Incorporating Adult Clinical Data into Pediatric Clinical Trials: A Robust Bayesian Approach

Satrajit Roychoudhury
Pfizer Inc.
ASA NJ Chapter 40th Annual Spring Symposium
Piscataway, NJ
June 28, 2019

GLOBAL PRODUCT DEVELOPMENT

Disclaimer

The views and opinions expressed herein are solely those of the presenters and are not necessarily those of Pfizer Inc. Any of these cannot and should not necessarily be construed to represent those of Pfizer Inc. or its affiliates.

Acknowledgement

- Beat Neuenschwander, Novartis Pharma AG
- Heinz Schmidli, Novartis Pharma AG
- Michael Branson, Celgene

Extrapolation and Prediction

- Extrapolation/Prediction common in clinical research
  - From historical control to concurrent control
  - From adults to children
  - From biomarker to clinical endpoint
  - From one drug to another
- Bayesian approaches are very natural for evidence synthesis and extrapolation/prediction
- Though the methodology is well developed, the use in practice is still rare

Regulatory Considerations

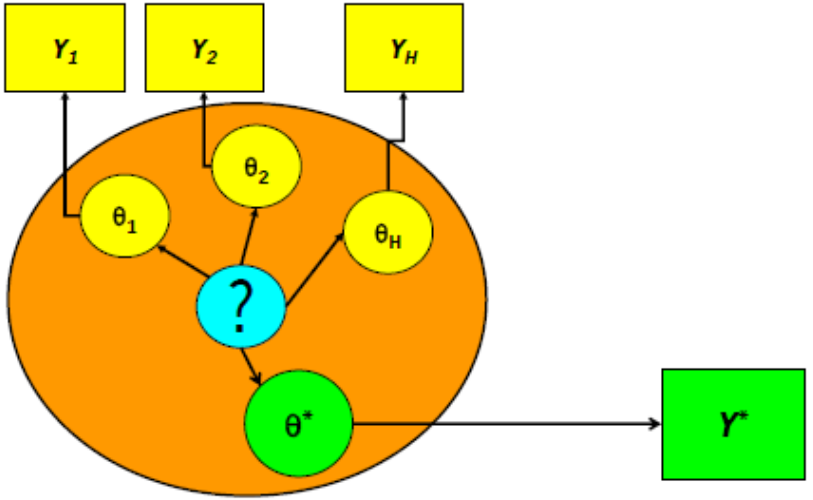
- EMA (2017) : Reflection paper on extrapolation of efficacy and safety in pediatric medicine development (draft)

... using Bayesian methods to either summarize the prior information for the extrapolation concept, or to explicitly borrow information (from adult trials, from control groups, from other pediatric clinical trials)

- FDA (2016): Leveraging existing clinical data for extrapolation to pediatric uses of medical devices

While Bayesian methods are described in this document, non-Bayesian methods can also be used for borrowing strength

Extrapolation: General Framework



- Meta-Analytic Approach
  - uses a model for all quantities, which involves a parameter model
  - infers the parameter of interest θ_*
    - at the design stage (without Y_*),
    - or at the end of the new trial (with Y_*),

Meta-Analytic (MA) Approaches

- ***Meta-Analytic-Predictive* (MAP)** is **prospective**
  - At design stage of current trial, perform meta-analysis of *co-data* and obtain distribution of θ_*

$$\textbf{MAP Prior: } \theta_* \mid Y_1,\ldots Y_C$$

  - Combine MAP prior with current trial data Y_* (Bayesian analysis)
- ***Meta-Analytic-Combined (MAC) is retrospective***
  - Perform a meta-analysis of all co-data and current trial data
  - Parameter of interest: the parameter in the actual trial

$$\theta_* \mid Y_1,\ldots Y_C, Y_*$$

MAP or MAC?

- ***Meta-Analytic-Predictive (MAP)***
  - MAP priors not analytically available (can be approximated by mixtures)
  - MAP approach is cumbersome for adaptive designs with concurrent co-data
- ***Meta-Analytic-Combined (MAC)***
  - No prior for θ_* required at design stage
  - Only one analysis required, can be (non-)Bayesian
- MAP and MAC are equivalent. This means
  - we can summarize MAP prior in protocol with all the historical co-data
  - and later do MAC analyses with historical and concurrent co-data

Pediatric Extrapolation

- Pediatric drug development faces substantial hurdles, including economic, logistical, technical, and ethical barriers
- An efficient design for pediatric may “extrapolate”
  - from adults to pediatric patients, between pediatric subpopulations
- Assumes that there is no need for formal proof of efficacy in the pediatric population
  - no substantial difference in proof of mechanism between adult and children (supporting PK/PD information)
- Meta-Analytic framework: a powerful tool for extrapolation
- However validation of extrapolation concept is key
  - use of predictive check to ensure data or model adequacy for extrapolation

