Borrowing from Adult Data for Pediatric Uses of Medical Devices

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Center for Devices and Radiological Health
Food and Drug Administration
Outline

• PMDSIA (2007)

• Forthcoming Draft Guidance “Extrapolation of Data for Pediatric Uses of Medical Devices”

• Examples of borrowing adult data.

• Guidance mentions borrowing from a single adult study.

• Conclusions
Pediatric Medical Device Safety & Improvement Act (PMDSIA) 2007

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 done for FDA approvals and clearances for marketing medical devices, as well as for study proposals.
Draft Guidance Document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

• 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.
Method for this Talk: Bayesian Hierarchical Models

- Typical Bayesian hierarchical models assume exchangeability of studies (across adult and pediatric populations).
- Should adult and pediatric studies be assumed exchangeable?
- In our suggestions, we put exchangeability not at a study level, but at a population level.
  - In doing so, borrowing is generally not as strong as when exchangeability is at the study level.
  - We need more than one adult study
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 Exchangeability

**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.

Most important step for using the “extrapolation” intended in the law/guidance.
Hypothetical Example:
SlimFix Device for Weight Loss
*Single Arm Study* for Adolescent Indication

Average Excess Weight Loss in Percentages (SE)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Weight Loss Percentage (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Study 1 (n=250)</td>
<td></td>
<td>42% (0.7%)</td>
</tr>
<tr>
<td>Adult Study 2 (n=150)</td>
<td></td>
<td>37% (0.9%)</td>
</tr>
<tr>
<td>Adolescent Study (n=20)</td>
<td></td>
<td><strong>20% (2.7%)</strong></td>
</tr>
</tbody>
</table>
Borrowing Across Studies
Adjusting for a covariate

Baseline “Size” variable

Percent Excess Weight Loss

○ Adolescent
○ Adult 1
○ Adult 2
Borrowing Across Studies
Adjusting for Covariates (Model 1)

\[ y_{spi} \sim N(x_i' \beta_{sp}, \tau_y), \text{ subj } i, \text{ study } s, \text{ pop } p \]

\[ \beta_{sp} \sim N(\mu_{\beta_p}, R_p) \quad \text{Studies within population } p \]

\[ \mu_{\beta_p} \sim N(\mu_{\beta_0}, R_0) \quad \text{Population coefficients} \]

\[ R_p \sim Wish(\gamma_p I, 2) \]

\[ R_0 \sim Wish(\gamma_0 I, 2) \quad \tau_y \sim gamma(0.001, 0.001) \]
Borrowing Across Studies
Adjusting for Covariates (Model 2)

\[ y_{spi} \sim N(x'_i \beta_{sp}, \tau_y), \text{ subj } i, \text{ study } s, \text{ pop } p \]

\[ \beta_{s1} \sim N(\mu_{\beta_1}, R_1) \]  
Studies within Adult Population

\[ \beta_{12}, \mu_{\beta_1} \sim N(\mu_{\beta_0}, R_0) \]  
One Pediatric Study, Adult population mean

\[ \mu_{\beta_0} \sim N(0, \epsilon I) \]

\[ R_1 \sim \text{Wish}(\gamma_1 I, 2) \]

\[ R_0 \sim \text{Wish}(\gamma_0 I, 2) \]
No Borrowing from Adult Studies Adjusting for “Baseline Size”

<table>
<thead>
<tr>
<th>Population</th>
<th>Study</th>
<th>Posterior Mean Percent Excess Weight loss (SD)</th>
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<tbody>
<tr>
<td>Adolescent Baseline “Size” = 0.85</td>
<td>Study 3 (n=20)</td>
<td>22.8% (5.1%)</td>
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<td>Adolescent Baseline “Size” = 0.60</td>
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<td>19.8% (3.1%)</td>
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</tbody>
</table>
Borrowing from Adult Studies \( (\gamma_0 = \gamma_1 = \varepsilon^{-1} = 100) \)

