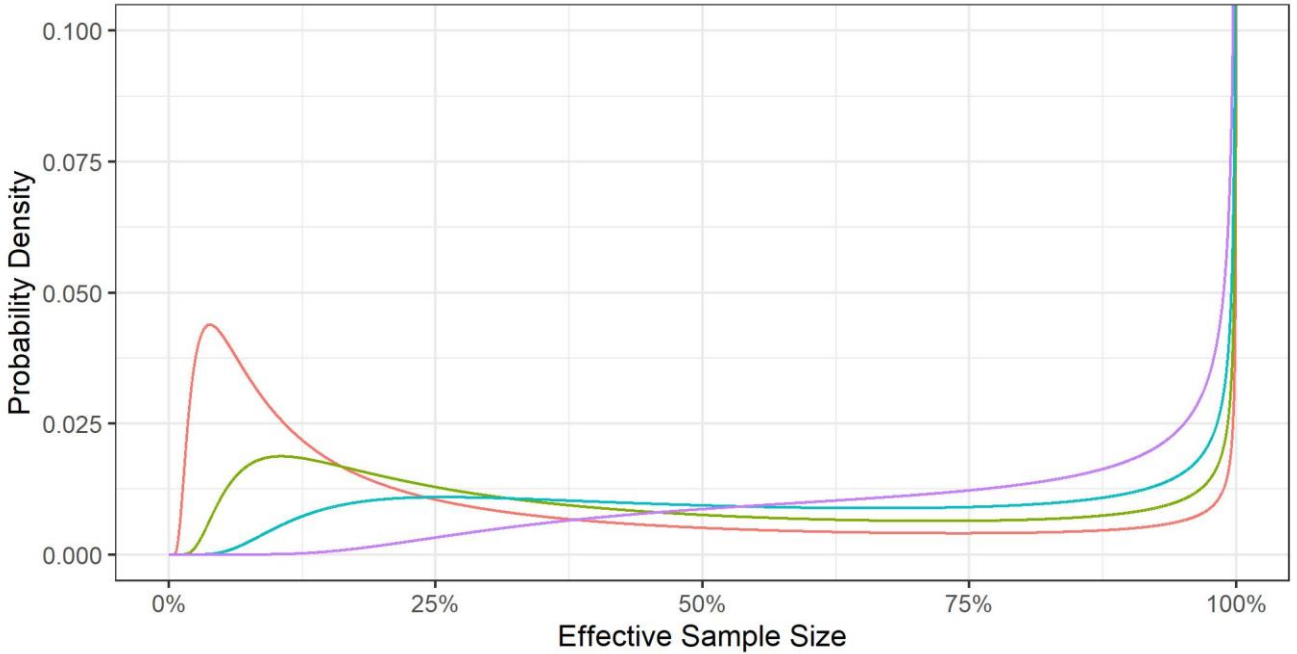
Inverse-Gamma (1/2)



Inverse-Gamma (2/2)



