American Course on Drug Development and Regulatory Sciences

Pediatric Drug Development Workshop

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University of California, San Francisco
Schools of Pharmacy and Medicine
Department of Bioengineering
and Therapeutic Sciences

Statistical Implications of Extrapolation on the Design and Analysis of Pediatric Clinical Trials

Presentation Developed By…

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Disclosures, Affiliations, and Acknowledgements

Disclosures

- Employed at Eli Lilly & Co.
- Lilly Pediatric Steering Committee for some introductory slides and helpful comments

Key Take-aways

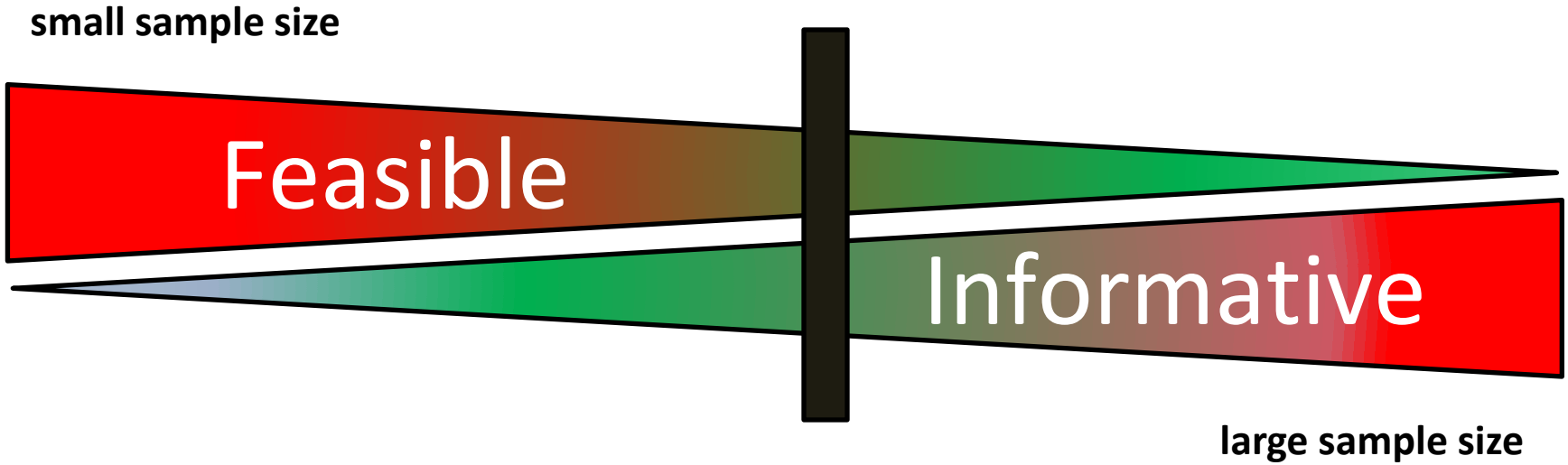
Extrapolation

- is triggered when the lead indication has a pediatric disease state that is similar in progression of disease and treatment response
- can minimize the requirements and accelerate timeline of the pediatric program
- requires designing adult program with some similarity in endpoints to pediatric program

Agenda

- ❑ Extrapolation
- ❑ Statistical implications of extrapolation
  - Bayesian Approach in partial extrapolation
  - Alternative designs for partial/no extrapolation
- ❑ Summary