<table>
<thead>
<tr>
<th>Population</th>
<th>Study</th>
<th>Posterior Mean Percent Excess Weight loss (SD) (Borrowing)</th>
<th>Posterior Mean Percent Excess Weight loss (SD) (No Borrowing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Study 1 (n=250)</td>
<td>37.6% (0.7%)</td>
<td></td>
</tr>
<tr>
<td>“Size”=0.85</td>
<td>Study 2 (n=150)</td>
<td>33.7% (0.9%)</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>Study 3 (n=20)</td>
<td>25.0% (3.0%)</td>
<td>22.8% (5.0%)</td>
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<tbody>
<tr>
<td>Adults</td>
<td>Study 1 (n=250)</td>
<td>30.1% (1.2%)</td>
<td></td>
</tr>
<tr>
<td>“Size”=0.60</td>
<td>Study 2 (n=150)</td>
<td>26.8% (1.6%)</td>
<td></td>
</tr>
<tr>
<td>Adolescents</td>
<td>Study 3 (n=20)</td>
<td>19.8% (3.1%)</td>
<td></td>
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</table>
Bayesian Effective Sample Size (Malec, 2001)

\[
ESS = n_{3,\text{ped}} \frac{\text{Var}(\mu_{3,\text{ped}} \mid Y_{3,\text{ped}})}{\text{Var}(\mu_{3,\text{ped}} \mid Y_{1,\text{adult}}, Y_{2,\text{adult}}, Y_{3,\text{ped}})}
\]

**Effective Sample Size in Adolescent 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 Adolescent Study (when “Size” = 0.60) = 40:**
20 subjects’ worth of information was borrowed from the adult studies (out of a possible 250 + 150 = 400)
## Borrowing from Adult Studies

### Not accounting for covariate

<table>
<thead>
<tr>
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<th>Adolescent (no borrowing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Study 1 (n=250)</td>
<td>41.4% (0.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study 2 (n=150)</td>
<td>37.4% (0.9%)</td>
<td></td>
</tr>
<tr>
<td>Adolescent</td>
<td>Study 3 (n=20)</td>
<td>21.1% (2.6%)</td>
<td>20.3% (3%)</td>
</tr>
</tbody>
</table>

**Effective Sample Size in Adolescent Study = 27:**

7 subjects’ worth of information was borrowed from the adult studies (out of a possible 250 + 150 = 400)
Adjusting for a covariate
Another Situation – “Influential” Outlier in Peds
### No Borrowing from Adult Studies Adjusting for “Baseline Size” (Outlier)

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<th>Posterior Mean Percent Excess Weight loss (SD)</th>
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<tbody>
<tr>
<td>Adolescent</td>
<td>Study 3 (n=20)</td>
<td>22.4% (8.4%)</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Size”=0.85</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adolescent
Posterior
Mean Slope = -0.04
SD = 0.32

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<td>Adolescent</td>
<td>Study 3 (n=20)</td>
<td>23.5% (5.1%)</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Size”=0.60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Borrowing from Adult Studies

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<tr>
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<th>Posterior Mean (SD) No borrowing</th>
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</thead>
<tbody>
<tr>
<td>Adults “Size”= 0.85</td>
<td>Study 1</td>
<td>37.7% (0.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study 2</td>
<td>33.8% (1.0%)</td>
<td></td>
</tr>
<tr>
<td>Adolescent “Size”= 0.85</td>
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<td>26.9% (3.2%)</td>
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<td>30.2% (1.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study 2</td>
<td>27.1% (1.6%)</td>
<td></td>
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<td>Adolescent “Size”= 0.60</td>
<td>Study 3 (n=20)</td>
<td>22.7% (2.3%)</td>
<td>23.5% (5.1%)</td>
</tr>
</tbody>
</table>
Borrowing from Adult Studies

**Effective Sample Size in Adolescent Study (when “Size” = 0.85) = 138:**
118 subjects’ worth of information was borrowed from the adult studies (out of a possible 250 + 150 = 400)

