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    - Forthcoming Pediatric Extrapolation Draft Guidance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

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.

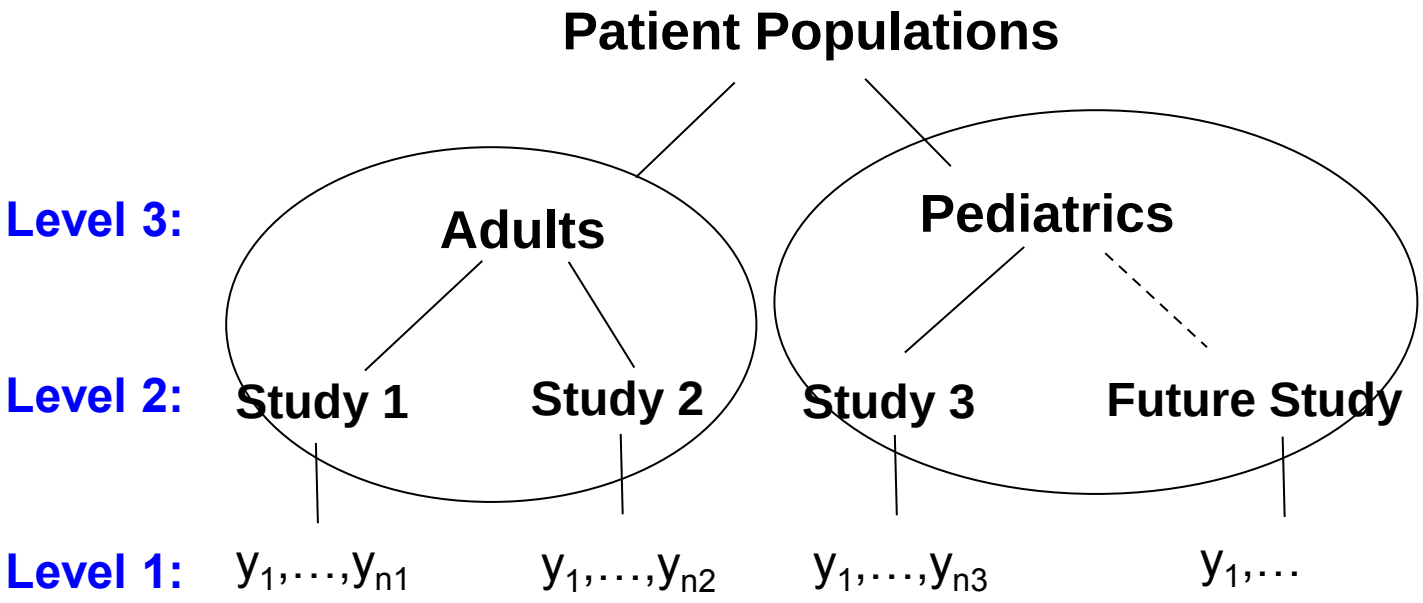
Draft Guidance Document "Extrapolation of Data for Pediatric Uses of Medical Devices"

- 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.

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



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

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.

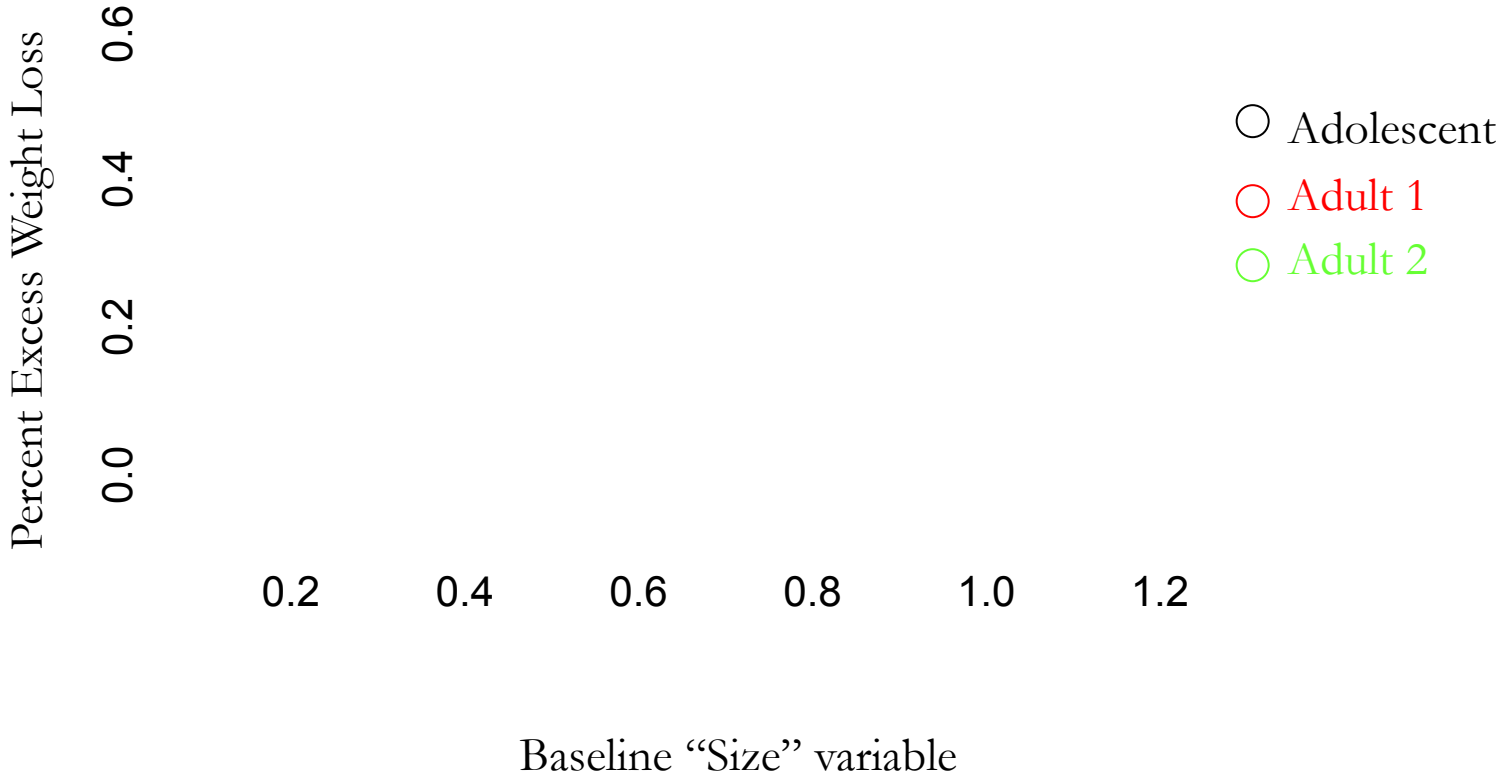
Hypothetical Example: SlimFix Device for Weight Loss

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



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%)**

Borrowing from Adult Studies

<u>Effective</u> 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)

<u>Effective</u> 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.