Pediatric Trial Design: Opportunities, Challenges, Bioethics and Innovation

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Lilly

Outline

- Regulatory Landscape
- New Guidance
- Bioethics and Pediatric Research
- Extrapolation
- Application and Examples
- Concluding Remarks + Q&A

US/EU Regulatory Landscape

USA

Pediatric Research Equity Act (2003, 2007): mandatory; no exclusivity; orphan indications exempt. **RACE Act** (2017) required if drug target is relevant in pediatric cancer

Best Pharmaceuticals for Children Act (2002, 2007): voluntary; exclusivity possible; written requests may be issued for orphan indications

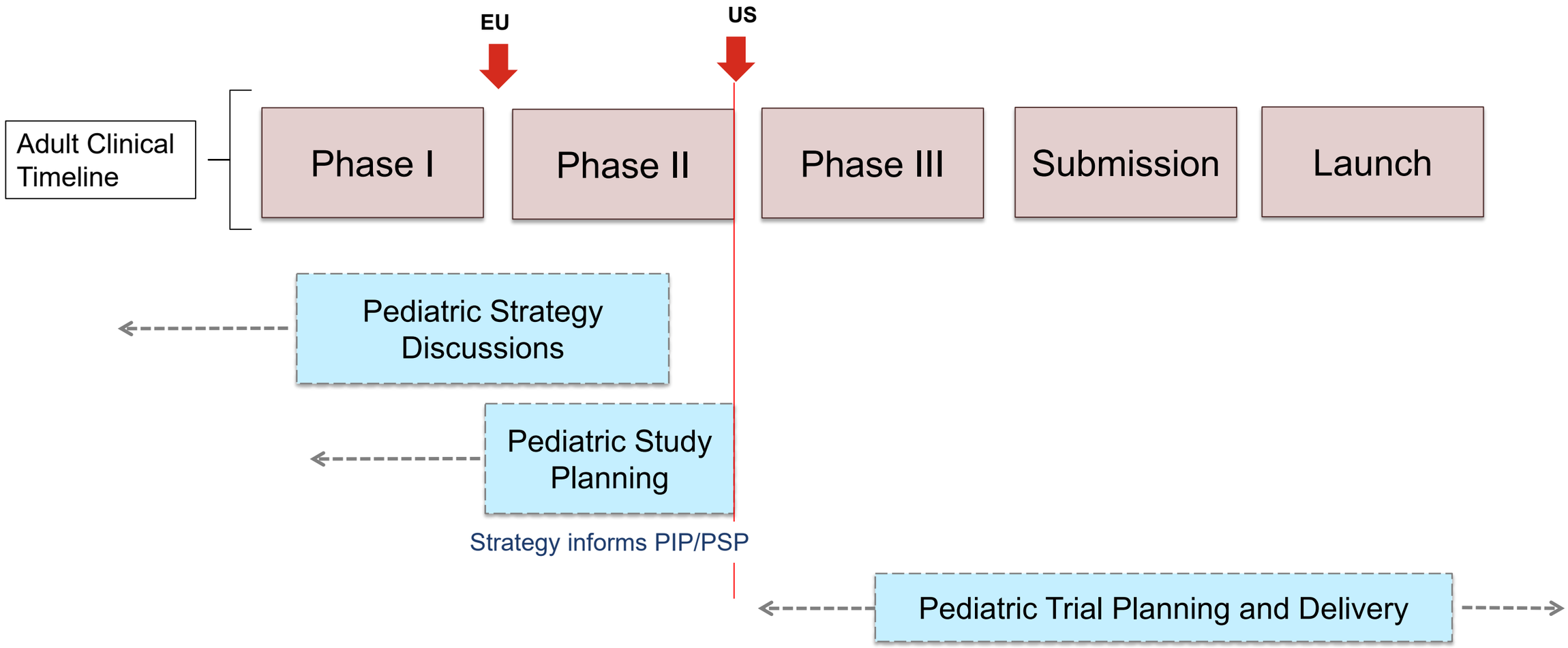
- Approved Pediatric Study Plan (PSP) and/or waiver are required for adult submission
- Failure to have an agreed PSP or waiver is considered a reason for refusal to file
- Potential 6 month exclusivity if voluntary Written Request (WR) commitments are met
- Priority review voucher if pediatric rare disease is first indication

EU

EMA Pediatric Regulation (2007): mandatory; 6-mo Supplementary Protection Certificate

- Approved Pediatric Investigation Plan (PIP) and/or waiver are required prior to adult marketing authorization application*
- Failure to comply with PIP requirements can result in delayed submissions, public disclosure and penalties
- Potential 6 month patent extension if agreed PIP commitments are met
- Actively considering additional legislative changes

General Development Timeline



Evolving Regulatory Landscape

2019

(2019) FDA Draft Guidance: Rare Pediatric Disease Priority Review Vouchers

2020

(2020) FDA Final Guidance: Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs

2022

(2022) ICH E11A Draft Guideline: Paediatric Extrapolation

(2022) FDA Draft Guidance: General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products

(2022) FDA Draft Guidance: Measuring Growth and Evaluating Pubertal Development in Pediatric Clinical Trials

(2022) FDA Draft Guidance: Ethical Considerations for Clinical Investigations of Medical Products Involving Children

