Bayesian Joint Modelling of Benefit and Risk in Drug Development

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EFSPI/PSDM Safety Statistics Meeting
Leiden 2017

Disclosure

- Maria Costa is an employee and shareholder of GSK

- Data presented is based on human research studies funded and sponsored by GSK

Outline

- Motivation
- Bayesian Joint Modelling of Mixed Outcomes
- Simulation Study
- A Case Study in Type 1 Diabetes
- Summary

Motivation

Quantitative Benefit-Risk as a Strategy for Risk Mitigation

- Goal of NDA Safety Review: To determine the significance of the adverse events and their impact on the approvability of the drug
  - "To show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labelling" (Food, Drug, and Cosmetic Act (Section 505))

- How do we know that the Benefit-Risk balance is "positive"? If positive, under which context (which population, etc)?

- How to enhance the transparency, reproducibility and communication of the Benefit-Risk balance of medicines?

- How to assess the impact of uncertainty in Benefit-Risk assessments?

Quantitative Benefit-Risk assessments can support decision makers with these questions...

Motivation

Multivariate Modelling, Bayesian Inference & Quantitative Benefit-Risk

Multivariate Modelling

- Potential for efficacy and safety signals to be linked via exposure to active drug
- Joint modelling of efficacy and safety endpoints enables efficient data driven BR analyses

Bayesian Inference

- Provides direct framework to build relevant and intuitive probability statements in the context of BR that can be used to quantify uncertainty and risk
- Bayesian updating mechanism naturally supports “Learn & Confirm” drug development paradigm – crucial when assessing BR

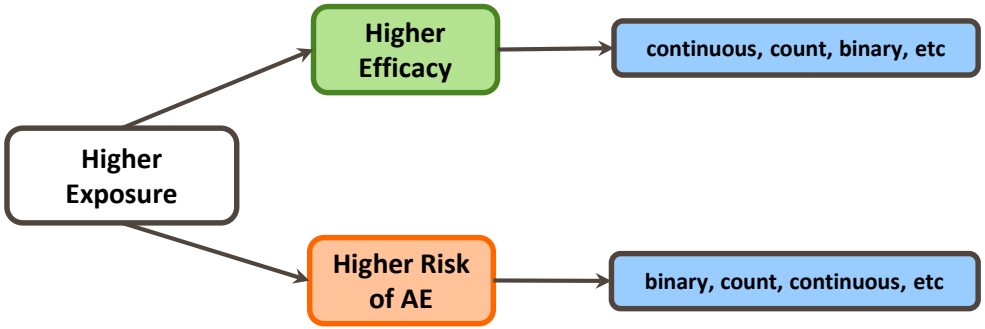
Quantitative Benefit-Risk Assessment

- Can help team gain insight into specific BR questions about key endpoints of interest
- Important to communicate BR to stakeholders in a way that supports decision-making
- Important to quantify uncertainty in BR profile – particularly if aim is to discharge risk

Bayesian Joint Modelling of Mixed Outcomes

Motivation

- Strength of efficacy and safety signals likely to be linked at subject level via exposure to active drug:



- Approach that accounts for observed correlation at subject level between efficacy and safety signals is desirable – more efficient and realistic assessment

- Often efficacy and safety endpoints modelled using different distributions

- Should focus on key endpoints – primary efficacy and key safety finding(s) identified by safety team?

Bayesian Joint Modelling of Mixed Outcomes

Approaches to Linking Mixed Outcomes: GLMM

- Option 1: Use generalised linear mixed models (GLMM)
  - Assume *J* different observations on same subject (each following some distribution)
  - For subject *i* with mean response $\boldsymbol{\mu}_i$, $\mathbf{g}(\boldsymbol{\mu}_i) = \mathbf{X}_i\,\mathbf{b} + \mathbf{Z}_i\,\mathbf{u}_i$, $\mathbf{u}_i \sim N(\mathbf{0}, \mathbf{G}(\mathbf{X}_i))$

