Bayesian Methods for Making Inferences about Rare Diseases in Pediatric Populations

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Outline

- Special problems with Studying Rare Diseases in Pediatric Populations.

- Bayesian Methods for solutions
  - Zero Numerator Problem with Rare Events
  - Borrowing Strength from Similar Studies to Boost Sample Size
    - Forthcoming Pediatric Extrapolation Draft Guidance
  - Bayesian Adaptive Designs for Shorter Trials

- Summary

Special Problems with Studying Rare Diseases in Pediatric Populations

- The pediatric population available for clinical trials is limited even when the condition/disease is not rare.
  - Informed consent might be more difficult in pediatrics.
  - Finding an appropriate control could be difficult.
  - Problematic: results more prone to variability and studies lack power
- Rare conditions or events may not occur in a finite collected sample of pediatric patients.
  - Problematic: Estimating an event rate is difficult with no events

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., adverse event rate from using a device) in order to form conclusions about the endpoint.

- Prior information typically comes from results of previous studies.

Overview of Bayesian Approach

- Often, prior information can be used to help estimate rare event rates and gain power for small populations.

- 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.

Special Problem #1

Rare conditions or events may not occur in a finite collected sample of patients.

Zero Numerator Problem

Example based on Chen & McGee (2008)

- A standard test or device has been shown to cause a serious reaction in about 15 of every 10,000 patients exposed to it (0.0015). A new improved test/device was used on 167 patients and none of them reported having the reaction.

- What can we say about the probability of a serious reaction for the new test/device? Is it really 0%?

Zero Numerator Problem
Example based on Chen & McGee (2008)

- "Rule of three" estimate of the upper bound of a 95% confidence interval is a conservative approximation: $3/n = 3/167 = 0.018$

- Approximation holds better with larger n.

- We would like a point estimate of the occurrence rate too.

- Bayesian methods can obtain this (even with small samples), as well as uncertainty intervals with direct probability interpretations.

Actual Submission (Zero Numerator): Essure™ System for Permanent Birth Control

- SSED: http://www.accessdata.fda.gov/cdrh_docs/pdf2/P020014b.pdf

- Micro-Insert that occludes the fallopian tubes

- Zero pregnancies were observed in pivotal study (n=632). However, because no birth control is 100% effective, an estimate of a 0% fertility rate at 12 months appears inaccurate.

- Bayesian Statistics/Models can help so that the estimate is not 0% when that is unrealistic.

Bayesian Estimate of Rare Event Rate

- Prior distribution placed on p, the probability of experiencing the event.

- Examples of prior distributions:
  - Prior mean is equal to the standard rate (e.g., 0.0015), and there is a 95% chance that p is less than 0.0075.

  - "Vague" Uniform prior distribution (equal probability that p falls anywhere between 0 and 1.0)

  - Hierarchical model: common method used in CDRH

Bayesian Estimate of Rare Event Rate

- Posterior Estimates (from posterior distribution)
  - Posterior mean rate is not 0%, but something more realistic and satisfying.
    - (Chen & McGee Example) The posterior mean is 0.00022, which is much less than 0.0015.
    - (Uniform prior) The posterior mean is 0.0016.
  - Posterior probability statements can be made:
    - (Chen & McGee Example) There is 96% posterior probability that the rate is lower than the standard rate of 0.0015.
    - (Uniform prior) There is 39% posterior probability that the rate is lower than the standard rate of 0.0015.

Special Problem #2:

The pediatric population available for clinical trials is limited.

Bayesian Methods can be used to gain power by combining prior studies with a current study.

Boost Sample size by "borrowing strength" (information) from prior studies

- By borrowing from appropriate prior information, the same decision might be reached with a smaller (recruitment) sample size.
  - The extent of borrowing depends on the similarity of previous studies with the current study.
  - If prior study results are different from current study result, then borrowing strength weakens (and can go to zero).

Bayesian Hierarchical Models

- "Borrow strength" from prior studies similar to a current study on an endpoint of interest.

  - Effective sample size boost: we borrow information provided by subjects in the prior studies

  - We don't know how much we will borrow until the current data become available.

- The model lets the *current and prior studies determine* how much to borrow.

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. (Are the studies comparable?)

- Ideally, it is decided upon before seeing *any* study results (even the prior study results).

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

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

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U.S. Food and Drug Administration
Protecting and Promoting Public Health