(2023) FDA Draft Guidance: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

(2023) EMA Draft Guidance: Stepwise PIP Pilot

(2023) FDA Draft Guidance: Research Involving Children as Subjects and Not Otherwise Approvable by an IRB

(2023) EMA Draft Reflection Paper: Establishing Efficacy Based on Single-Arm Trials Submitted as Pivotal Evidence in a Marketing Authorization

(2023) FDA Draft Guidance: How to Comply with the Pediatric Research Equity Act

(2023) HC Draft Guidance: Submitting Pediatric Studies and Pediatric Development Plans

2023

ICH harmonisation for better health

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Health Canada Santé Canada

Bioethics & Pediatric Research

Scientific Necessity

Prospect of Direct Benefit

Maximize Info;
Minimize Risk;
Minimize Patients

Bioethics: Scientific Necessity

- "Children should not be enrolled into a clinical investigation unless their participation is necessary to answer an important scientific and/or public health question directly relevant to the health and welfare of children."
- When it is scientifically necessary to conduct pediatric trials, the **trials must be well designed**. Poorly designed trials expose children to unnecessary risk and may be considered unethical.

- For products that are being developed for use in adults and children, if effectiveness in adults can be extrapolated to children, then effectiveness studies in adults should be conducted to minimize the need to collect effectiveness data in children.

- Key elements of well-designed clinical investigations include the selection of appropriate control groups and study endpoints relevant in the pediatric population.
- Studies that are not well-designed expose children to unnecessary risks, are unlikely to yield informative study results and as a result may be considered unethical.

Bioethics: Prospect of Direct Benefit

- "The potential benefit to the individual child from exposure to the research intervention or procedure in the clinical investigation in question.“
- Risk must be justified by potential benefit; proposed dose and duration of treatment must be sufficient to offer PDB

- Should result from the research intervention or procedure being studied and not from ancillary interventions or procedures, such as physical exams done as part of the trial
- The risk is justified by the anticipated benefit to the child, but the relation of the anticipated benefit to the risk is at least as favorable as any available alternatives
- The proposed dose (particularly for drugs) and duration of exposure to the intervention or procedure are adequate to offer a potential clinical benefit to the individual child
- For a medical device clinical investigation, the device characteristics should be compatible with the child’s age and developmental stage such that a benefit is anticipated

Bioethics: Maximize Info, Minimize Risk and Patients

- "Clinical investigations involving children should be designed to maximize the amount of information gained and minimize the number of subjects involved."
- Principle of Scientific Necessity is not limited to initiating pediatric research, but also applies when right-sizing that research

Minimal Risk

- probability and magnitude of harm or discomfort anticipated are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests
- interpreted as those risks encountered in the daily life of normal, average, healthy children living in safe environments and indexed to the experiences of children of the same age and developmental stage as the subject population
- duration of exposure to the risk, the characteristics of the risk, and the reversibility of harm should be considered

Minor Increase over Minimal Risk

- slight increase over minimal risk that poses no significant threat to the child's overall health or well-being
- Any potential harms should be expected to be transient and reversible
- the probability for severe pain, discomfort, or harm should be extremely small or nonexistent

Additional Considerations

Initiation of Pediatric Studies

- **Effectiveness in adults does not need to be established before studies in children may begin**
- Early inclusion of children in medical product development or initiation of trials directly in children may be appropriate
- Nonclinical studies, bench testing, modeling and simulation, literature, and prior adult information (eg: PK, PK/PD) may be used to assess the potential risks and benefits of initiating pediatric investigations

Design Considerations

- Any dose planned for use in a pediatric clinical investigation should have the potential to have a therapeutic effect based on available scientific information
- Investigations should be of sufficient duration to offer potential clinical benefit
- Adaptive designs could combine prospectively planned dose ranging or titration with continues dosing after a dose is established
- **Adult studies should be designed to minimize the amount of information needed in pediatrics**

Innovation as a Driver for Efficiency

- Challenge: develop efficient designs while balancing the ethics of enrolling children as a vulnerable population.
- Response: Innovative techniques such as extrapolation have come into focus

Extrapolation:

An approach to providing evidence in support of the safe and effective use of drugs in the pediatric population when it can be assumed that the **course of the disease and the expected response to a medicinal product would be sufficiently similar** in the pediatric and reference or source population (ICH E11)

- Goal: reduce the need for pediatric exposure by leveraging prior information and developing analysis models that take this information into account.

ICH E11A Extrapolation Overview

- Disease similarity between reference and target populations is not a yes or no question. A continuum of similarity or dissimilarity may exist and the extrapolation approach should reflect that continuum.
- Extrapolation is an iterative process of understanding existing information, identifying gaps/uncertainties, and developing ways to generate additional information to fill those gaps.
- A discussion on extrapolation of safety data should be included in the extrapolation concept and a comprehensive safety plan should be included in the extrapolation plan
- Inclusion of adolescents in adult trials may accelerate pediatric data gathering. Disease similarity evaluation between adolescents and younger children is needed if using adolescent data as a bridge from adults to younger children.