- Random effect $\mathbf{u}_i$ is shared across all *J* observations for subject *i* thus modelling potential correlation

- When $g_j(.)$ is not identity function the fixed effects **b** are conditional on random effects $\mathbf{u}_i$
  - Monte Carlo integration can be used to obtain marginal population effects – important when making inferences at the population level

- Constraints may be necessary to ensure identifiability for certain distributions

Bayesian Joint Modelling of Mixed Outcomes

Approaches to Linking Mixed Outcomes: Copulas

- Option 2: Use copulas
  - Copulas - distribution functions used to form new multivariate distributions given set of marginal distributions of interest (which are preserved)
  - E.g., $H(y_1,y_2) = C(F(y_1), G(y_2) \mid \theta)$, with F(.) and G(.) the CDF of the marginal distributions of y_1 and y_2
  - $C(. , . \mid \theta)$ is the copula function (e.g., Gaussian CDF)
  - θ measures association between y_1 and y_2
- Directly obtain marginal population effects for parameters of interest
- Choice of copula C(.) may impact results through different dependency assumptions
- Difficult to interpret beyond 3 dimensions (non-unique model definition)

Simulation Study

Set Up

- Two treatment arms: new drug (treatment 2) vs comparator (treatment 1)

- Endpoints and parameters:

BR Endpoints	Endpoint Type	Parameter Values	Correlation between endpoints
Primary efficacy endpoint	Continuous, N (μ, σ^2)	$\mu_1 = -150$ $\mu_2 = -50$	$\rho_1 = 0.1$ $\rho_2 = 0.6$
Key AE endpoint - AESI	Binary, Bernoulli (p)	$p_1 = 0.1$ $p_2 = 0.4$	

- Comparisons of interest as follows: $\mu_2 - \mu_1$ and $p_2 - p_1$

- Non-informative priors assumed for all model parameters

- 100 simulated datasets generated

- Bayesian inference performed using MCMC

Joint Modelling, Benefit-Risk and Decision-Making

Use of Clinical Thresholds for Go/No-go Decisions

- Aim is to assess the level of evidence (i.e., posterior probability) associated with BR profiles of interest and to understand trade-off between efficacy & safety

- Different BR profiles can be set up using range of clinically meaningful efficacy and safety thresholds:
  - Δ_e represents *minimum* improvements in efficacy with the new drug relative to comparator
  - Δ_s represents *maximum* increases in risk with the new drug relative to comparator

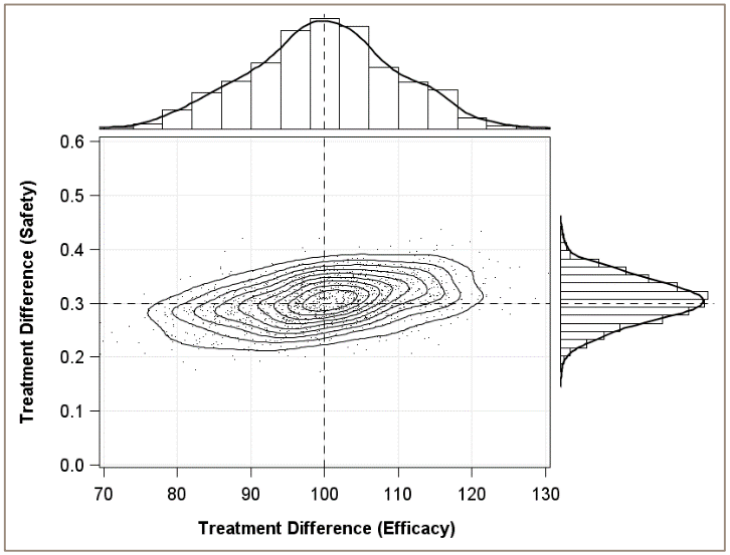
- Δ_e and Δ_s are independent and set by the project team - can be viewed as clinical Go/No-go boundaries

- Trade-off between efficacy and safety represented by following probability statement:
  - Prob ($\mu_2 - \mu_1 > \Delta_e$ and $p_2 - p_1 < \Delta_s$ | Data, prior)

