Use of historical data
Methods, applications and implementation
with the R package RBesT
Heinz Schmidli and Sebastian Weber

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Outline - Methods

• Evidence synthesis and prediction
• Use of historical controls
• Extrapolation from adults to children
• Robustness
• Probability of Success
• Conclusions
Evidence synthesis and prediction

Introduction

• Evidence synthesis and prediction/extrapolation

  From source to target
  – From historical control to concurrent control
  – From historical adult trials to trial in children
  – From historical trials on one drug to trial in a similar drug
   ...

• Historical clinical trials as main source of information

• Hierarchical models very natural for evidence synthesis and prediction
Evidence synthesis and prediction

Bayesian approaches

Regulators open to Bayesian approaches in some areas

EMA (2012) Concept paper on extrapolation of efficacy and safety in medicine development (draft).

Some efficacy data are considered necessary in the target population the nature of which depending on the degree of extrapolation from the source population. Such a scenario could be supported by *Bayesian* statistical approaches using prior information from the source population(s).

EMA (2016) Reflection paper on extrapolation of efficacy and safety in paediatric medicine development (draft).

... using Bayesian methods to either summarise the prior information for the extrapolation concept, or to explicitly borrow information (from adult trials, from control groups, from other paediatric clinical trials).

FDA (2016) Leveraging existing clinical data for extrapolation to pediatric uses of medical devices.

*While Bayesian methods are described in this document, non-Bayesian methods can also be used for borrowing strength.*
Evidence synthesis and prediction

Framework

Hierarchical model to link parameters (hyper-parameter $\phi$)

Bayesian inference on unknowns $\theta_*$ ($\theta_1, \ldots, \theta_J, \phi$)
Use of historical controls

Case study

• **Disease**
  Ankylosing spondylitis

• **Test treatment**
  Secukinumab (monoclonal antibody)

• **Endpoint**
  Binary: response at week 6

• **Traditional clinical trial design**
  – Secukinumab (n=24) vs. Placebo (n=24)
  – Fisher’s exact test

However: 8 similar historical placebo-controlled clinical trials with different test treatments

Could this historical placebo information be used?
Use of historical controls

Case study

J=8 historical placebo-controlled trials

# responders on placebo

$Y_j \sim \text{Binomial}(\pi_j, n_j)$

$\theta_j = \text{logit}(\pi_j)$

Planned clinical trial

# responders on placebo

$Y_* \sim \text{Binomial}(\pi_*, n_*)$

$\theta_* = \text{logit}(\pi_*)$

Simplest hierarchical model to link parameters

$\theta_*, \theta_1, ..., \theta_J \mid \mu, \tau \sim N(\mu, \tau^2)$

Meta-Analytic-Predictive (MAP)

Mean $\mu$

Between-trial standard deviation $\tau$

Hyper-parameter $\phi = (\mu, \tau)$

Spiegelhalter et al. (2004)
Neuenschwander et al. (2010)
Schmidli et al. (2014)
## Use of historical controls

### Case study

<table>
<thead>
<tr>
<th>Historical studies</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td></td>
</tr>
<tr>
<td>Study 3</td>
<td>$\pi_1$</td>
</tr>
<tr>
<td>Study 4</td>
<td>$\pi_2$</td>
</tr>
<tr>
<td>Study 5</td>
<td>$\pi_3$</td>
</tr>
<tr>
<td>Study 6</td>
<td>$\pi_4$</td>
</tr>
<tr>
<td>Study 7</td>
<td>$\pi_5$</td>
</tr>
<tr>
<td>Study 8</td>
<td>$\pi_6$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prediction</th>
<th>$\pi_7$</th>
</tr>
</thead>
<tbody>
<tr>
<td>New study</td>
<td>$\pi_8$</td>
</tr>
</tbody>
</table>

### Meta-analytic-predictive (MAP)

$$\theta_j = \text{logit}(\pi_j)$$

$$\theta^* = \text{logit}(\pi^*)$$

$$\theta^*, \theta_1, \ldots, \theta_J \mid \mu, \tau \sim N(\mu, \tau^2)$$

### Prior information for Placebo in new study

Placebo response rate
Use of historical controls

Case study

Bayesian primary analysis

- **Prior Placebo**: Derived from 8 historical trials (N=533), using a Meta-Analytic-Predictive (MAP) approach
  \[
  \text{Beta}(11,32) \quad \text{worth} \quad 43 = 11 + 32 \text{ patients}
  \]

