EFSP1 & BBS “Small populations and level of evidence”

Bayesian analysis for small sample size trials using informative priors derived from historical data

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27 Jun 2018
Introduction
Planning a trial in patients with ΔF508 mutation in cystic fibrosis at early clinical development

// Cystic fibrosis is a multi-organ disorder
// Caused by gen mutations, cystic fibrosis transmembrane conductance regulator (CFTR) channels are affected; most frequent mutation is ΔF508
// Today survival depends on status of lung disease, median age of survival is 40 years
// Rare disease: Affects ≈1 out of 3000 newborns of Northern European ancestry, ≈30000 patients with CF in USA
// At early clinical development, trials are conducted to evaluate the treatment potential of drug
// Desire to conduct trials with small sample sizes
// Large challenges in recruiting patients for trials in rare disease like cystic fibrosis
// Limit number of patients to be exposed to drug without proven clinical benefit
// Fast decision making to avoid delaying development of potential efficacious drug
// Utilize historical information by using Bayesian approach
// Replace real patients by “virtual” patients → reduce sample size
Trial design and historical data

Early clinical development trial in patients with ΔF508 mutation in cystic fibrosis

- Randomized, placebo-controlled, parallel group trial in cystic fibrosis patients with by ΔF508 mutation
- Primary variable: Change of sweat chloride (Cl) content from baseline
  - Sweat Cl content is established diagnostic and biomarker for clinical trials for cystic fibrosis
- Primary objective: Evaluate reduction of sweat Cl content from baseline under treatment vs. placebo
- Approach: Use historical data to reduce number of patient with ΔF508 mutation for placebo treatment
  - Historical data for change from baseline of sweat Cl content (mmol/L) in patients treated with placebo

<table>
<thead>
<tr>
<th>Source</th>
<th>Gender</th>
<th>Age</th>
<th>FEV1 pred.</th>
<th>Genotype</th>
<th>Time</th>
<th>N</th>
<th>Mean</th>
<th>St. dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clancy et.al., Thorax (2012)</td>
<td>F &amp; M</td>
<td>18 - 54</td>
<td>&gt;= 40%</td>
<td>F508del-CFTR, homozygote</td>
<td>Day 14</td>
<td>17</td>
<td>1.75</td>
<td>7.7</td>
</tr>
<tr>
<td>Flume et.al., Chest (2012)</td>
<td>F &amp; M</td>
<td>12 - 52</td>
<td>&gt;= 40%</td>
<td>F508del-CFTR, homozygote</td>
<td>Day 15</td>
<td>26</td>
<td>-0.04</td>
<td>8.1</td>
</tr>
<tr>
<td>Boyle et.al., Lancet (2014)</td>
<td>F &amp; M</td>
<td>&gt;= 18</td>
<td>&gt;= 40%</td>
<td>F508del-CFTR, homozygote</td>
<td>Day 14</td>
<td>21</td>
<td>-1.7</td>
<td>8.7</td>
</tr>
</tbody>
</table>

- Selection of data based on external expert feedback (status of 2015)
  - Similar changes for both genotypes for placebo
  - Inclusion of recent articles to ensure comparable measurement procedure for sweat Cl
- Between trial-variability for mean and potentially for standard deviation
Deriving prior distribution from historical data sources

Using meta-analytical prediction to deal with between-trial variability

// Deriving prior distribution for placebo by simple pooling of historical data ignores between-trial variability

// Would lead to overestimation of existing information

// Meta-analytical prediction (MAP) approach allows deriving of prior distribution while taking uncertainty due to between-trial variability into account [Neuenschwander et al. (2010), Schmidli et al. (2014)]

1. Bayesian random-effect meta analysis on historical data for trial parameter, e.g. means

2. Predicted posterior distribution for parameter $\theta^*$ in new trial

Predicted posterior distribution

= Hyper distribution + uncertainty in estimates of $\mu$ and $\tau^2$

// Predicted posterior distribution for parameter $\theta^*$ in new trial reflects all information about this parameter
Modelling estimates for mean and variance for placebo in trials

MAP: Model for Bayesian random-effect meta analysis for sweat Cl content

\[ y_{ij}, \ i = 1, \ldots, n_j \] of patient \( i \) in trial \( j \) is normal distributed with unknown, trial-specific mean \( \vartheta_j \) and variance \( \sigma_j^2 \)

\[ y_{ij}|\vartheta_j, \sigma_j^2 \sim N(\vartheta_j, \sigma_j^2) \]