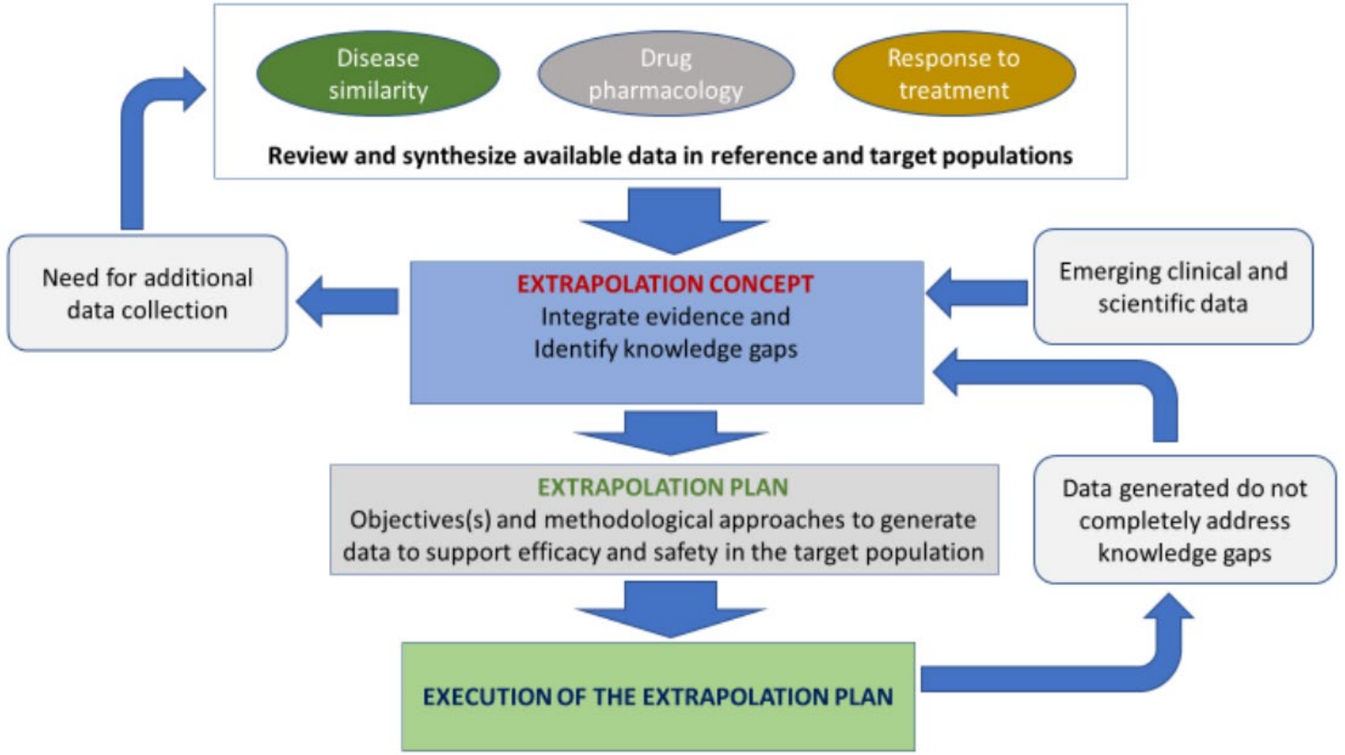


Figure 2: Pediatric Extrapolation Framework: E11A Pediatric Extrapolation | FDA

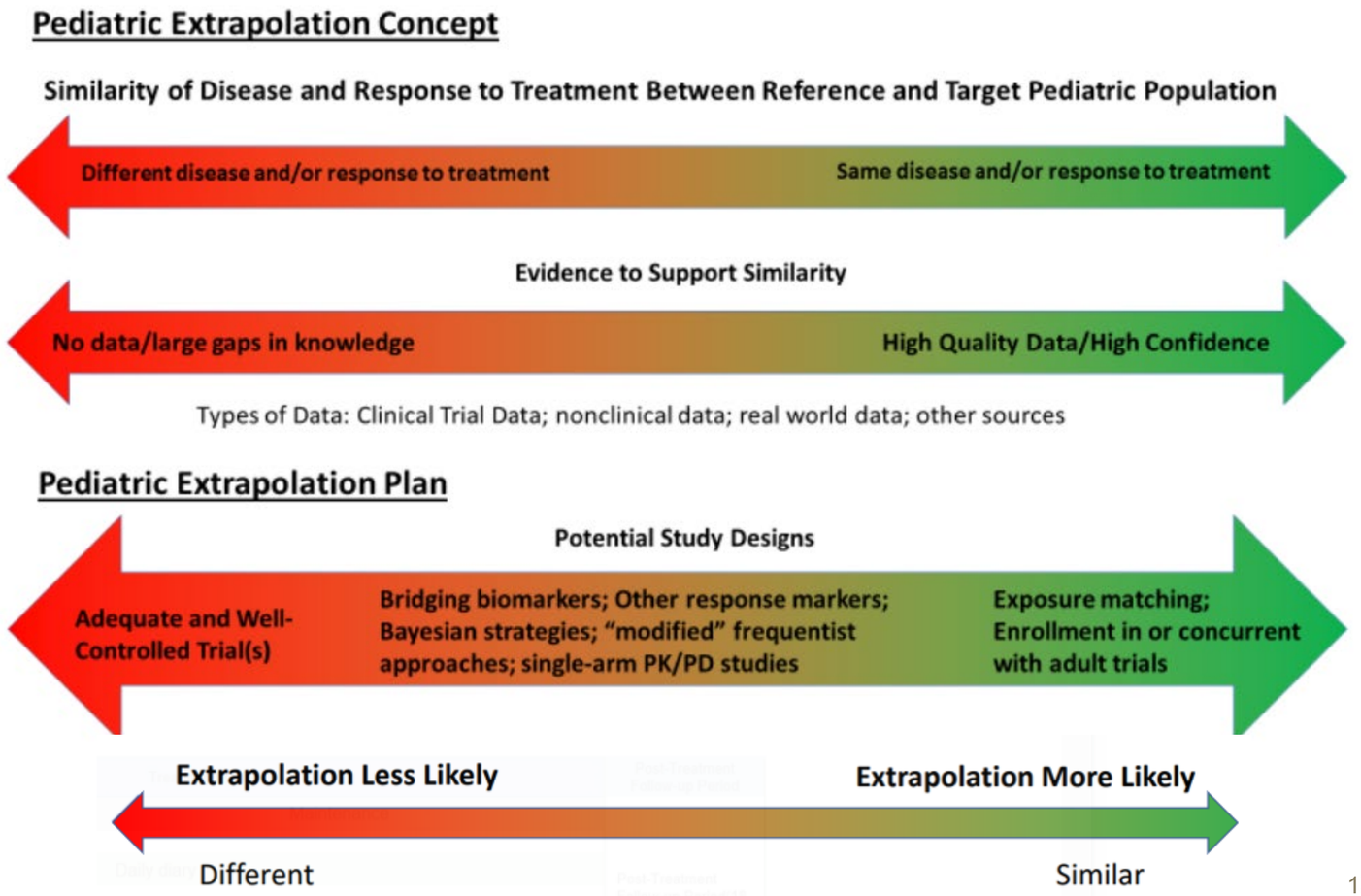
Extrapolation as a Continuum

Extrapolation has gone from a categorical phenomenon to being described on a continuum of similarity and dissimilarity

Whether the course of disease and expected response to treatment can be considered sufficiently similar between a target and a reference population is not a "yes" or "no" question

Extrapolation should address the uncertainties, and the level of uncertainty should inform the trial design

Figure 1: Pediatric Extrapolation Approach



Pediatric Extrapolation Concept

Development of a pediatric extrapolation concept requires an understanding of the factors that influence the similarity of disease, the pharmacology of the drug and the response to therapy as well as the safety of use in all the relevant populations.

- Disease Similarity
- Drug (Pharmacology) Similarity
- Similarity to Response of Treatment
- Sources and Types of Existing Data
- Safety Considerations in the Extrapolation Concept

Assessing disease similarity

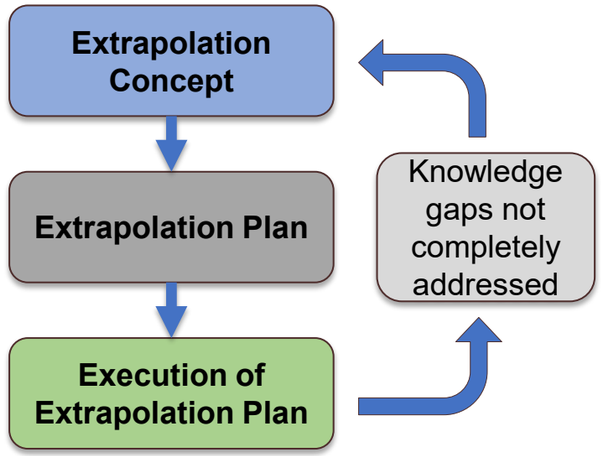
- Manifestations of disease/diagnostic criteria
- Measurements used to define disease
- Subtypes of disease (e.g. defined by severity, genetics or molecular markers)
- Other factors that define the disease (e.g., genetic/epigenetic)
- Clinical course of disease
- Endpoints and/or biomarkers to measure disease progression
- Measuring short-term outcomes
- Measuring long-term outcomes
- Available treatments
- Treatment effects on course of disease

Extrapolation of Safety

- What is the **age-range** of pediatric patients to be studied as part of the safety extrapolation?
- What **amount/quality of safety data** is available from the reference population?
- Are there **known on- or off-target effects** of the investigational drug relevant to pediatric safety?
- Are data needed to account for **age-specific short- and longer-term adverse effects** in pediatric populations, which may not have been identified in studies in the reference population?
- How does the expected **treatment duration and treatment effect size** compare?
- How do the **expected drug exposures** compare?
  Does the exposure needed to target a specific PD effect or clinical response predict a specific toxicity in the target pediatric population?
- What information is already known from **non-clinical sources** that can be leveraged to the target population?
- Are there other **differences between the reference and target population** that could limit the extrapolation of safety (e.g., a background therapy used in a target population that may potentiate a safety signal but is not used in the reference population)?

