Innovative Analytic Approaches in the Context of a Global Pediatric IBD Drug Development

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Topics

- Rationale for "right sizing" pediatric trials
- Extrapolation and innovative analytics as tools for "right sizing" trials
- Extrapolation and innovative analytics must be guided by awareness of regulatory expectations
- Bayesian strategies in concurrent adult & adolescent trials
- Comments on the use of placebo
- Piloting real world data in an area where extrapolation is expected
- Design and analysis in staggered development of different cohorts

Timely label update requires the right amount of pediatric patients to answer a public health question.
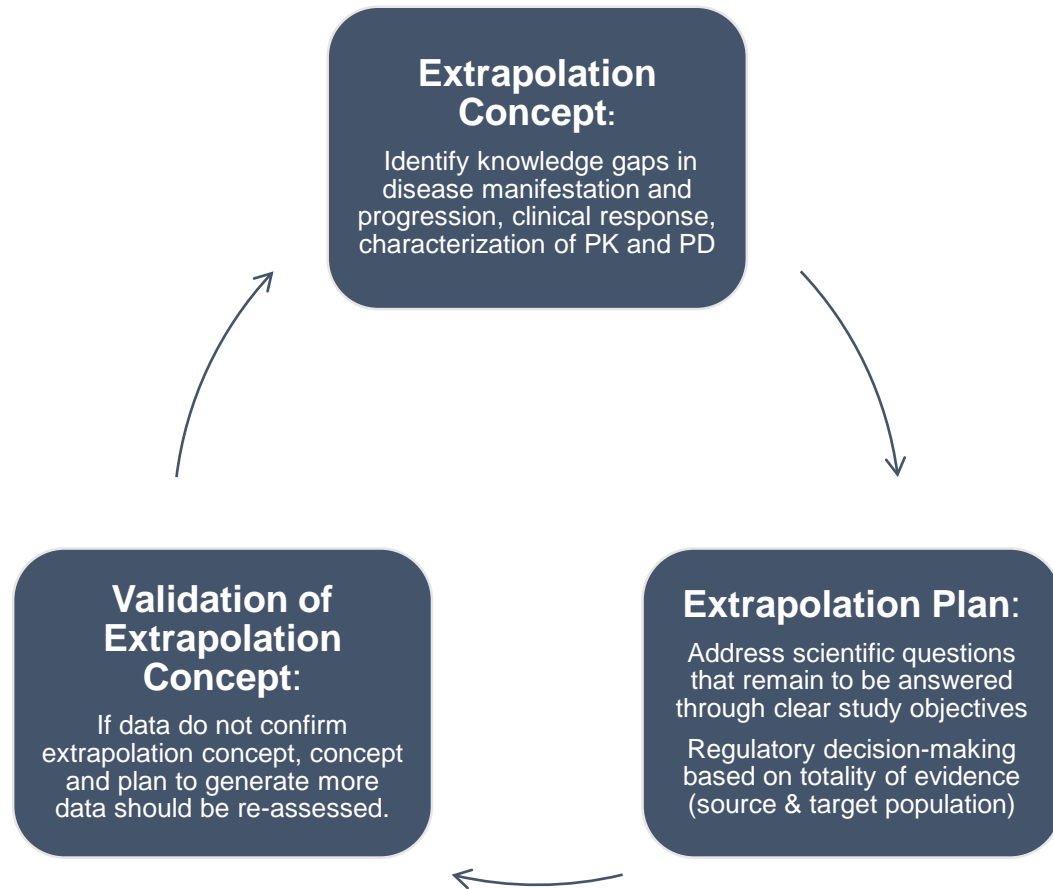
- **Right amount of pediatric patients in a trial to provide sufficient information for labelling.**
  - Too small a trial cannot sufficiently provide answer to public health question of interest.
  - Too large a trial risks of not being completed on a timely basis and thus loses social value.
- **Right amount of patients implies extrapolation and/or innovative analytics to maximally extract new information from the least amount of patients**

Goldilocks Principle

Right amount of pediatric patients is grounded on ethics that children are a vulnerable population.

Extrapolation: Evidence synthesis, identification of knowledge gaps/uncertainty, prediction within that gap, validation of prediction

Extrapolation Concept:
Identify knowledge gaps in disease manifestation and progression, clinical response, characterization of PK and PD

Extrapolation Plan:
Address scientific questions that remain to be answered through clear study objectives
Regulatory decision-making based on totality of evidence (source & target population)

Validation of Extrapolation Concept:
If data do not confirm extrapolation concept, concept and plan to generate more data should be re-assessed.