Finding balance

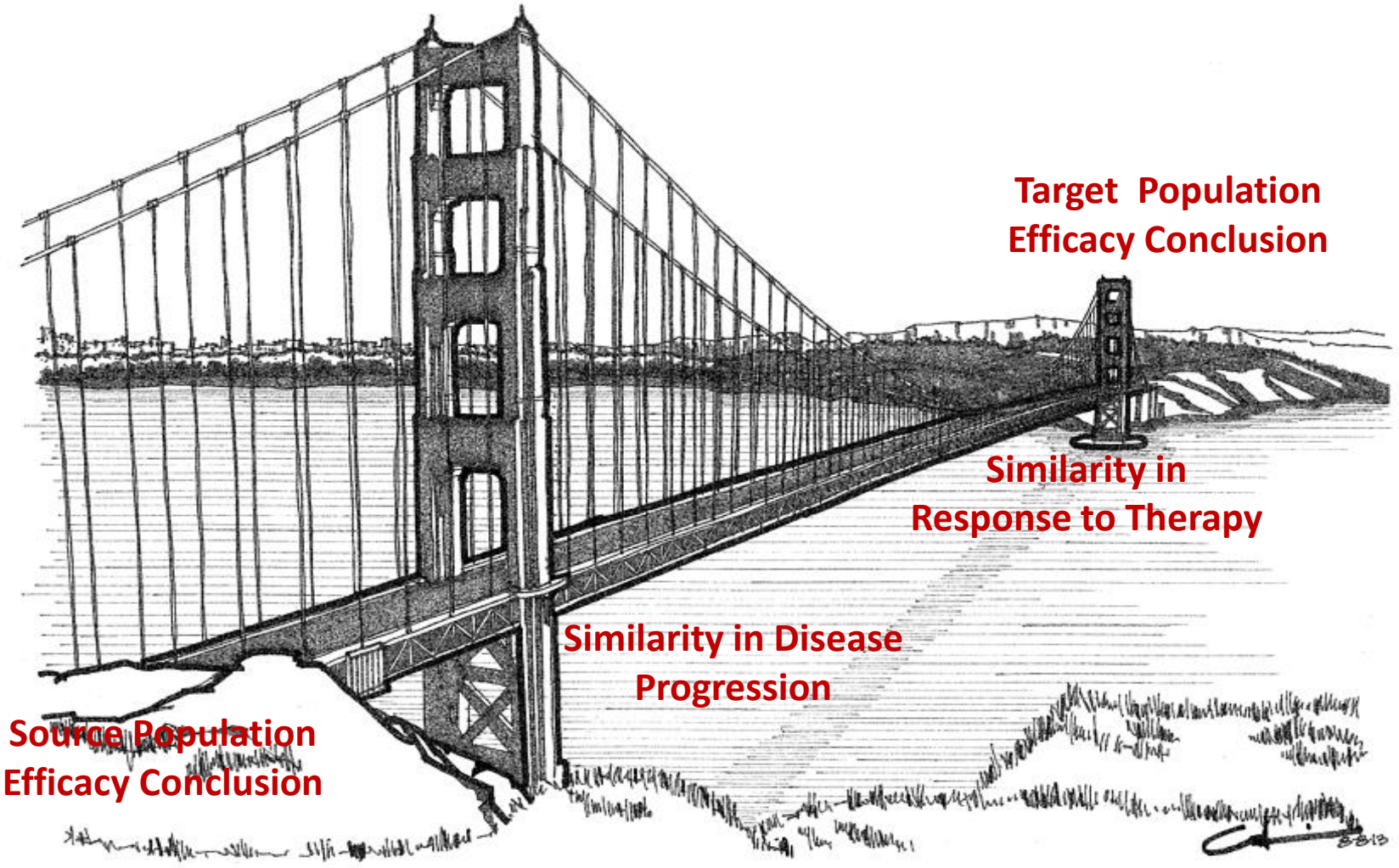


Need to minimize number of subjects enrolled in pediatric clinical trials and the need to maximize the usefulness of the data obtained, while ensuring that the trials are **feasible**, **robust**, and **interpretable**. – Dunne et al. (2011)

Pediatric Drug Development current regulatory landscape

Obligation, Incentive, & Extrapolation

Extrapolation



Data Sources for Extrapolation

Sufficient quality data on:

- ❑ Adult indication for (similar) pediatric indication
- ❑ Other pediatric age groups
- ❑ Related pediatric indications
- ❑ External data
- ❑ Preclinical efficacy
- ❑ Formulations of same active ingredient

FDA/CDER Decision Tree

	Full Extrapolation	Partial Extrapolation	No extrapolation
Similar progression of disease	Yes	Yes	No
Similar response to treatment	Yes	Yes	No
Similar exposure-response	Yes	Uncertain	No
Concentration predictive of response	Yes	Uncertain	No
Clinical Development	**Supportive data**	**Optimized programme**	**Full programme**

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Current practice

- ❑ **Uncontrolled; open-label**
- ❑ **Controlled; arbitrary sample size**
- ❑ Non-inferiority trials
- ❑ Studies powered on surrogate endpoint
- ❑ Modeling

Example 1: balsalazide

Mild to Moderate Ulcerative Colitis

Adults ≥18 y	Children 5-17 y
▪ R, DB, PG (2 doses : 2.25 g/day and 6.75 g/day; Azacol) in 154 patients (50, 53, 51) ▪ Improvement in stool blood, stool frequency, sigmoidoscopy at week 8	▪ R, DB, PG (2 doses: 2.25 g/day and 6.75 g/day) in 68 patients ▪ Modified Sutherland UC Activity Index (MUCAI) at week 8

Statistical reviewer notes: Sample size based on feasibility rather than statistical power

Example 1: balsalazide

Endpoint	2.25 g/day	6.75 g/day	p-value
Adult (improvement in)			
Stool blood	35%	55%	0.045
Stool frequency	25%	49%	0.013
Sigmoidoscopy	52%	74%	0.031
Children			
MUCAI decrease ≥ 3	37%	45%	0.623

Adapted from FDA Clinical review

Clinical reviewer notes: "…the **clinical response rate for the primary endpoint in children thus seems to correlate reasonably well with the response rate seen in adults** (where the primary endpoint was reduction of rectal bleeding and improvement of at least one other assessed symptom) and would indicate that **Colazal is similarly effective** in improving symptoms in children and in adults."