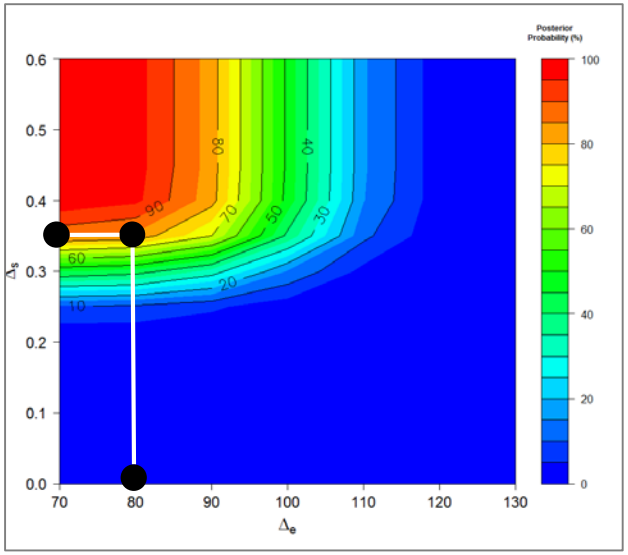
Simulation Study

Results for a typical simulated dataset

Posterior Distribution for $\mu_2 - \mu_1$ and $p_2 - p_1$
(Joint and Marginal)



BR Contour
Prob ($\mu_2 - \mu_1 > \Delta_e$ and $p_2 - p_1 < \Delta_s$ | Data)



Elliptical shape of joint posterior reflects correlation between μ_2 and p_2

Example: 84% posterior probability that difference active vs comparator in risk of an AE is *at most* 0.35 (Δ_s =0.35) and in efficacy *at least* 80 units (Δ_e =80)

Simulation Study

Impact of correlation

- To assess impact of correlation on Prob ($\mu_2 - \mu_1 > \Delta_e$ and $p_2 - p_1 < \Delta_s$ | Data, prior) simulations were run for different values of ρ_2
- We fix $\Delta_e = 100$ and $\Delta_s = 0.3$

ρ_2	GLMM Model	Gaussian Copula Model
0	24.95%	26.06%
0.2	23.06%	23.93%
0.4	20.72%	21.68%
0.6	18.42%	19.77%
0.75	17.89%	19.57%

- Increasing values of ρ_2 leads to lower posterior probability values for the BR profile defined by $\Delta_e = 100$ and $\Delta_s = 0.3$
  - Accounting for correlation results in more realistic BR assessments