Pediatric Medical Device Safety & Improvement Act (PMDSIA) 2007

- To improve the process for the development of needed pediatric medical devices.
- Allows determination of a pediatric indication for a medical device, using adult data, if:
  - Similar Course of Disease or Condition, or
  - Similar Effect of Device
- "Extrapolation" of a device's effect or safety may be made:
  - From adults to pediatric patients
  - Between pediatric subpopulations
- Can potentially be made for approvals and clearances (PMAs, HDEs, 510Ks), as well as during the IDE stage.
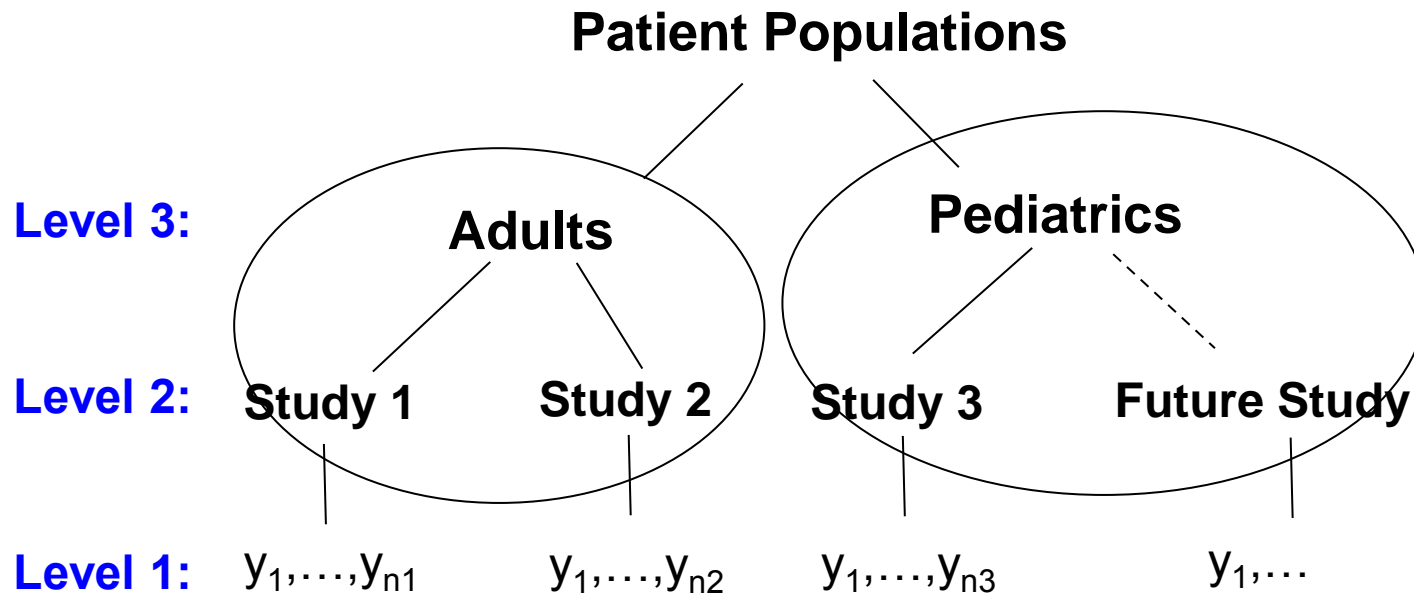
Draft Guidance Document
"Extrapolation of Data for Pediatric Uses of Medical Devices"

- General Factors for Consideration for Extrapolation:
  1. *Similarity* of Adult Population/Response Data with future Pediatric Response Data
     - Will there be differences in device characteristics, disease process, or patient characteristics that will likely make responses to treatment with device different for the pediatric population than adults?
  2. *Quality* of Adult Data
     - How were the data collected, assigned to treatments? (Recent final CDRH Guidance)
- The higher the similarity and quality, the more likely extrapolation will be appropriate for regulatory submissions. If both are low, we cannot rely on adult data for pediatric indication.

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Are Adult and Pediatric Studies Exchangeable?

- Obvious Differences in physiology
- Study Conduct Differences
  - 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

Patient Populations

Level 3: **Adults** **Pediatrics**

Level 2: **Study 1** **Study 2** **Study 3** **Future Study**

Level 1: $y_1, \ldots, y_{n1}$ $y_1, \ldots, y_{n2}$ $y_1, \ldots, y_{n3}$ $y_1, \ldots$

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

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Conditional Exchangeabilty

- **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, and hence borrow strength from adults to pediatrics.