Example 2: infliximab

Moderate to Severe Ulcerative Colitis

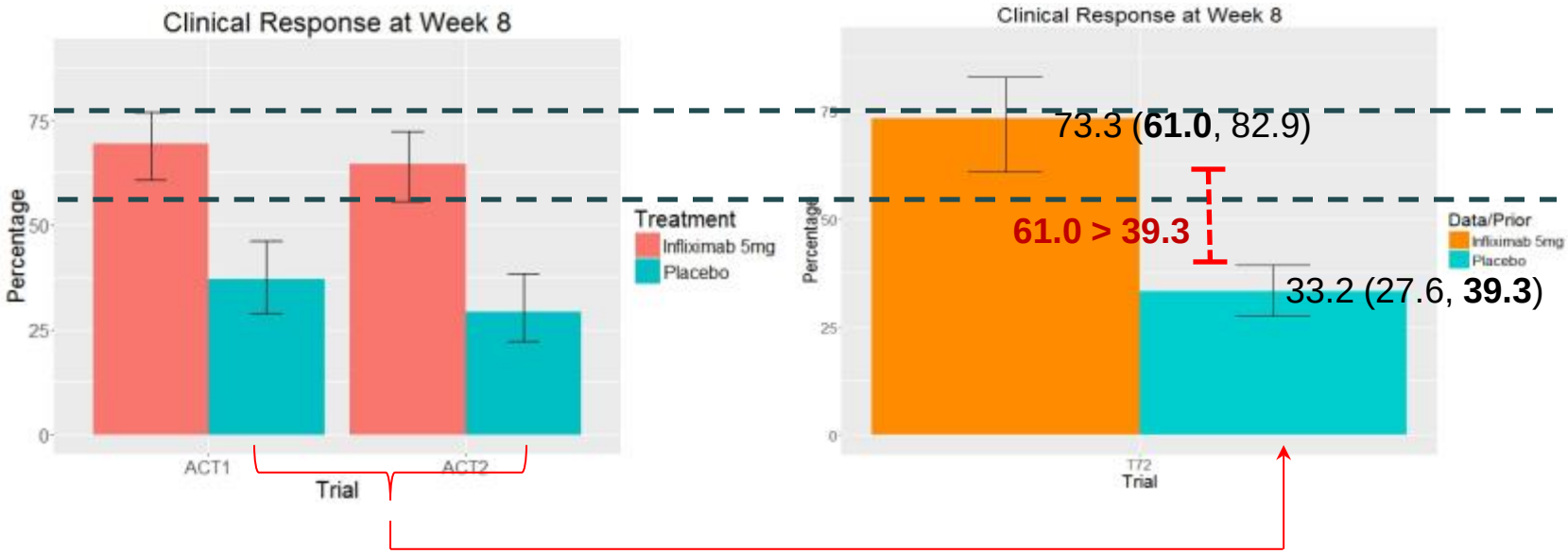
Adults ≥18 y	Children 6-17 y
▪ R, DB, PG (2 dose regimens; placebo) ▪ Mayo score at week 8	▪ OL induction phase; R maintenance phase (2 dose regimens) ▪ Mayo Score and PUCUI at week 8

Example 2: infliximab

	ACT 1	ACT 2	T72
	Infliximab 5mg/kg	Infliximab 5mg/kg	Infliximab 5mg/kg
Endpoint	N = 121	N = 121	N = 60
Clinical response	84 (69.4%)	78 (64.5%)	44 (73.3%)
Clinical remission	47 (38.8%)	41 (33.9%)	24 (40.0%)
Mucosal healing	75 (62.0%)	73 (60.3%)	41 (68.3%)

Summary level data obtained from Rutgeerts et al, 2005[9], and Hyams, et al., 2012[10]. Placebo response not shown.

Example 2: infliximab



Step 1: **Assume** combined placebo response in adults is the same as placebo response in pediatrics.
Step 2: **Check** pediatric clinical response within reasonable range of adult response.
Step 3: Compare confidence interval limits.