Quantifying All Available Evidence

- Setting: Confirmatory evidence available for adult and sparse data available for pediatric
- Objective: to propose a quantitative approach that
  - allows comparing the available evidence available for children to a confirmatory standard
  - complements and improves qualitative decisions
- Disclaimer: what follows
  - is not meant to replace the standard confirmatory approach
  - it is meant to complement it

Predictive Evidence Threshold Scaling (PETS)

Three requirements

- a confirmatory standard: (hypothetical) data $Y_{(C)}$
- a metric to compare available or actual evidence Y_E to $Y_{(C)}$
- a metric-based rule to decide whether non-confirmatory data is sufficiently strong
  (e.g., evidence from small pediatric patients and adult patients)

Hierarchical Structure

- Actual, non-confirmatory data $\mathbf{Y_E}$ from J sources
  - estimates $Y_1, Y_2, \ldots Y_J$
  - standard errors $s_1, s_2, \ldots s_J$
  - **parameters** $\theta_1, \theta_2, \ldots \theta_J$
- Hypothetical (minimal) confirmatory evidence $\mathbf{Y_{(C)}}$
  - e.g., two significant trials; or one in Pediatrics, Oncology, Rare disease
  - estimates $Y_{(1)}, Y_{(2)}$
  - standard errors $s_{(1)}, s_{(2)}$
  - **parameters** $\theta_{(1)}, \theta_{(2)}$
- These effect parameters differ (heterogeneity!)

Metrics for Evidence Quantification

- Metric to compare actual and hypothetical confirmatory evidence
  - metric should be trial-independent (not the effect parameter of one of the trials in the database)
  - choice: probability of a «positive» effect θ_P in a new trial

$$pr(\theta_P > 0 \mid data)$$

  - note: inequality cutoff may be non-zero (e.g. NI trials)
  - heterogeneities to account for:
    - heterogeneity across data sources (actual or confirmatory)
    - predictive heterogeneity

Three Heterogeneities

- Heterogeneities: deviations from mean value μ
  - for effect parameters in actual trials τ_E
  - for effect parameters in confirmatory trials τ_C
  - for effect parameter in new trial τ_P

$$\theta_1, \theta_2, \ldots, \theta_J \approx \theta_P \approx \theta_{(1)}, \theta_{(2)}$$

$$\Downarrow$$

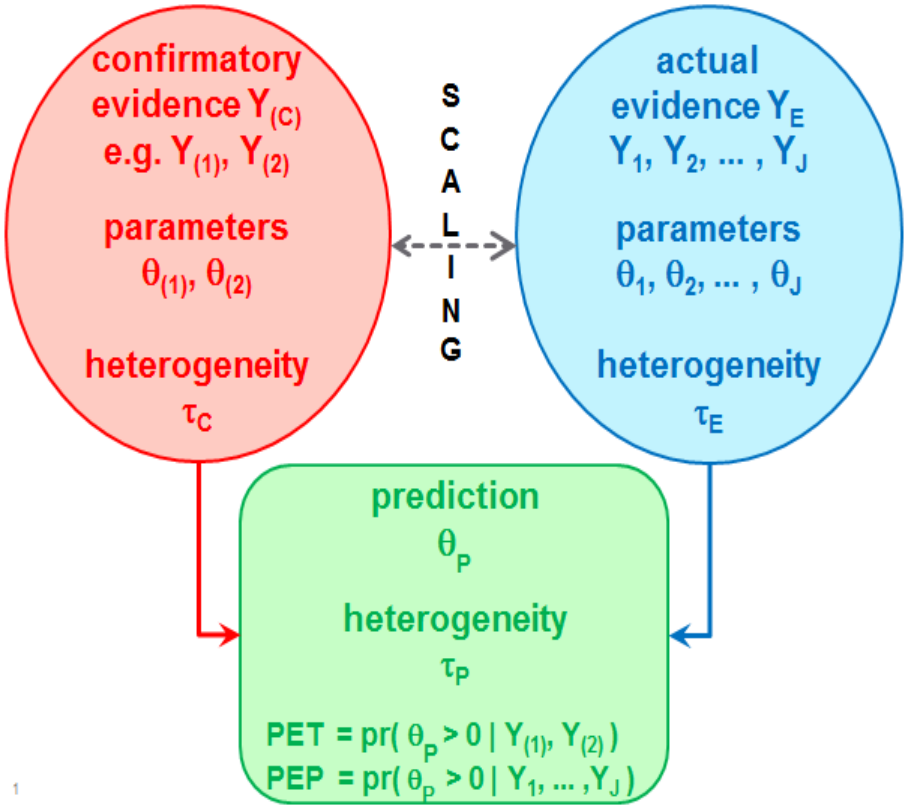
If parameters are similar, the actual evidence Y_E will have higher confirmatory relevance