NB: Despite the concept of an iterative approach, rarely is there an iteration in a PIP/PSP. In fact, plans (key elements) have to be approved and modified only later if infeasible.
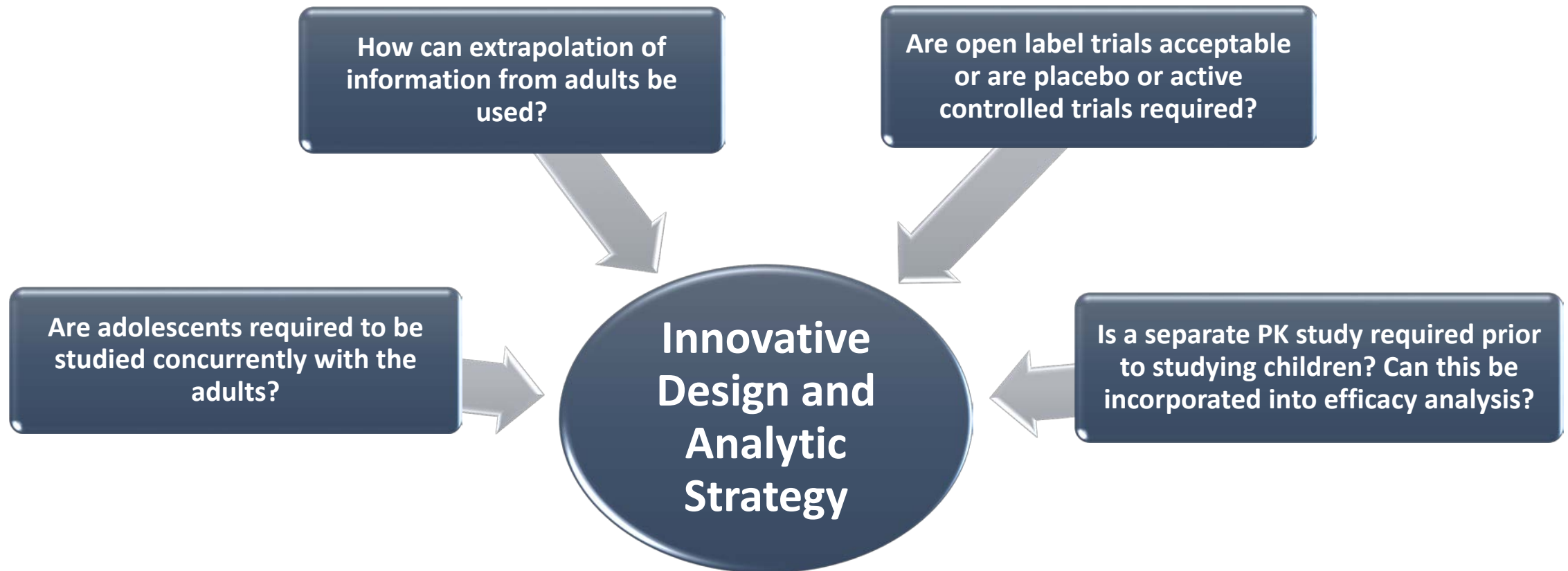
Concept:
- "Quantify" evidence synthesized in source population and how much of that information is translatable to the target population. Say that is **X (known)**.
- How much information is still needed to achieve certain precision? What are the knowledge gaps that still need to be filled? Say **Z** is the required target information (**generally unspecified**)

Plan: Conduct a trial with informational value **Y** in the target population so that **X + Y = Z.**
- Size **Y** such that it only needs the right number of patients to fill the gap or uncertainty

Validate: Check whether information in **Y** is consistent with what was seen in **X** (source population).

Extrapolation and innovative analytic approaches must be informed with varying degree of receptivity across regulatory agencies.


How can extrapolation of information from adults be used?

Are open label trials acceptable or are placebo or active controlled trials required?

Are adolescents required to be studied concurrently with the adults?

Innovative Design and Analytic Strategy

Is a separate PK study required prior to studying children? Can this be incorporated into efficacy analysis?

Proposals to use extrapolation and innovative analytics can result in protracted and resource-intensive discussion with the fallback of taking a conservative approach when last minute negotiations fail.

Bayesian approach in a concurrent addendum adolescent study in an adult IBD Fixed Design Induction + RW trial

Analytical options if adolescents are part of the adult trial:

- If the two cohorts complete enrollment at the same time then analysis should be with respect to the whole intent-to-treat population
  - Ensure agreement on sufficient (and feasible) number of adolescent patients that provides high probability of completing enrollment simultaneously

Adults   Adolescents

Control

ITx

RCT in Adults   Addendum RCT in Children
(12–18 yrs old)

- As long as pre-specified, if the adolescent cohort lags in enrollment
  - Analyze two cohorts independently, if powered sufficiently
  - Use Bayesian approach, if not powered sufficiently
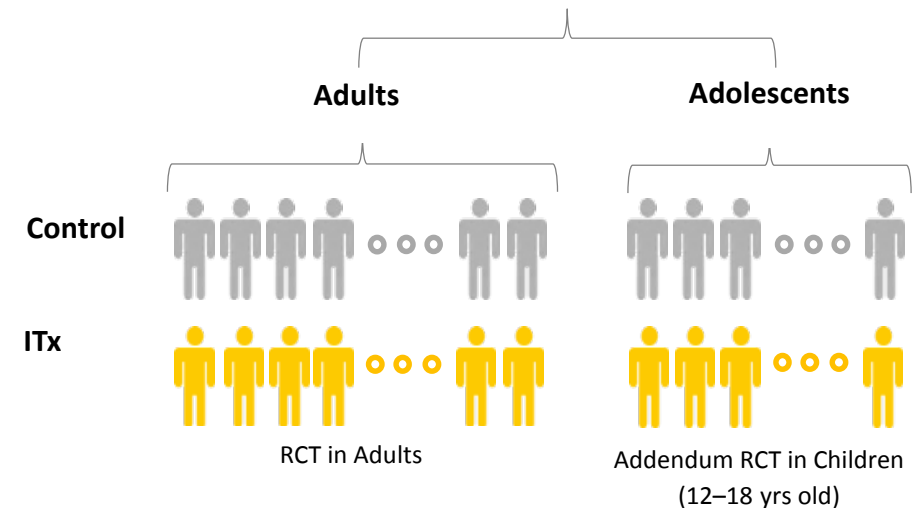
NB: Simultaneous development between adults and adolescents require (1) proof of direct benefit from Phase 2 adults and (2) early considerations about timing of juvenile tox and dose/formulation so that it is ready by end-of-phase 2.