- **Prior Test Treatment**: Weakly informative
  \[
  \text{Beta}(0.5,1) \quad \text{worth} \quad 1.5 = 0.5 + 1 \text{ patients}
  \]

Design:

Secukinumab (n=24) vs. Placebo (n=6)

Results:

14/23 Secukinumab vs. 1/6 Placebo, \( p(\delta > 0 \mid \text{data}) > 99.8\% \)

Baeten et al. (2013) *Lancet*
Use of historical controls

Summary

• Benefits
  Allows to reduce number of placebo patients in new trial
  – Decreases cost
  – Shortens trial duration
  – Facilitates recruitment
  – May be more ethical in some situations
  } Faster decisions

• Risks
  – Prior-data conflict
  – Excessive type I error inflation

Mitigated by using robust priors, adaptive designs
Extrapolation from adults to children
Example for evidence synthesis and extrapolation

- Full extrapolation: \( p(\theta_* | Y_1, ... , Y_J) \)
- Partial extrapolation: \( p(\theta_* | Y_1, ... , Y_J, Y_*) \)
- No extrapolation: \( p(\theta_* | Y_*) \)

\( \theta_* \), \( \theta_1, ..., \theta_J \mid \mu, \tau \sim N(\mu, \tau^2) \)

Clinical trial in adults of test treatment vs control, with treatment effect \( \theta_j \)

J clinical trials in adults of test treatment vs control, with treatment effect \( \theta_j \)

Clinical trial in children of test treatment (children version) vs control, with treatment effect \( \theta_* \)

Models to link parameters

- Full extrapolation: \( p(\theta_* | Y_1, ... , Y_J) \)
- Partial extrapolation: \( p(\theta_* | Y_1, ... , Y_J, Y_*) \)
- No extrapolation: \( p(\theta_* | Y_*) \)

\( \theta_* \mid \mu_*, \tau_* \sim N(\mu_*, \tau_*^2) \)
Extrapolation from adults to children

Illustrative example - treatment of venous thromboembolic events (VTE)

• Considered clinical trial in children
  – Test: low molecular weight heparin
  – Control: unfractionated heparin, followed by oral anticoagulation

  Binary primary endpoint: recurrent VTE (3 months)

• 14 similar historical clinical trials in adults
  Test vs Control, recurrent VTE (3 months) available
  Erkens and Prins (2010) Cochrane Database of Systematic Reviews

• Similar efficacy in children and adults seems plausible
  – Individualized dosing based on biomarkers and body weight
  – Same mode of action

  Full extrapolation?

Comparable setting discussed by Gerß et al. (2012)
Extrapolation from adults to children
Treatment of venous thromboembolic events (VTE)

Recurrent VTE (3 months)
Test vs Control:
Log(odds ratio) $\theta_j$

Historical trials in adults

Favors Test
Favors Control

14 Public
Extrapolation from adults to children

Treatment of venous thromboembolic events (VTE)

Recurrent VTE (3 months)

Test vs Control:
Log(odds ratio) $\theta_j$

Meta-Analytic-Predictive (MAP) model
$\theta_*, \theta_1, \ldots, \theta_J \mid \mu, \tau \sim N(\mu, \tau^2)$
Extrapolation from adults to children

Treatment of venous thromboembolic events (VTE)

Recurrent VTE (3 months)

Test vs Control:
Log(odds ratio) $\theta_j$

Meta-Analytic-Predictive (MAP) model
$\theta_*, \theta_1, \ldots, \theta_J | \mu, \tau \sim N(\mu, \tau^2)$

MAP prior $p_{\text{MAP}}(\theta_*) = p(\theta_* | Y_1, \ldots, Y_J)$
Extrapolation from adults to children

Treatment of venous thromboembolic events (VTE)

MAP prior

\[ p_{\text{MAP}}(\theta^*) = p(\theta^* | Y_1, ..., Y_J) \]

Approximated by mixture of normal distributions (solid line)

\[ 0.71 \, \mathcal{N}(-0.36,0.18^2) + 0.29 \, \mathcal{N}(-0.41,0.42^2) \]
Extrapolation from adults to children

Treatment of venous thromboembolic events (VTE)

• MAP approach to extrapolate from adults to children
  MAP prior $p_{\text{MAP}}(\theta^*)$ derived from total of 6551 adults (14 studies)

• Trial in children
  Recurrent VTE (3 months): Test 2/36 vs Control 4/40
  Massicotte et al. (2003) planned N=352, actual N=78

