Bayesian Meta-Analysis in Drug Safety Evaluation

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Outline

• Personal Experience on Bayesian Applications in Drug Safety Evaluation

• Specific Examples on Bayesian Meta-analysis
  – Meta analysis for rare adverse event data
  – Meta-experimental design in evaluating CV risk for T2DM drug development

• Summary
  – Advantages of Bayesian Meta-analysis
  – Caveats and Recommendations
Current Use of Bayesian Methods in Industry

• Medical Device Industry
  – Regulatory support
    • Final FDA guidance released in Feb, 2010
    – It has been used regularly in support of clinical trial design and regulatory submission

• Biopharmaceutical Industry
  – Regulatory submission has been rare
  – Effectively used in
    • Early phase clinical trial design and monitoring for internal decision making
    • Analysis with complex modeling
Some Areas of Bayesian Impact/Applications

• **Clinical trial design**
  – Calculate posterior Pr (Success) to make E2L decision
  – Use of good prior information (historical data used via hierarchical modeling) appreciably reduced the size and the length of a trial
  – Use prediction to plan pilot and confirmatory studies as a whole
  – Bayesian adaptive design / dose finding

• **Clinical trial sequential monitoring**
  – Use posterior probability to continuously monitor an event of interest in a Phase 2 trial
  – Bayesian sequential monitoring plan to incorporate risk-benefit assessment for a clinical trial

• **Analysis (hierarchical modeling)**
  – Various applications in drug safety evaluation
  – Evidence synthesis/meta-analysis
Some Challenges in Drug Safety Evaluation

• How to detect unexpected adverse drug reactions while handling the multiplicity issue properly?
• How to synthesize data from different trials, or even different sources?
• How to deal with rare events?
• How to evaluate multi-dimensional, complex safety information as a whole?
• Can we monitor a potential safety issue in a continuous manner during a trial so patients can be better protected?
Specific Examples of Bayesian Applications in Safety Assessment

- Case 1: Clinical trial signal detection
- Case 2: Meta analysis for rare adverse event data
- Case 3: Meta-experimental design in evaluating CV risk for T2DM drug development
- Case 4: Joint modeling of longitudinal and time-to-event data
- Case 5: Continuously monitoring an adverse event of interest in a clinical trial

There are many more examples …
Case Studies

Meta analysis for rare adverse event data

Example 1: Nissen Meta-analysis with Bayesian Fixed Effect Model

Example 2: Bayesian Survival Meta-analysis Using Individual Patient Data
Statistical Issues with Meta-Analysis for Rare AE Data

- Standard inferences for meta-analysis rely on large sample approximations. They may not be accurate and reliable when
  - sample sizes from individual studies are small
  - total number of studies is small
  - total number of events is small
- Some serious AEs are often sparse, leading to zero events being observed in one arm or even both arms for some studies
- The problem with lack of power in evaluating heterogeneity is amplified when the number of studies is only modest or an event of interest is rare
Example 1: Nissen Meta-Analyses

- Rosiglitazone (RSG) is a hypoglycemic drug licensed in 1999 for treating patients with type 2 diabetes mellitus
- Nissen meta-analyses* included 48 (Ph 2,3,and 4) RCTs with a similar duration between treatment groups, and at least 24 weeks of drug exposure
  - Primary outcomes: MI and CV death
  - 6 trials with zero events of MI and CV death were excluded so 42 trials were used in the analysis
  - Of 42 studies, 38 reported at least one MI and 23 reported at least one CV death
  - Peto method was used (excluding double-zero studies)