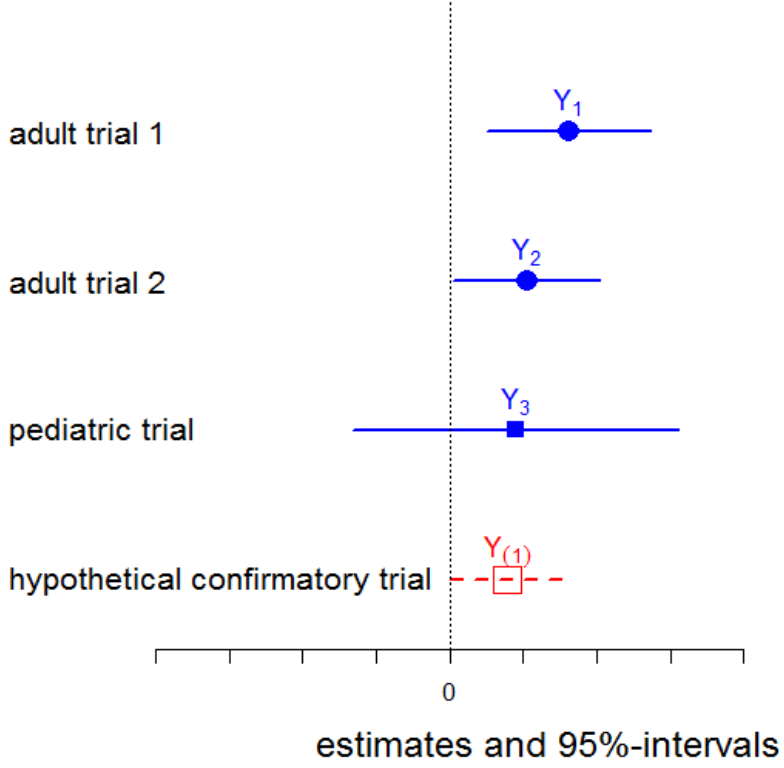
If parameters differ considerably, evidence will be discounted due to larger heterogeneity

Predictive Evidence Probability (PEP) and Threshold (PET)

- Scaling of Y_E vs. $Y_{(C)}$
- For the actual evidence
  - *predictive evidence probability* (PEP): pr($\theta_P > 0 \mid Y_E$)
  - predictive probability of «positive effect» in a new trial
- For the (hypothetical) confirmatory evidence
  - *predictive evidence threshold* (PET): pr($\theta_P > 0 \mid Y_{(C)}$)
- How large are PEP and PET?
- Default rule for sufficient evidence: PEP ≥ PET

