Challenges in Pediatric Study Design and Analysis, and Some Potential Solutions

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Outline

- Pediatric Study Challenges
- PMDSIA 2007 and Draft Guidance
- Potential Design and Analysis Solutions
  - Borrowing/Extrapolating from adult data
  - Adaptive Designs
  - Use of Historical Controls
- Conclusions

Challenges that Affect Design and Analysis of Pediatric Clinical Trials

1. **Small Sample Sizes**
   - Diseases can have a low incidence in pediatrics (hard to find pediatric subjects).
   - Informed consent might be more difficult in pediatrics.
   - Problematic: results more prone to variability and studies lack power
2. **There might not be a suitable control group**
   - Reluctance to have pediatric patients assigned to control
   - An approved active control might not be available for pediatrics.
   - A placebo might not be ethical.

- Design and analysis methods can be used to deal with consequences of "small n" trials and/or lack of control group.

Pediatric Medical Device Safety & Improvement Act 2007

To improve the process for the development of needed pediatric medical devices.

- Allows Determination of Pediatric Effectiveness Based on:
  - Similar Course of Disease or Disease Condition as for adults, or
  - Similar Effect of Device on Adults.
- Extrapolation of effectiveness may be made:
  - From adults to pediatric patients
  - Between pediatric subpopulations
- Is limited to approved devices (PMAs & HDEs)

Draft Guidance Document "Extrapolation of Effectiveness for Pediatric Uses of Medical Devices"

- Explains CDRH's implementation and interpretation of the PMDSIA law.
- Introduces a framework for decisions about whether extrapolating from adult data is appropriate.
- Provides suggestions for study designs and analyses.
- Expected to be issued in draft form by the end of 2012.

Challenge #1:
Small Sample Sizes

Overview of Bayesian Approach

- The Bayesian approach describes a method for learning from evidence as it accumulates.
- The method combines prior information with current study information on an endpoint of interest (e.g., success rate from using a device) in order to form conclusions about the endpoint.

Overview of Bayesian Approach

- Prior information typically comes from results of previous studies.
- In short, a way to combine the past (**prior**) with the present (**current study**) to make decisions about the future (**posterior** conclusions).
- FDA "*Guidance for the Use of Bayesian Statistics in Medical Device Trials*" released in final form February, 2010.

Bayesian Hierarchical Models

- Allow us to "borrow strength" from previous studies to make inferences about pediatric population.
  - "Strength" = information from the results in the previous studies
    - patients = information --->sample size boost
  - The **extent** of borrowing depends on the similarity of prior results with the pediatric population.
  - Borrowing is not all-or-none.
  - Most important: previous studies can primarily be on adults

Assumption of *Exchangeability* is Required for the Hierarchical Model

- Exchangeability of studies means that knowing a result would not divulge which study it came from.
  - Practically, it translates to comparability of studies or similarity of studies, with respect to an endpoint of interest.

- Ideally, it is decided upon prior to seeing any study results.

Assumption of *Exchangeability* is Required for the Hierarchical Model

- To decide whether exchangeability of prior and current studies can be assumed, we need clinical input.