Bayesian approach can be incorporated in extrapolation in such a way that it only borrows information when is similarity of response is validated

Question: How can we validate efficacy in children if we are combining efficacy conclusion from source population with efficacy information from children's trial?
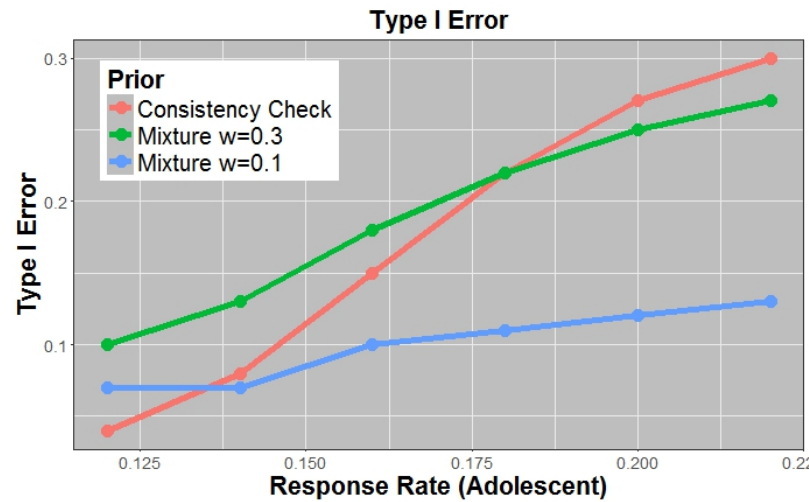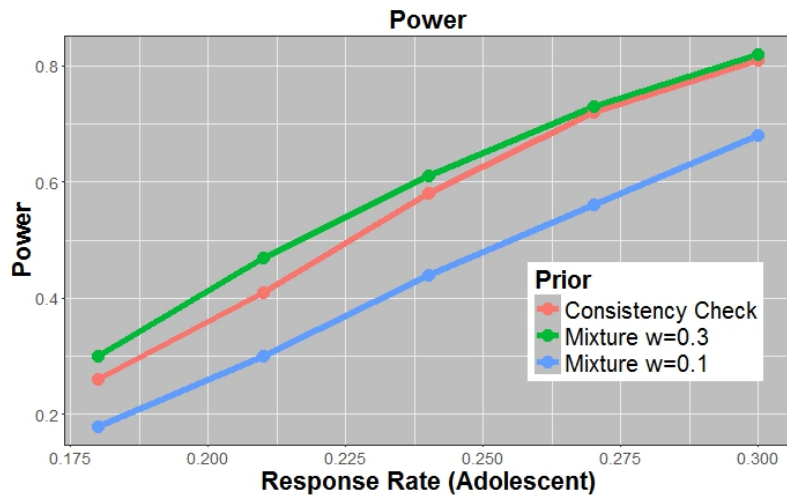
Method 1: Mixture Prior
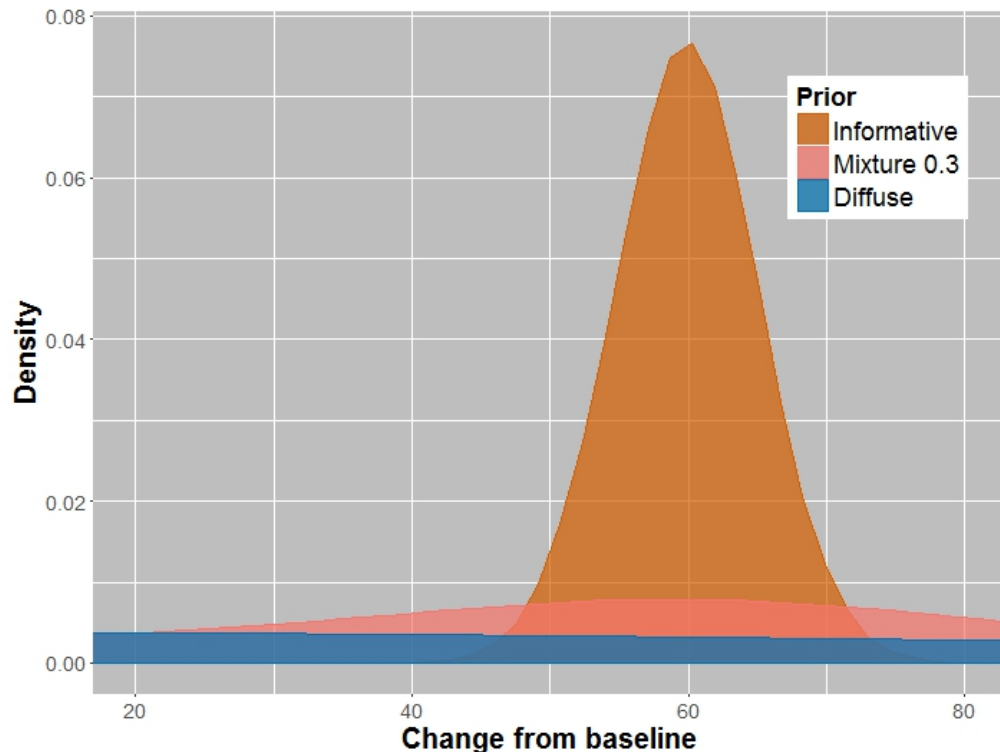
Method 2: Consistency Check

Trt treatment response point estimate in children is above the lower bound of the 95% CI of Trt treatment response in adolescents