PETS Framework

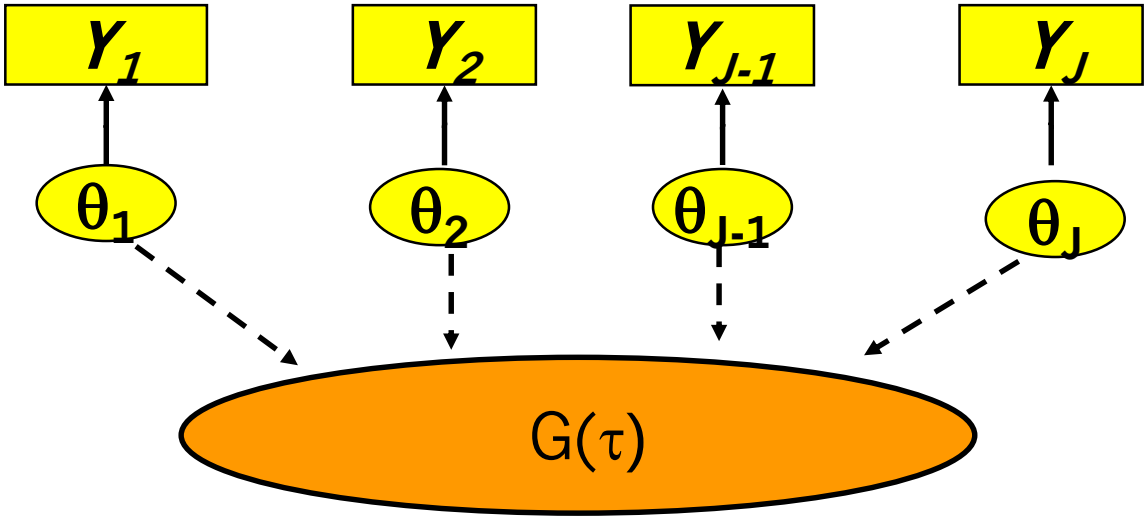




Combining Heterogeneous Evidence: Hierarchical model

- Most clinical literature uses two extreme models
  - **No pooling:** Separate inference for each tumor type (stratified analysis) - *"Low power for small sample size situations"*
  - **Complete pooling:** grouping in the data is irrelevant, i.e. imposing restriction that all tumor type effects are same – "optimistic borrowing"
- Bayesian hierarchical modeling is a specific methodology may be used to combine information of different strata.
- **Exchangeable/Hierarchical model** lies between these two extreme cases
  - "Shrinkage": the estimates are pulled towards a common mean

A Meta-Analytic Framework for Co-Data



- data (sampling) model $Y_j \mid \theta_j \sim F(\theta_j)$
- parameter model $\theta_1,\ldots, \theta_J, \theta_* \mid \tau \sim G(\tau)$:Exchangeability
- too restrictive if relevance of *co-data* differs
- Possible Extension: adjustment with covariates → Partial exchangeabilty

Normal-Normal Hierarchical Model

- The normal-normal hierarchical model (NNHM)
  - (approximately) normally distributed estimates Y
  - normally distributed parameters θ
- Heterogeneities: parameter τ_C, τ_P, τ_E
  - similar (or equal) small confirmatory and predictive heterogeneity, $\tau_C \approx \tau_P$, since confirmatory setting is more revevant
  - two approaches
    - assumed parameters $\rightarrow$ sensitivity analyses for plausible scenarios
    - or uncertain parameters $\rightarrow$ prior distributions on parameters
    - choices must be sensible (depend on the context)

Normal-Normal Hierarchical Model

- NNHM with differential heterogeneity
  - data model $Y_k|\theta_k, s_k^2 \sim N(\theta_k, s_k^2)$, $Y_{(k)}|\theta_{(k)}, s_{(k)}^2 \sim N(\theta_{(k)}, s_{(k)}^2)$
  - parameter model $\theta_k|\mu, \tau_k^2 \sim N(\mu, \tau_E^2)$, $\theta_{(k)}|\mu, \tau_C^2 \sim N(\mu, \tau_C^2)$
  - prediction $\theta_p|\mu, \tau_p^2 \sim N(\mu, \tau_p^2)$
  - note: standard NNHM uses a common τ
- Two calculations with NNHM: PET and PEP
  - PET: pr($\theta_p > 0$ | confirmatory data $Y_{(C)}$)
  - PEP: pr($\theta_p > 0$ | actual data Y_E)

NNHM PET and PEP Calculations for Fixed Heterogeneities

- PET and PEP calculation for fixed τ parameters
  - Bayesian with flat prior for μ

$$\boldsymbol{\theta_P | Y_1, \ldots \sim N(\hat{\mu}, \frac{1}{w_+} + \tau_p^2)}$$

$$\hat{\mu} = \sum_k w_k Y_k \, / w_+$$

$$w_k = \frac{1}{s_k^2 + \tau_k^2} \quad \text{(precisions)}$$

$$w_+ = \sum_k w_k \quad \text{(total precision)}$$

  - «equivalent» classical result: $\boldsymbol{\hat{\theta}_P = \hat{\mu}, \quad \widehat{se}^2 = \frac{1}{w_+} + \tau_p^2}$

Extensions

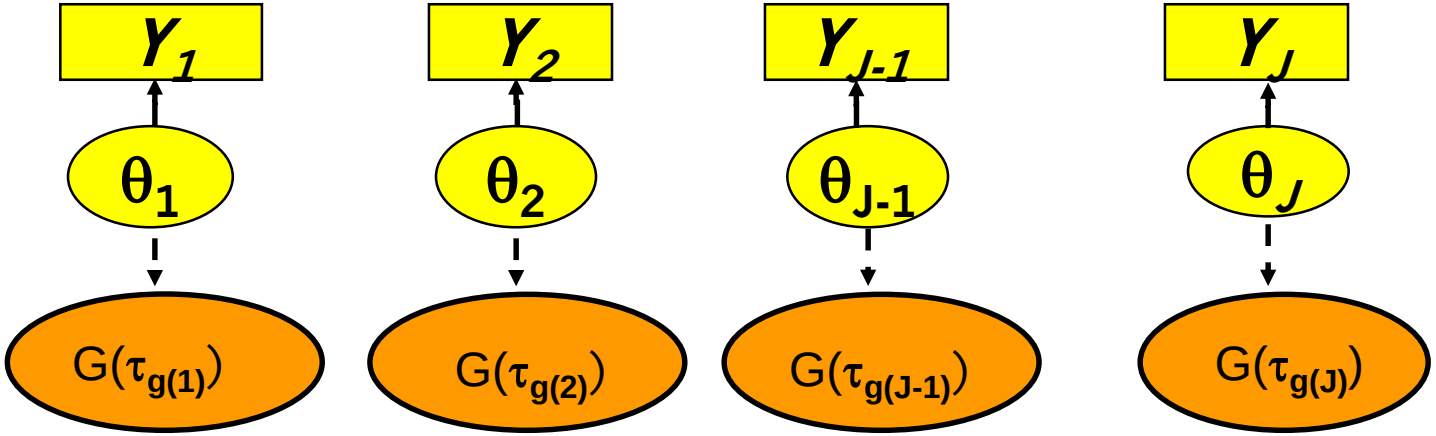
- Other sampling models
- Analyses with uncertainty for τ
- Inclusion of covariates
- Individual patient data
- ...
- **Systematic biases**