Observed mean response \( M_j \) of trial \( j \) follows a normal distribution

\[ M_j|\vartheta_j, \sigma_j^2 \sim N\left(\vartheta_j, \frac{\sigma_j^2}{n_j}\right) \]

Observed variance of response \( S_j^2 \) of trial \( j \) follows a “scaled” \( \chi^2 \)-distribution

\[ S_j^2|\sigma_j^2 \sim \chi^2(n_j - 1, \sigma_j^2) \]

i.e. \( S_j^2/\sigma_j^2 \sim \chi^2(n_j - 1) \) follows a \( \chi^2 \)-distribution with \( n_j - 1 \) degree of freedom
Modelling the unknown means of sweat Cl content in trials

For modelling the means $\vartheta_j$ of the trials, a normal distribution is used with unknown mean $\mu$ and variance $\tau^2$ as hyper distribution

$$\vartheta_j | \mu, \tau^2 \sim N(\mu, \tau^2)$$

Weak informative prior distributions for hyper distribution parameters are used

- Mean $\mu \sim$ Normal distribution
  - mean = 0, variance = 5^2
- Variance $\tau^2 \sim$ Gamma distribution
  - mean = 1.5^2, CV = 100%

Use of informative priors to cope with small numbers of historical trials [Wandel et al. (2017), Friede et al. (2017)]

- Values were chosen to restrict $\mu$ and $\tau^2$ on plausible values while avoiding “over domination”
- Evaluation of impact of informative priors in meta-analysis by sensitivity analysis
For modelling the variance $\sigma_j^2$ of the trials, an inverse-gamma distribution is used as hyper distribution.

To allow easier assessing of between-trial variability of variance, the inverse gamma distribution is reparametrized by the mean $\delta^2$ and the coefficient of variation $\varepsilon$:

$$
\sigma_j^2 | \delta^2, \varepsilon \sim \text{Inv-}\Gamma(2 + 1/\varepsilon^2, \delta^2 (1 + 1/\varepsilon^2))
$$

Weak informative prior distributions for hyper distribution parameters are used:

- Mean $\delta^2 \sim \text{Gamma distribution}$
  - mean = $8^2$, CV = 100%
- Coefficient of variation $\varepsilon \sim \text{Gamma distribution}$
  - mean = 20%, CV = 100%

Remark: For common variance, $\sigma^2 = \sigma_j^2$, replace hyper-distribution by inverse-gamma distribution for $\sigma^2$ as prior distribution.

Affects mainly variance estimates of studies, small impact on marginal posterior for trial means.
Results of Bayesian meta-analysis for sweat Cl content for placebo

Results of first step of meta-analytical prediction

// Posterior distribution for parameter of hyper-distributions are derived by MCMC simulations

// Assessment of posterior probabilities provide insight about “reproducibility” of endpoints

// Trial means $\vartheta_j$
  // Located around $\mu \approx 0$
  // Small between-trial variability, $\tau \approx 1$

// Variance of trials $\sigma_j^2$
  // Located around $\delta^2 \approx 8^2$
  // Negligible between-trial variability, $\varepsilon \approx 4\%$

// Remark: Peaks in histogram for $\delta$ indicate convergence issues in MCMC simulation caused by limited information from data due to few studies $\rightarrow$ need for informative priors
Information about mean and variance of future trials

Results of prediction step of meta-analytical prediction

Knowledge about mean $\vartheta^*$ and variance $\sigma^{*2}$ of a future trial is reflected by the hyper distributions taking uncertainties in distribution parameters into account.

Predicted posterior distribution for $\vartheta^*$ and $\sigma^{*2}$ is a representation for the available information.

MC samples for $\vartheta^*$ and $\sigma^{*2}$ are derived from hyper distribution using MCMC parameter samples.

Marginal predicted posterior distribution for trial mean $\vartheta^*$ and standard deviation $\sigma^*$

<table>
<thead>
<tr>
<th>Parameter</th>
<th>mean</th>
<th>sd</th>
<th>q1</th>
<th>median</th>
<th>q3</th>
<th>90%-range low</th>
<th>90%-range up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of new trial $\vartheta^*$</td>
<td>-0.11</td>
<td>1.54</td>
<td>-0.98</td>
<td>-0.11</td>
<td>0.76</td>
<td>-2.58</td>
<td>2.37</td>
</tr>
<tr>
<td>Standard deviation of new trial $\sigma^*$</td>
<td>8.04</td>
<td>0.56</td>
<td>7.65</td>
<td>8.01</td>
<td>8.38</td>
<td>7.21</td>
<td>9.02</td>
</tr>
</tbody>
</table>
Deriving prior distribution for sweat Cl content for Bayesian analysis