Pbo treatment response point estimate in children is below the upper bound of the 95% CI of Pbo treatment response in adolscents
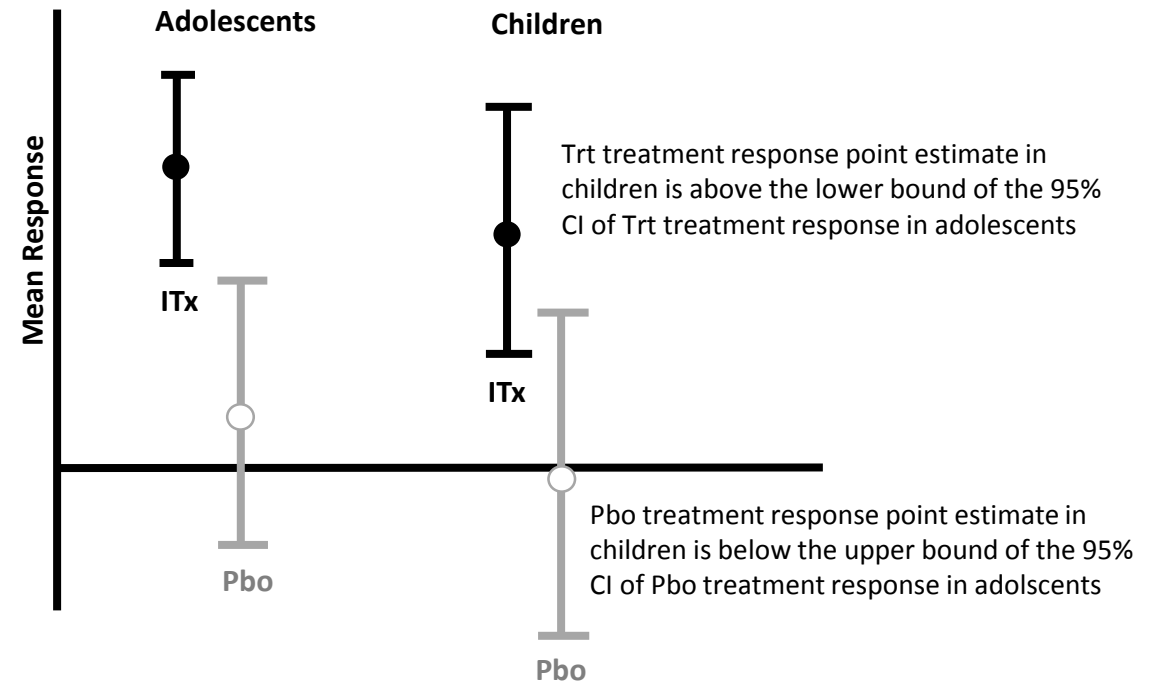
In the application of extrapolation, bias may be more important than type I error

NB: (1) In extrapolation, because there is preponderance of similarity of response, type I error will always be inflated! What is important is to ensure that bias in the estimates is not inflated as well.

(2) If Type I error needs to be controlled at a certain level, borrowing has to be limited. (Counterintuitive to extrapolation)

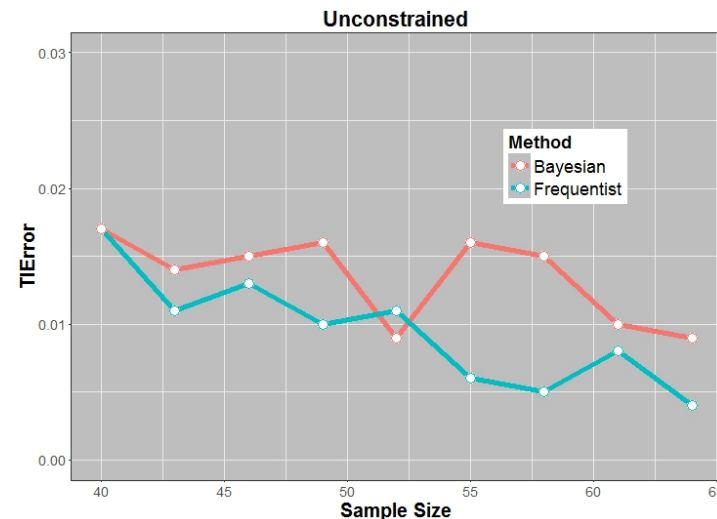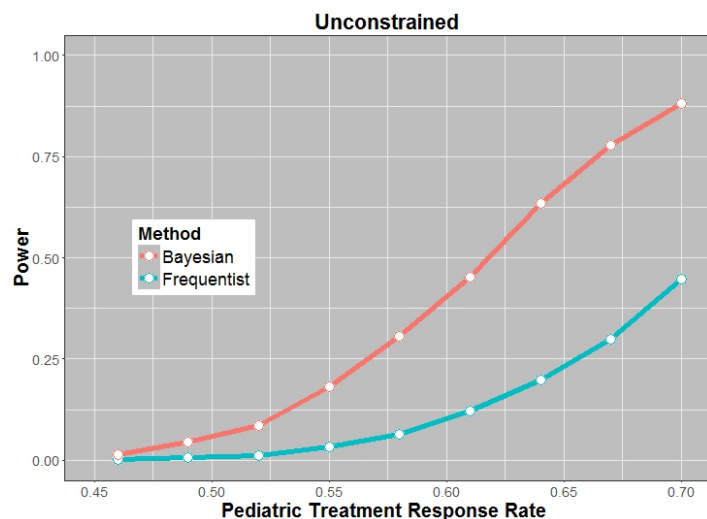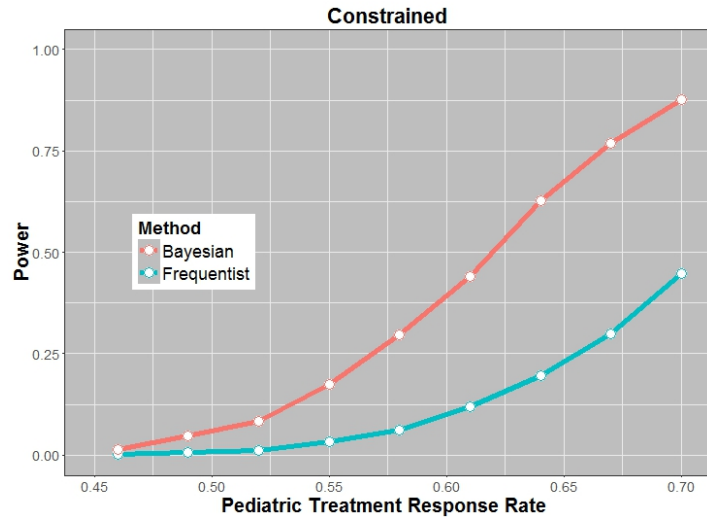# Open label adolescent in concurrent adult and adolescent IBD Fixed Design Induction + RW trial