Extensions: systematic biases

- So far: no systematic biases assumed, all distributions centered at μ
- (Sensitivity) analyses with systematic biases
  - allow for trial-specific biases $\boldsymbol{\delta_k}$
  - require judgement about plausible bias scenarios
  - simple model extension

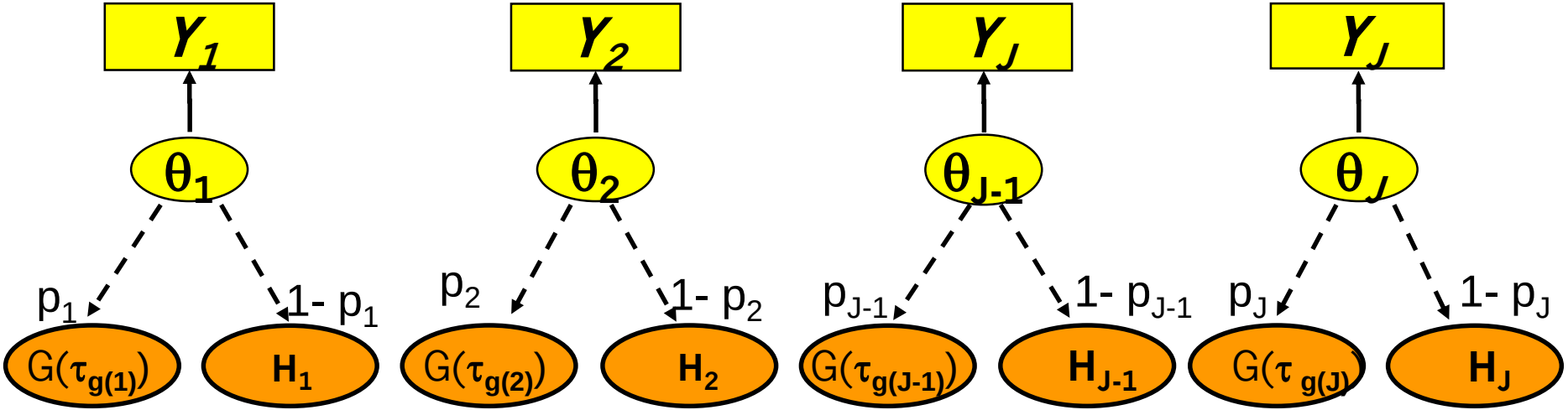
$$\boldsymbol{\theta_k|\mu, \tau_k^2, \delta_k \sim N(\mu + \delta_k, \tau_k^2)}$$

Flexible Meta-analytic Approach for Co-data



- Extension: $\theta_j \sim G(\tau_{g(j)})$ $g(j) \in \{1,...,G\}$, $j = 1,...J,_*$ Differential discounting
- For example:
  - G=2 for observational and randomized *co-data*
  - note: the larger G, the less information for between-trial sd $\tau_1,..,\tau_G$

A Robust Meta-analytic Approach for Co-data



- **Robustification**: $\theta_j \sim p_j\, G(\tau_{g(j)}) + (1- p_j)\, H_j : g(j) \in \{1,...,G\}, j = 1,...J,_*$
- Allows for nonexchangeable parameters to add robustness