• Extrapolation from adults to children

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>exp($\theta^*$)</th>
<th>Prob</th>
<th>Effective sample size (ESS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median (95% prob. interval)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full</td>
<td>0.69 (0.37, 1.19)</td>
<td>94%</td>
<td>1030</td>
<td></td>
</tr>
<tr>
<td>Partial*</td>
<td>0.68 (0.38, 1.09)</td>
<td>96%</td>
<td>1199</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.48 (0.06, 2.84)</td>
<td>78%</td>
<td>78</td>
<td></td>
</tr>
</tbody>
</table>

* Using $\theta^*, \theta_1, ..., \theta_J | \mu, \tau \sim N(\mu, \tau^2)$

18 Public
Robustness

Relevance of source data

• Prior $p(\theta^*)$ derived from adults considered to be relevant for children, however...

  “... think it possible that you may be mistaken.”  Cromwell

• Robust prior $p_{\text{Robust}}(\theta^*) = (1-\varepsilon) p_{\text{MAP}}(\theta^*) + \varepsilon p_{\text{Vague}}(\theta^*)$
  – Mixture of prior derived from adults and vague prior
  – Value $\varepsilon$ chosen to reflect scepticism on relevance of adult data
  – Robust priors are heavy-tailed, and hence discarded in case of clear prior-data conflict  O’Hagan and Pericchi (2012), Schmidli et al. (2014)

Solid line: $p(\theta^*)$
Dashed line: $p_{\text{Robust}}(\theta^*)$ with $\varepsilon=0.2$
Robustness
Prior-data conflict - hypothetical

"Bayesian - One who, vaguely expecting a horse and catching a glimpse of a donkey, strongly concludes he has seen a mule".

Stephen Senn
Robustness

Prior-data conflict - hypothetical

Robust prior          Posterior / Conflicting Likelihood

Robust prior essentially discarded in case of clear prior-data conflict
Extrapolation from adults to children

Summary

• Benefits
  Allows to reduce number of children in new trial
  – More ethical in many situations
  – Facilitates recruitment
  – Shortens trial duration
  – Decreases cost

  } Faster decisions

• Risks
  – Prior-data conflict
  – Excessive type I error inflation

Mitigated by using robust priors, adaptive designs
Probability of Success

Introduction

Success in a ...

• Clinical trial
  – Statistically significant efficacy result
  – Observed response rate on drug > 60%
  – Less observed AE than in active control
  ...

• Clinical development program
  – Target product profile – meet “base”/“upside” case
  – Drug approval
  – Drug reimbursement
  – ...

Probability of Success
Planning a Phase 3 trial

- Historical data/information available
- Success (yes/no) could be evaluated if data were known...
  E.g. success: p-value < 2.5% (one-sided)
- Uncertainty on data, hence uncertainty about success

**Probability of success (PoS)** 0-100%

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**Phase 3 trial**

<table>
<thead>
<tr>
<th></th>
<th>Experimental drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data $Y_E^*$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data $Y_P^*$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Phase 1, 2 results
Publications
Clinical trial data
Expert knowledge

...
**Probability of Success**

*Planning a Phase 3 trial: Evaluating PoS*

Bayesian framework

*Prediction*: predictive distribution of future data \( Y^* = (Y^*_E, Y^*_P) \)

E.g. 10’000 times:

- sample \( Y^*(i) \) from predictive distribution
- Calculate success \( S(i) \) (1/0)
- Probability of Success \( \text{PoS} \approx \Sigma S(i) / 10’000 \)

In simple cases: analytical evaluation rather than simulation
Probability of Success

Example: interim analysis in Phase 3

• Two phase 3 trials A and B running in parallel
  – endpoint survival
  – 379 events (n): α=2.5%, 90% power for log-hazard ratio log(0.75)
  – interim analysis when at least 150 deaths occurred in each of the trials

• Two historical trials
  1) a small proof-of-concept trial, and 2) a randomized phase 2 trial

• Interim decisions
  – based on probability of success (PoS)
  – stop phase 3 trial if PoS < 10% (e.g.)