Statistical Considerations

Extrapolation requires…

- ❑ **Quality data**
- ❑ **Some similarity in endpoint or design**
  - Some common endpoint
  - Modeling to account for difference
  - Consistency of effect in source-target population

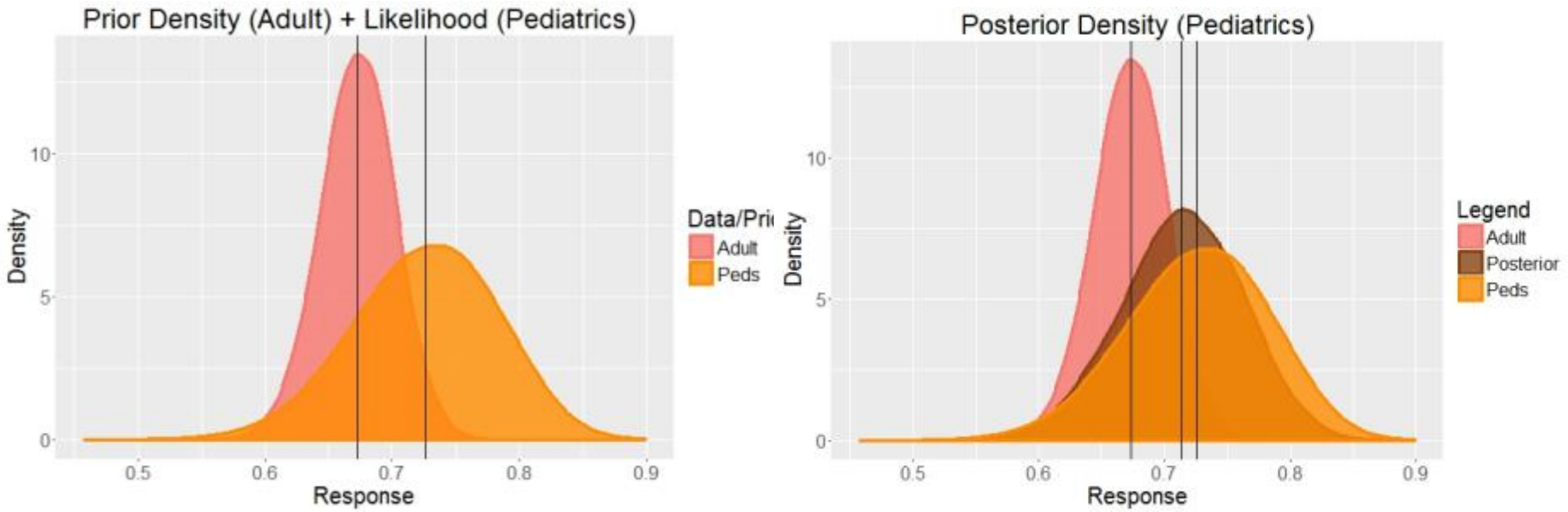
How is extrapolation of information and conclusion from adults to pediatrics structurally done?

“Bayesian” extrapolation

Design Trial

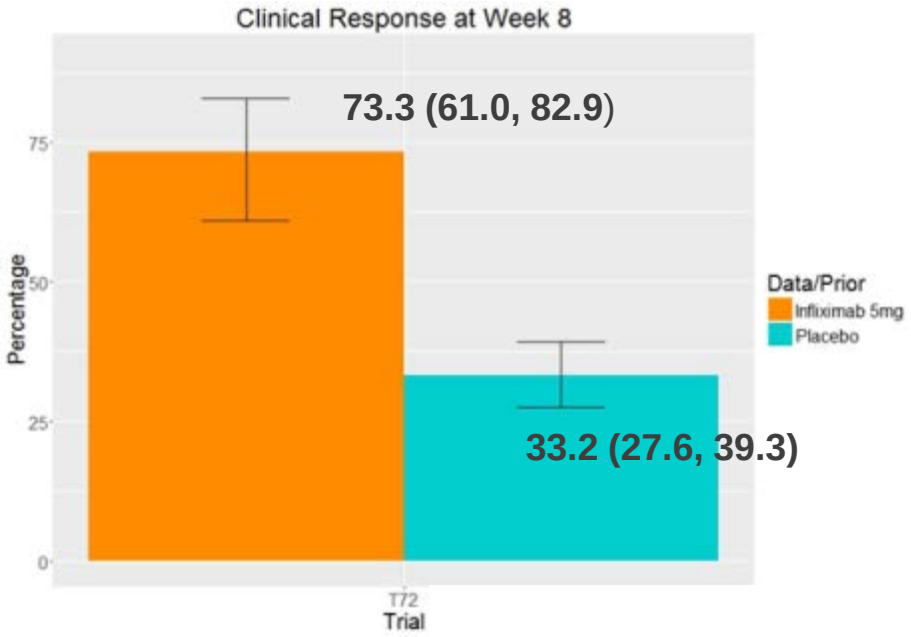
- ❑Specify a prior using adult data: $q_S(\theta_E) \propto L(\theta_E|Source\ Data)\pi(\theta_E)$
- ❑Conduct pediatric trial + compute likelihood: $L(\theta_E|target\ Data)$
- ❑Apply Bayes theorem (likelihood + prior) to estimate of pediatric response

