A Regulator's Perspective on Pediatric Bayesian Methods

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- I have no conflicts of interest to report.
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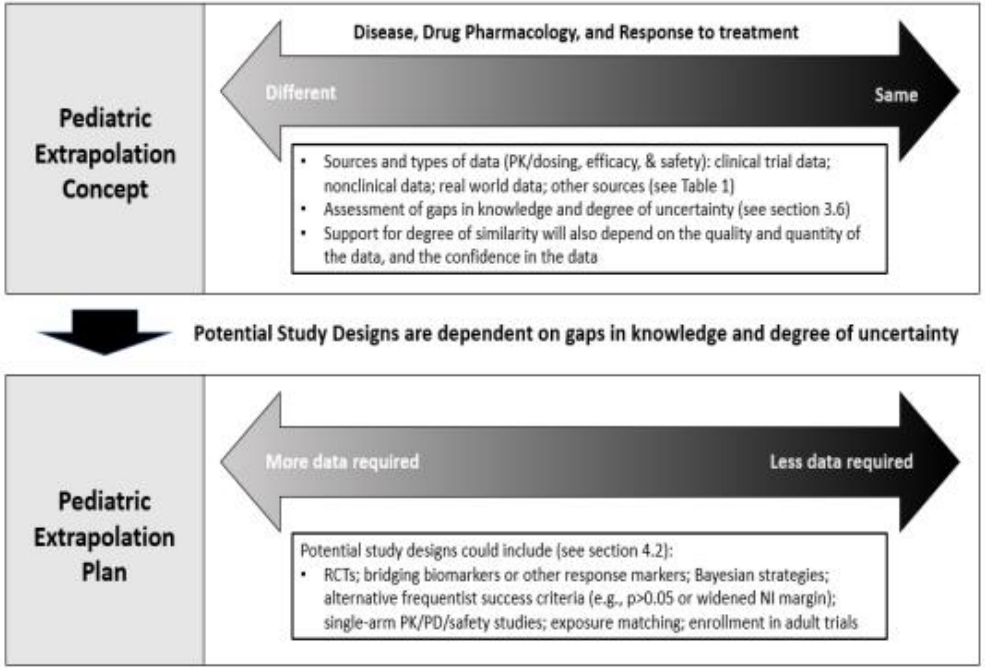
Pediatric Extrapolation Regulatory History

- Long history of extrapolation (1994 Pediatric Labeling Rule)
  - "New § 201.57(f)(9)(iv) provides that a pediatric use statement may be based on adequate and well-controlled studies in adults, provided that the course of the disease and the drug effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients."

Pediatric Extrapolation as a Continuum



From E11A Pediatric Extrapolation.

Bayesian Trials in Pediatrics

- Goodman and Sladky in 2005 proposed using a Bayesian approach to analyses pediatric trials.
- A Bayesian approach forces us to explicitly deal with:
  - The quality of the adult data and its relevance to children.
  - The quality and quantity of the children's data
  - How to represent the prior knowledge based on adult and children's data.
- "Bayesian methods must be preceded by a judgment that the biological processes involved in both disease and treatment are deemed to be related in the two populations."

