EFSPI & 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

Source	Gender	Age	FEV1 pred.	Genotype	Time	N	Mean	St. dev.
Clancy et.al., Thorax (2012)	F & M	18 - 54	>= 40%	F508del-CFTR, homozygote	Day 14	17	1.75	7.7
Flume et.al., Chest (2012)	F & M	12 - 52	>= 40%	F508del-CFTR, homozygote	Day 15	26	-0.04	8.1
Boyle et.al., Lancet (2014)	F & M	>= 18	>= 40%	F508del-CFTR, homozygote	Day 14	21	-1.7	8.7
Ramsey et.al., N Engl J Med (2011)	F & M	12 - 53	31.6 - 98.2	G551D-CFTR, homozygote	Day 15	74	-0.15	7.8

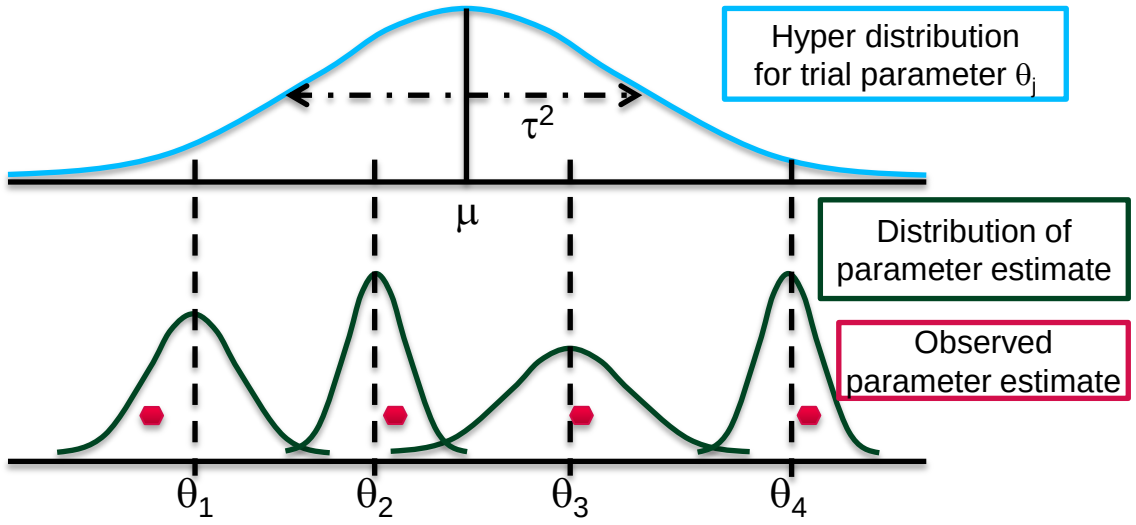
  - Selection of data based on external expert feedback (status of 2015)
    - Similar changes for both genotypes for placebo
    - Inclusion of recent articles to ensure comparable measurement procedure for sweat Cl
  - Between trial-variability for mean and potentially for standard deviation

Deriving prior distribution from historical data sources

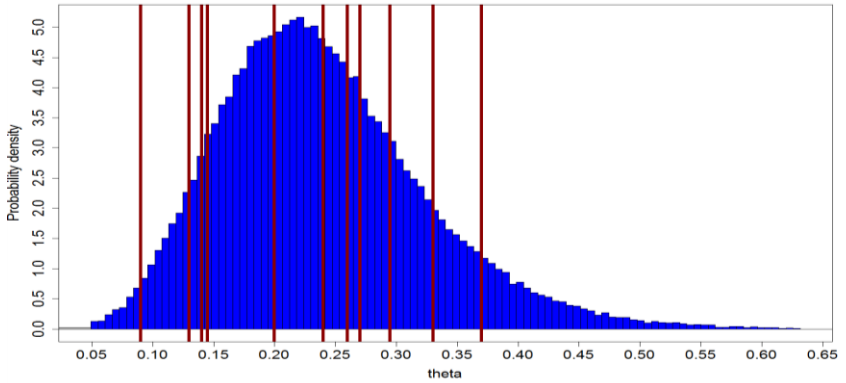
Using meta-analytical prediction to deal with between-trial variability