$$q_{T,S}(\theta_E) \propto L(\theta_E|Target\ Data)q(\theta_E)$$



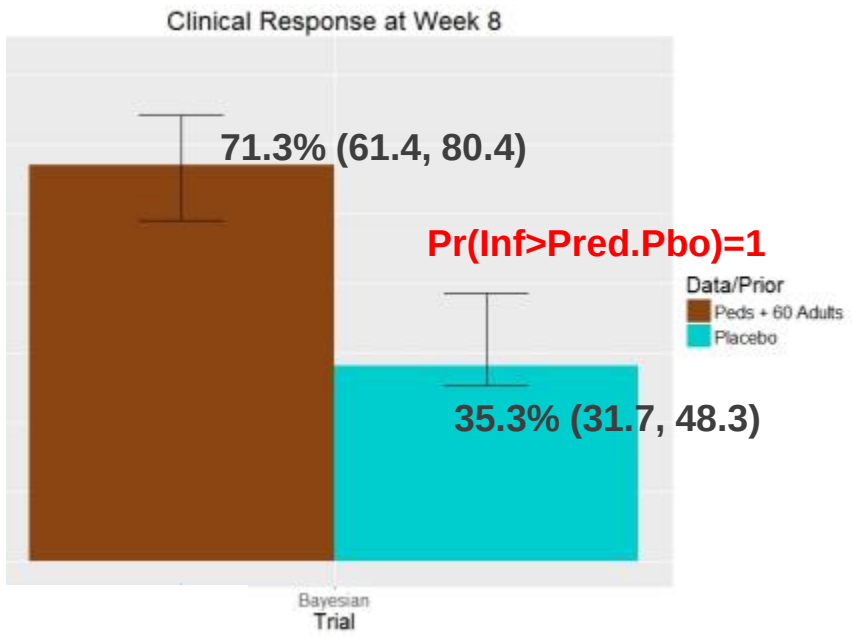
Example 2: infliximab

"Cursory"



$$q_S(\theta_P) \propto L(\theta_P|Source\ Data)\pi(\theta_P)$$

Bayesian



$$\theta_P^* \sim q_S(\theta_P)$$

$r_P^* \sim Bin(\theta_P^*, n_T)$, U^* is 95% CI of θ based on the sample , $\tau = E(U^*)$

Bayesian extrapolation can be more conservative!

“Bayesian” extrapolation

Bayesian approach formalizes what **pediatricians** do when they **combine the results from large adult trials with the results of smaller pediatric trials to make treatment decisions**.”

- Schoenfeld et al. 2009

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US Regulations: 21 CFR50, subpart D

Risk Pathways:

§ 50.51 “Clinical investigations not involving greater than minimal risk”

§ 50.52 “Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects”

§ 50.53 “Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition. The risk represents a minor increase over minimal risk”

Applied via component analysis

Single-Arm Trials

Hypothesis: $H_0: \theta \leq \theta_0 \; vs \; H_1: \theta > \theta_0$

- θ_0 is the upper bound of adult placebo response; Historical Evidence of Sensitivity to Drug Effects (HESDE)
- Useful if large effects of treatment are seen in early clinical studies
- Where to get θ_0?
  - Upper bound of placebo response confidence interval in adults
  - Upper bound of credible interval derived from the **predictive distribution of placebo response** from a sample of comparable size as the number of children given the treatment
  - Estimate of **placebo response via counterfactuals** from quality registry data

Single-Arm Trials

- Indirect comparison with adult placebo may be inadequate if there are changes over time in supportive care/quality of diagnostic staging techniques

- Potential solutions
  - Pediatric trial needs to be concurrent to the adult trial
  - Use predictive distribution of placebo instead of confidence interval

Mean Resp*	Unconditional Power					
	N=60		N=80		N=100	
	Carry-over placebo	Predicted placebo	Carry-over placebo	Predicted placebo	Carry-over placebo	Predicted placebo
0.70	0.973	0.937	0.996	0.981	0.998	0.993
0.60	0.706	0.417	0.843	0.561	0.916	0.719
0.50	0.215	0.027	0.360	0.066	0.415	0.105
0.40	0.018	0.000	0.024	0.000	0.042	0.000
0.33	0.001	0.000	0.003	0.000	0.004	0.000

