Predictive Evidence Threshold Scaling:
does the evidence meet a confirmatory standard?

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Abstract

Making better use of evidence is one of the tenets of modern drug development. This calls for an understanding of the evidential strength of non-confirmatory evidence relative to a confirmatory standard. *Predictive evidence threshold scaling (PETS)* provides a framework to do so. Under *PETS*, the evidence meets a confirmatory standard if the predictive probability of a positive effect reaches the predictive evidence threshold from hypothetical confirmatory data. Obtaining these probabilities requires hierarchical models with plausible heterogeneity and bias assumptions. After introducing the methodology, I will discuss two examples. The first is childhood Guillain-Barré syndrome, with sparse children data enriched with adult data. The second is breakthrough designation, illustrated by a recent FDA approval of Crizotinib for non-small-cell-lung-cancer based on phase I and II data. The examples suggest that the evidential strength of non-confirmatory data can meet a confirmatory standard. This is reassuring for modern drug development, which exploits various types of evidence to inform licensing decisions.

Outline

- Scope & Objective
- Predictive Evidence Threshold Scaling (PETS)
  - Idea
  - Methodology
- Examples
  1) Crizotinib for NSCLC
  2) Plasmapheresis for childhood Guillain-Barré syndrome
- Conclusions

Scope and Objective

Scope & Objective

Problem statement

- Problem
  - For a treatment effect parameter θ, we want to compare the evidential strength of two data sources Y_E and Y_C
  - Which one provides more evidence for a treatment effect?
- Question:
  - Why? If we have two relevant data sources, why don't we combine them to inform θ?
- Answer:
  - Only one is observed (Y_E), the other (Y_C) is hypothetical

Scope & Objective

Example 1: breakthrough therapy designation

- Breakthrough therapy
  - an FDA designation that expedites drug development (FDA Safety and Innovation Act, July 9, 2012)
  - unmet clinical
  - *real world evidence (RWE),* data outside well-controlled clinical trials, can be used
  - effect sizes are large
- How does RWE (Y_E) compare to a confirmatory standard (Y_C)?

Scope & Objective

Example 1: Crizotinib in non-small-cell lung cancer (NSCLC)

- Promising NSCLC progression-free survival (PFS) data: median 8-9 months

Trial	median (95%-CI)	y (s)*
PROFILE 1001	9.7 (7.7, 12.8)	2.272 (0.130)
PROFILE 1005	8.1 (6.8, 9.7)	2.092 (0.091)

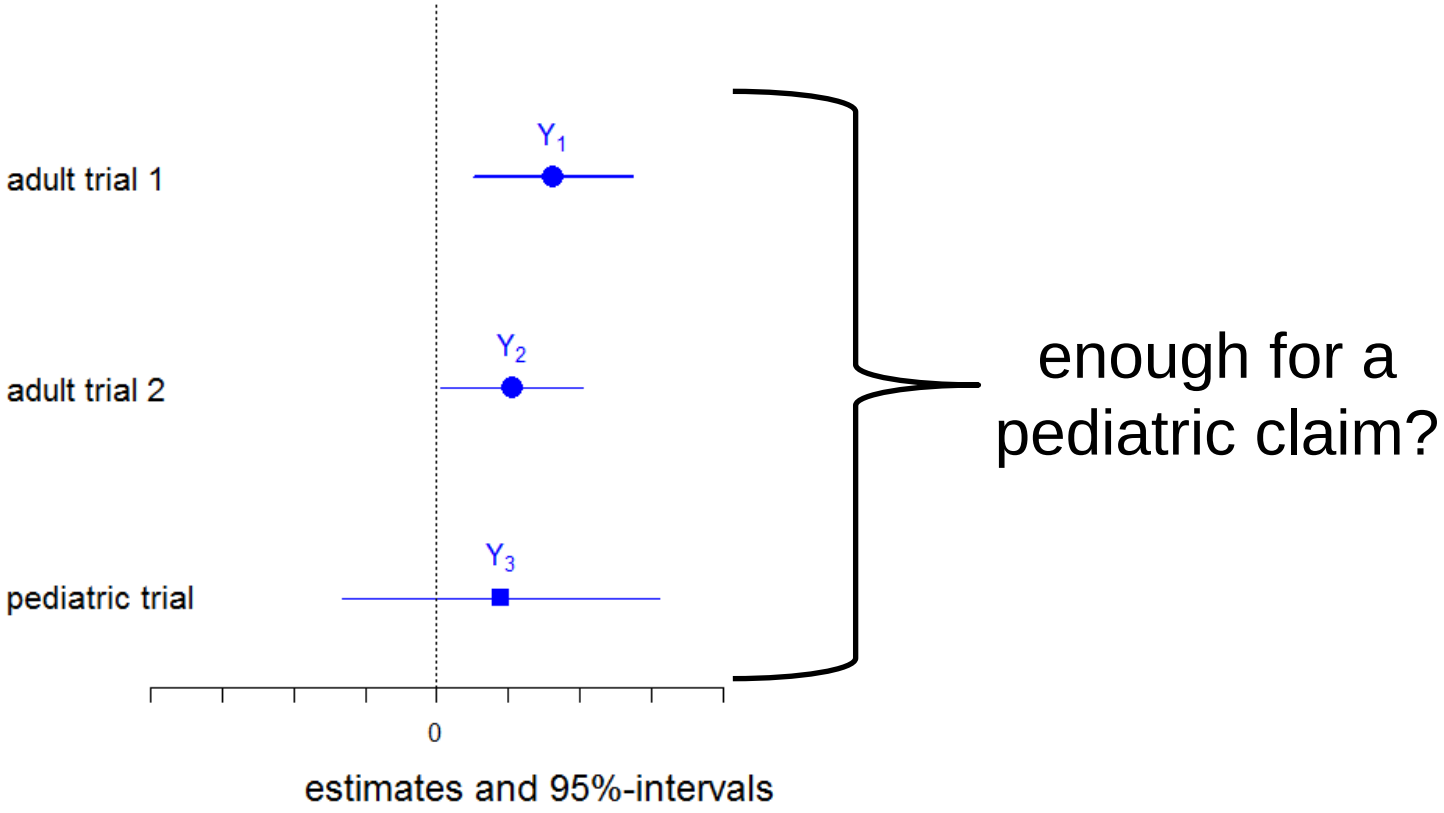
* normal approximation: est (se) of log-median PFS