* Nissen and Wolski, NEJM, 2007
Results from Nissen Meta-Analyses

MI

N = 38; OR = 1.43; 95% CI: (1.03, 1.98); p-value = 0.03

CV Death

N = 23; OR = 1.64; 95% CI: (0.98, 2.74); p-value = 0.06

Courtesy Dr. Lu Tian
# CVD Results Based on Bayesian Fixed Effect Model

<table>
<thead>
<tr>
<th></th>
<th>Fixed Effect (n=23)</th>
<th>Fixed Effect (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR</strong></td>
<td>1.73</td>
<td>1.68</td>
</tr>
<tr>
<td><strong>95% Credible Set</strong></td>
<td>[0.99, 2.86]</td>
<td>[0.95, 2.81]</td>
</tr>
<tr>
<td><strong>Pr (OR &gt; 1)</strong></td>
<td>0.97</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Pr (OR &gt; 1.2)</strong></td>
<td>0.89</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>Pr (OR &gt; 1.5)</strong></td>
<td>0.65</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Pr (OR &gt; 2.0)</strong></td>
<td>0.25</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>RD (%)</strong></td>
<td>0.08</td>
<td>-0.05</td>
</tr>
<tr>
<td><strong>95% Credible Set</strong></td>
<td>[-0.02, 0.20]</td>
<td>[-0.15, 0.04]</td>
</tr>
<tr>
<td><strong>Pr (RD &gt; 0)</strong></td>
<td>0.94</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Pr (RD &gt; 0.05%)</strong></td>
<td>0.72</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Pr (RD &gt; 0.1%)</strong></td>
<td>0.37</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Pr (OR &gt; 0.2%)</strong></td>
<td>0.03</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Example 2: Bayesian Survival Meta-Analysis with Individual Patient Data (IPD)

• Case study: a cross-company meta-analysis to investigate the short-term cancer risk in 3 TNF (tumor necrosis factor) inhibitors

• 74 RCTs of TNF inhibitors across multiple indications (n = 22,904)

• Results:
  – All cancers excluding NMSC (non-melanoma skin cancer): RR = 0.99 (95% BCI 0.61-1.68)
  – NMSC: RR = 2.02 (95% BCI 1.11-3.95)

Challenges in This Meta-analysis

• Re-analyzing RCTs for outcomes not originally planned, and comparing data across sponsors (as opposed to pre-planned meta-analyses of emerging data, using pre-defined safety endpoints)
  – Although centralized, blinded adjudication was used, the adjudication of many events was based on minimal information
• Dealing with rare events
• Using individual patient data (with covariates) with time-to-event endpoints with non-constant hazards over time

Meta-analysis of rare events based on RCTs is a powerful tool but poses a series of methodological challenges that require due attention and action
Bayesian hierarchical piecewise exponential survival models were used

- Dividing time into (0-3, > 3mos) with constant hazard in each interval, allowing for relaxing the proportional hazards assumption
- Assessing class effects and drug-specific effects among 3 anti-TNF agents
- Investigating differences in ‘sponsor-specific control-group effect’
- Taking into account patient-level covariates, between study heterogeneity, and time-dependent covariates
Advantages of Bayesian Meta-Analyses for Rare AE Data

• Provide a powerful framework to model the uncertainty of all parameters
  – e.g. complex hierarchical piecewise exponential survival models
• ‘Exact’ methods allow meta-analyses without the need for continuity correction
• Inferences based on the exact full posterior distributions, relaxing the assumption of normality of the outcome (not sensible for rare event data)
• Straightforward and flexible to assess clinical important difference with different scales
Practical Considerations of Bayesian Meta-Analysis for Rare AE Data

• Non-informative priors may lead to convergence failure due to very sparse data
  – Weakly informative priors may be used to solve this issue, e.g.

<table>
<thead>
<tr>
<th>Prior</th>
<th>Mean log(OR)</th>
<th>Std Dev</th>
<th>Translated Est. Mean HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.7</td>
<td>2</td>
<td>2 (0.04, 110)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1 (0.02, 55)</td>
</tr>
<tr>
<td>3</td>
<td>0.7</td>
<td>0.7</td>
<td>2 (0.5, 8.2)</td>
</tr>
</tbody>
</table>

• Sensitivity analyses with regard to the choice of priors need to be performed
Case Study

Meta-experimental design in evaluating CV risk for T2DM drug development*

* Ibrahim, Chen, Xia and Liu, Biometrics, 2011.
Background – CV Evaluation of New Therapies to Treat Type 2 Diabetes (T2DM)

- FDA Guideline for Evaluating CV risk in a T2DM Product (12/2008) calls for a program-wide meta-analysis of CV outcomes
  - a meta-analysis of the randomized phase 2 and phase 3 studies, or
  - an additional single, large postmarketing safety trial.