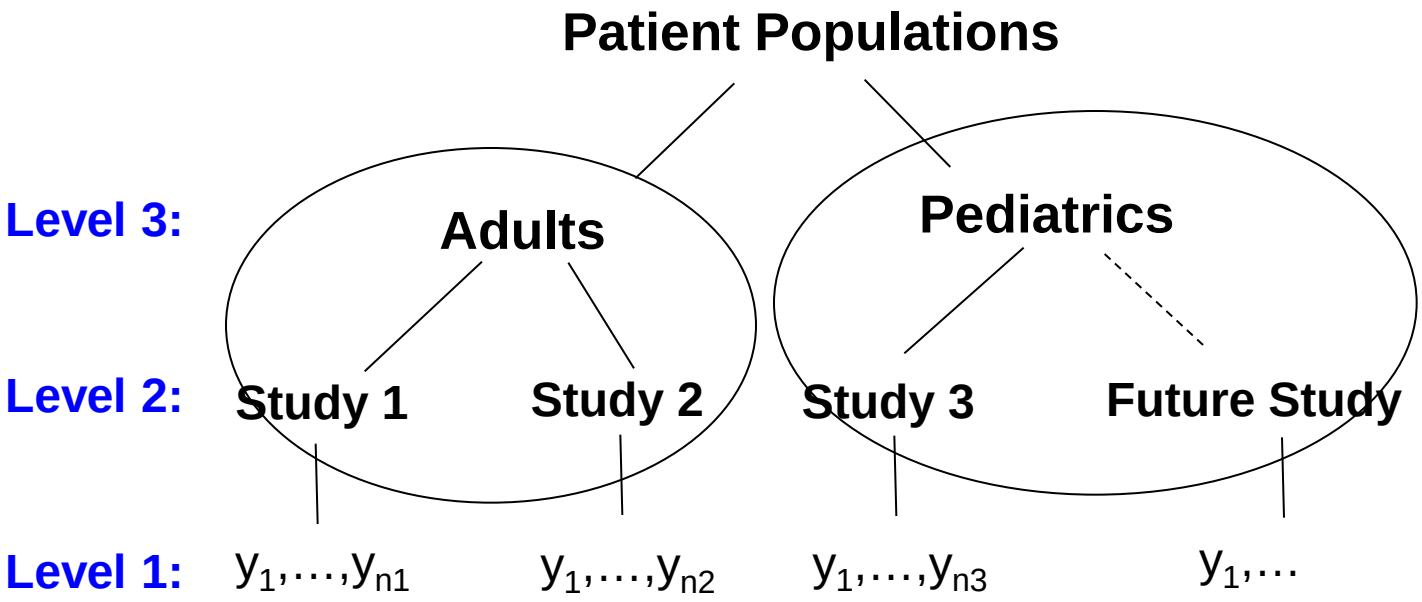
  – ***CDRH clinicians and engineers*** compare previous studies with proposed study for similarity in relevant factors, including

device used	patient population
protocol	inclusion/exclusion criteria
prognostic factors	patient management
proximity	operator training/experience

Are Adult and Pediatric Studies Exchangeable?

- Enrollment might differ between adult and pediatric studies.
- Informed consent might differ between adult and pediatric studies.
- Treatment or handling in the trial might differ between adult and pediatric studies.
- With these dissimilarities, how can we still borrow from adult studies?

Three-level Hierarchical Model Structure:
Studies *within Patient Populations* are Exchangeable



Level 1: Patients (y) exchangeable within studies
Level 2: Studies exchangeable within patient populations.
Level 3: Patient populations are exchangeable.

Hypothetical Example: QuickFix Device for Pain

- Question: What is the device effect in a pediatric population?
  - Primary endpoint is score on Pain-free Scale (0 – 100%).
- Two prior RCTs in adults (1:1 randomization)
  - Study 1: N=250, Study 2: N=150
- One RCT in pediatrics: 1:1 randomization, **N = 20**
- Study Hypothesis:
  - Device is superior to a control in reducing pain in a pediatric population.
- Sample size is too small to make precise inference.

Hypothetical Example: QuickFix Device for Pain

Observed mean (Device – Control) difference in percentages

Adult Study 1 (n=250)	Adult Study 2 (n=150)	Ped Study (n=20)
20.1%	18.9%	16.6%

Assumption: We have accepted the adult studies as relevant for borrowing.