Sources and Types of Existing Data

- Both quantity and quality of data must be considered to evaluate the similarities and differences between the reference and target populations.
- All available data should be used to establish the extrapolation concept and formulate the extrapolation plan
- Sources:
  - Clinical data
  - Nonclinical data
  - Real World data
  - Other sources (systematic reviews, meta-analyses)



Example 1: Extrapolation

Study Info

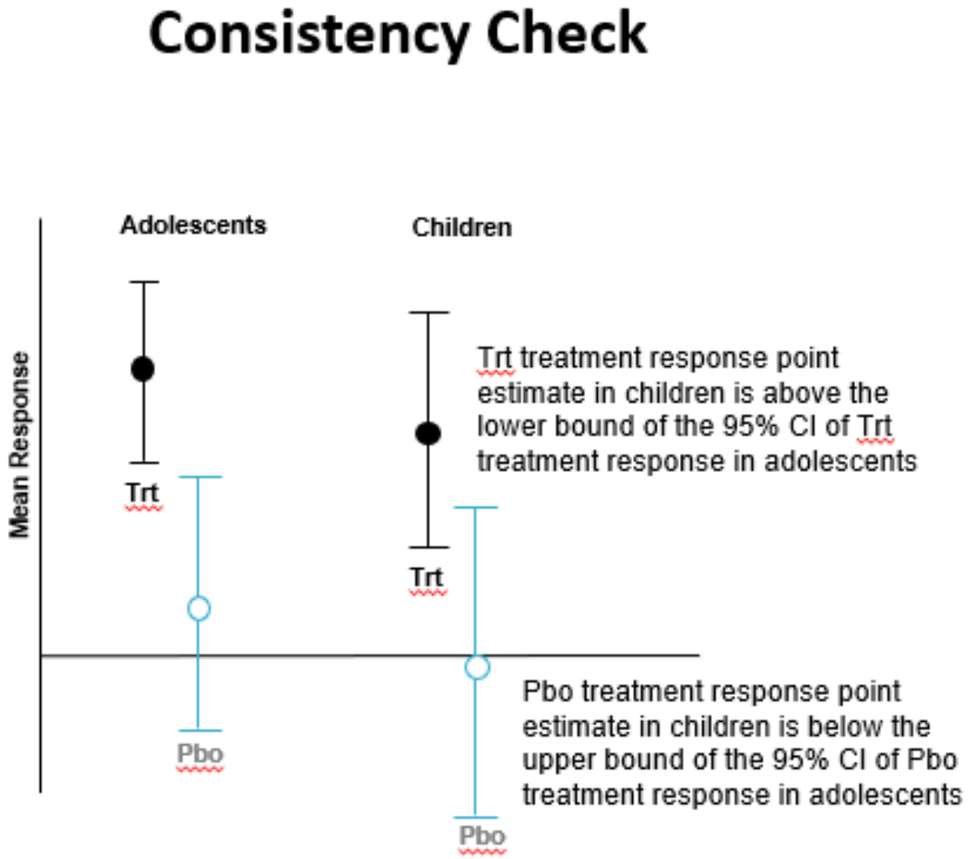
- Phase 3
- Indication exists in adults and pediatrics
- Non-rare disease
- Treatments approved in adults and pediatrics
- First in class therapy

Design

- Open-label PK lead in
- Randomized, controlled trial (Treatment vs. Control)
- Extrapolation from adolescents to children
- Bayesian analysis - mixture prior

Justification of Data Borrowing

- Before we borrow information from the older group of patients, we need to check that the treatment responses in the younger group are similar or *consistent* with the treatment responses in the older group.
- If responses are consistent, we borrow information from the older group via an informative prior
- If responses are not consistent, we use a non-informative prior instead (no data from the older group is used in analysis)



How does a consistency check fit into the extrapolation paradigm?

Data to Support Extrapolation

- Clearly define source population: older pediatric patients
- Planned (or ongoing) adult trials: completed phase 2 adult trial; ongoing phase 3 trials (at the time of PIP negotiation)
- One planned pediatric trial

Extrapolation Concept

- List of what is known about IP
  - Adults and pediatrics with indication have similarities in disease manifestation, aetiology, pathophysiology, and response to existing therapies
  - Similar target populations to be enrolled in the adult studies and the pediatric study

- List of what is unknown about IP that will be important in finalizing a study design
  - Anticipated that a positive effect in adults will mean a positive effect in older pediatric patients.
  - Anticipated that a positive effect in older pediatric patients will mean a positive effect in younger pediatric patients.

- How uncertainty will be mitigated
  - Assumption of similarity of expected results in older and younger patients, will be validated by the inclusion of a consistency check on the prior information.