 Generally may not need a PMC CV trial

 Generally need a PMC CV trial

 A large safety P3 study is needed
An Overview of the New Bayesian Meta-experimental Design Approach

- Using survival models to assess whether the size of a clinical development program is adequate to evaluate a safety endpoint, after accounting for between study heterogeneity
- Extending the fitting and sampling priors of Wang and Gelfand (2002) to Bayesian meta-analysis design with a focus on controlling the type I error and power
- Proposing the partial borrowing power prior to incorporate the historical survival meta-data into the statistical design
- Applying the proposed methodology to the design of a phase 2/3 development program including a non-inferiority clinical trial for CV risk assessment in T2DM studies
A Hypothetical Design of Phase 2/3 Meta Studies with Two Categories

<table>
<thead>
<tr>
<th>Category 1: Randomized Efficacy Superiority Studies</th>
<th>Control Group</th>
<th>Experimental Drug</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2a – 4 weeks (5 doses, placebo)</td>
<td>25</td>
<td>125</td>
<td>150</td>
</tr>
<tr>
<td>Phase 2b – 24 weeks (3 doses, active control, placebo)</td>
<td>140</td>
<td>210</td>
<td>350</td>
</tr>
<tr>
<td>Phase 3 – 24 weeks (3 doses, placebo)</td>
<td>100</td>
<td>300</td>
<td>400</td>
</tr>
<tr>
<td>Phase 3 – 24 weeks (4 doses, placebo)</td>
<td>75</td>
<td>300</td>
<td>375</td>
</tr>
<tr>
<td>Phase 3 add on therapy – 24 weeks (3 doses, placebo)</td>
<td>185</td>
<td>555</td>
<td>740</td>
</tr>
<tr>
<td>Phase 3 add on therapy – 24 weeks (2 doses, placebo)</td>
<td>250</td>
<td>500</td>
<td>750</td>
</tr>
<tr>
<td>Phase 3 add on therapy – 24 weeks (2 doses, placebo)</td>
<td>188</td>
<td>376</td>
<td>564</td>
</tr>
<tr>
<td>Aggregated level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample size of the above 7 studies</td>
<td>963</td>
<td>2,366</td>
<td>3329</td>
</tr>
<tr>
<td>Assumed annualized event rate of death/MI/stroke</td>
<td>1.2%</td>
<td>1.2%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Expected endpoints</td>
<td>5</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Probability of upper 95% CI on HR &lt; 1.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category 2: Randomized CV outcome study (2 year equal enrollment, minimal of 2 years follow up)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>5,000</td>
<td>5,000</td>
<td>10,000</td>
</tr>
<tr>
<td>Assumed annualized event rate of death/MI/stroke</td>
<td>1.5%</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Expected endpoints</td>
<td>226</td>
<td>226</td>
<td>452</td>
</tr>
<tr>
<td>Probability of upper 95% CI on HR &lt; 1.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined Categories 1 &amp; 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expected endpoints</td>
<td>231</td>
<td>238</td>
<td>469</td>
</tr>
<tr>
<td>Probability of upper 95% CI on HR &lt; 1.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Historical Meta Data Used to Formulate Priors for the Control Arm

