Bayesian Evidence Synthesis for Extrapolation in Clinical Research

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38th Annual Conference of the ISCB
9-13 July 2017, Vigo
Outline

• Extrapolation/Prediction
  – Use of historical controls
  – Extrapolation from adults to children

• Robustness

• Type I error

• Further applications

• Conclusions

Acknowledgements

*Beat Neuenschwander, Simon Wandel*
*David Spiegelhalter, Anthony O’Hagan*
Extrapolation/Prediction

Introduction

• Extrapolation/Prediction common in clinical research

  From source to target
  – From historical control to concurrent control
  – From adults to children
  – From biomarker to clinical endpoint
  – From one drug to another
  ...

• Clinical trials as main source of information

• Hierarchical models very natural for evidence synthesis and extrapolation/prediction
Extrapolation/Prediction

Bayesian approaches

Regulators open to Bayesian approaches

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.
Extrapolation/Prediction
Framework for evidence synthesis and extrapolation

Hierarchical model to link parameters (hyper-parameter $\phi$)
$$p(\theta_*, \theta_1, ..., \theta_J | \phi)$$

Bayesian inference on unknowns $\theta_*$ ($\theta_1, ..., \theta_J$)
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

\[ Y_1, Y_2, \ldots, Y_J \]

\[
\begin{align*}
\theta_1, \theta_2, \ldots, \theta_J & \mid \mu, \tau \sim N(\mu, \tau^2) \\
\theta_* & = \text{logit}(\rho_*) \\
Y_* & \sim \text{Binomial}(\rho_*, n_j) \\
Y_j & \sim \text{Binomial}(\rho_j, n_j)
\end{align*}
\]

J=8 historical placebo-controlled trials

# responders on placebo

Spiegelhalter et al. (2004)
Neuenschwander et al. (2010)
Schmidli et al. (2014)

Meta-Analytic-Predictive (MAP)

Mean \( \mu \)

Between-trial standard deviation \( \tau \)
Use of historical controls

Case study

Historical studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo group</th>
<th>Meta-analytic-predictive (MAP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>( \pi_1 )</td>
<td>( \theta_j = \logit(\rho_j) )</td>
</tr>
<tr>
<td>Study 2</td>
<td>( \pi_2 )</td>
<td>( \theta_* = \logit(\rho_*) )</td>
</tr>
<tr>
<td>Study 3</td>
<td>( \pi_3 )</td>
<td>( \theta_*, \theta_1, \ldots, \theta_J \mid \mu, \sigma \sim N(\mu, \sigma^2) )</td>
</tr>
<tr>
<td>Study 4</td>
<td>( \pi_4 )</td>
<td>Prior information for Placebo in new study</td>
</tr>
<tr>
<td>Study 5</td>
<td>( \pi_5 )</td>
<td></td>
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<tr>
<td>Study 6</td>
<td>( \pi_6 )</td>
<td></td>
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<tr>
<td>Study 7</td>
<td>( \pi_7 )</td>
<td></td>
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<tr>
<td>Study 8</td>
<td>( \pi_8 )</td>
<td></td>
</tr>
<tr>
<td>New study</td>
<td>( \pi_* )</td>
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</tbody>
</table>

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
  Beta(11,32) worth 43=11+32 patients

– Prior Test Treatment Weakly informative
  Beta(0.5,1) worth 1.5=0.5+1 patients

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

Results:
  14/23 Secukinumab vs. 1/6 Placebo, p(d>0 | 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

\[ p(\theta^* | Y_1, ..., Y_J) \]

\[ p(\theta^* | Y_1, ..., Y_J, Y^*) \]

\[ p(\theta^* | Y^*) \]

\[ \theta^*, \theta_1, ..., \theta_J | \mu, \sigma^2 \sim N(\mu, \sigma^2) \]

\[ \theta^* | \mu^*, \sigma \sim N(\mu^*, \sigma^2) \]

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

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

Models to link parameters

\[ \phi \]

\[ \theta_1, \theta_2, ..., \theta_J \]

\[ Y_1, Y_2, ..., Y_J, Y^* \]

\[ Y^*_1, Y^*_2, ..., Y^*_J, Y^*_* \]
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) $\theta_j$

Favors Test

Favors Control
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
$\theta_*, \theta_1, \ldots, \theta_J \mid \mu, \sigma^2 \sim N(\mu, \sigma^2)$
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
$\theta_*, \theta_1, \ldots, \theta_J | \mu, \omega \sim N(\mu, \omega^2)$