Open label trial in adolescent cohort:

- **Pro**: More feasible from enrollment standpoint; more likely to finish concurrently with adults
- **Con**: Lack internal validity for validating efficacy over placebo in adolescents
- **Primary comparison**:
  - Whether adult ITx responses are similar to adolescent ITx response*;
  - Possible co-primary is superiority over a *threshold*
- **Additional comparison**: <u>Descriptive analysis for randomized withdrawal due to small sample sizes</u>. Can use *Bayesian analysis* if RW is similar to adults.
- **NB**: RW usually precludes feasibility; can use primary comparison on both induction and maintenance

Control

ITx

Adults

Adolescents

RCT in Adults

Open label Addendum in Adolescents (12–18 yrs old)
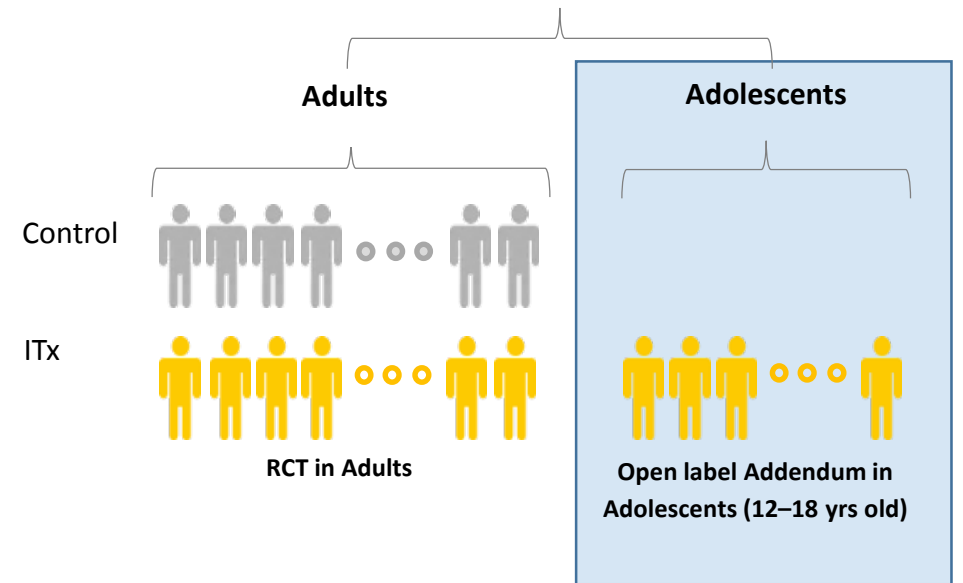
*Primary comparison promotes rigor/uniformity in the conduct of clinical trials for adolescents so that results are consistent with adults.

# Bayesian approach provides significant power gains for minimal simulated type I error increase.
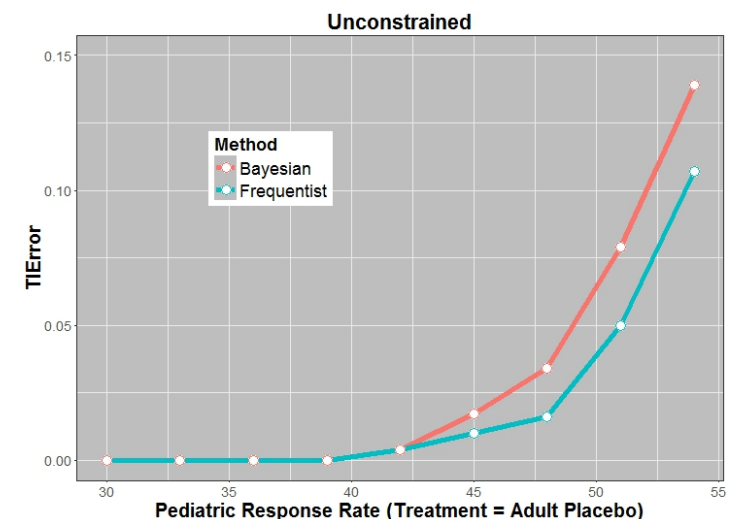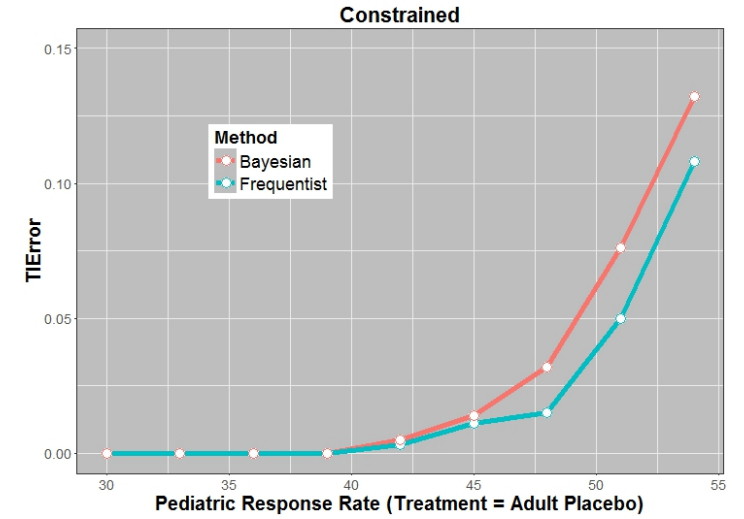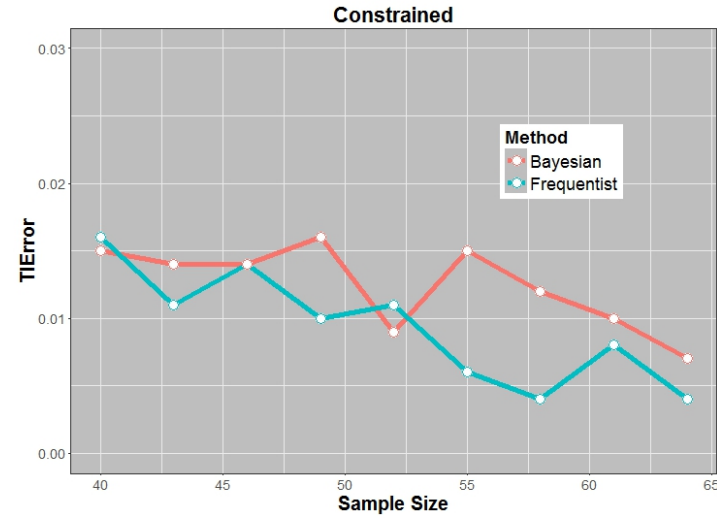
Significant power gains

