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• PMDSIA 2007 and Draft Guidance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Draft Guidance Document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

<table>
<thead>
<tr>
<th>Adult Study 1 (n=250)</th>
<th>Adult Study 2 (n=150)</th>
<th>Ped Study (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.1%</td>
<td>18.9%</td>
<td><strong>16.6%</strong></td>
</tr>
</tbody>
</table>

Assumption: We have accepted the adult studies as relevant for borrowing.
<table>
<thead>
<tr>
<th>Population</th>
<th>Study</th>
<th>Posterior Mean Difference (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatrics</td>
<td>Study 3 (n=20)</td>
<td>16.6% (9%)</td>
</tr>
</tbody>
</table>

### Borrowing from Adult Studies

<table>
<thead>
<tr>
<th>Population</th>
<th>Study</th>
<th>Posterior Mean Difference (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Study 1 (n=250)</td>
<td>20% (1%)</td>
</tr>
<tr>
<td></td>
<td>Study 2 (n=150)</td>
<td>19% (1%)</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>Study 3 (n=20)</td>
<td>16.8% (3%)</td>
</tr>
</tbody>
</table>

**Effective Sample Size in Study 3 = 180:**
160 “subjects” were borrowed from the adult studies (out of 250+150 = 400)
Conditional Exchangeability

• 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 \( \text{ESS}_1 \) 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.