  - phase I expansion (PROFILE 1001) and phase II single-arm trial (PROFILE 1005)
  - typical (control) median-PFS is 3 to 4 months
  - FDA granted breakthrough designation
  - How do these data compare to a confirmatory standard?

Scope & Objective

Example 2: extrapolation from adults to pediatrics

Assume with have promising adult evidence for a treatment effect. How much pediatric data is needed?



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Scope & Objective

Quantifying Real World Evidence

- Setting: actual **RWE Y_E** for a clinical endpoint
- Objective: to propose a quantitative approach that
  - allows comparing the actual evidence **Y_E** to a confirmatory standard
  - complements and improves qualitative decisions
- Disclaimer: what follows
  - is not meant to replace the standard confirmatory approach
  - is meant to complement it

Predictive Evidence Threshold Scaling

Idea

Predictive Evidence Threshold Scaling (PETS)

Three requirements

Three requirements

1. a *confirmatory standard:* (hypothetical) data $\mathbf{Y_{(C)}}$
2. a *metric* to compare $\mathbf{Y_E}$ to $\mathbf{Y_{(C)}}$
3. a *rule* to decide whether the non-confirmatory data is sufficiently strong

PETS

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** $\boldsymbol{\theta_1, \theta_2, \ldots \theta_J}$
- Hypothetical (minimal) confirmatory data $\mathbf{Y_{(C)}}$
  - e.g., two significant trials; or one in Oncology
  - estimates $Y_{(1)}, Y_{(2)}$
  - standard errors $s_{(1)}, s_{(2)}$
  - **parameters** $\boldsymbol{\theta_{(1)}, \theta_{(2)}}$
- The effect parameters differ (heterogeneity!)

PETS

Metric

- 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)

PETS

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, the evidence will be discounted due to larger heterogeneity

PETS

Predictive Evidence Probability (PEP) and Threshold (PET)

- Scaling of Y_E vs. $Y_{(C)}$
- For the actual evidence Y_E

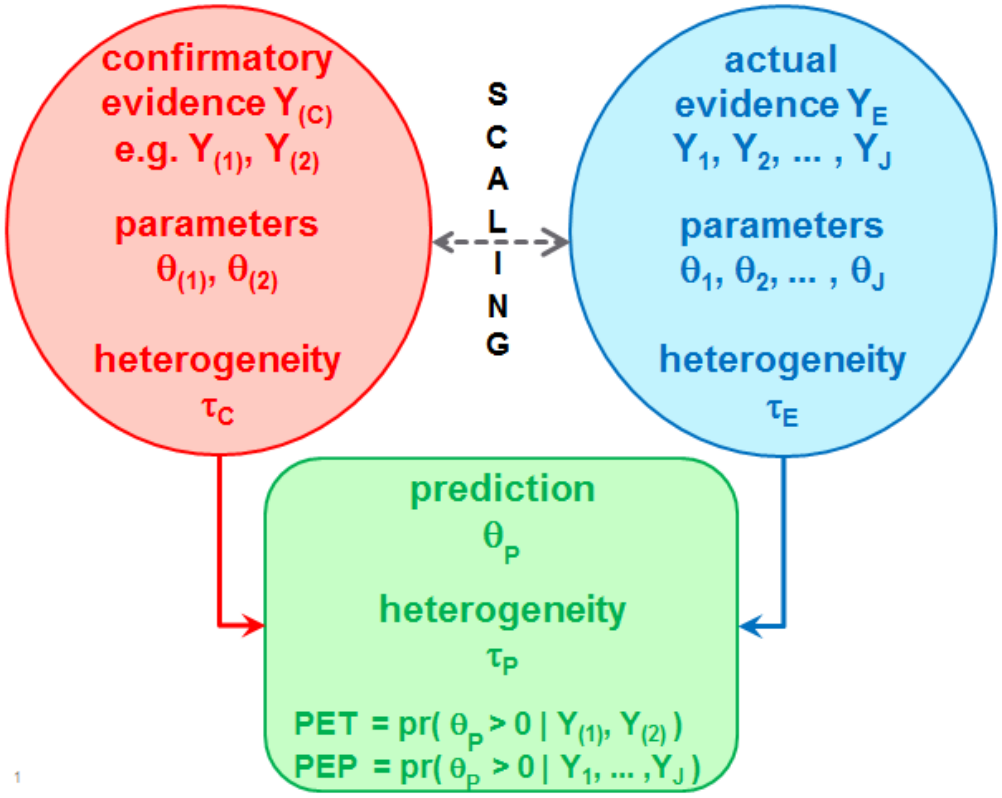
  PEP (predictive evidence probability) $\quad pr(\theta_P > 0 \mid Y_E)$