Prior distributions for τ's

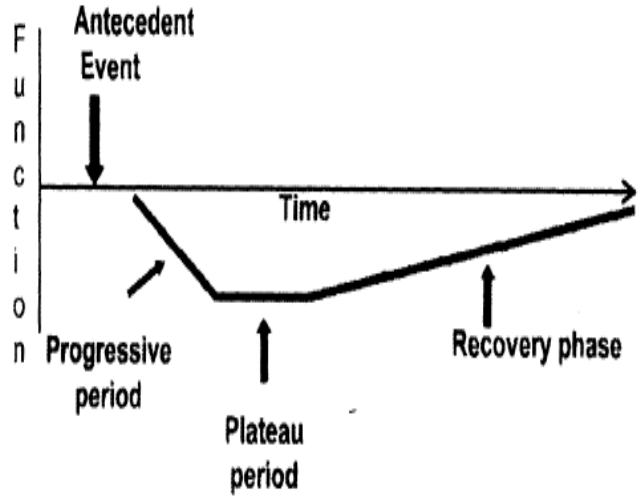
- Since the number of trials (J) is usually small, priors matter
- Recommendations (Spiegelhalter 2004, Gelman 2006)
  - use priors that put most of their probability mass on plausible values
- Example: Between-trial standard deviations on log-hazard-ratio scale

	Heterogeneity					
	Very large	Large	Substantial	Moderate	Small	Very small
τ	1	0.5	0.25	0.125	0.062	0.031
$\exp(\theta_{97.5\%})/\exp(\theta_{50\%})$	7.1	2.66	1.63	1.28	1.13	1.06

Example: Pediatric Trial on Guillain-Barre Syndrome

- Guillain-Barre syndrome (GBS) is a rare disease
- Affecting about 6,000 to 9,100 people in the U.S. each year
  - annual incidence rate of GBS was 1.51 per 100,000 children
  - most common paralytic illness of children
- Most common primary symptoms are
  - weakness, pain, ataxia, difficulty with balance
  - bent legs, flexed hips and lancinating pain
  - unwillingness or inability to walk

Disease and Endpoint



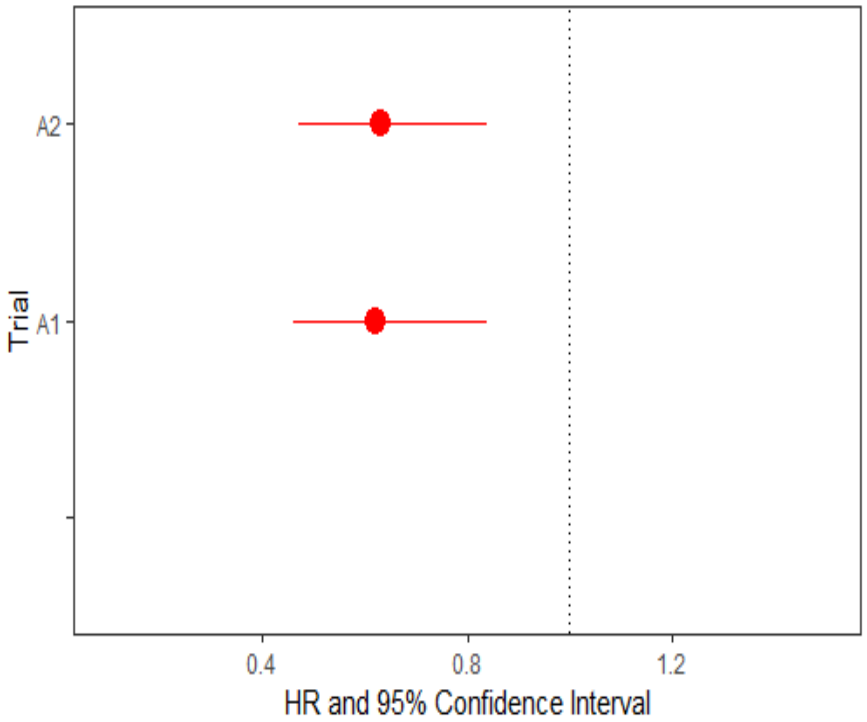
Source: Goodman and Sladky, Clinical Trials 2005

- Autoimmune disease with 4 stages
- The severity of GBS is assessed with a clinical grading scale
  - Grade 1: Minor signs or symptoms
  - Grade 2: Can walk 5 m independently
  - Grade 3: Walk 5 m with support
  - Grade 4: Chairbound
  - Grade 5: On ventilator for all or part of day
- Need for treatment: Grade 3 or above
- **Endpoint**: time to recover ambulation
  - defined as the ability to walk at least 5 m without assistance (grade 2 or lower)

Treatment Options

- Two main treatment option for GBS are
  - **Intravenous Immunoglobulin (IVIg) therapy:** this is treatment with a blood product that helps to decrease the immune system's attack on the nervous system.
  - **Plasmapheresis or plasma exchange (PE):** this is a procedure to remove the fluid part of the blood (plasma) and replace it with other fluids. This may help reduce the symptoms of the disease
- Plasmapheresis is a complex procedure that can be hard to do on children
  - it is difficult to perform well powered study for pediatric population
  - how to use all available information?