MAP prior $p_{MAP}(\theta_*) = p(\theta_* | Y_1, \ldots, Y_J)$
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>Prob OR&lt;1</th>
<th>Effective sample size (ESS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full</td>
<td>0.69 (0.37, 1.19)</td>
<td>94%</td>
<td>1030</td>
</tr>
<tr>
<td>Partial*</td>
<td>0.68 (0.38, 1.09)</td>
<td>96%</td>
<td>1199</td>
</tr>
<tr>
<td>No</td>
<td>0.48 (0.06, 2.84)</td>
<td>78%</td>
<td>78</td>
</tr>
</tbody>
</table>

* Using $\theta_*, \theta_1, \ldots, \theta_J | \mu, \omega \sim N(\mu, \omega)$
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

Conjugate prior  Posterior  Conflicting Likelihood

"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
Type I error
Scientific judgement

• Incompatible - can’t have both!
  Strict type I error control vs. Borrowing strength from external data

• Strict type I error control not always required
  – Early phase trials (phase I, IIa, IIb)
  – Some phase III settings – two examples

  ÁMonotherapy treatment for epilepsy: FDA requires single arm phase III trial with historical control
  French et al. (2010) Epilepsia

  ÁNon-inferiority trials: superiority to placebo indirectly established based on historical trials
  FDA Guidance (2016) “In the absence of a placebo arm, knowing whether the trial had assay sensitivity relies heavily on external (not within-study) information, giving NI studies some of the characteristics of a historically controlled trial.”
Further applications

Non-inferiority trials

Example data from FDA guidance on NI trials (2016)
NI trial SPORTIF V for prevention of stroke T vs C

T test treatment C active control P placebo

\[ \theta^*_T - \theta^*_C \]
Further applications

Non-inferiority trials

Historical trials only: C vs P

\[(\theta^*_P - \theta^*_C), (\theta^*_P - \theta^*_C), ..., (\theta^*_P - \theta^*_C) \sim N(\mu_{PC}, \tau^2_\delta)\]

Non-inferiority trial only: T vs C

Study 1
Study 2
Study 3
Study 4
Study 5
Study 6
Population
Prediction NI study
NI study

\[\theta^*_C - \theta^*_P\]

\[\theta^*_T - \theta^*_C\]

Risk Ratio

0.0625 0.1250 0.2500 0.5000 1.0000 2.0000 4.0000
Further applications

Non-inferiority trials

Historical trials only: C vs P

\((\theta^*_P - \theta^*_C), (\theta^*_1 - \theta^*_1), \ldots, (\theta^*_P - \theta^*_C) \sim N(\mu_{PC}, \tau^2_\delta)\)

\[ \theta^*_C - \theta^*_P \]

\[ \theta^*_T - \theta^*_C \]

Non-inferiority trial only: T vs C

Historical trials and non-inferiority trial: T vs P

\[ \theta^*_T - \theta^*_P \]

Study 1
Study 2
Study 3
Study 4
Study 5
Study 6

Population
Prediction NI study

NI study

0.0625 0.1250 0.2500 0.5000 1.0000 2.0000 4.0000

Risk Ratio

Gamalo et al. (2016)

*J Biopharm Stat*

Gamalo et al. (2016) J Biopharm Stat
Further applications

Comparative effectiveness

Prevention of serious vascular events (stroke, myocardial infarction, death from vascular causes)

Antiplatelet regimens: T (aspirin+dipyridamole), C (thienopyridine), P (aspirin), A (aspirin+thienopyridine), B (background therapy)

Network meta-analysis:
24 historical trials to predict C vs T OR 1.19 (0.98, 1.43)

PRoFESS trial C vs T
C 1333/10181
T 1333/10151

Pr(observed OR<1 | hist) = 4.5%

Further applications

Disease subtypes/subgroups

Phase II cancer trial: Assess efficacy of imatinib in patients with one of 10 different subtypes of advanced sarcoma

- Considerable borrowing across all subgroups for EX, EXNEX-1, EXNEX-2
- Substantial precision gains

Neuenschwander et al. (2016) *Pharm Stat*
Further applications
Surrogate endpoints

Treatment effects on
• Lesions (biomarker)
• Relapses (clinical)

23 placebo-controlled studies (40 arms)

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