*Placebo response is 33%; adult sample size is 225 with 2:1 randomization; adult response = pbo response - 0.10

Single-Arm Trials

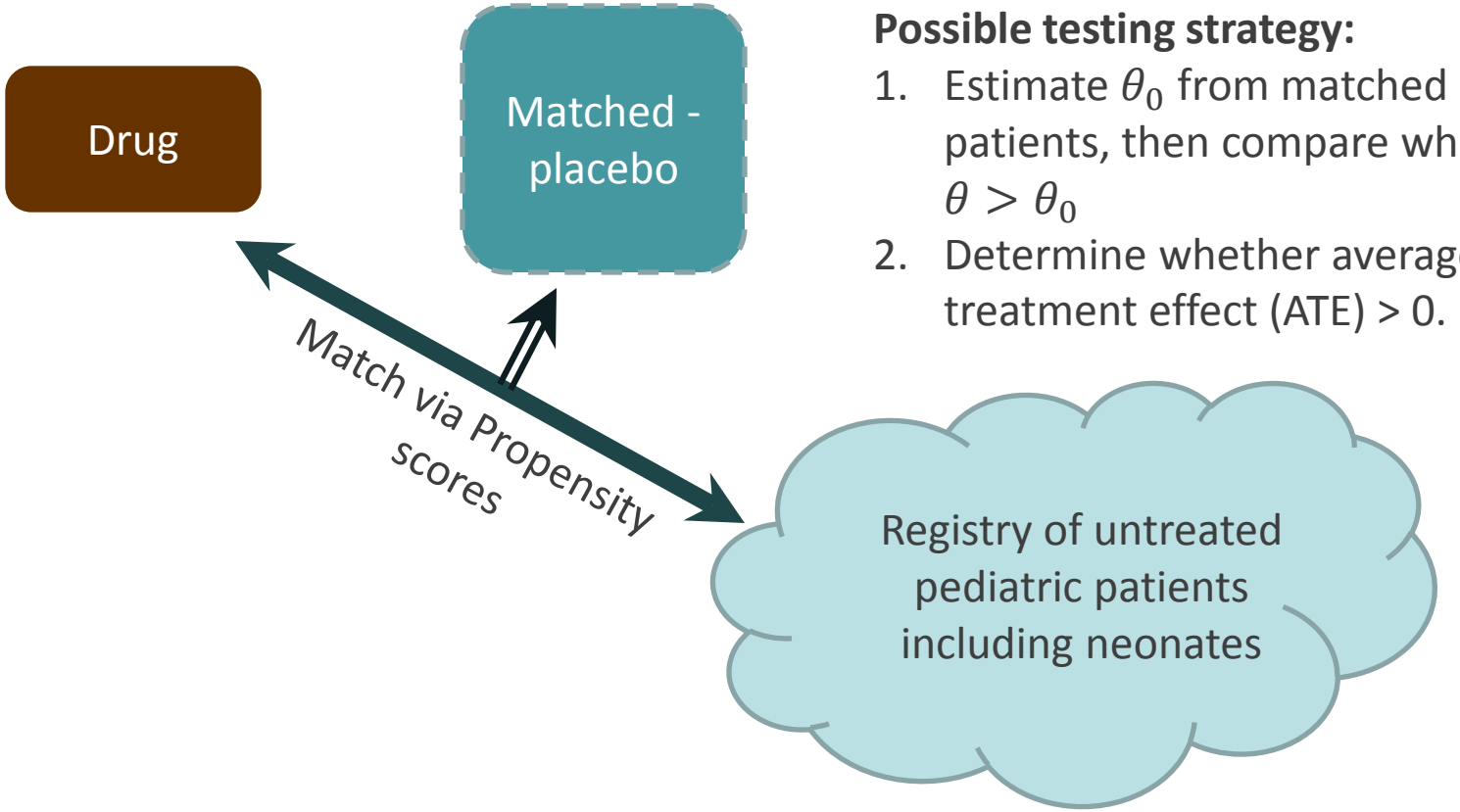
θ_0 determined through counterfactuals

"Threshold-crossing": A Useful Way to Establish the Counterfactual in Clinical Trials?