JUSTIFYING THE DECISION TO BORROW EXAMPLE: PEDIATRIC TYPE 2 DIABETES

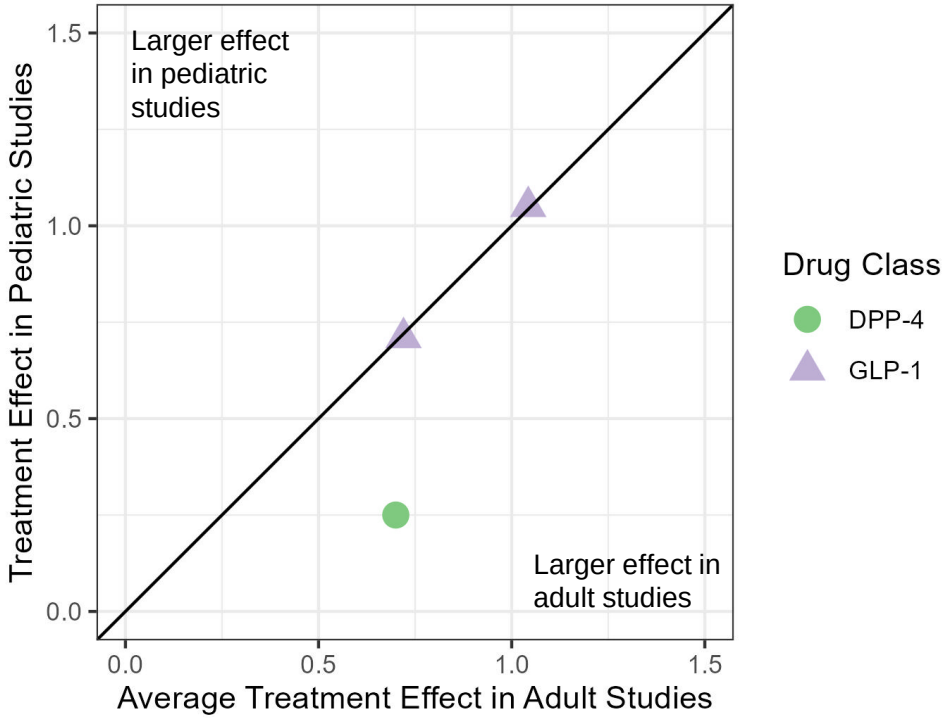
Background

- Since 2020, we started to see completed pediatric trials for newer type 2 diabetes drugs (DPP-4, SLGT2, GLP1)
- Some of these pediatric studies did not find a statistically significant difference.
- We decided to evaluate the completed programs to examine whether there were any lessons that could be applied to future programs to reduce the number of failed trials.

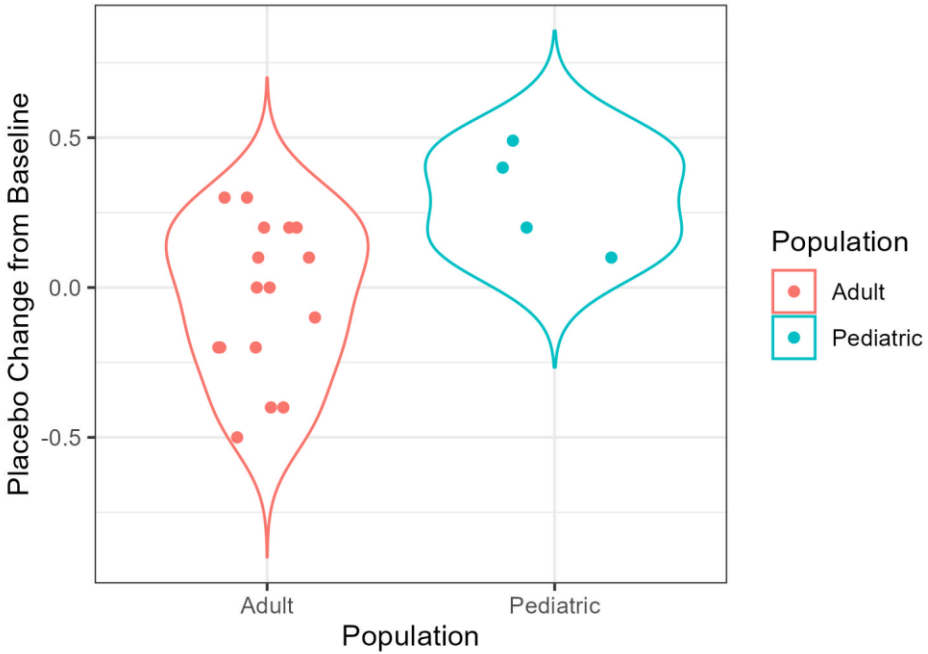
Pediatric Variability

Study Drug	Assumed SD and Planned Study Power	Observed SD and Retrospective Power
Sitagliptin	SD = 1.1% Power=82%	SD = 1.6% Retrospective Power=51%
Sitagliptin and Metformin	SD = 1.1% Power=86%	SD = 1.4% Retrospective Power=67%
Colesevelam	SD = 1.0% Power=80%	SD = 1.5% Retrospective Power=46%
Liraglutide	SD = 1.2% Power=80%	SD = 1.8% Retrospective Power=46%
Extended release Exenatide	SD = 1.0%, Power=74%	SD = 1.5% Retrospective Power=41%