- 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 θ^* in new trial



Predicted posterior distribution
= Hyper distribution + uncertainty in estimates of μ and τ^2

- Predicted posterior distribution for parameter θ^* 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

- Response $y_{ij},\ i = 1, \ldots, n_j$ of patient *i* in trial *j* is normal distributed with unknown, trial-specific mean ϑ_j and variance σ_j^2

$$y_{ij}|\vartheta_j, \sigma_j^2 \sim N\left(\vartheta_j, \sigma_j^2\right)$$

  - Observed mean response M_j of trial *j* follows a normal distribution

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

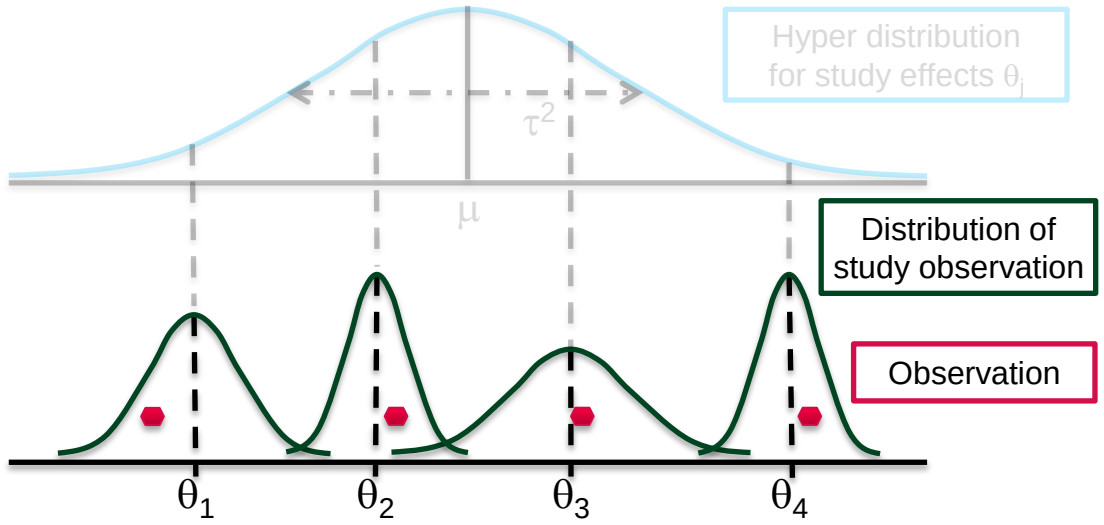
  - Observed variance of response S_j^2 of trial *j* follows a "scaled" χ^2-distribution

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

    i.e. $S_j^2/\sigma_j^2 \sim \chi^2(n_j - 1)$ follows a χ^2-distribution with $n_j - 1$ degree of freedom

Bayesian random-effect meta analysis on historical data

- Modelling of observations (e.g. trial means)



Modelling the unknown means of sweat Cl content in trials

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

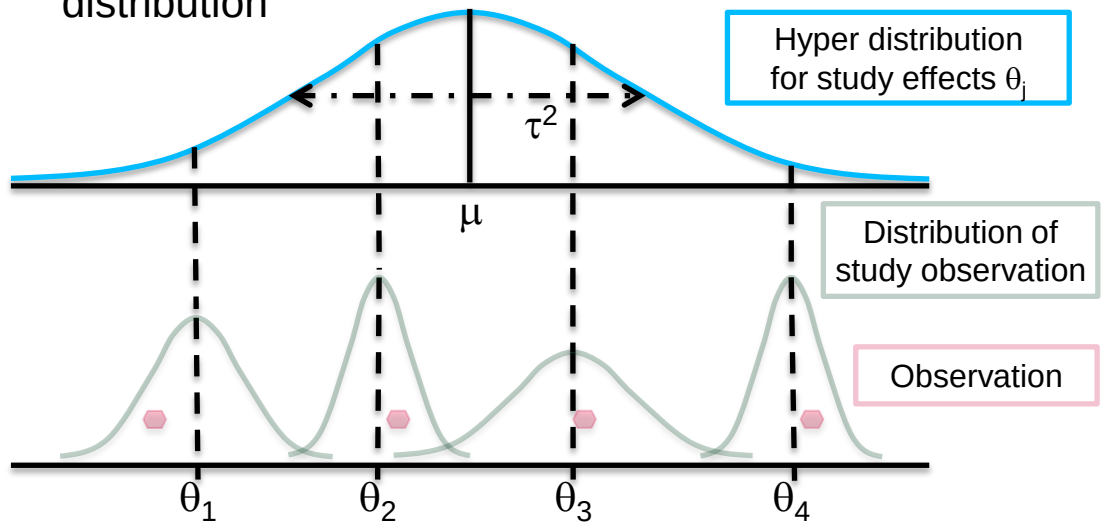
- For modelling the means ϑ_j of the trials, a normal distribution is used with unknown mean μ and variance τ^2 as hyper distribution