**Effective Sample Size in Adolescent Study (when “Size” = 0.60) = 99:**
79 subjects’ worth of information was borrowed from the adult studies (out of a possible 250 + 150 = 400)
Model Exploration and Operating Characteristics
When does the model borrow more or less? (follow ideas in Schoenfeld, et al., 2009)

• Fix $R_0$, $R_1$, and estimate $\tau_y$. Let $\varepsilon^{-1} \to \infty$

\[
E(\beta_P \mid X_p, X_A, \hat{\beta}_A, \hat{\beta}_y, R_0, R_1, \hat{\tau}_y) = \\
\begin{bmatrix}
2R_0^{-1} + R_1^{-1} + (X_A^T X_A)^{-1} / \hat{\tau}_y
\end{bmatrix}^{-1} \left(2R_0^{-1} + R_1^{-1} + (X_A^T X_A)^{-1} / \hat{\tau}_y\right)^{-1} + X_p^T X_p \hat{\tau}_y \right]^{-1} \hat{\beta}_A + \\
\hat{\tau}_y \left( X_p^T X_p \right) \left(2R_0^{-1} + R_1^{-1} + (X_A^T X_A)^{-1} / \hat{\tau}_y\right)^{-1} + X_p^T X_p \hat{\tau}_y \right]^{-1} \hat{\beta}_y
\]

\[
Var(\beta_P \mid X_p, X_A, R_0, R_1, \hat{\tau}_y) = \left[2R_0^{-1} + R_1^{-1} + (X_A^T X_A)^{-1} / \hat{\tau}_y\right]^{-1} + X_p^T X_p \hat{\tau}_y \right]^{-1}
\]

• In example, $E(R_0) = E(R_1) = 100I$
Operating Characteristics

• Hypotheses:

\[ H_0 : E(y_p | X = x) = x^T \beta_p \leq \rho \]

\[ H_1 : E(y_p | X = x) = x^T \beta_p > \rho \]

• Alternative: Expected percent excess weight loss exceeds \( \rho \), when baseline “size” is \( x \).

• Power computed as a function of \( R \) (precision) matrices.

• Used adult data from example.
Operating Characteristics

• Obtain posterior probability of $H_1$ using approximate normality of posterior distribution of $\beta_p$

• If posterior probability exceeds a threshold (0.975, say), conclude success.

• Power function is the probability of concluding success, given value of $\beta_p$ and adult data (taken as a single data set), as well as generated adolescent baseline size data.

• Power function has approx. analytical form.
Operating Characteristics – Type I Error Rate

\[ \text{Power}\left((1, 0.80)^T \beta_P = 20\%\right) \]

\[
R_0^{-1} = \begin{pmatrix}
\rho_0 & 0.5 * \rho_0 \\
0.5 * \rho_0 & \rho_0 \\
\end{pmatrix}
\]

\[
R_1^{-1} = \begin{pmatrix}
\rho_1 & 0.5 * \rho_1 \\
0.5 * \rho_1 & \rho_1 \\
\end{pmatrix}
\]
Operating Characteristics – Type I Error Rate

\[
\text{Power}\left((1, 0.80)^T \beta_p = 20\%\right)
\]

\[
R_0^{-1} = \begin{pmatrix}
\rho_0 & 0.5 \times \rho_0 \\
0.5 \times \rho_0 & \rho_0
\end{pmatrix}
\]

\[
R_1^{-1} = \begin{pmatrix}
\rho_1 & 0.5 \times \rho_1 \\
0.5 \times \rho_1 & \rho_1
\end{pmatrix}
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Operating Characteristics – Type I Error Rate

\[ \text{Power}\left( (1, 0.80)^T \mathbf{\beta}_p = 20\% \right) \]

\[ \mathbf{R}_0^{-1} = \begin{pmatrix} \rho_0 & 0.5 \times \rho_0 \\ 0.5 \times \rho_0 & \rho_0 \end{pmatrix} \]