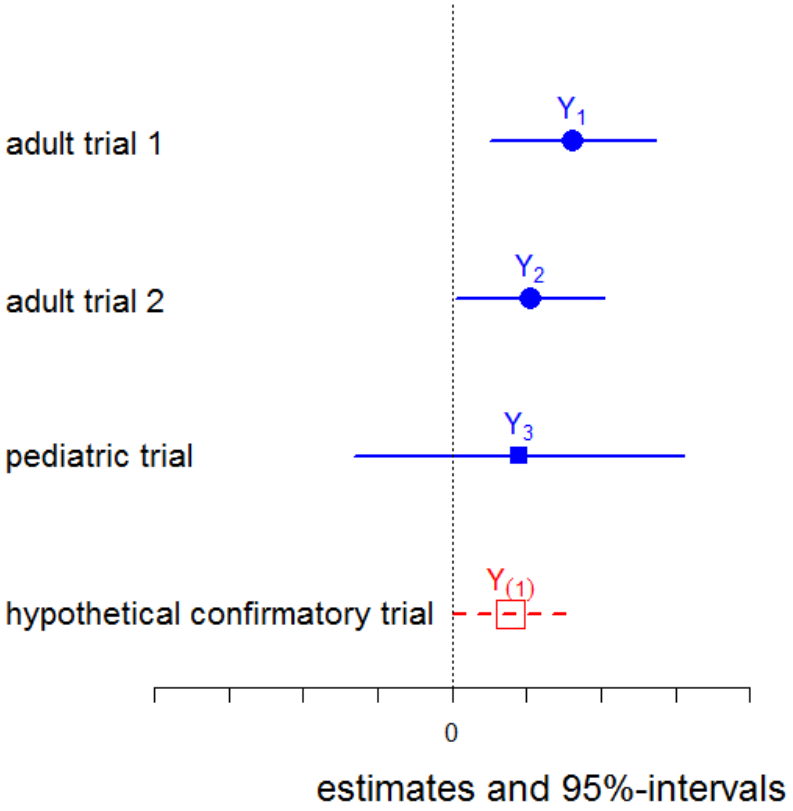
  - predictive probability of a «positive effect» (in a new trial)
- For the (hypothetical) confirmatory evidence $Y_{(C)}$

  PET (predictive evidence threshold) $\quad pr(\theta_P > 0 \mid Y_{(C)})$
- How large are PEP and PET? Is PEP $\geq$ PET

PETS

PETS framework: summary





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Predictive Evidence Threshold Scaling

Methodology

PETS

Methodology: hierarchical model

- The normal-normal hierarchical model (NNHM)
  - (approximately) normally distributed estimates Y
  - normally distributed parameters θ
- Heterogeneity parameters 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, with prior distributions on parameters
    - choices must be sensible (context-specific)

PETS

Normal-normal hierarchical model and predicted effect θ_P

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

PETS

NNHM PET and PEP calculations for fixed heteogeneities

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

PETS

Extensions

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

PETS

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

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

  - biases
    - can be fixed (scenarios) or uncertain (priors)
    - but must be plausible

Example 1:

Breakthrough Designation

Crizotinib for NSCLC

Crizotinib

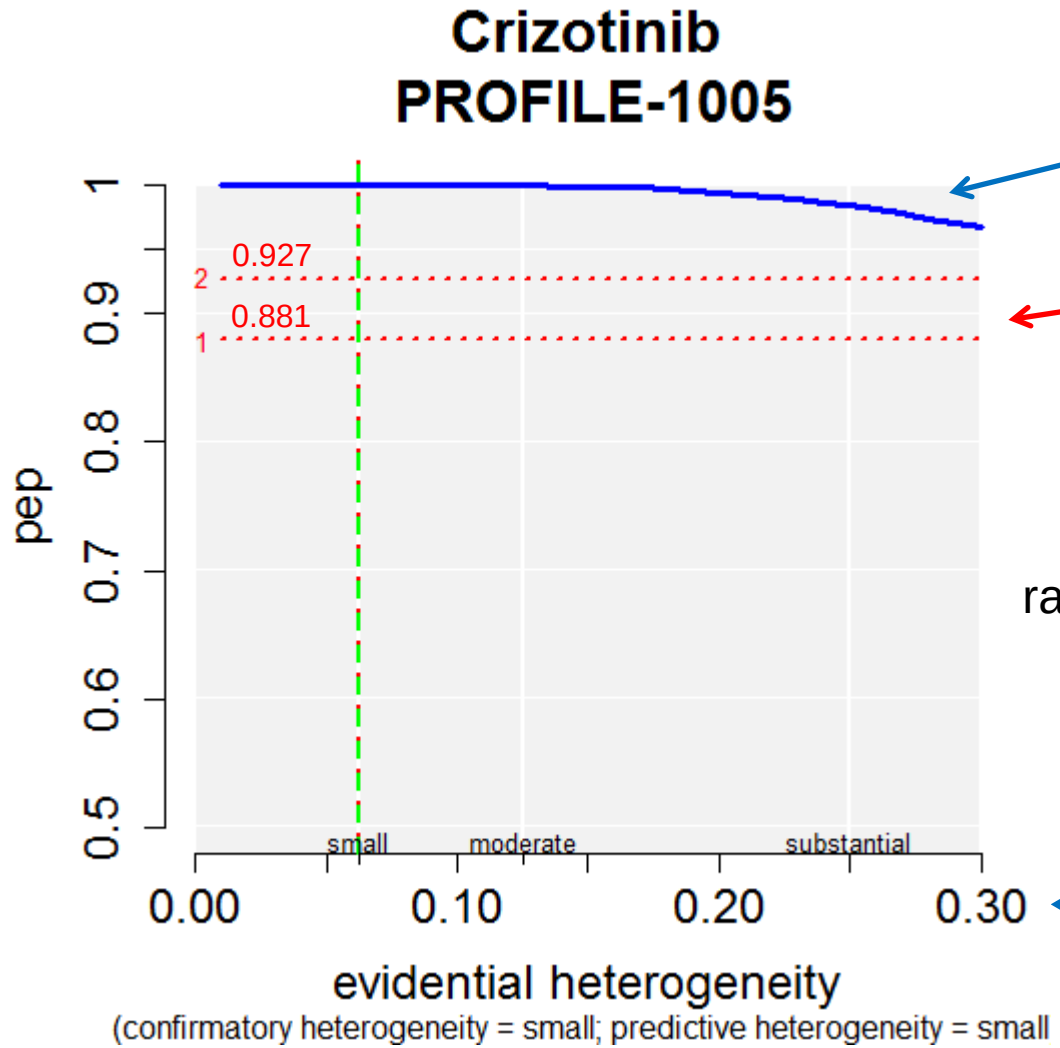
Data

Trial	median (95%-int)	y (s)
actual data		
PROFILE 1001	**9.7 (7.7, 12.8)**	**2.272 (0.130)**
PROFILE 1005	**8.1 (6.8, 9.7)**	**2.092 (0.091)**
hypothetical confirmatory data (one trial)		
CONF*	5.12 (4.5, 5.83)	1.635 (0.066)

* one confirmatory trial with 225 events;
H_0: θ = log(4.5 months); σ=1; one-sided p-value = 0.025.

Crizotinib

PETS graph: PEP vs. PET (single-arm analyses)



PEP

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

PET

(for 1 or 2 conf. trials)

pr($\theta_P > 0 \mid Y_{(C)}$)

<u>Conclusion</u>

PEP dominates PET for a wide range of evidential heterogeneities

evidential heterogeneity τ_E «no to substantial»