No Borrowing from Adult Studies

Population	Study	Posterior Mean Difference (SD)
Pediatrics	Study 3 (n=20)	**16.6% (9%)**

Borrowing from Adult Studies

Population	Study	Posterior Mean Difference (SD)
Adults	Study 1 (n=250)	20% (1%)
	Study 2 (n=150)	19% (1%)
Pediatrics	Study 3 (n=20)	**16.8% (3%)**

Effective Sample Size in Study 3 = 180:

160 "subjects" were borrowed from the adult studies (out of 250+150 = 400)

Conditional Exchangeabilty

- Often, one or more important covariates is needed to facilitate borrowing of strength from adults to pediatrics.
- **Important for pediatrics**: ***Growth*** or size of the patient might influence effectiveness of the device.
- If the covariate is measured in all studies, we can assume exchangeability across populations, conditional on this covariate.

Adaptive/Flexible Designs

- Trial designs that allow modifications during the course of a trial without negatively impacting false positive error rate.
- Adaptations are performed at an interim look, based on revised estimates of variance and/or treatment effect, or external information.
- Examples
  - Change criteria for entry into trial
  - Dropping/Adding an arm
  - Change randomization ratio
  - Sample size re-estimation
  - Stop early for effectiveness or futility
- ***Specific adaptations should be pre-specified in order to be carried out without complications/concerns from regulators.***
- Interim looks should be performed by an independent third party

Bayesian adaptive sample size using predictive probability

- **Predictive Probability**: Probability of unobserved outcomes for future patients (enrolled or not yet accrued) midcourse in a trial, given observed data.
- Predictive probability can give the probability of trial success before all patients finish the trial.

Bayesian Predictive Probability

- Might be used to predict a clinical outcome from a valid surrogate.
- Might be used to stop a trial prematurely (for success or futility).
- Might be used to stop accrual of patients into the trial.
- **Key point**: Often lead to shorter trials.

Challenge #2: Limited Availability of a Control Group

Non-Randomized Control

- Physicians, guardians, etc might be less willing to randomize the treatment applied to pediatric patients.
- A non-randomized control allows physicians to treat pediatric patients as needed.
- Non-randomized groups introduce selection bias.
- **Propensity score matching**: match device subjects with control subjects based on similar estimated probability of being assigned to the device group.
  - The probability is estimated using measured baseline covariates.
  - Can correct for or "untangle" selection bias if the bias is explained by measured baseline covariates.

Historical Control

- Pivotal Study:
  - New Device versus Active Control (e.g., previous version of device)
- Control: use data from historical studies
- What is an appropriate historical control?
  - Equivalence of eligibility criteria across arms.
  - The time difference between the historical and treatment assessments cannot be too wide.
  - Availability of patient-level data from historical control.
- **Propensity score matching**: match device subjects with historical control subjects based on similar estimated probability of being assigned to the device group.

Historical Control + Current Control

- Pivotal Study:
  - New Device versus Control
- Control: **Enroll some *current* control subjects, but also borrow strength from historical control**
- Assume Historical *Control* and Current *Control* groups are exchangeable.
- Requires fewer new subjects for control group.

How many current controls are needed? Information-Balanced Randomization

- One could borrow historical control data from previous study, but also enroll concurrent controls from pivotal study to achieve a certain randomization ratio.
- If 2n subjects are to be randomized 1:1 to device and control, one can adjust the allocation to the concurrent control according to the similarity of historical and concurrent controls.
- The greater the similarity between concurrent and historical controls, the fewer number of concurrent controls needed.

Information-Balanced Randomization: Adjust Randomization Ratio

- 2n total subjects are needed.
- Begin with a 1:1 randomization ratio.
- At an interim look, with n_1 subjects per group, compute ESS_1 and update the randomization ratio:

$$1:1-\left(\frac{\text{ESS}_1-n_1}{n_1}\right)$$

- **Goal is to randomize fewer new subjects to current control, if appropriate.**

Conclusions

- CDRH is committed to apply PMDSIA for pediatric medical devices.
- Statistical methods can be used to borrow from adult data to make decisions about pediatric effectiveness.
- Alternatives to the randomized control group:
  - Historical control
  - Non-randomized control
- Adaptive Designs can lead to shorter trials.
- Clinical Input is needed to make these methods work best.