**Type I error decrease with increasing sample size**

Minimal Type I error increase when ITx → Pbo

# Umbrella design in adult and adolescent IBD Fixed Design Induction + RW trial

- **Pro**: Not necessarily concurrent; Pools placebo in to increase inferential precision; has internal validity for efficacy determination due to concurrent placebo
- **Con**: Not so feasible from enrollment standpoint
- **Primary comparison**:
  - Difference between treatment and placebo in the cohort or
  - Whether adult ITx responses are similar to adolescent ITx response*;
  - Possible co-primary is superiority over a *threshold*
- **Additional comparison**: Descriptive analysis for randomized withdrawal due to small sample sizes. Can use *Bayesian analysis* if RW is similar to adults
- **NB**: For treat-through design, can use primary comparison only; for open-label children trial, primary analysis will depend on cohort
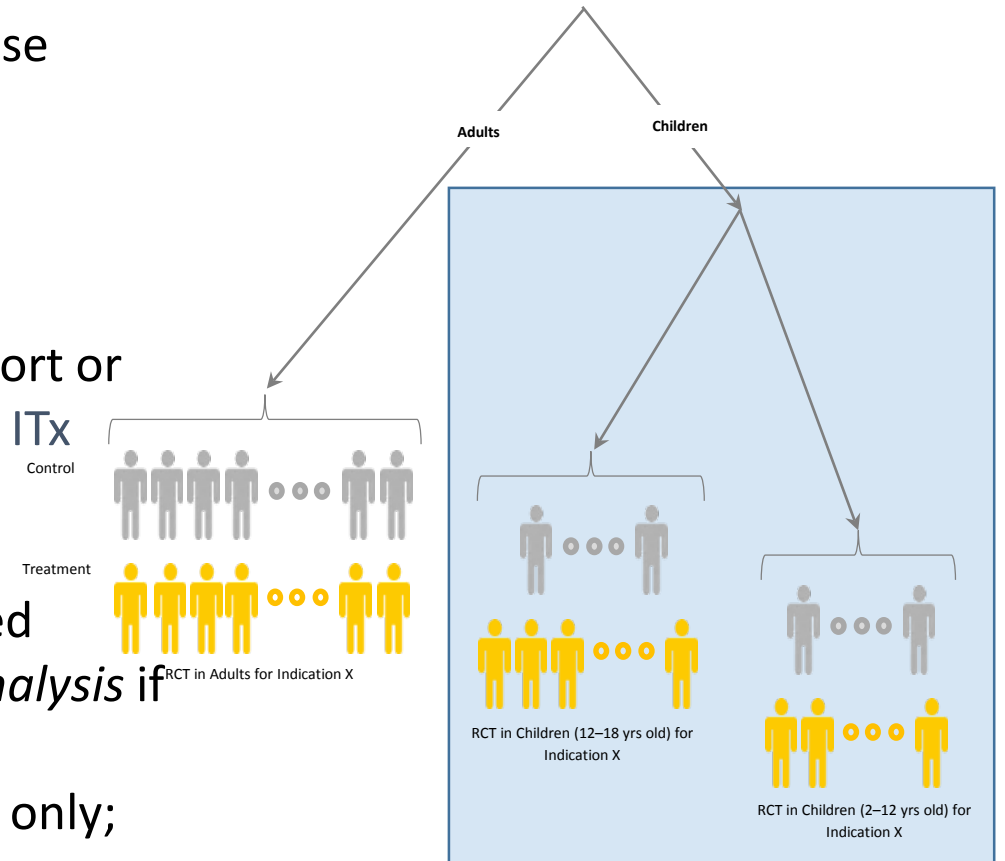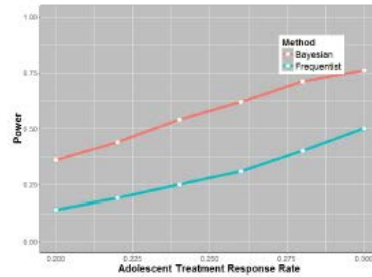
In hierarchical models including multiple cohorts, the simulated type I error may not be inflated
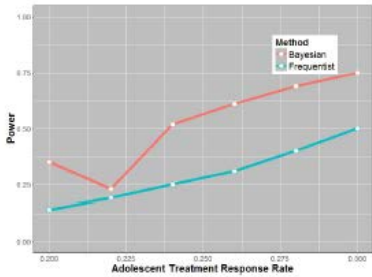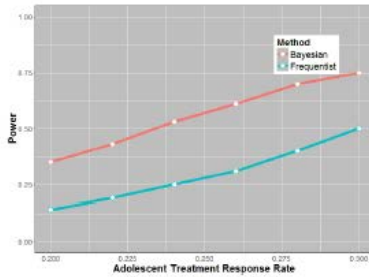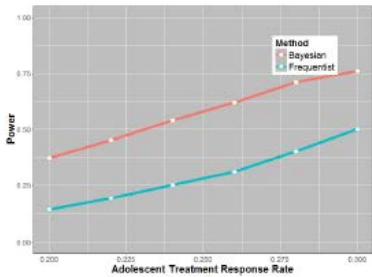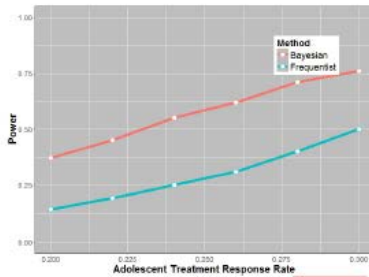