Half Normal Prior



$$HN\left(0, \sigma = \frac{\tau}{\sqrt{2}\,\mathrm{erf}^{-1}(0.5)}\right)$$

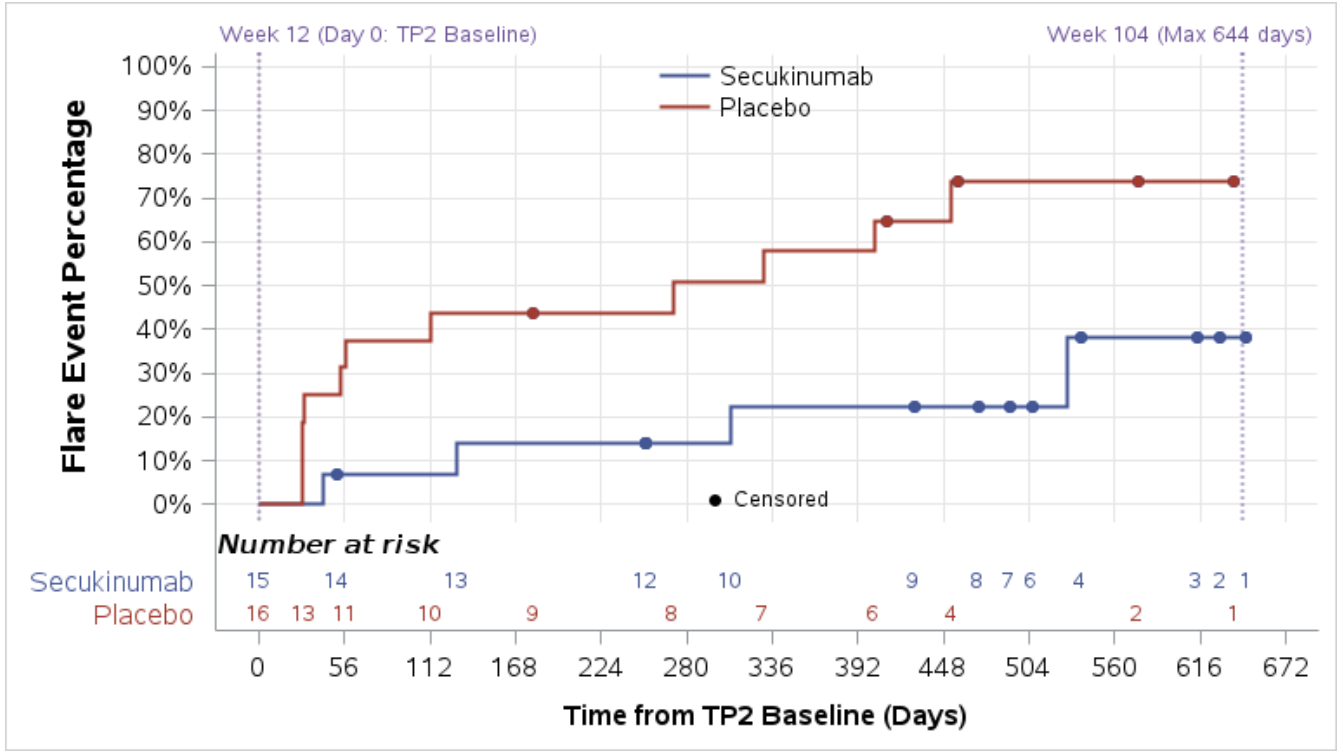
Example

- A trial was conducted to study the efficacy of secukinumab in treating two types of arthritis in pediatric patients: enthesitis related arthritis and juvenile psoriatic arthritis.
- All enrolled patients were treated with secukinumab and patients who responded were randomized to either continue receiving secukinumab or be treated with placebo.
- For both populations, the primary endpoint was time to disease flare.