Example 2: Historical Data and Probability of Success

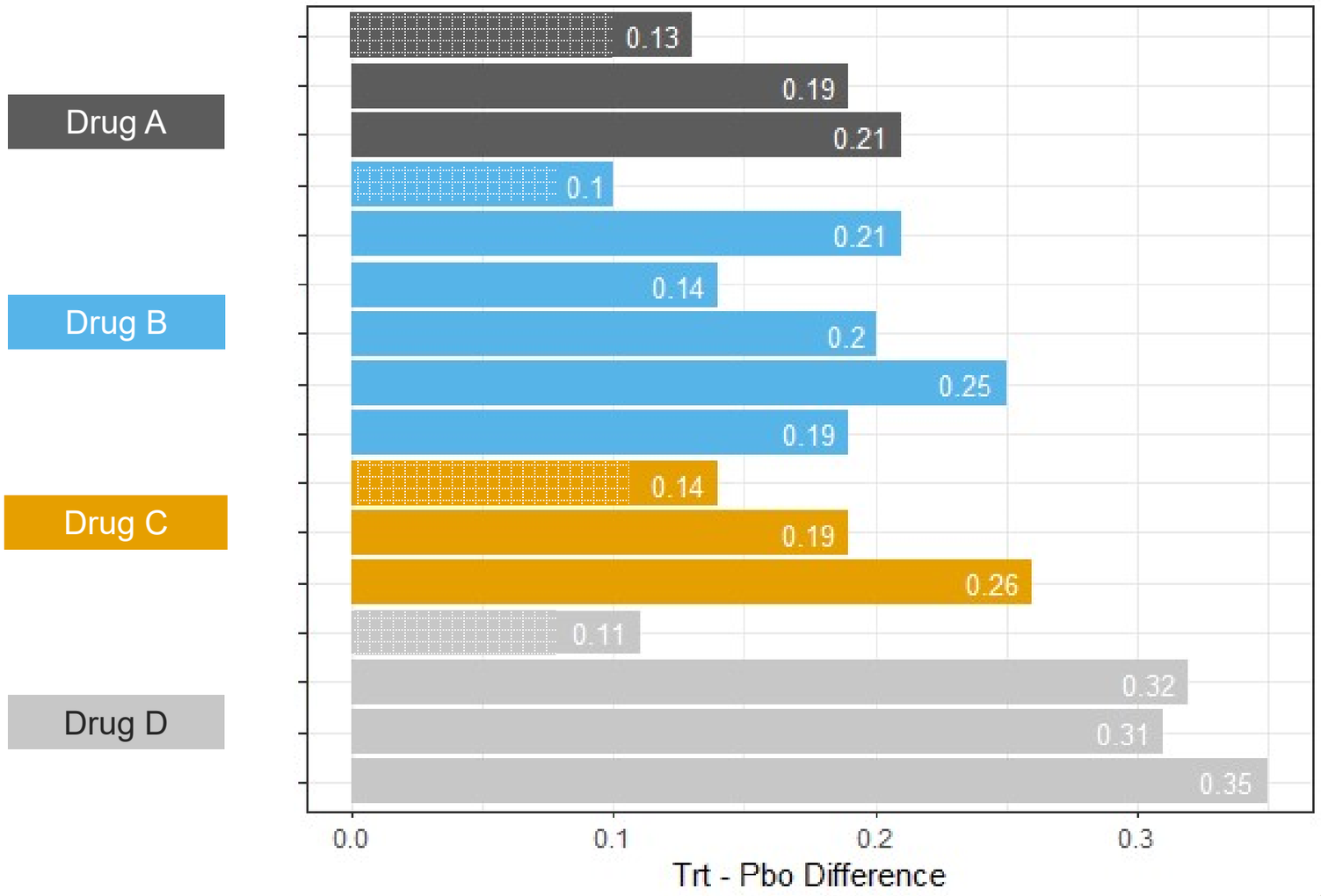
Incorporating Historical Data into Pediatric Design

- Historical data is an important consideration in developing response rate assumptions within pediatric trial design and it can be incorporated into a design framework in multiple ways.
- Here, a case example is presented for an indication in which both adult and pediatric historical data exist. A weighted average approach and a Bayesian meta-analysis approach are presented to compare response rates in pediatric studies with those from adult studies examining the same medications and dosages.
- Summary of endpoints and ped/adult design:
  - The primary endpoint is a pain freedom rate with 4 treatment groups (Low dose, Mid dose, High dose, Pbo).
  - The pooled treatment effect (Drug-Pbo) for high dose in adults is 0.20.
  - The assumed pediatric treatment effect for high dose is 0.12 (based on peds historical data) which yields approximately 80% power for sample size of 700 and assumed Pbo response of 0.16.

Historical Data Summary

The first bar in every color grouping represents the pediatric treatment effect (Trt-Pbo difference). Only studies with designs similar to the peds drug design are considered. Note that pediatric treatment effect are less than adult treatment effects.

The goal is to leverage historical data to inform beliefs about the peds data (how much lower is the expected peds treatment effect relative to the adults?)



Leveraging historical data to inform perspective on Adult to Pediatric discounting

- We expect the pediatric treatment effect to be lower than that observed in adults. How much lower?
- Some ways to answer this question:
  1. Calculate a ratio of treatment effect weighted averages from historical data (ped/adults)
  2. Borrow an approach from meta-analysis and model the distribution of the discounting between historical adult and pediatric treatment effects.

Method 1: Weighted Average Approach

Steps:

1. For each dose, obtain the weighted average of treatment effects in pain freedom rates for adult and pediatric studies separately.
2. Calculate the ratio of the weighted averages (ped/adult).
3. Calculate the weighted average of the ratios to obtain the proportion of discounting from adults to peds.

Dose	Weighted Avg Diff Adults	Weighted Avg Diff Peds	Ratio (Peds/Adults)
Drug A	0.20	0.13	0.65
Drug B	0.20	0.09	0.45
Drug C	0.22	0.14	0.64
Drug D	0.32	0.08	0.25

The average of the ratios is 0.49.