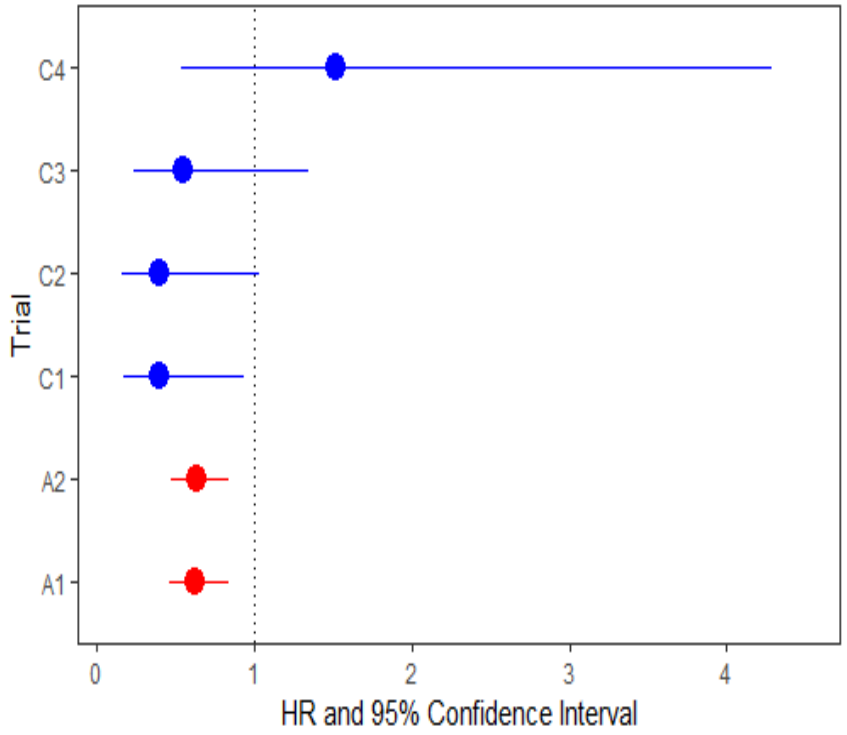
Adult Data of Plasmapheresis



- Two large randomized trials PE vs placebo
  - substantial decrease in the median time to unassisted walking
  - Highly significant HR

Trial	N	HR	95% CI
A1: McKhann (1985)	245	0.62	(0.46, 0.84)
A2: Raphael (1987)	220	0.63	(0.47, 0.84)

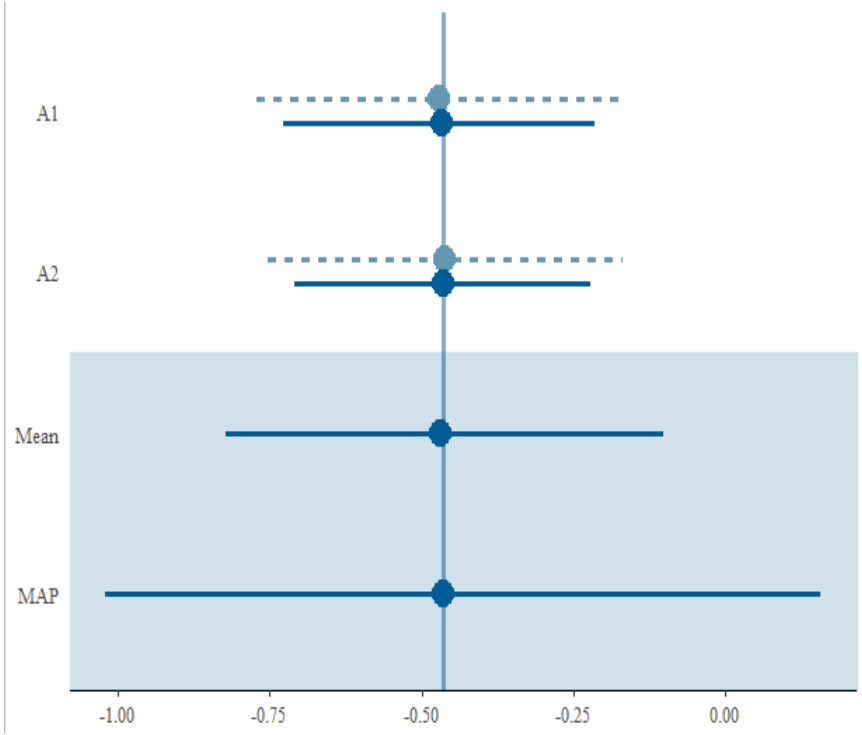
Adult and Pediatric Data of Plasmapheresis



- Four small observational pediatric trials are available
  - evidence is promising but sparse!