fixed $\tau_C = \tau_P = 0.0625$

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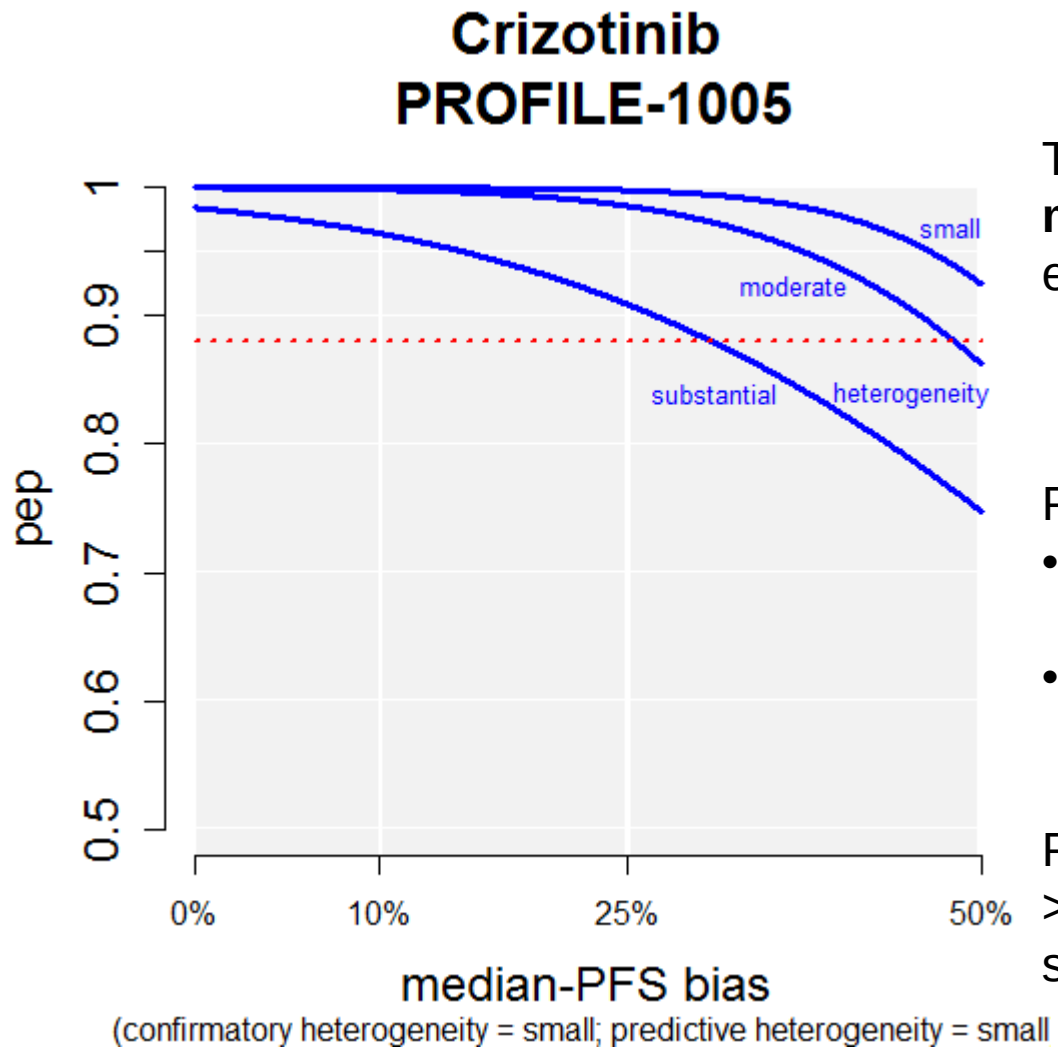
Crizotinib

Phase II trial: systematic bias sensitivity analyses



Heterogeneities

Three blue lines are for **small**, **moderate**, and **substantial** evidential heterogeneity (τ_E)

Conclusions

PEP dominates PET

- for small to substantial heterogeneity if bias is <25%
- for small to moderate heterogeneity if bias <50%

PEP is not sufficient if bias is > 25% and heterogeneity is substantial (plausible?)

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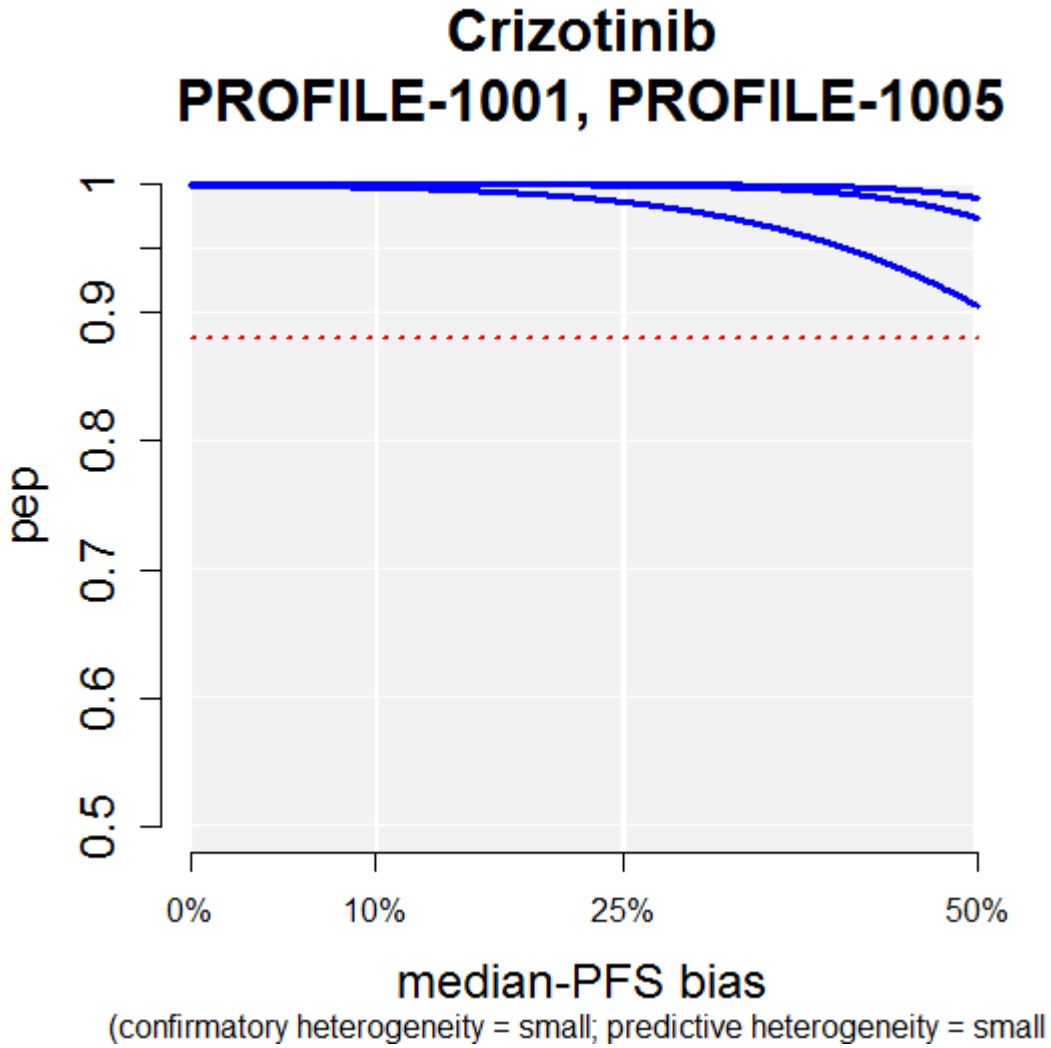
Crizotinib