This means the pediatric treatment effect for pain freedom rates is less than half of that in adult studies.

Multiplying 0.49 by the adult high dose treatment effect yields a response assumption for the peds treatment effect informed by historical data.

Method 2: Bayesian Meta-Analysis

Steps:

1. Model the distribution of the historical adult mean treatment effects for each drug. For each effect y_{ij} and standard error SE_j,

$$y_{ij} \sim N(\boldsymbol{\alpha_i}, SE_j) \ ,$$

where *i* is the *i*-th treatment effect and *j* is the study index for each treatment.

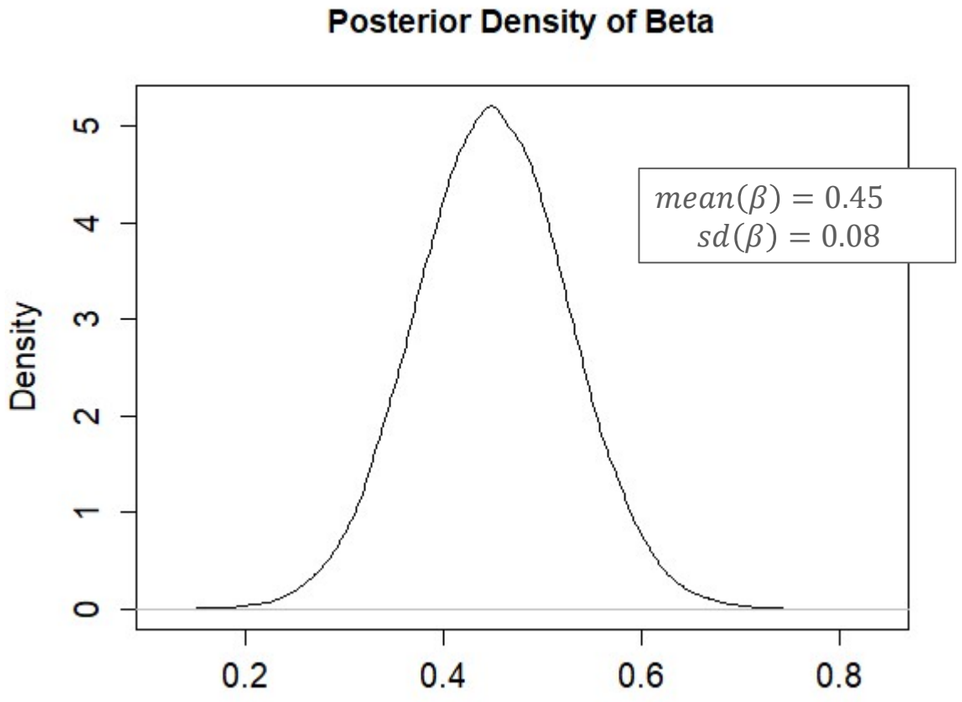
2. The estimates for the historical adult treatment effects inform the historical pediatric model. For each pediatric treatment effect x_{ij},

$$x_{ij} \sim N(\boldsymbol{\alpha_i} * \beta, SE_j) \text{ where } \beta \sim U(0,100).$$

3. Use the distribution of β in step 2 to generate pediatric data as a discounted version of the adult data (α_A is adult high dose treatment effect).

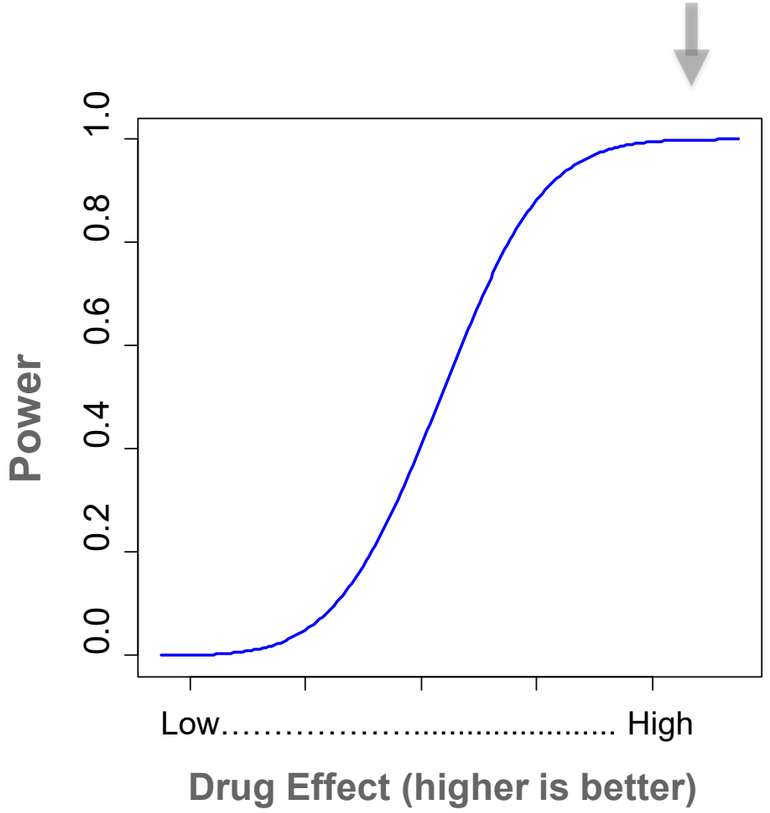
$$x_{LY} \sim N(\alpha_A \cdot \beta, SE)$$