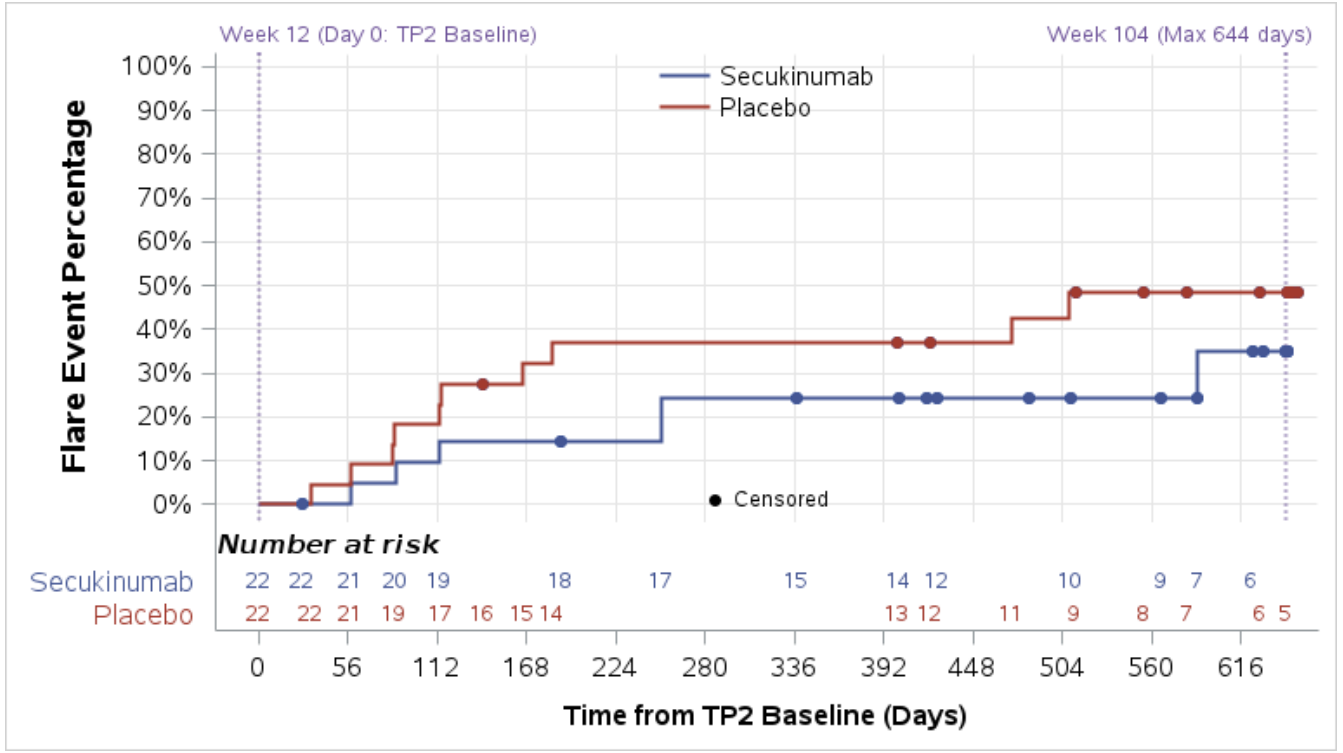
Study Results

Population	Secukinumab: # of Flare Events/ # of Subjects (% Subjects with Flare)	Placebo: # of Flare Events/ # of Subjects (% Subjects with Flare)	Hazard Ratio Estimate (95% CI)	Stratified Log-rank test (One -sided nominal p-value)
Pooled Stratified by Population (JPsA/ERA)	10/37 (27%)	21/38 (55%)	0.28 (0.13, 0.63)	<0.001
Pooled Unstratified by Population	10/37 (27%)	21/38 (55%)	0.33 (0.15, 0.70)	0.001
JPsA Alone	4/15 (27%)	11/16 (69%)	0.15 (0.04, 0.56)	<0.001
ERA Alone	6/22 (27%)	10/22 (45%)	0.47 (0.17, 1.32)	0.081

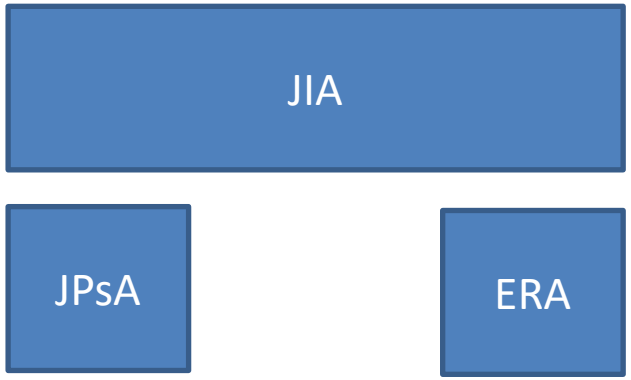
JPsA Results



ERA Results


Week 12 (Day 0: TP2 Baseline)
Week 104 (Max 644 days)
Flare Event Percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Secukinumab
Placebo
Censored
Number at risk
Secukinumab 22 22 21 20 19 18 17 15 14 12 10 9 7 6
Placebo 22 22 21 19 17 16 15 14 13 12 11 9 8 7 6 5
0 56 112 168 224 280 336 392 448 504 560 616
Time from TP2 Baseline (Days)

Hierarchical Bayesian Model



- Model:

$$\log\left(\widehat{HR}_{JPsA}\right) \sim N\left(\theta_{JPsA}, \hat{\sigma}^2_{JPsA}\right) \text{ and } \log\left(\widehat{HR}_{ERA}\right) \sim N\left(\theta_{ERA}, \hat{\sigma}^2_{ERA}\right)$$

$$\theta_{JPsA}, \theta_{ERA} \sim N(\mu, \tau^2)$$

Estimating the Standard Deviation

- To estimate the standard deviation, we used the following formula for the pooled data:

$$\sigma = \sqrt{r_t \left(\frac{1}{r_e} + \frac{1}{r_c} \right)}$$

- Where r_t was the total number of observed events, and r_e and r_c are the number of events in the experimental and control arms.

$$\sigma = \sqrt{31 \left(\frac{1}{10} + \frac{1}{21} \right)} = 2.14$$

Rothmann, M.D., B.L. Wiens, and I.S. Chan, *Design and analysis of non-inferiority trials*. 2011: CRC press.