Trial	N	HR	95% CI
A1: McKhann (1985)	245	0.62	(0.46, 0.84)
A2: Raphael (1987)	220	0.63	(0.47, 0.84)
C1: Epstein et al (1990)	23	0.40	(0.17, 0.94)
C2: Lamont et al (1991)	24	0.40	(0.16, 1.03)
C3: Jansen et al (1993)	19	0.55	(0.23, 1.34)
C4: Graf et al (1999)	15	1.52	(0.54, 4.29)

Using Adults Data in Pediatric Evidence



- Prediction using two adult data supports the outcome of C1-C4

Caculation of PETS scenario analyses: assumptions

- Scenario assumptions for heterogeneities/biases
  - actual trials
    - 3 heterogeneity scenarios for adult/children trials:
      - moderate/small, substantial/moderate, large/substantial
    - 3 bias scenarios for children trials
      - 0% (no bias), 10% bias, 25% bias
  - one confirmatory trial in children
    - 200 events => A HR of 0.758 need to be observed for statistical significance
    - confirmatory heterogeneity = small

$\Rightarrow$ PET = 0.95

  - predictive heterogeneity = small

PETS scenario analyses: results

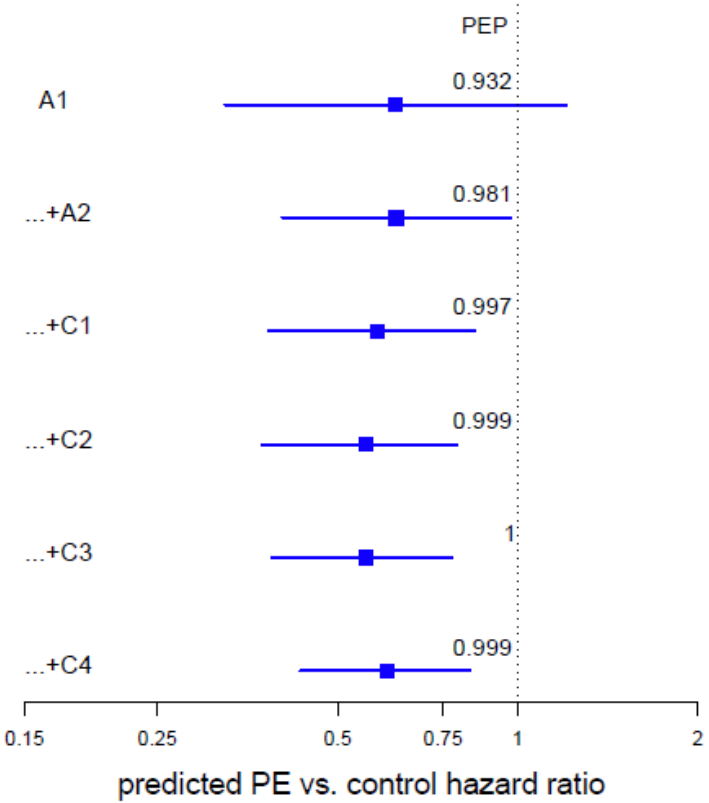
	heterogeneity: adult/children		
bias (trials C1-C4)	moderate/small	substantial/moderate	large/substantial
	adult trials		
	0.999	0.985	0.894
	adult trials + children trial 1		
no	1	0.997	0.98
10%	1	0.996	0.974
25%	1	0.994	0.958

- Extrapolation based on adult data only is insufficient if heterogeneity is large/substantial: PEP = 0.894
- With data from first children trial (C1), PEP > PET for all scenarios
- Conclusion: strong adult data combined with sparse pediatric data provides sufficient evidence

Bayesian PETS analyses

- Alternative to fixed scenarios: prior distributions on
  - heterogeneities: log-normal priors on τ parameters
  - biases: normal priors on δ parameters
- PETS results
  - are similar if priors cover the range of the fixed scenarios used previously
  - are shown cumulatively on next slide:
    trial A1, trials A1+A2, trials A1+A2+C1, etc.
- Finally we performed an analysis where we allowed 50% chance of non-exchangeabity for each trial
  - PEP = 0.978

Bayesian PETS analyses: cumulative results



Conclusions

- Increasing pressure on the pharmaceutical industry
  - scope for innovation is broad (for policy and science)
  - one aspect is to better use the evidence, which includes pediatric extrapolation (21st Century Cures Act)
  - this is challenging and requires that

1) data are accessibe
2) data quality is understood
3) data are properly analyzed (hierarchical modeling)
4) results of the analysis are properly interpreted

- PETS contributes to the inferential 3) and 4)
- Can be extended to complex model

Thank You!!