\[ \mathbf{R}_1^{-1} = \begin{pmatrix} \rho_1 & 0.5 \times \rho_1 \\ 0.5 \times \rho_1 & \rho_1 \end{pmatrix} \]
Operating Characteristics - Power

\[
\text{Power}\left((1, 0.80)^T \beta_p = 27\%ight)
\]

\[
R_0^{-1} = \begin{pmatrix}
\rho_0 & 0.5^* \rho_0 \\
0.5^* \rho_0 & \rho_0
\end{pmatrix}
\]

\[
R_1^{-1} = \begin{pmatrix}
\rho_1 & 0.5^* \rho_1 \\
0.5^* \rho_1 & \rho_1
\end{pmatrix}
\]
Operating Characteristics - Power

Power\left( \left(1, 0.80\right)^T \mathbf{\beta}_p = 27\% \right)

\mathbf{R}_0^{-1} = \begin{pmatrix} \rho_0 & 0.5 \times \rho_0 \\ 0.5 \times \rho_0 & \rho_0 \end{pmatrix}

\mathbf{R}_1^{-1} = \begin{pmatrix} \rho_1 & 0.5 \times \rho_1 \\ 0.5 \times \rho_1 & \rho_1 \end{pmatrix}
Operating Characteristics - Power

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\[
\mathbf{R}_1^{-1} = \begin{pmatrix} \rho_1 & 0.5 \times \rho_1 \\ 0.5 \times \rho_1 & \rho_1 \end{pmatrix}
\]
Other Options to Incorporate More Information

• Order constraints, if applicable. For example, the slope of the relationship between baseline size and percent excess weight-loss may be “known” to be higher or lower for adolescents than for adults.

• Non-linear relationships between response and covariate.
Summary Statements

• CDRH is committed to applying PMDSIA for pediatric medical devices.

• Statistical methods can be used to borrow from existing adult data to make decisions about pediatric effectiveness.

• Extrapolation really means borrowing
  – Technical “extrapolation” would extrapolate the adult slope to pediatrics.
  – Model 2 allows for flexibility in both intercepts and slopes across populations.
Backup
“Extrapolation of Safety and Effectiveness Data for Pediatric Uses of Medical Devices”

• What should a company prepare for if they wish to extrapolate?
  – How is the pediatric population different from the adult population?
  – What covariates are expected to modify the effect of the device on pediatric population? Are these covariates measured in the adult data set? Suggest a model that relates the covariates to treatment response.
  – Explain the source of the adult data, study design, variables measured.
  – Propose a statistical model for borrowing from adult data.
Potential Methods/Models

• Bayesian Hierarchical modeling (multiple authors)
  – Prior studies are assumed exchangeable with current study

• Bayesian power priors (Ibrahim & Chen, 2000)
  – Prior is likelihood from historical data, raised to a power.

• Bayesian commensurate priors (Hobbs, et al., 2012)
  – Historical data are on same level as current data (no down-weighting). Current study mean is centered at the historical study mean, with precision that determines the commensurability of the studies.

• Propensity score methods (Normand, 2011)
Complete Overlap in Covariate
Most Amount of Borrowing

Baseline “Size” variable

Percent Excess Weight Loss

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

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<tr>
<th>Population</th>
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<td>Adolescent Baseline</td>
<td>Study 3 (n=20)</td>
<td>23.8% (14.7%)</td>
</tr>
<tr>
<td>“Size”=0.60</td>
<td></td>
<td><strong>No data here</strong>...</td>
</tr>
</tbody>
</table>
## Borrowing from Adult Studies