Prior Selection

- For example, suppose we want to target an effective sample size of 7.5 events (50% discounting):

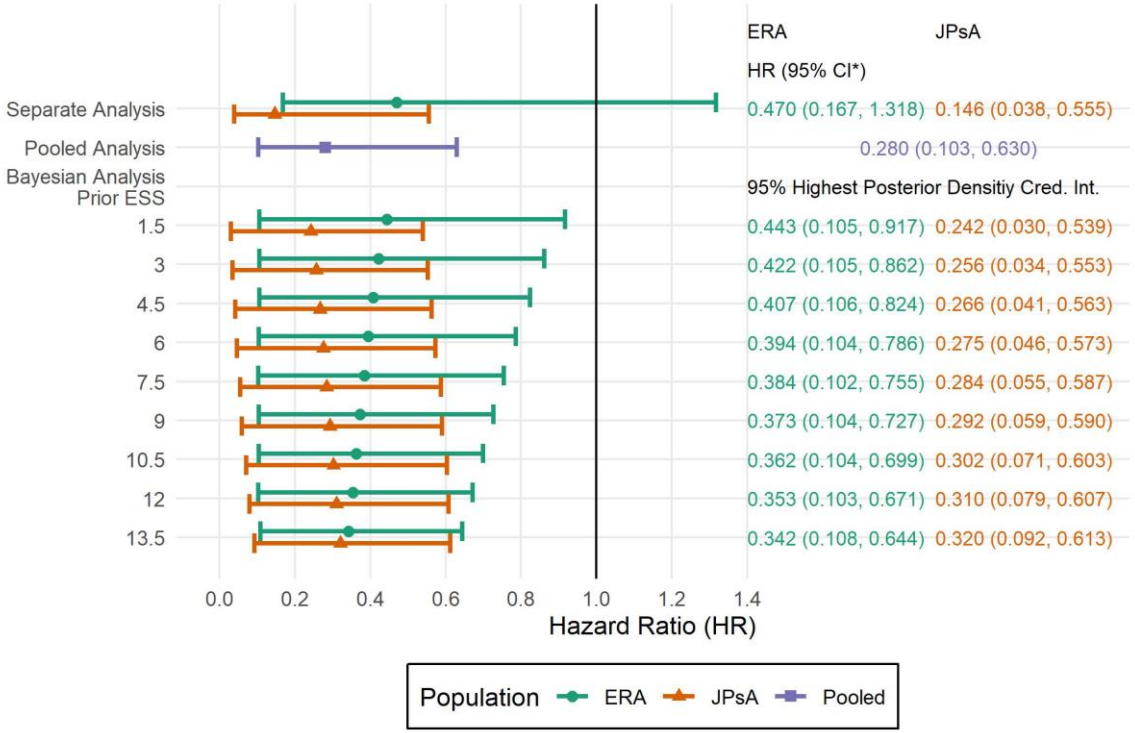
$$\tau_{7.5} = 2.14 * \sqrt{\frac{(15 - 7.5)}{2 * 15 * 7.5}} = 0.39$$

- Rather than using a fixed value, we wanted to use a prior distribution for τ to reflect the uncertainty. We chose a $\text{half}-\text{normal}(0, \sigma^2)$ prior with $\text{mean} = \tau_{7.5}$.

$$\text{Half-normal mean} = \frac{\sigma\sqrt{2}}{\sqrt{\pi}} = \tau_{7.5}$$

$$\sigma^2 = \frac{\pi}{2}\tau_{7.5}^2 = 0.24$$

Analysis Results



Example Conclusion

- Applying this Bayesian method allowed us to get a more complete picture between the planned extremes of pooling and separate analyses.
- This demonstrates the value of this type of method in master protocols where the same treatment is explored for multiple related populations under a single protocol.

Conclusion

- Bayesian methods offer an opportunity to reduce the practical burdens of trials for multiple disease subtypes.
- These methods allow us to evaluate the relationship between groups with more flexibility.
- In general, the key challenge is calibration of the value/relevance of the borrowed information.

Acknowledgements

- Eiji Ishida
- Yun Wang
- Mark Rothmann

References

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- E11A Pediatric Extrapolation – https://www.fda.gov/media/161190/download
- FDA Impact Story https://www.fda.gov/drugs/regulatory-science-action/impact-story-using-innovative-statistical-approaches-provide-most-reliable-treatment-outcomes
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