*Bias sensitivity analyses **using both trials***



Heterogeneities

Three blue lines are for **small**, **moderate**, and **substantial** evidential heterogeneity (τ_E)

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Crizotinib

Later confirmatory data were consistent with earlier data

Median-PFS results		
Trial	median (95%-int)	y (s)
actual non-confirmatory data		
PROFILE 1001	**9.7 (7.7, 12.8)**	**2.272 (0.130)**
PROFILE 1005	**8.1 (6.8, 9.7)**	**2.092 (0.091)**
hypothetical confirmatory data		
CONF	5.12 (4.5, 5.83)	1.633 (0.066)
later confirmatory data		
PROFILE 1007*	**7.7 (6.0, 8.8)**	

* Randomized phase 3 trial PROFILE-1007 with standard 2nd line chemotherapy (pemetrexed or taxotere) confirmed the effect of Crizotinib. **Median PFS for chemotherapy: 3 (2.6, 4.3)**

Crizotinib

Complication: single-arm vs. randomized

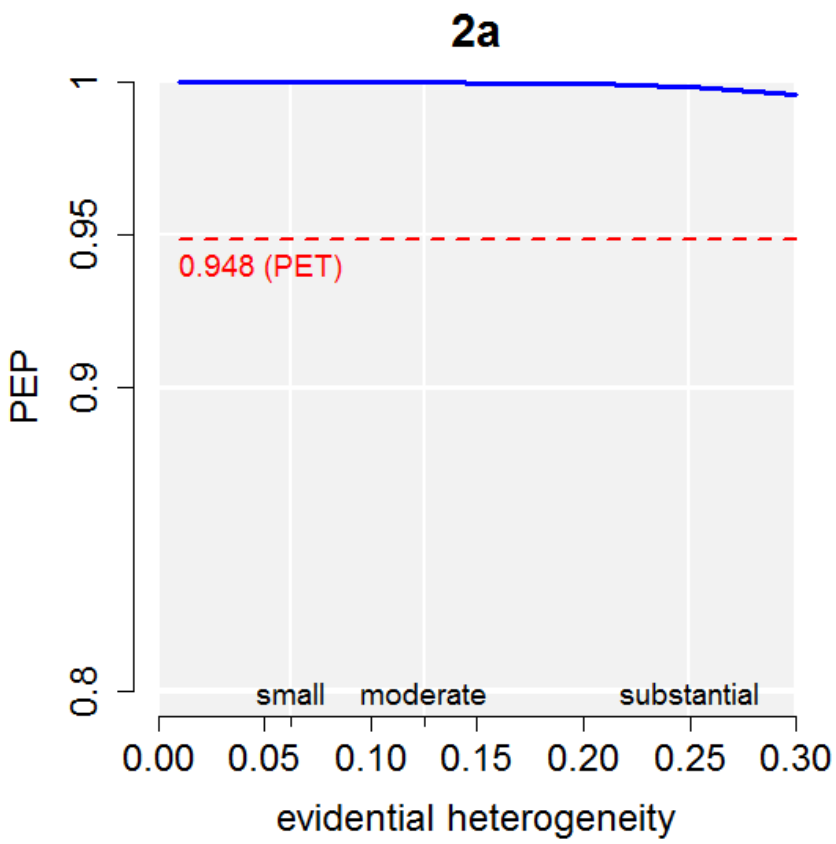
- Phase I and II trials were single-arm
- PETS analyses compared Crizotinib to a fixed control median of 4.5 months
- What about the randomized setting?
  - hazard-ratio Critzotinib vs. SoC. Two scenarios
    1. assuming a fixed control effect: median = 4.5 months
    2. **assuming uncetain control effect: median = 4.5 months (worth ~ 50 events)**
  - results qualitatively similar to single-arm PETS analyses