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

- Weak informative prior distributions for hyper distribution parameters are used
  - Mean μ ~ Normal distribution
    - mean = 0, variance = 5^2
  - Variance τ^2 ~ 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 μ and τ^2 on plausible values while avoiding “over domination”
    - Evaluation of impact of informative priors in meta-analysis by sensitivity analysis

Bayesian random-effect meta analysis on historical data

- Modelling trial parameters (e.g. means) by hyper distribution



Modelling the unknown variance of sweat Cl content in trials

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

- For modelling the variance σ_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 δ^2 and the coefficient of variation ε

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

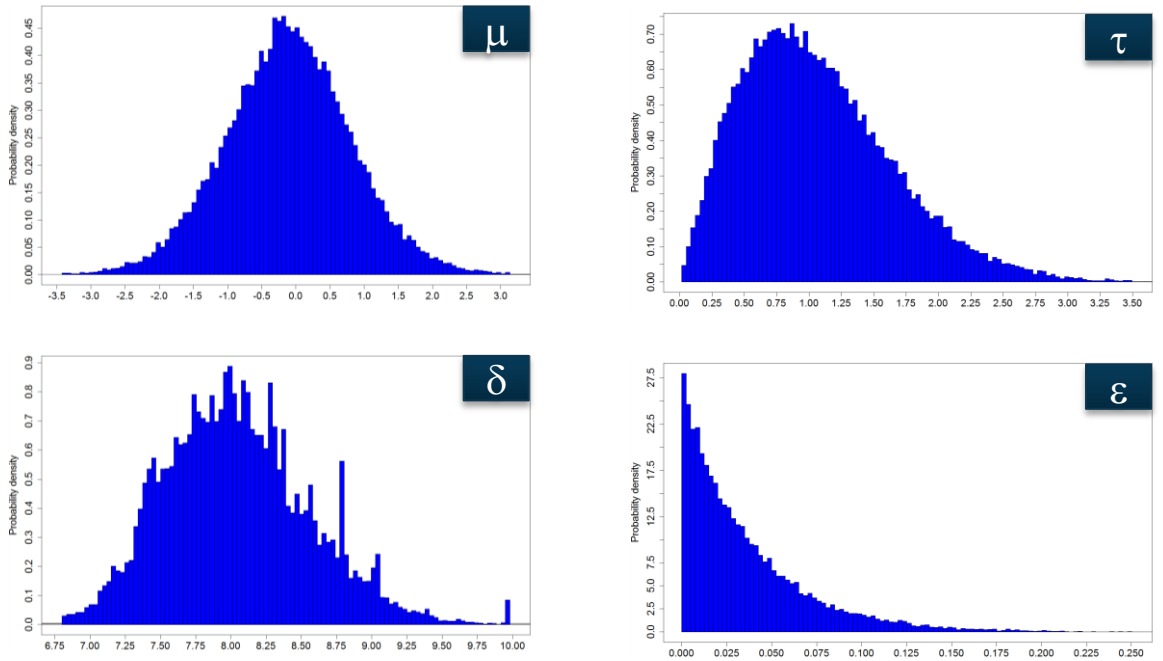
- Weak informative prior distributions for hyper distribution parameters are used
  - Mean δ^2~ Gamma distribution
    - mean = 8^2, CV = 100%
  - Coefficient of variation ε~ Gamma distribution
    - mean = 20%, CV = 100%