Simulation Study: Dose-Response

Motivation & Set up

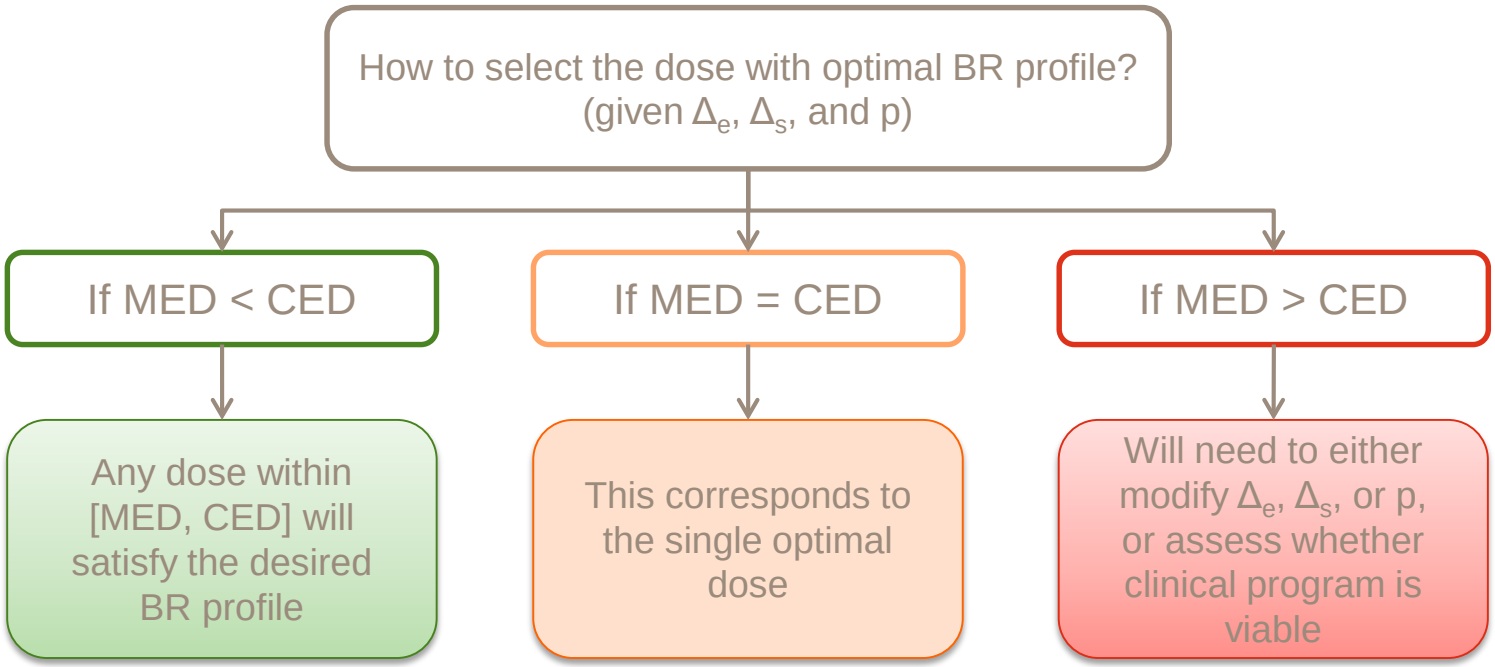
- Choosing dose with optimal BR profile is major hurdle in drug development
  - Too high dose may result in an unacceptable risk profile
  - Too low dose may decrease the chances of achieving the desired level of efficacy in a phase 3 trial
  - 16% of NME applications fail due to uncertainty related to dose selection (Sacks et al, 2014)

- Previous simulation study expanded to dose-response setting:
  - Same 2 endpoints for efficacy and safety
  - 5 active doses (from d2 = 0.3 to d6 = 6 units) and comparator (d1 = 0)
  - Correlation ρ_d between efficacy and safety at subject-level increases with dose such that $\rho_{d1} = 0$, and $\rho_{d1} \sim 0.6$
  - Emax model (3 parameter) used to generate data for efficacy
    - $E_0 = -150$, Emax = 150, $ED_{50} = 0.5$
  - Linear regression model on probit scale used to generate safety data
    - Prob (AE in dose d) = $p_d = \Phi(-1.28 + 0.26 \times d)$
  - Bayesian inference via MCMC