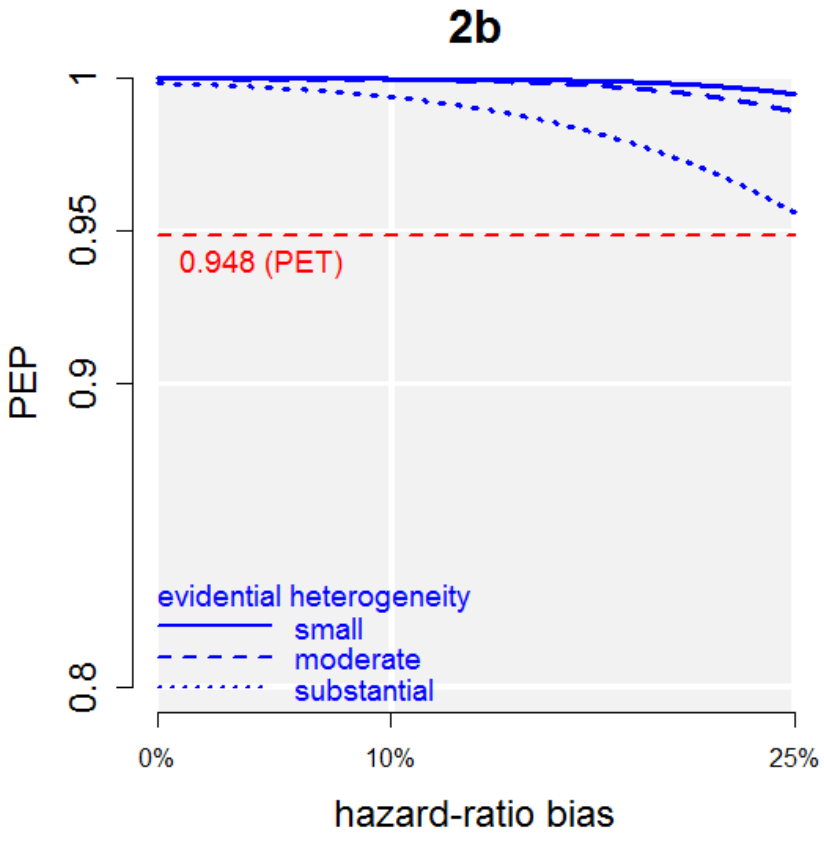
Crizotinib

PETS for hazard-ratio scale (uncertain control median)

without bias

with bias
(3 heterogeneity scenarios)





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Example 2:

Extrapolation from Adults to Pediatrics

Plasmapheresis for Guillain-Barré Syndrome (GBS)

Source: Goodman & Sladky (2004)

Plasmapheresis for childhood GBS

Introduction

- Guillain-Barré syndrome
  - a rare neurologic disease
  - affects all age groups, but is more common in children
  - main treatments:
    - ***plasmapheresis (plasma exchange, PE)***
    - *intraveneous immune globulin (IVIg)*
  - Both treatments were shown to be effective in adults and then used in children off-label
- Here, we apply PETS to ***PE***
  - to predict efficacy in children, using adult data (and sparse children data)

Plasmapheresis for childhood GBS

Data

- A1-2: 2 trials in adults in the 1980s
- C1-C4: 4 small trials in children in the 1990s
- Endpoint: time to independent walking
- Does the evidence from these trials meet a confirmatory standard? For example, for trials A1, A2, and C1

	HR	95%-CI	y	s
A1. McKhann 1985	0.62	(0.46-0.84)	-0.472	0.153
A2. Raphael 1987	0.63	(0.47-0.84)	-0.461	0.149
C1. Epstein 1990	0.4	(0.17-0.94)	-0.916	0.434
C2. Lamont 1991	0.4	(0.16-1.03)	-0.916	0.481
C3. Jansen 1993	0.55	(0.23-1.34)	-0.598	0.455
C4. Graf 1999	1.52	(0.54-4.29)	0.419	0.529

Plasmapheresis for childhood GBS

PETS scenario analyses: assumptions

- Scenario assumptions for heterogeneities/biases
  - Y_E: 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
  - Y_C: one confirmatory children trial (1-sided p-value=0.025)
    - 200 events
    - confirmatory heterogeneity = small

    $\Rightarrow$ PET = 0.95
  - predictive heterogeneity = small

Plasmapheresis for childhood GBS

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 1st children trial (C1), PEP > PET for all scenarios
- Conclusion: strong adult data combined with sparse pediatric data provides sufficient evidence