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

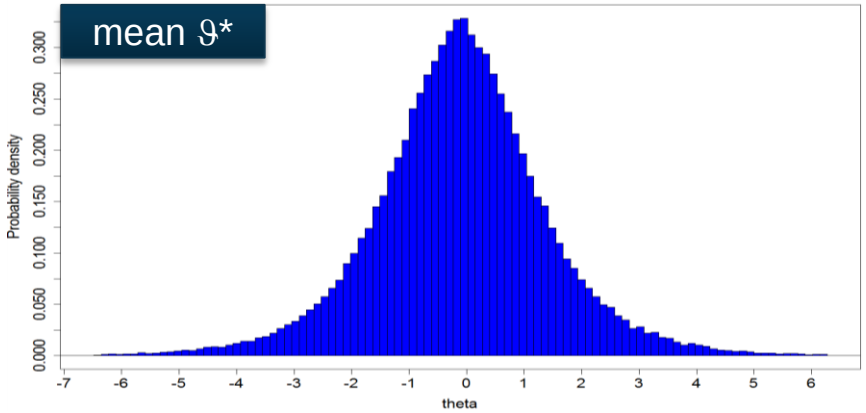
- Posterior distribution for parameter of hyper-distributions are derived by MCMC simulations
- Assessment of posterior probabilities provide insight about “reproducibility” of endpoints
  - Trial means ϑ_j
    - Located around $\mu \approx 0$
    - Small between-trial variability, $\tau \approx 1$
  - Variance of trials σ_j^2
    - Located around $\delta^2 \approx 8^2$
    - Negligible between-trial variability, $\varepsilon \approx 4\%$
  - Remark: Peaks in histogram for δ indicate convergence issues in MCMC simulation caused by limited information from data due to few studies → need for informative priors

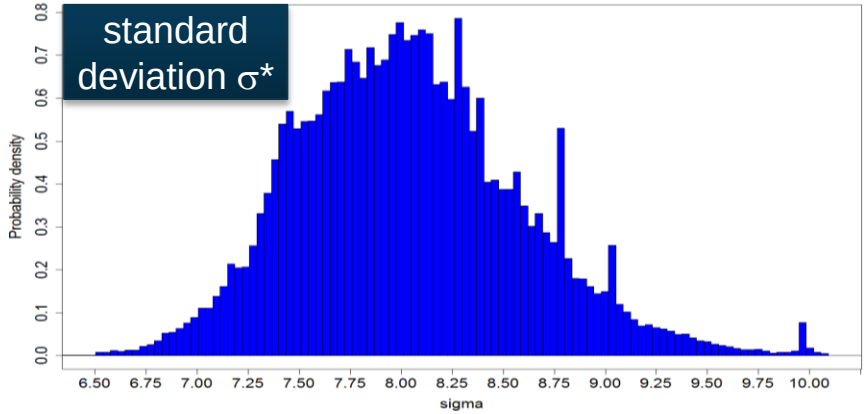


Information about mean and variance of future trials

Results of prediction step of meta-analytical prediction

- Knowledge about mean ϑ^* and variance σ^{*2} of a future trial is reflected by the hyper distributions taking uncertainties in for distribution parameters into account
  - Predicted posterior distribution for ϑ^* and σ^{*2} is a representation for the available information
  - MC samples for ϑ^* and σ^{*2} are derived from hyper distribution using MCMC parameter samples
- Marginal predicted posterior distribution for trial mean ϑ^* and standard deviation σ^*





Parameter	mean	sd	q1	median	q3	90%-range_low	90%-range_up
Mean of new trial ϑ*	-0.11	1.54	-0.98	-0.11	0.76	-2.58	2.37
Standard deviation of new trial σ*	8.04	0.56	7.65	8.01	8.38	7.21	9.02

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 ϑ^* and σ^{*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-χ^2 distribution to MC samples of predicted posterior distribution