• Evaluating PoS without/with co-data
  – *Without*: e.g. for phase 3 trial A, use just interim data from trial A for PoS
  – *With*: e.g. for trial A, use also interim data from trial B and historical trials
**Probability of Success**

*Example: interim analysis in Phase 3*

Data available at interim analysis for HR \( \theta \)

<table>
<thead>
<tr>
<th>Study</th>
<th>deaths</th>
<th>HR (95%-int)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Proof-of-concept</td>
<td>8</td>
<td>( \theta_1 ) 0.70 (0.18,2.80)</td>
</tr>
<tr>
<td>2. Phase 2</td>
<td>85</td>
<td>( \theta_2 ) 0.75 (0.49,1.15)</td>
</tr>
<tr>
<td>3. Phase 3 study A</td>
<td>162</td>
<td>( \theta_3 ) 0.83 (0.61,1.13)</td>
</tr>
<tr>
<td>4. Phase 3 study B</td>
<td>150</td>
<td>( \theta_4 ) 0.78 (0.57,1.07)</td>
</tr>
</tbody>
</table>

- **Success** = statistical significance
  - PoS = predictive power (Spiegelhalter et al., 1986)

- **Evaluating PoS for Phase 3 study B**
  - classical conditional power \( CP(\theta_4) = p(\text{final p-value}<0.025 \mid \theta_4, \text{interim data}) \)
  - PoS = \( \int CP(\theta_4) \ p(\theta_4 \mid \text{interim data}) \ d \theta_4 \)
  - Posterior distribution \( p(\theta_4 \mid \text{interim data}) \) may be evaluated without or with co-data
  - With co-data: \( \theta_1,\theta_2,\theta_3,\theta_4 \mid \mu,\tau \sim N(\mu,\tau^2) \)
## Probability of Success

*Example: interim analysis in Phase 3*

<table>
<thead>
<tr>
<th>Study</th>
<th>deaths</th>
<th>HR (95%-int)</th>
<th>log(HR) (sd)</th>
<th>pr(HR&lt;1)</th>
<th>PoS</th>
<th>ESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Proof-of-concept</td>
<td>8</td>
<td>0.70 (0.18,2.80)</td>
<td>-0.36 (0.71)</td>
<td>0.69</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2. Phase II</td>
<td>85</td>
<td>0.75 (0.49,1.15)</td>
<td>-0.29 (0.22)</td>
<td>0.91</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>3. Phase III study A</td>
<td>162</td>
<td>0.83 (0.61,1.13)</td>
<td>-0.19 (0.16)</td>
<td>0.88</td>
<td>0.45</td>
<td>162</td>
</tr>
<tr>
<td>4. Phase III study B</td>
<td>150</td>
<td>0.78 (0.57,1.07)</td>
<td>-0.25 (0.16)</td>
<td>0.94</td>
<td>0.64</td>
<td>150</td>
</tr>
</tbody>
</table>

**stratified analyses**

<table>
<thead>
<tr>
<th>Study</th>
<th>deaths</th>
<th>HR (95%-int)</th>
<th>log(HR) (sd)</th>
<th>pr(HR&lt;1)</th>
<th>PoS</th>
<th>ESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Phase III study A</td>
<td>162</td>
<td>0.80 (0.63,1.04)</td>
<td>-0.22 (0.13)</td>
<td>0.95</td>
<td>0.51</td>
<td>254</td>
</tr>
<tr>
<td>4. Phase III study B</td>
<td>150</td>
<td>0.79 (0.61,1.01)</td>
<td>-0.24 (0.13)</td>
<td>0.97</td>
<td>0.65</td>
<td>252</td>
</tr>
</tbody>
</table>

**co-data analysis**

ESS=effective sample size (number of events)

- PoS without co-data (stratified analyses) or with co-data
- Borrowing strength from co-data to support decision making

Neuenschwander et al. (2016)
Probability of Success

MAP or MAC?

Two approaches for evidence synthesis

• Meta-Analytic-Predictive (MAP) is prospective
  – At design stage of current trial, perform MA of co-data and obtain distribution of $\theta$. MAP Prior $p(\theta | Y_1, \ldots, Y_J)$
  – For the analysis, combine MAP prior with current trial data $Y^*$

• Meta-Analytic-Combined (MAC) is retrospective
  – Perform a meta-analysis of all co-data and current trial data
  – Parameter of interest is the parameter in the actual trial $\theta^*$
    $p(\theta^* | Y_1, \ldots, Y_J, Y^*)$

• MAP and MAC give identical results!

• PoS evaluation
  – At design stage, MAP has to be used
  – At analysis stage, more convenient of MAP or MAC can be used
Conclusions

• Hierarchical models flexible and useful for
  – synthesis of evidence from various sources
  – extrapolation to target

• Bayesian framework natural for
  – Inclusion of prior information
  – Inference and prediction

• Scepticism on relevance of source data can be taken into account
References