H-G Eichler[1], B Bloechl-Daum[2], P Bauer[3], F Bretz[4], J Brown[5], LV Hampson[6], P Honig[7], M Krams[8], H Leufkens[9], R Lim[10], MM Lumpkin[11], MJ Murphy[12], F Pignatti[1], M Posch[3], S Schneeweiss[13], M Trusheim[14] and F Koenig[3]

A central question in the assessment of benefit/harm of new treatments is: how does the average outcome on the new treatment (the factual) compare to the average outcome had patients received no treatment or a different treatment known to be effective (the counterfactual)? Randomized controlled trials (RCTs) are the standard for comparing the factual with the counterfactual. Recent developments necessitate and enable a new way of determining the counterfactual for some new medicines. For select situations, we propose a new framework for evidence generation, which we call "threshold-crossing." This framework leverages the wealth of information that is becoming available from completed RCTs and from real world data sources. Relying on formalized procedures, information gleaned from these data is used to estimate the counterfactual, enabling efficacy assessment of new drugs. We propose future (research) activities to enable "threshold-crossing" for carefully selected products and indications in which RCTs are not feasible.

Alternative Study designs

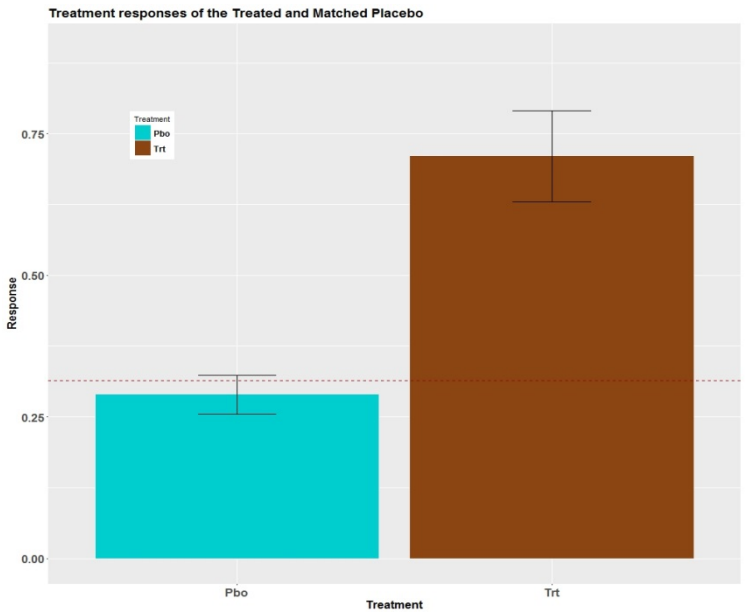


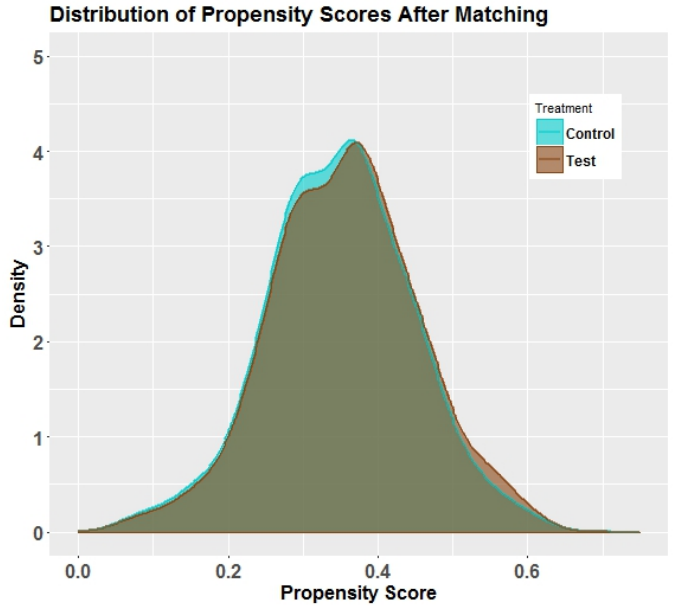
Possible testing strategy:

1. Estimate θ_0 from matched pbo patients, then compare whether $\theta > \theta_0$
2. Determine whether average treatment effect (ATE) > 0.

Registries may be established to evaluate the natural history of a disease, meaning its characteristics, management, and outcomes with and/or without treatment.

Single-Arm Trials





- Matching observations are not selected on the basis of their response but on the basis of a preselected set of baseline covariates.
- May require restricting search to contemporaneous registry data.
- Requires that the registry and the treated children have similar collected measurements (endpoint and baseline).

aglucosidase alfa (Myozyme)

- Indication: improved survival and invasive ventilator-free survival with infantile-onset Pompe disease
- Study 1602:
  - 18 ptx [1.2mo – 7.3mo] randomized to 2 doses of Myozyme
  - Comparator: 62 untreated ptx serving as historical control;
- Historical control group has clinical status similar to entry criteria of the Study; included all subjects who died within the first few months of life
- Statistician noted: “The use of matched control…would have permitted a more appropriate statistical analysis.”
  - Applicants analyses compared proportion of survivors/survival rates by age

Summary

- Explore ways to exploit extrapolation in pediatric drug development.