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

  - Trial mean for placebo: Amount of information corresponds to ≈28 patients (kappa = 27.8)
    - ≅ 20% of total sample size in historical trials (N=138)
      → information reduction caused by between-trial variability
  - Trial variance for placebo: Amount of information corresponds to ≈107 patients (dof = 106.3)
    - ≅ 80% of total sample size
      → 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)]

Evaluation of treatment potential of drug using Bayesian approach

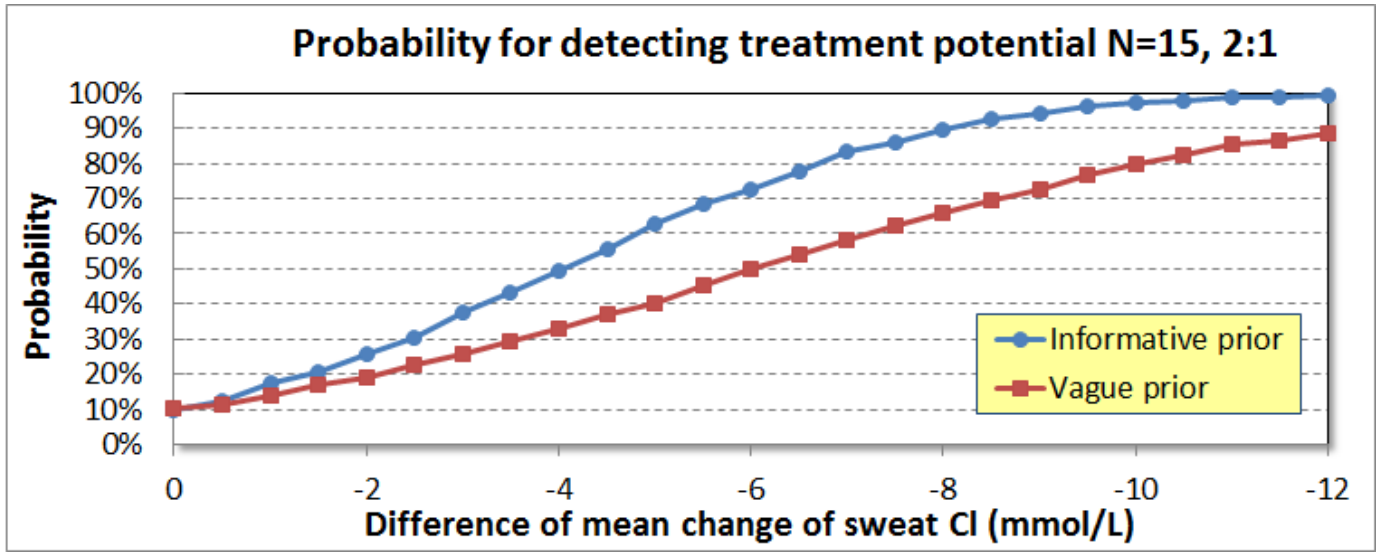
- Assessment of treatment potential by Bayesian analysis: Evaluate difference in mean change of sweat Cl content from baseline between drug and placebo $\vartheta_{drug} - \vartheta_{placbo}$

  - Marginal posterior probability for mean change of sweat Cl from baseline for placebo ϑ_{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 ϑ_{drug}
    - Vague prior information
  - Posterior distribution for mean difference $\vartheta_{drug} - \vartheta_{placbo}$
    - MC sampling from marginal posterior distributions for ϑ_{placbo} and ϑ_{drug}
    - Take differences of MC samples for drug and placebo

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 $\vartheta_{drug} - \vartheta_{placbo}$
  - Coping with uncertainty about ϑ_{placbo} and ${\sigma_{placbo}}^2$: Sample parameters and averaging probability using prior distribution derived by MAP [Walley et.al. (2015)]; for drug higher variability is assumed $\sigma_{drug} = 1.1 \cdot \sigma_{placbo}$

- Sample size determination
  - 2:1 randomization
  - $n_{drug} = 10$ and $n_{placebo} = 5$
  - $\vartheta_{drug} - \vartheta_{placbo}$ = -8 mmol/L
    → ≈ 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