Use predicted posterior distribution for future trial from MAP to derive prior information

// The predicted posterior distribution for $\theta^*$ and $\sigma^2$ reflects all prior information for mean and variance
// Use predicted posterior distribution as prior distribution for placebo
// Derive analytical form for prior distribution by fitting a Normal – Inv-$\chi^2$ distribution to MC samples of predicted posterior distribution

$$\theta_{\text{placebo}}, \sigma_{\text{placebo}}^2 \sim \text{Normal} – \text{Inv}–\chi^2(\text{mean} = -0.1, \text{kappa} = 27.8, \text{dof} = 106.3, \text{sd}^2 = 8^2)$$

// Trial mean for placebo: Amount of information corresponds to $\approx 28$ patients ($\text{kappa} = 27.8$)
// $\approx 20\%$ of total sample size in historical trials ($N=138$)
$\rightarrow$ information reduction caused by between-trial variability

// Trial variance for placebo: Amount of information corresponds to $\approx 107$ patients ($\text{dof} = 106.3$)
// $\approx 80\%$ of total sample size
$\rightarrow$ small information reduction due to negligible between-trial variability

// Remark: To cope with long tails and/or shape deviations from standard distribution, deflate prior distribution (information loss) or use approximation by mixture distribution [Schmidli et al. (2014)]
Assessment of treatment potential by Bayesian analysis: Evaluate difference in mean change of sweat Cl content from baseline between drug and placebo $\theta_{drug} - \theta_{placbo}$

- Marginal posterior probability for mean change of sweat Cl from baseline for placebo $\theta_{placbo}$
  - Incorporate prior information for placebo derived by MAP procedure
    - Based on expert feedback, no further deflation of prior despite potential domination over data
- Marginal posterior probability for mean change of sweat Cl from baseline for drug $\theta_{drug}$
  - Vague prior information
- Posterior distribution for mean difference $\theta_{drug} - \theta_{placbo}$
  - MC sampling from marginal posterior distributions for $\theta_{placbo}$ and $\theta_{drug}$
  - Take differences of MC samples for drug and placebo

Evaluation of treatment potential of drug using Bayesian approach

- Treatment potential
  - $\text{Prob}(\theta_{drug} - \theta_{placbo} < 0 | \text{data}) \geq 90\%$
- Insufficient potential
Operational characteristic of assessment of treatment potential

// Capability of planned trial to detect treatment potential is evaluated by trial simulations
// Assess probability for detecting treatment potential for fixed difference in means $\theta_{\text{drug}} - \theta_{\text{placbo}}$
// Coping with uncertainty about $\theta_{\text{placbo}}$ and $\sigma_{\text{placbo}}^2$: Sample parameters and averaging probability using prior distribution derived by MAP [Walley et.al. (2015)]; for drug higher variability is assumed $\sigma_{\text{drug}} = 1.1 \cdot \sigma_{\text{placbo}}$

// Sample size determination
// 2:1 randomization
// $n_{\text{drug}} = 10$ and $n_{\text{placebo}} = 5$
// $\theta_{\text{drug}} - \theta_{\text{placbo}} = -8$ mmol/L
// $\Rightarrow \approx 90\%$ probability for detecting treatment potential on average

// Incorporation of prior information increases probability to detect treatment potential
// Allows designing trial with smaller sample sizes and unbalanced randomization
Summary and conclusions

// Trials with small sample sizes are desired in rare disease, in particular at early stage of development

// Incorporation of historical information might allow reduction of patient numbers
  // Bayesian approach provides formal framework for incorporation of prior information in trial analysis
  // Relevant sample size reduction can be achieved for small trials allowing imbalanced designs

// Selection of historical data is a crucial step when deriving prior information for Bayesian analysis
  // Close interaction with clinicians and experts is essential
  // Meta-analytical prediction is a useful approach to derive prior distributions from historical source
    // Cope with between-trial variability, thus prevents overestimation of information
    // Usually effective sample size of derived prior distribution is much smaller than total sample size
    // Provides additional insight about e.g. mean and variance of treatment response
  // Meta-analysis on few historical trials is feasible when incorporating (weak) informative priors
    // Evaluate impact of incorporating informative prior by sensitivity analysis
  // Domination of prior information in analysis and deflation of prior distribution needs to be considered
Thank you!

Bye-Bye