Pediatric vs Adult Treatment Effect



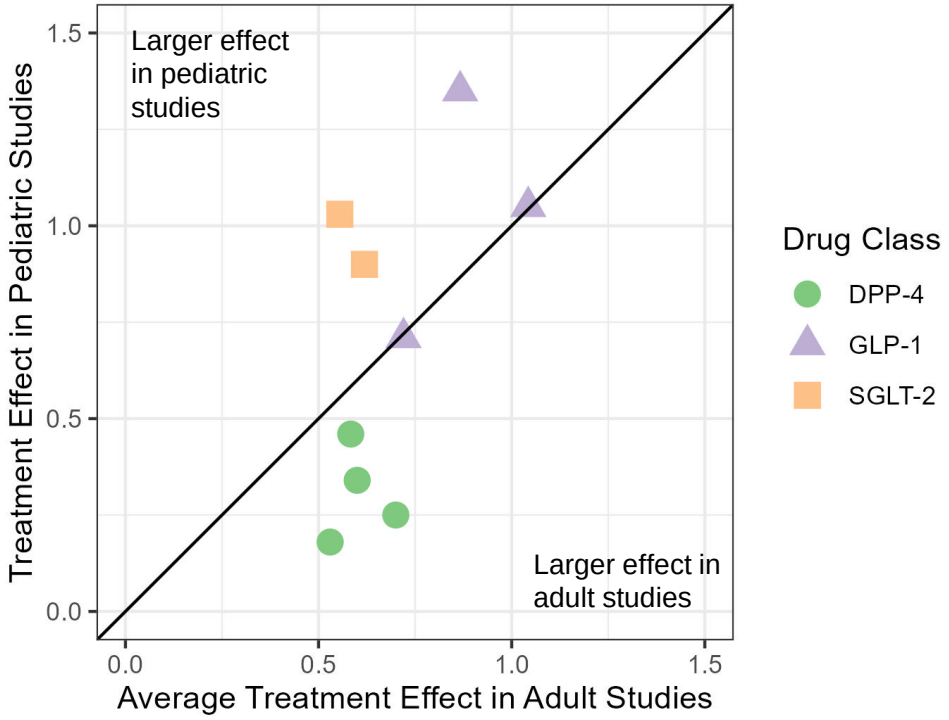
Pediatric Vs Adult Placebo Effect



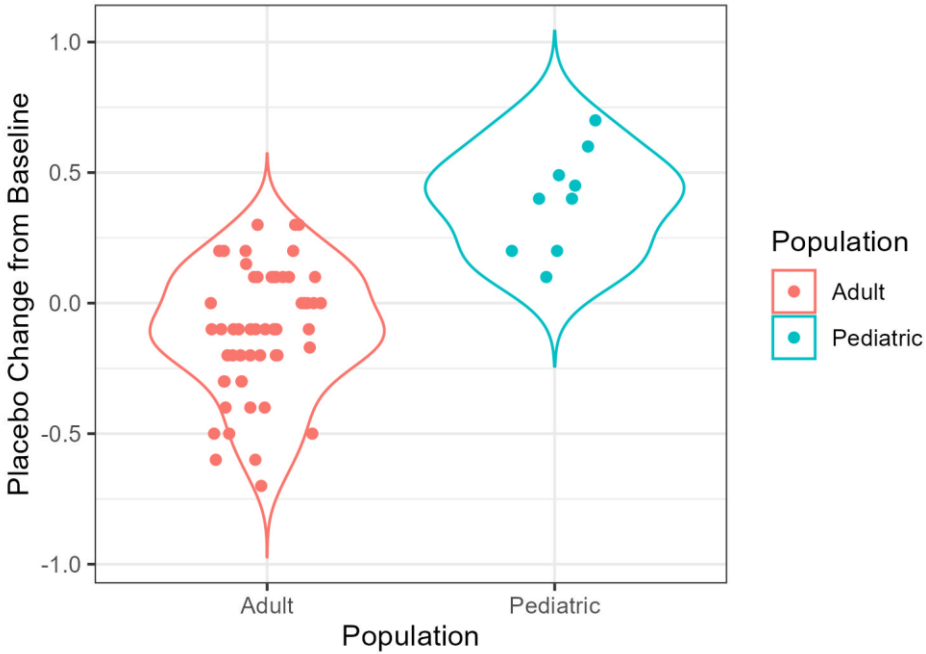
Lessons Learned – Summary

- Pediatric patients are more variable than adult patients which means pediatric studies need to be larger than comparative adult studies.
- Disease progression over the course of the trial is also different, with apparent trend of increasing HbA1c in placebo treated pediatric patients.
- For 2/3 completed pediatric trials, we saw similar magnitudes of treatment effect suggesting using prior information could be reasonable.
- Result: Recommended using a Bayesian analysis in analyses of pediatric type 2 diabetes studies.