<table>
<thead>
<tr>
<th>Study (publication year)</th>
<th>Group</th>
<th>N</th>
<th>Events</th>
<th>Total patient year</th>
<th>Annualized event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxagliptin (2009)</td>
<td>Total control</td>
<td>1251</td>
<td>17</td>
<td>1289</td>
<td>1.31%</td>
</tr>
<tr>
<td>Liraglutide (2009)</td>
<td>placebo</td>
<td>907</td>
<td>4</td>
<td>449</td>
<td>0.89%</td>
</tr>
<tr>
<td></td>
<td>Active control</td>
<td>1474</td>
<td>13</td>
<td>1038</td>
<td>1.24%</td>
</tr>
<tr>
<td>ACCORD (2008)</td>
<td>Standard therapy</td>
<td>5123</td>
<td>371</td>
<td>16000</td>
<td>2.29%</td>
</tr>
<tr>
<td>ADVANCE (2008)</td>
<td>Standard therapy</td>
<td>5569</td>
<td>590</td>
<td>27845</td>
<td>2.10%</td>
</tr>
</tbody>
</table>
# Power and Type I Error for Meta-Design

<table>
<thead>
<tr>
<th>Model</th>
<th>$a_0$</th>
<th>$n_{18} = n_{28} = 4000$</th>
<th>$n_{18} = n_{28} = 4500$</th>
<th>$n_{18} = n_{28} = 5000$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Power</td>
<td>Type I Error</td>
<td>Power</td>
</tr>
<tr>
<td>Random Effects</td>
<td>0</td>
<td>0.765</td>
<td>0.043</td>
<td>0.811</td>
</tr>
<tr>
<td></td>
<td>0.00625</td>
<td>0.787</td>
<td>0.047</td>
<td>0.831</td>
</tr>
<tr>
<td></td>
<td>0.0125</td>
<td>0.801</td>
<td>0.050</td>
<td>0.843</td>
</tr>
<tr>
<td></td>
<td>0.015</td>
<td>0.805</td>
<td>0.051</td>
<td>0.846</td>
</tr>
<tr>
<td></td>
<td>0.025</td>
<td>0.814</td>
<td>0.054</td>
<td>0.855</td>
</tr>
<tr>
<td></td>
<td>0.0375</td>
<td>0.819</td>
<td>0.055</td>
<td>0.860</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>0.821</td>
<td>0.057</td>
<td>0.862</td>
</tr>
<tr>
<td></td>
<td>0.075</td>
<td>0.826</td>
<td>0.058</td>
<td>0.865</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>0.829</td>
<td>0.059</td>
<td>0.867</td>
</tr>
</tbody>
</table>
Summary of Bayesian Meta-Design

• The proposed Bayesian method allows for
  – planning sample size for a phase 2/3 development program in the meta-analytical framework by accounting for between-study heterogeneity
  – incorporating prior information for the underlying risk in the control population through the partial borrowing power prior
• We assess the operating characteristics (type I error and power) of the Bayesian meta-design via simulations
  – recommended by the FDA Bayesian device trials guidance
• Further extension on Bayesian sequential meta-design has been published (Chen, et al, SIM, 2014)
Advantages of using Bayesian statistics for meta-analysis

• Provides a unified framework for synthesizing evidence from multiple data sources/studies/treatments in a formal, consistent and coherent manner, taking all the uncertainty at different levels into account
  – Ability of handling complex problems (e.g. IPD, non-constant hazards)
• Allows formal incorporation of other sources of evidence by utilizing prior distributions
• Provides direct probability statements about true treatment effects under different scales (e.g. OR, RR, or RD)
• Provides prediction of the treatment effect in a new trial
• Appealing for rare event meta-analysis
  – Models modulate the extremes in the zero event setting
  – Avoid the need for continuity correction
  – Bayesian inference is based on the full posterior distributions, relaxing the assumption of normality
Caveats and Recommendations

• **Caveats**
  – Careful specification of prior distributions and form of the model (e.g. form of hierarchy)
  – Computational intensity

• **Recommendations**
  – Bayesian expertise should be sought
  – Sensitivity analyses against a range of priors and model structures
References

References

Thank you!