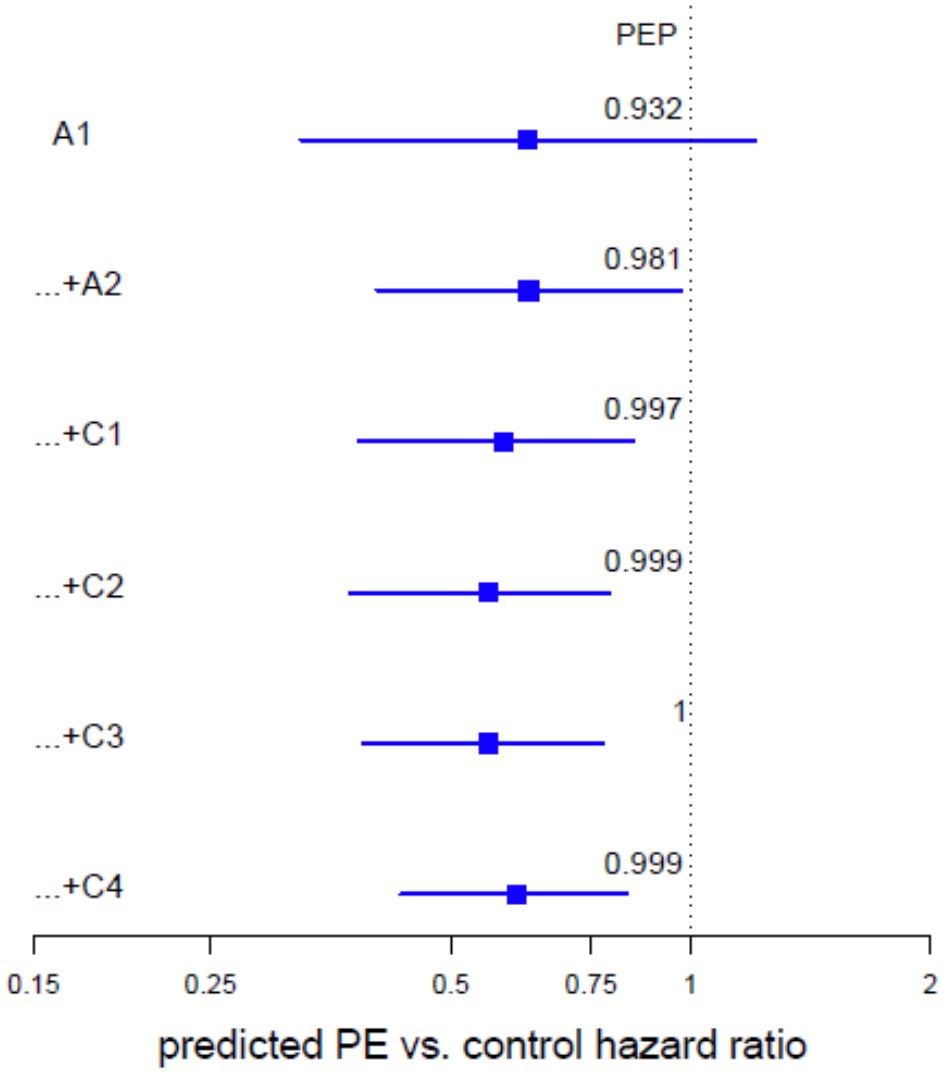
Plasmapheresis for childhood GBS

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.

Plasmapheresis for childhood GBS

Bayesian PETS analyses: cumulative results



Note:
PET = 0.95

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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 real-world evidence (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)
  - NNHM: the basic model (extensions possible)

Conclusions

- PETS has limitations
  - although quantitative, PETS requires contextual judgement about plausible *heterogeneities* and *biases*
  - for these, robustness of PEP>PET is needed
- Examples
  1. robust PETS results for Crizotinib, which clearly support FDA's breakthrough designation
  2. PETS supports intuition that strong adult data combined with sparse children data suffices for a pediatric claim
- NNHM can be easily implemented in *R* (for fixed scenarios) and *WinBUGS/JAGS/Stan* (for priors)

References

- 21st Century Cures Act., May 19, 2015. http://docs.house.gov/meetings/IF/IF00/20150519/103516/BILLS-1146ih.pdf.
- A Blueprint for Breakthrough: Exploring Utility of Real World Evidence (RWE). Friends of Cancer Reserach, Washington DC, June 16, 2016. http://www.focr.org/sites/default/files/pdf/RWE%20-%20Project%20PRE-MEETING%20DRAFT.pdf
- The Food and Drug Administration Safety and Innovation Act (FDASIA), July 9, 2012. http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/ucm20027187.htm
- Camidge et al. (2012). Activity and safety of crizotinib in patients with ALK-positive non-small-cell-lung cancer: updated results from a phase I study. Lancet.
- Eichler et al. (2015). From adaptive licensing to adaptive pathways: delivering a flexible life-span approach to bring new drugs to patients. Clin Pharm & Ther
- Goodman, Sladky (2004). A Bayesian approach to randomized controlled trials in children utilizing information from adults: the case of Guillain-Barré syndrome. Clinical Trials
- Kesselheim, Darrow (2015). FDA designations for therapeutics and their impact on drug development and regulatory review outcomes. Clin Pharm & Ther

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References

- Kim et al. (2012). Results of a global phase II study with crizotinib in advanced ALSK-posiitive non-small-cell lung cancer (NSCLC). J Clin Oncol.
- Oye et al. (2015). The next frontier: fostering innovation by improving health data access and utilization. Clin Pharm & Ther
- Neuenschwander, Roychoudhury, Schmidli (2016). Using co-data in clinical trials. Statistics in Biopharmaceutical Research.
- Neuenschwander, Roychoudhury, Branson. Predictive evidence threshold scaling: does the evidence meet a confirmatory standard? Submitted to Statistics in Biopharmaceutical Research.
- Schneeweiss et al. (2011). Assessing the comparative effectiveness of newly marketed medications: methodological challenges and implications for drug development. Clin Pharm & Ther
- Spiegelhalter, Abrams, Myles (2004). Bayesian Approaches to Clinical Trials and Health-Care Evaluations. Wiley.
- Woodcock (2012). Evidence vs. Access: can twenty-first-century drug regulation refine the tradeoffs? Clin Pharm & Ther