Simulation Study: Dose-Response

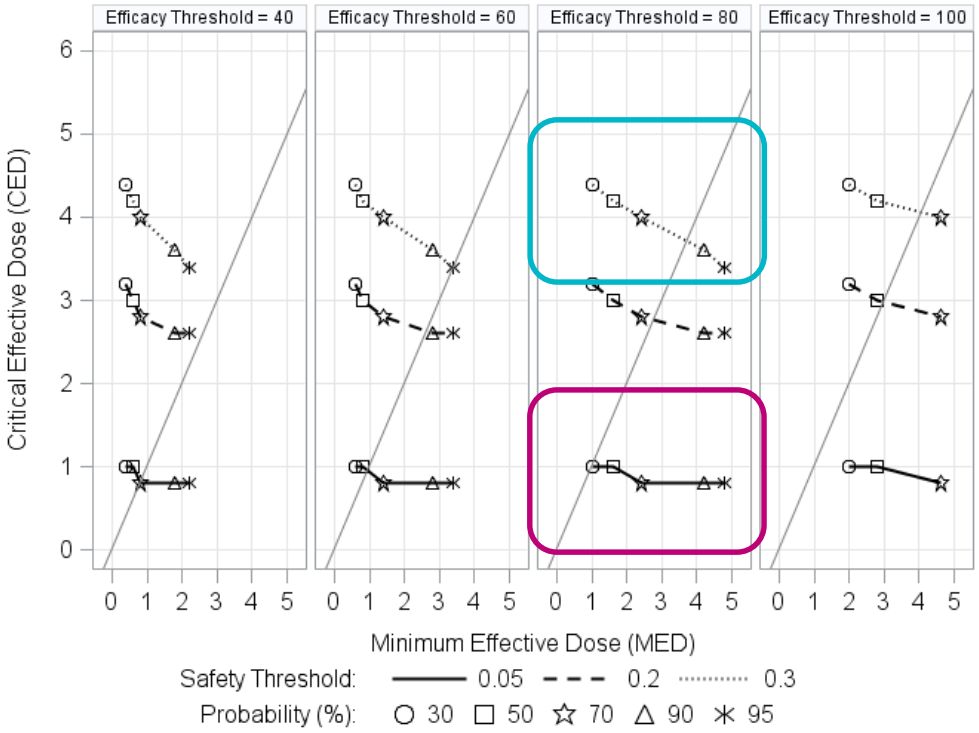
Minimum Effective Dose vs Critical Effective Dose

- We define the following quantities:
  - Minimum Effective Dose (MED) = the *smallest dose* d that produces an improvement of size Δ_e or larger compared to placebo with posterior probability > p%
  - Critical Effective Dose (CED) = the *largest dose* d that produces an increase in toxicity no greater than Δ_s compared to placebo with posterior probability > p%



Simulation Study: Dose-Response

Choosing the dose with optimal BR profile – results for a typical simulated dataset



If Δ_e=80 Δ_s= 0.3 and p = 70% then MED = 2.5 and CED = 4.0

Any dose in the range [2.5, 4.0] can be considered "optimal"

If Δ_s= 0.3 is considered too high increase in risk of AE and team sets Δ_s= 0.05, then MED ≤ CED *only* if p = 30%

This means there will be considerably *more uncertainty* with this more stringent BR profile

- In general, as Δ_e increases and Δ_s decreases, MED ≤ CED only by *lowering* the posterior probability p% - so the team will need to accept *more uncertainty* going to phase 3
- If existing correlation is not accounted for, data may erroneously suggest that MED ≤ CED with high probability p, when in fact this is not the case (simulation results not shown)

Case Study

Treatment X for New Onset Type 1 Diabetes

- Treatment X was a monoclonal antibody targeting CD3 receptors that was being developed as a potential treatment for new-onset (<3 months) Type 1 diabetes mellitus
  - Significant associated morbidity and mortality (neuropathy, ischemic heart disease, among others)

- A clinical trial (PoC) was designed to assess efficacy and safety of X over an 18 month period in patients with new-onset type 1 diabetes

  - *Primary efficacy* endpoint was the decline of C-peptide levels at 6 months (measurement of beta-cell function) – treated as continuous outcome

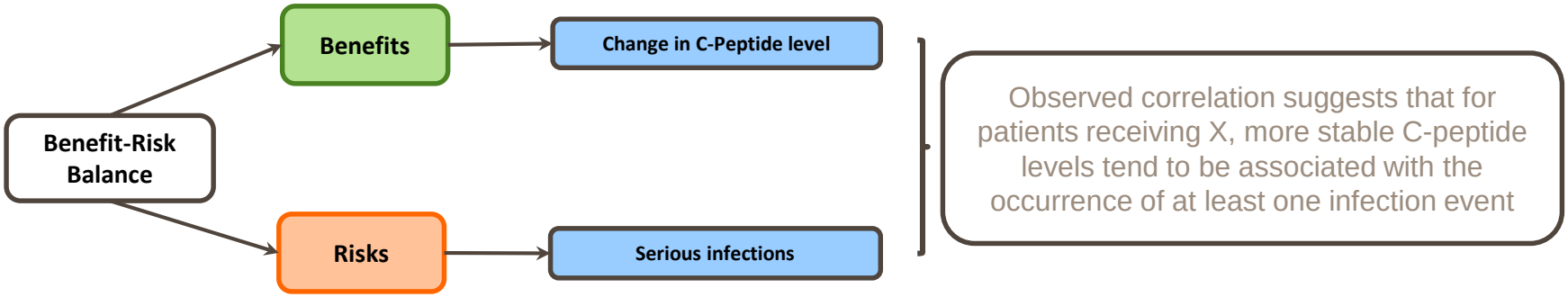
  - *Key safety* events of interest included infection and Cytokine Release Syndrome (CRS) – treated as binary outcomes