- Plan ahead and strategically –
  - If extrapolation is used, ensure adult clinical trial efficacy outcomes can be supportive of pediatric efficacy outcomes;
  - Should I need a registry data; what measurements should my pediatric trial have

- Push the boundaries of innovative/alternative design

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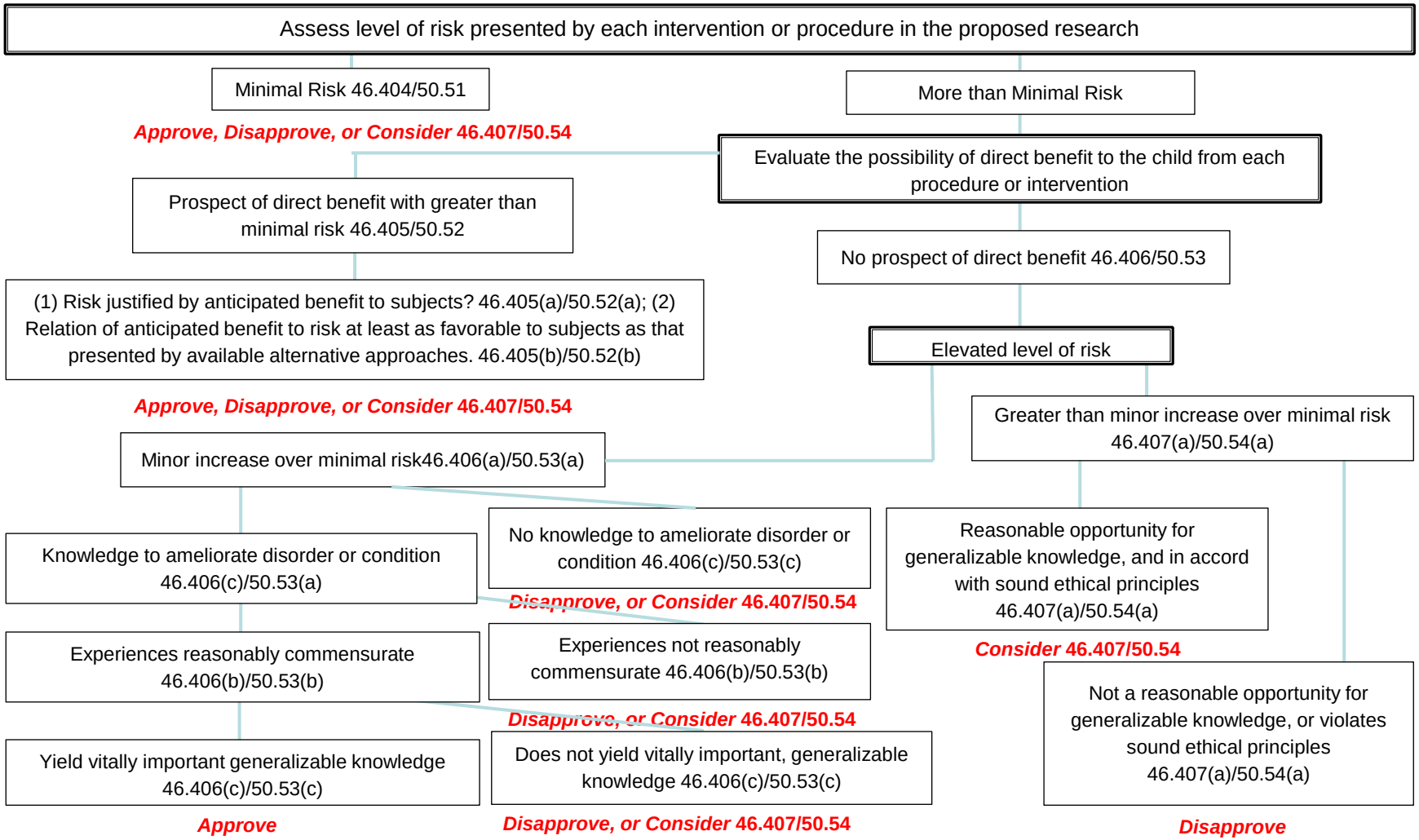
IRB Evaluation 21 CFR § 50



Adapted from: Field, M. J., R. E. Behrman. 2004. *Ethical conduct of clinical research involving children*. Washington, DC: National Academies Press