Pediatric vs Adult Treatment Effect



Pediatric Vs Adult Placebo Effect



MAIN CHALLENGES OF BORROWING

Hardest Part of Borrowing

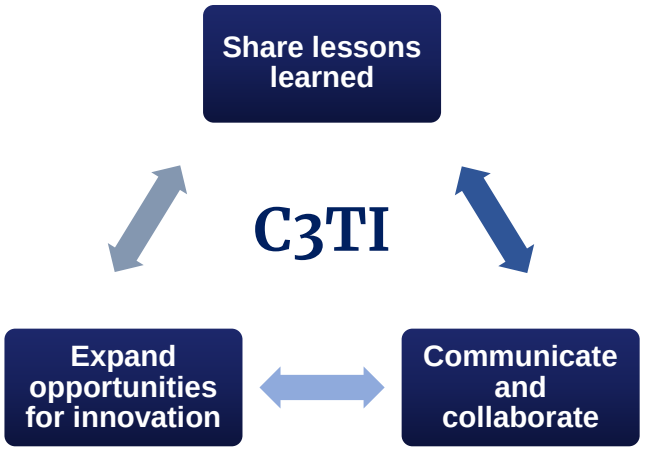
- Deciding how much borrowing is appropriate and aligning the prior with this decision is the most challenging part of the process.
- It requires discussion and compromise between multiple disciplines and organizations.
- Development and education on tools and language to facilitate this process is crucial.

Process Needs

- Need to collaborate to develop and use easily interpretable, direct measures of borrowing that ensure clear communication.
- Traceability and transparency of decisions are also crucial communication considerations.

CDER Center for Clinical Trial Innovation (C3TI)

Mission: To promote existing and future CDER clinical trial innovation through enhanced communication and collaboration



Learn more

www.fda.gov/C3TI

CDERclinicaltrialinnovation@fda.hhs.gov

Key Activities:

- Demonstration program to scale adoption of innovation
- Internal and external communication and engagement
- Single point-of-contact for innovation-related questions
- Knowledge sharing

C3TI Demonstration Program

- Offers a mechanism for early engagement between CDER and sponsors of clinical trials implementing select innovative approaches.
- Open to selected sponsors conducting innovative clinical trials under a pre-investigational new drug application (pre-IND) or IND with CDER. These trials should be intended to support new drug approvals or changes to approved drug labeling.
- C3TI prioritized three initial demonstration project areas:
  - Bayesian Statistical Analysis
  - Selective Safety Data Collection
  - Streamlined Trials Embedded in clinical Practice
- If selected, sponsors will benefit from enhanced communication with CDER staff (review team members and relevant subject matter experts) to support critical milestones such as protocol development and study start-up. The nature and frequency of communication will vary based on the specific innovations being applied.

To learn more about the demonstration program, including proposal eligibility criteria and the submission process, visit www.fda.gov/C3TI.

Bayesian Statistical Analysis (BSA)

Overview

- Aims to **increase experience** in Bayesian statistical methods in simple trials settings across sponsors, CDER clinical reviewers, and CDER statisticians.
- Participation provides sponsors with additional CDER support to **align on the statistical analysis plan**, ensuring it robustly supports drug safety and efficacy evaluations while improving trial efficiency.

Eligibility Criteria

- A phase 3 efficacy or safety trial with simple design, such as a trial with a non-adaptive or straightforward sequential design.
- The Bayesian analysis may be used for:
  - Pre-specified primary analysis
  - Supplemental analysis of the primary endpoint in the overall study population and/or in relevant subgroups (i.e. subgroup analysis).
  - Trial monitoring

Bayesian Guidance

- PDUFA VII Commitment:
  - By the end of FY 2025, FDA will publish draft guidance on the Use of Bayesian Methodology in Clinical Trials of Drugs and Biologics.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