- A total of 73 subjects had C-peptide levels recorded at 6 months (39 received X, 34 placebo)

Case Study – Treatment X for New Onset Type 1 Diabetes

1 Efficacy & 1 Safety Endpoint – Bayesian Inference of Multivariate Model

- For safety, focus initially on risk of infection, modelled as binary outcome



- GLMM and Bayesian inference used to obtain parameter estimates of interest

	Parameter	Posterior Median	95% Credible Interval
Efficacy	CFB C-Peptide X - Placebo	0.63	(0.27, 0.99)
Safety	Prob (Infection) X - Placebo	0.24	(0.07, 0.42)

CFB = Change from baseline at 6 months

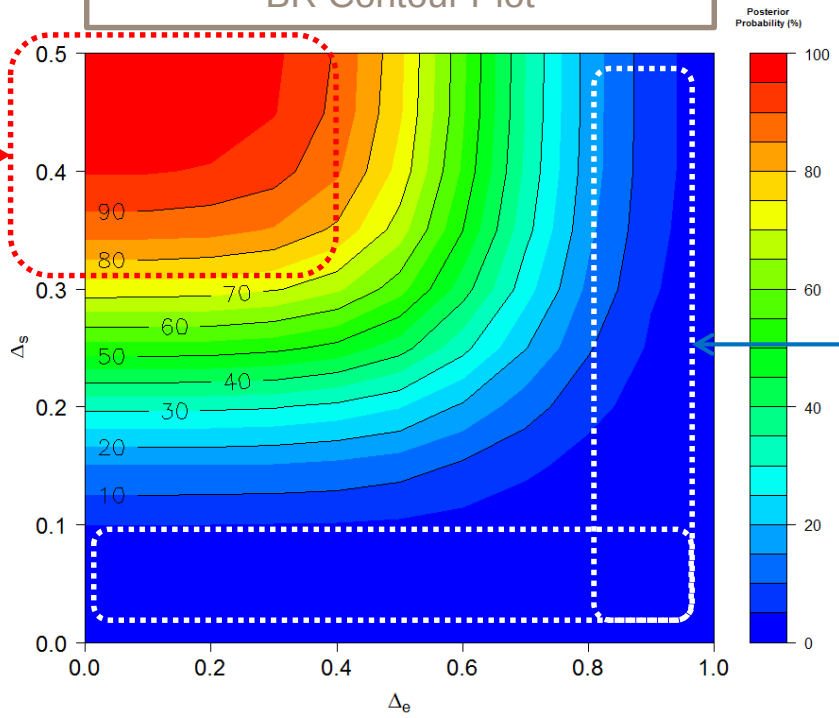
Patients receiving X have more stable levels of C-Peptide