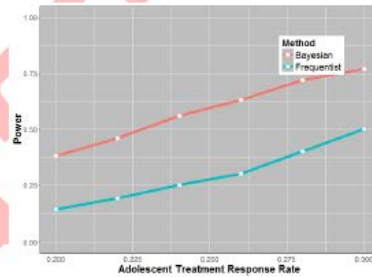(a) Child Trt Resp = 0.20
(b) Child Trt Resp = 0.22
(c) Child Trt Resp = 0.24
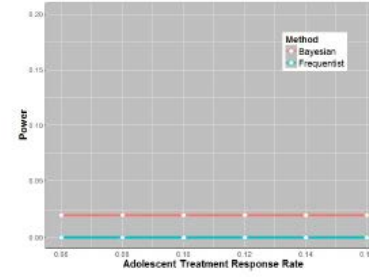(d) Child Trt Resp = 0.26
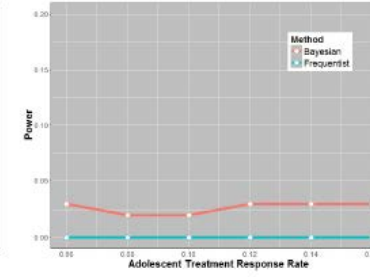(e) Child Trt Resp = 0.28
(f) Child Trt Resp = 0.30

Power for detecting superiority in adolescents as a function of adolescent's treatment response when children's treatment response is fixed. Placebo response for both children and adolescents are kept at 0.10

(a) Child Trt Resp = 0.06
(b) Child Trt Resp = 0.08
(c) Child Trt Resp = 0.10
(d) Child Trt Resp = 0.12
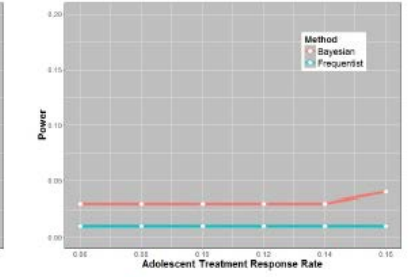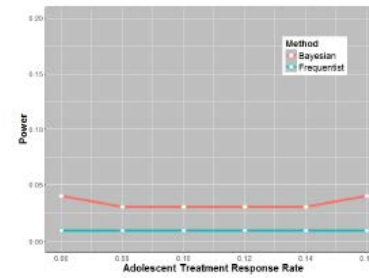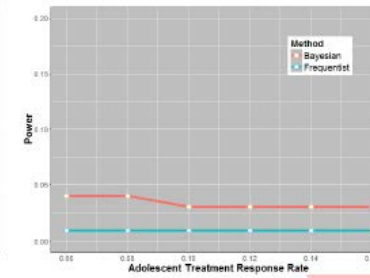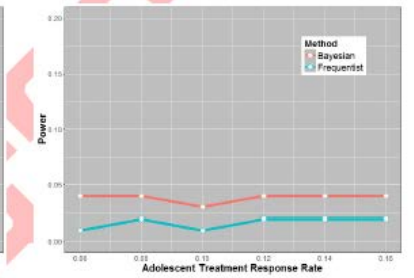(e) Child Trt Resp = 0.14
(f) Child Trt Resp = 0.16

Type I error for detecting superiority in adolescents as a function of adolescent's treatment response when children's treatment response is fixed. Placebo response for both children and adolescents are kept at 0.10

Placebo in the induction phase and use of randomized withdrawal limits enrolment: Some comments on the design and analysis

- Having placebo in induction phase for adolescents can make it hard to enroll adolescents
  - If placebo cannot be used, should adding an active control provide information?
  - Can the use of registry data on the use of standard of care provide threshold for efficacy?
  - UC is an area where extrapolation holds, RWD can be a good choice here!

- Randomized withdrawal maybe difficult to justify especially when an adolescent patient has responded
  - Question, should maintenance of response be confirmed to be similar to adults as well?

Piloting use of RWD in cases where extrapolation is already established

UC (FDA Guidance) and Crohn's (EMA Guideline) are similar in adult and pediatric patients.