Hypothetical Example:
SlimFix Device for Weight Loss
Single Arm Study

Average Excess Weight Loss in Percentages

Adult Study 1 (n=250)	Adult Study 2 (n=150)	Adolescent Study (n=20)
41%	34%	20%

Borrowing Across Studies
Adjusting for a covariate

Percent Excess Weight Loss

Baseline "Size" variable

○ Adolescent
○ Adult 1
○ Adult 2
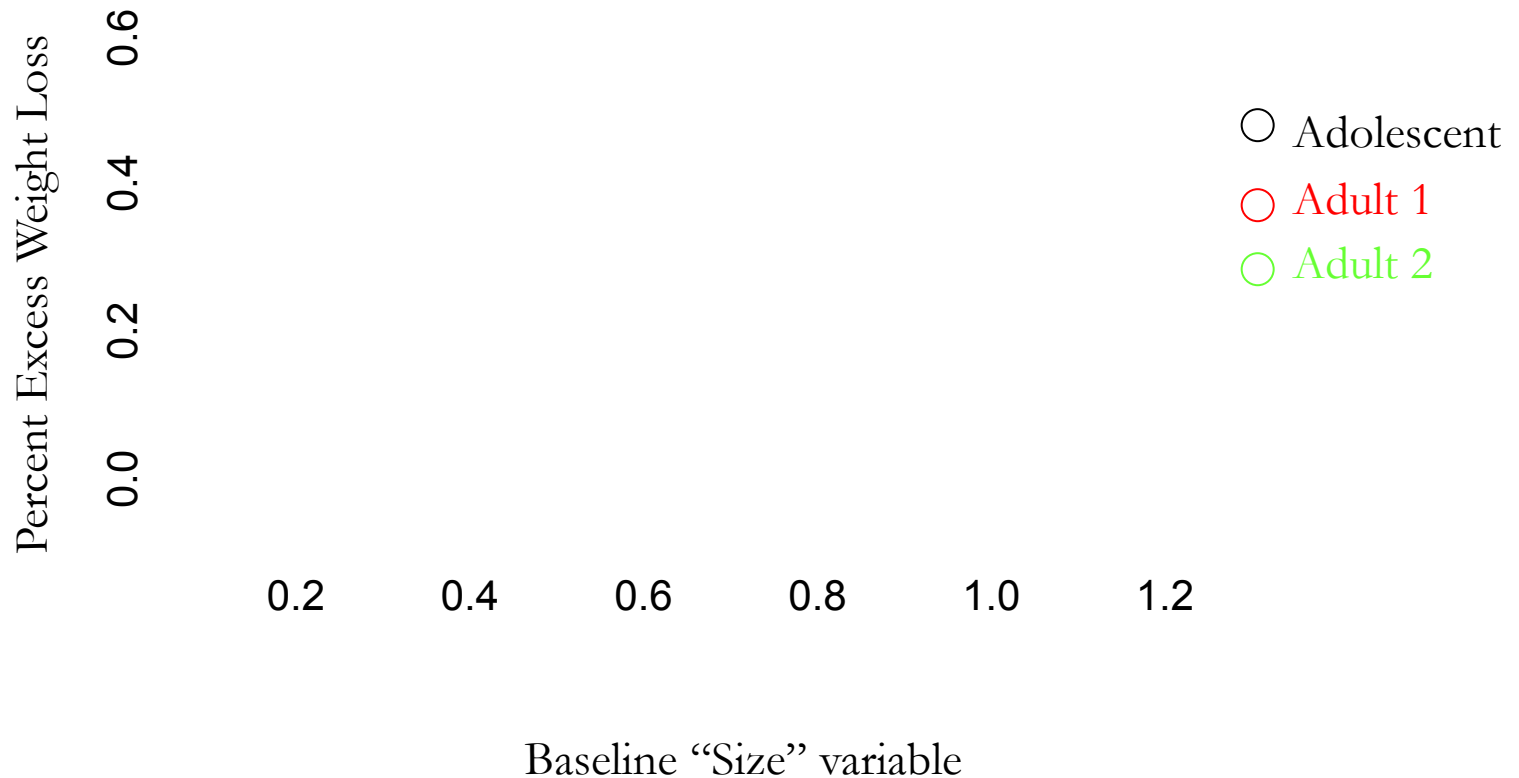
No Borrowing from Adult Studies Adjusting for "Baseline Size"

Population	Study	Posterior Mean Percent Excess Weight loss (SD)
Adolescent **Baseline "Size"=0.85**	Study 3 (n=20)	**22.8% (5.1%)**

Population	Study	Posterior Mean Percent Excess Weight loss (SD)
Adolescent **Baseline "Size"=0.60**	Study 3 (n=20)	**19.8% (3.1%)**

Borrowing from Adult Studies

Population	Study	Posterior Mean Percent Excess Weight loss (SD)
Adults "Size"=0.85	Study 1 (n=250)	38.7% (0.7%)
	Study 2 (n=150)	33.0% (0.9%)
Adolescent "Size"=0.85	Study 3 (n=20)	**24.3% (3.0%)**

Population	Study	Posterior Mean Percent Excess Weight loss (SD)
Adults "Size"=0.60	Study 1 (n=250)	32.2% (1.7%)
	Study 2 (n=150)	27.4% (1.9%)
Adolescent "Size"=0.60	Study 3 (n=20)	**20.0% (2.2%)**

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Borrowing from Adult Studies

Effective Sample Size in Pediatric Study (when "Size" = 0.85) = **58**:
38 subjects' worth of information was borrowed from the adult studies
(out of a possible 250 + 150 = 400)

Effective Sample Size in Pediatric Study (when "Size" = 0.60) = **40**:
20 subjects' worth of information was borrowed from the adult studies
(out of a possible 250 + 150 = 400)

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 Distribution** describes what the unobserved outcomes for future patients (enrolled or not yet accrued) will be midcourse in a trial, given the observed patients' data.

- This distribution provides the **predictive 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 early (for success or futility).

- Might be used to stop accrual of patients into the trial.

- **Key point**: Often lead to shorter trials or smaller trials.

Summary Statements

- Bayesian Methods can handle difficulties with studying rare conditions in pediatric populations.

    – More realistic estimates of rare event rates

    – Borrow strength from adult data to make decisions about device performance in pediatrics. (Adult clinical data may be available from previous marketing applications).

- Adaptive Designs and Predictive Probability may shorten lengthy trials.