Patients receiving X have higher risk of serious infection

Case Study – Treatment X for New Onset Type 1 Diabetes

1 Efficacy & 1 Safety Endpoint – Benefit-Risk Assessment

BR Contour Plot



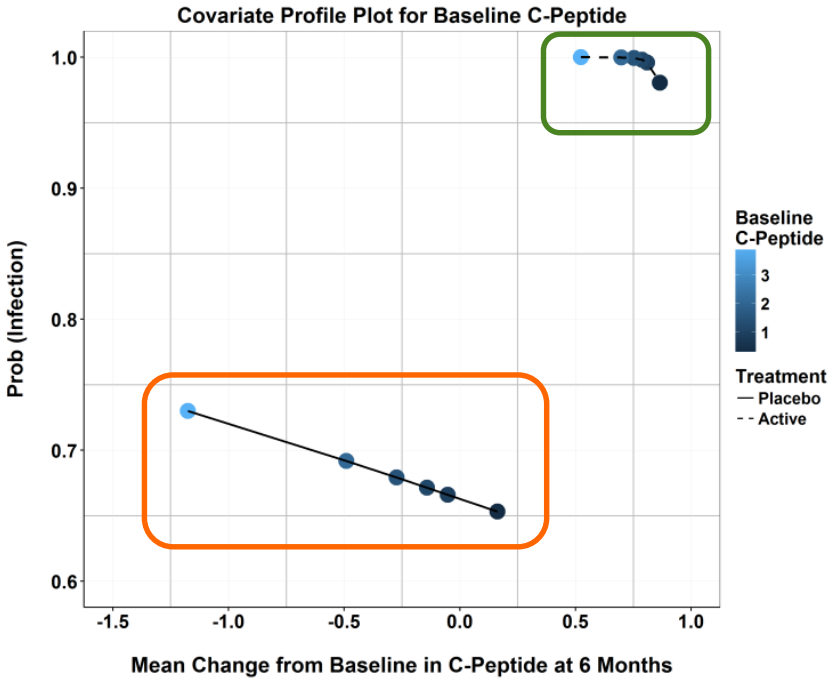
BR profiles with "high" posterior probability correspond to scenarios with a substantial increase in risk of infection

The data does not support BR profiles for which $\Delta_e > 0.8$ and $\Delta_s < 0.1$

Case Study – Treatment X for New Onset Type 1 Diabetes

1 Efficacy & 1 Safety Endpoint – Benefit-Risk Assessment

- "Given a patient's baseline C-peptide level, what is his/her likely BR profile with drug X compared to placebo?"



- The BR profile of X is robust to a patient's baseline C-Peptide level
- In placebo group, subjects with lower baseline C-Peptide levels have a more favourable BR profile

Case Study – Treatment X for New Onset Type 1 Diabetes

Benefit-Risk Assessment

- Does the BR assessment of drug X PoC study support further development?
  - BR analysis presented here suggests that high efficacy levels with low increases in risk are unlikely (< 10% probability)

- GSK run phase 3 program with lower dose of drug X – studies failed to achieve their primary endpoints, although risk profile improved
  - This is coherent with BR analysis conducted on PoC data – could the expensive and time consuming phase 3 program been avoided by looking quantitatively at chances of positive benefit-risk profile?

Summary

- Bayesian inference based on joint models of mixed outcomes is a powerful tool for Benefit-Risk assessment
  - Explore dependency between benefit and risk thresholds for decision-making
  - Joint (and conditional) probabilistic statements that help quantify risk in development program
  - Predicting responses for a new subject conditional on what was learned from study data

- Benefit-Risk profile is a combination of two different quantities:
  - Set of thresholds for efficacy and safety – define Benefit-Risk profile of interest (qualitative)
  - Level of evidence (posterior probability) to support Benefit-Risk profile – quantify risk (quantitative)

- Methods have been successfully applied to 3-dim setting as well (mixture of continuous, binary and count endpoints)
  - Beyond 3 dimensions it is difficult to interpret and visualise quantitative BR assessments

References

- Costa & Drury (2017), Bayesian Joint Modelling of Benefit and Risk in Drug Development (submitted)

- Costa et al (2017), The Case for a Bayesian Approach to Benefit-Risk Assessment, Therapeutic Innovation & Regulatory Science, doi: 10.1177/2168479017698190

- Saks et al (2014), Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000-2012. *JAMA*, **311**:378-384

Acknowledgements

- Thomas Drury
- Nigel Dallow
- Graeme Archer
- Nicky Best
- James Roger

Thank you