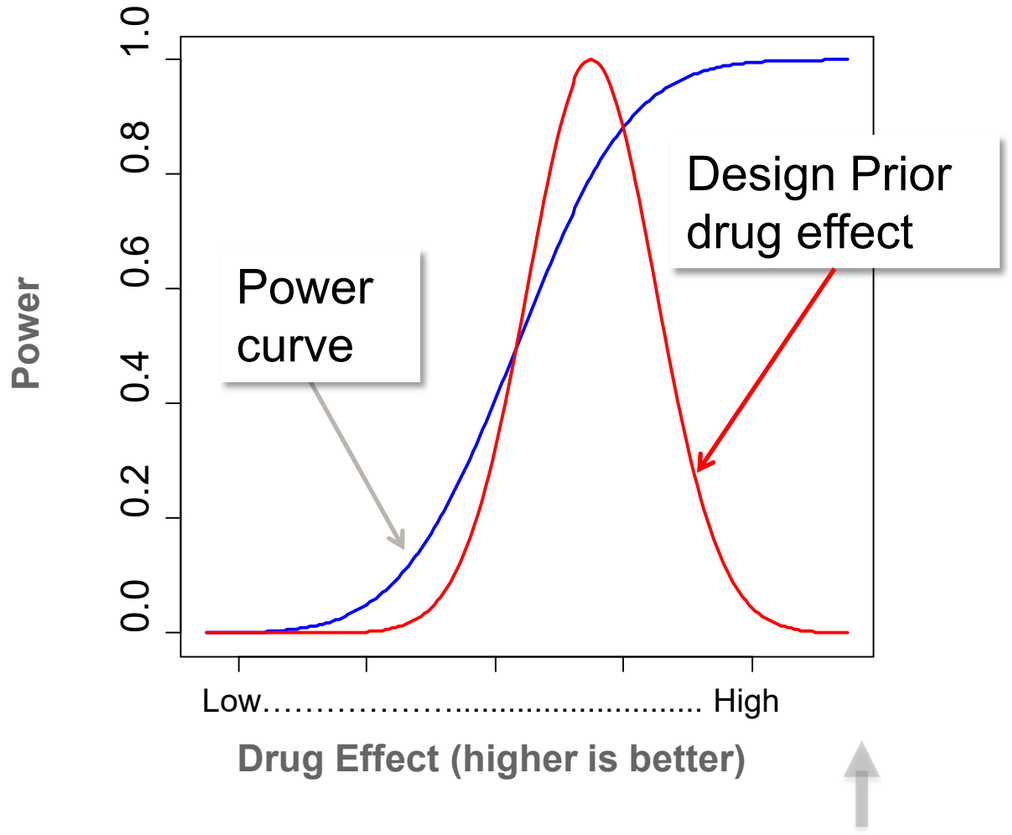
4. Calculate the probability of success (PrSS).



Explaining PrSS to non-statisticians

- The study design and decision criteria define a power curve
- This is the probability of success if the drug effect is known
- But prior to a study, the drug effect is not known so neither is placement on the curve





The current data informs where the effect is likely to land on the curve

1. Add in the uncertainty in the magnitude of the drug effect
2. Average the power over the possible drug effect to get PrSS

Example 2: Results and Conclusions

- Incorporating adult and pediatric historical information into pediatric study design can inform calculations for study power and probability of trial success.
  - The initial assumption for the high dose pediatric delta was 0.12 based on averaging historic pediatric results, which yields greater than 80% power for a pediatric sample size of 700.
  - However, in looking at the historical trends in adult and pediatric migraine programs, pediatric responses are consistently lower than those of adults.
  - Leveraging historical information and what is known about high dose in adults, a Bayesian meta-analysis approach yields an expected high dose pediatric treatment effect of 0.09 and a probability of trial success of 0.58 assuming a pediatric sample size of 700.
- A note on criteria for historical data use to ensure similarity in placebo response and placebo-treatment differences:
  - Consider only historical pediatric studies that utilize a design similar to that proposed by the sponsor and only adult/peds programs that study the same medications and dose exposures.

Concluding Remarks

- In the past researchers have focused efforts on minimizing the size of pediatric programs, leveraging extrapolation when possible.
- Thinking on extrapolation is evolving, as represented in ICH E11A, and investigators are advocating for more flexible trial designs and statistical methods to right-size pediatric programs to address areas or large uncertainty, sometimes accepting more risk of error than in traditional development programs.
- Innovative designs cannot be at the expense of the safety and ethical benefit to participants. In many cases it is not ethical to run small programs that cannot address the scientific question, and in other instances it is not ethical to conduct large trials that generate small amounts of new and relevant information.
- Pediatric programs can be made more efficient by designing adult programs to minimize the unknowns in children. Encourage your teams to reach out to pediatric experts for pediatric trial design & when setting objectives in adult trials that will be used to trigger pediatric trials.

Questions?