<table>
<thead>
<tr>
<th>Population</th>
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<th>Posterior Mean Percent Excess Weight loss (SD)</th>
<th>Effective Sample Size (ESS) in Adol Study</th>
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<tbody>
<tr>
<td>Adults “Size”=0.85</td>
<td>Study 1 (n=250)</td>
<td>38.2% (1.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study 2 (n=150)</td>
<td>33.4% (1.2%)</td>
<td></td>
</tr>
<tr>
<td>Adolescent</td>
<td>Study 3 (n=20)</td>
<td>31.9% (2.6%)</td>
<td>ESS = 133</td>
</tr>
<tr>
<td>“Size”=0.85</td>
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<td></td>
<td></td>
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</tbody>
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<td></td>
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<td>26.6% (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Adolescent</td>
<td>Study 3 (n=20)</td>
<td>25.5% (4.3%)</td>
<td>ESS = 234</td>
</tr>
<tr>
<td>“Size”=0.60</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Very Little Overlap in Covariate
Least Amount of Borrowing

Percent Excess Weight Loss

Baseline “Size” variable

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

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<td>Adolescent Baseline</td>
<td>Study 3 (n=20)</td>
<td>18.3% (2.7%)</td>
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</tr>
<tr>
<td></td>
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<td>25.7% (3.0%)</td>
<td>ESS = 38</td>
</tr>
</tbody>
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<tr>
<td></td>
<td>Study 3 (n=20)</td>
<td>19.1% (2.4%)</td>
<td>ESS = 26</td>
</tr>
</tbody>
</table>
Adjusting for a covariate

Another Situation – Attenuation of High Slope

Percent Excess Weight Loss

Baseline “Size” variable

- Adolescent
- Adult 1
- Adult 2
No Borrowing from Adult Studies
Adjusting for “Baseline Size”

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<td>Study 3 (n=20)</td>
<td>50.3% (6.1%)</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Size”=0.85</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adolescent
Posterior
Mean Slope = 0.57
SD = 0.29

<table>
<thead>
<tr>
<th>Population</th>
<th>Study</th>
<th>Posterior Mean Percent Excess Weight loss (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescent</td>
<td>Study 3 (n=20)</td>
<td>36.1% (3.1%)</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Size”=0.60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Borrowing from Adult Studies

### Adults

<table>
<thead>
<tr>
<th>Population</th>
<th>Study</th>
<th>Posterior Mean Percent Excess Weight loss (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults “Size”=0.85</td>
<td>Study 1 (n=250)</td>
<td>39.3% (0.9%)</td>
</tr>
<tr>
<td></td>
<td>Study 2 (n=150)</td>
<td>32.4% (1.1%)</td>
</tr>
</tbody>
</table>

### Adolescents

<table>
<thead>
<tr>
<th>Population</th>
<th>Study</th>
<th>Posterior Mean Percent Excess Weight loss (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescents “Size”=0.85</td>
<td>Study 3 (n=20)</td>
<td>46.1% (3.1%)</td>
</tr>
</tbody>
</table>

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Adolescent
Posterior Mean
Slope = 0.36
SD = 0.10

<table>
<thead>
<tr>
<th>Population</th>
<th>Study</th>
<th>Posterior Mean Percent Excess Weight loss (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults “Size”=0.60</td>
<td>Study 1 (n=250)</td>
<td>31.2% (1.8%)</td>
</tr>
<tr>
<td></td>
<td>Study 2 (n=150)</td>
<td>25.8% (2.2%)</td>
</tr>
<tr>
<td>Adolescents “Size”=0.60</td>
<td>Study 3 (n=20)</td>
<td>37.1% (2.3%)</td>
</tr>
</tbody>
</table>
Borrowing from One Adult Study

- Populations are confounded with Studies: Cannot have a population level and a study level
- Can still adjust for covariates: Might be necessary in order to borrow across populations.
- Need an informative prior on between-study precision (or analogous measure), regardless of methodology.
Borrowing from One Adult Study: Alternatives

- Partial Borrowing Power prior (Chen et al., 2012)
- Commensurate Prior (Hobbs, et al., 2012)
- Borrowing from historical control group only
  - Active control may not be available/approved for pediatrics.
  - Use a historical control (perhaps from adult study) for pediatrics (with propensity score adjustment)
  - Borrow from a historical control, along with “Information-balanced” randomization to enroll some current pediatric controls.