1. Real-World Data Source
2. Cohort Selection Criteria
3. Endpoint Selection
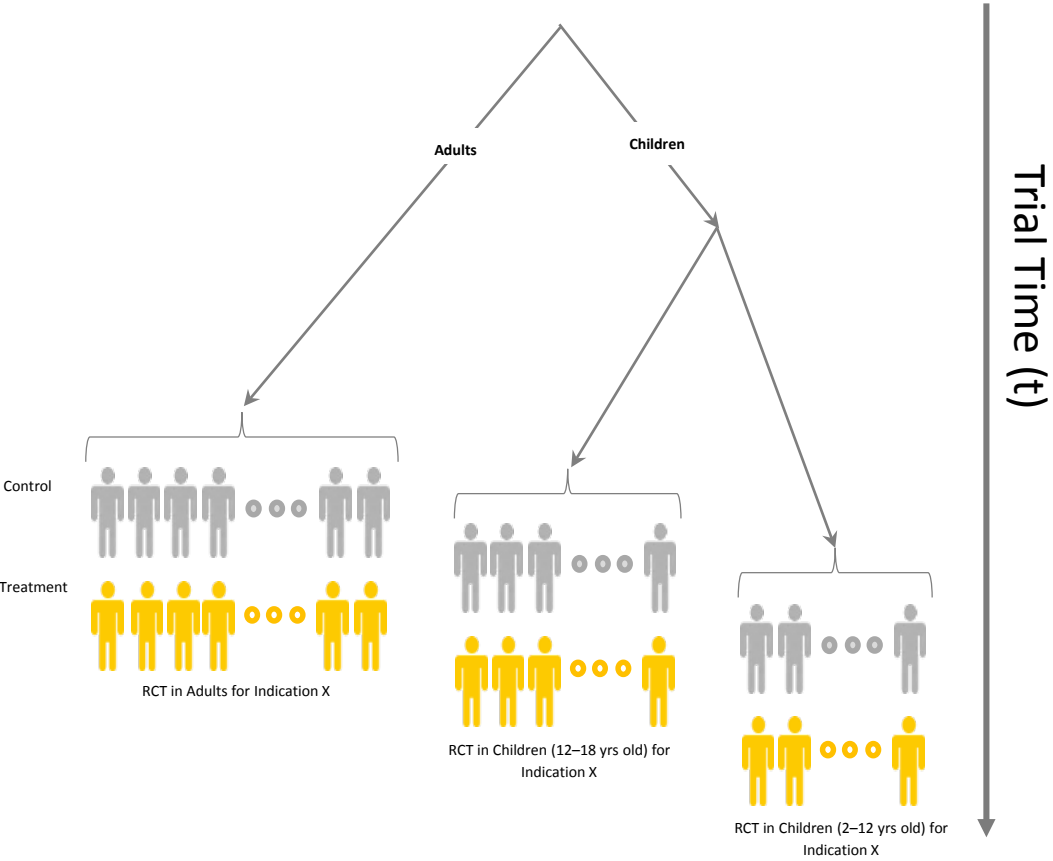4. Statistical Approach: matching; incorporation of RWE

Design decisions are inter-dependent and made prospectively

Planning phase

- Prospective design and analysis
- Target external data; quality and Validation
- Remove outcome from baseline measurements in target data

Trial phase

- Run trial; collect baseline measurements
- Investigate overlap and balance in baseline measurements
- Perform efficacy analysis according to pre-specified analysis plan
- Perform sensitivity analysis

Lin, J., Gamalo-Siebers, M., & Tiwari, R. (2018). Propensity score matched augmented controls in randomized clinical trials: A case study. *Pharmaceutical statistics*, *17*(5), 629-647.

Most of the analytical strategies still hold even if adolescents cannot be enrolled concurrently with adults. In fact, they can even be made more precise!

Adults

Children

Trial Time (t)

Control

Treatment

RCT in Adults for Indication X

RCT in Children (12–18 yrs old) for Indication X

RCT in Children (2–12 yrs old) for Indication X

Proportion of adolescent patient or children can be calibrated to how much information is needed to extend conclusion toward children.

Adults

R

ITx

Control

1:1

Interim

R

Control

ITx

X:1
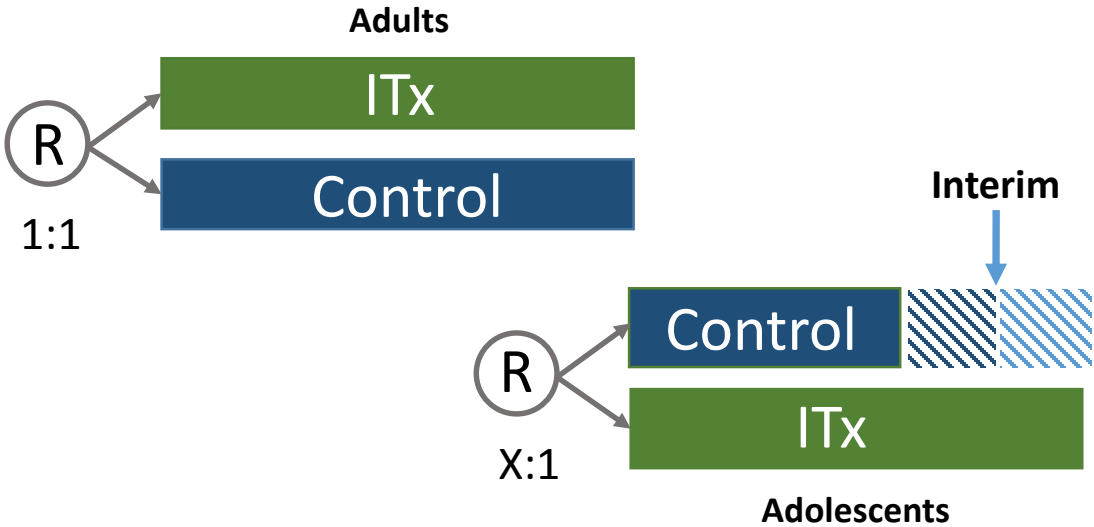
Adolescents

- Enroll n_{CTRL} adolescents
- At interim, calculate number needed to further treat using EHSS

Data from PK Lead-in can be used as prior for primary analysis

Key Messages

- Ethics of studying children implies we need to be innovative to extract sufficient information to warrant labelling for pediatric patients with the right number of patients.

- Extrapolation and innovative analytics requires timely planning and engagement with regulatory agencies across regions to forge a collaborative approach toward acceptance of the said approaches.

- UC and Crohn's should be areas where RWD can be of most help given concerns of using placebo and where extrapolation is already expected.