Bayesian Joint Modelling of Benefit and Risk in Drug Development

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Decision Making in Drug Development

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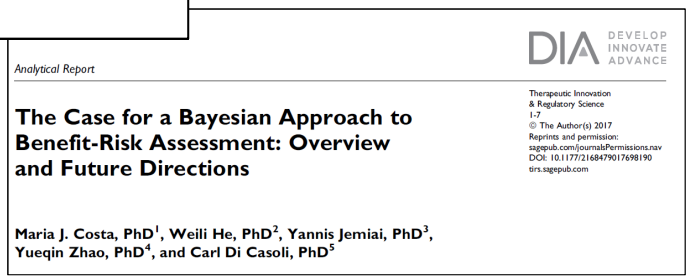
References

Joint work with **Tom Drury (GSK)**



2

Outline

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

3

Motivation

- How to **assess** whether an **intervention is efficacious**?
  - Typically this means that clinical endpoints of interest reach statistical significance
  - *"...For comparison, at week 24, 56.1% of patients in treatment group had gained ≥15 letters from baseline compared with 12.3% of patients in the sham group* ***(P < .001)****."*

4

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- How to **assess** if the **benefit-risk profile is 'positive'** for the patient population studied?
  - Is there a **trade-off** between efficacy and safety? If so, for **which endpoints**?
  - Are there **subgroups** of patients for whom the new intervention has a **better benefit-risk profile**?

5

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  - Are there **subgroups** of patients for whom the new intervention has a **better benefit-risk profile**?

- **Quantitative benefit-risk assessment** can help **address** some of these **questions**

6

Motivation

Quantitative Benefit-Risk (BR) Assessment

- Can help teams 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**

7

Motivation

Multivariate Modelling

- Potential for **efficacy** and **safety** signals to be **linked** via exposure to active drug
- **Joint modelling of key efficacy and safety** endpoints enables efficient data driven BR analyses & can account for mixture of endpoints (continuous, binary, count, etc)

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Bayesian Inference

- Framework to build **relevant** and **intuitive** probability statements that can **quantify uncertainty** and risk
- Bayesian updating mechanism naturally supports "**Learn & Confirm**" drug development paradigm – crucial when assessing BR

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9

Bayesian Joint Modelling of Mixed Outcomes – GLMM

- **Option 1**: Use generalized linear mixed models (GLMM)
  - Assume ***J* different outcomes** on same subject (each following some distribution)
  - For subject *i* with mean response $\boldsymbol{\mu}_i$, $g(\boldsymbol{\mu}_i) = \boldsymbol{X}_i\,\boldsymbol{b} + Z_i\,u_i$, $u_i \sim N(0, f(\boldsymbol{X}_i))$

10

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- Random effect u_i is **shared** across all *J* observations for subject *i* thus **modelling potential correlation between efficacy and safety outcomes**

11

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- Random effect u_i is **shared** across all *J* observations for subject *i* thus **modelling potential correlation between efficacy and safety outcomes**
- If $g(\boldsymbol{\mu}_i) \neq$ identity, fixed effects $\boldsymbol{b}$ are **conditional** on random effects 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

12

Bayesian Joint Modelling of Mixed Outcomes – Copulas

- **Option 2**: Use copulas
  - Copulas are distribution functions used to **build new multivariate distributions** given set of marginal distributions of interest (which are preserved)
  - E.g., $H(y_1, y_2) = C(F(y_1), G(y_2) \mid \boldsymbol{\theta})$, where:
    - $F(.)$ and $G(.)$ are the CDFs of the marginal distributions of $y_1$and y_2, respectively
    - $C(.,. \mid \boldsymbol{\theta})$ is the copula function (e.g., Gaussian CDF)
    - $\boldsymbol{\theta}$ measures association between $y_1$and y_2

13

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- Possible to directly obtain **marginal population effects** for parameters of interest
- **Choice of copula** $C(.,. \mid \boldsymbol{\theta})$ may impact results through **different dependency assumptions**
- **Challenging** to interpret **beyond 3 dimensions** (non-unique model definition)

14

Joint Modelling, Benefit-Risk and Decision-Making

- Aim of BR assessment is two fold:
  - **Assess evidence** associated with **BR profiles of interest** (e.g., quantified through a posterior probability)
  - Understand **trade-off between efficacy & safety**

15

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- Define different **BR profiles** using **clinically meaningful** efficacy and safety **thresholds**:
  - $\boldsymbol{\Delta_e}$ represents **minimum improvements in efficacy** with the new drug relative to comparator
  - $\boldsymbol{\Delta_s}$ represents **maximum increases in risk** with the new drug relative to comparator

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

16

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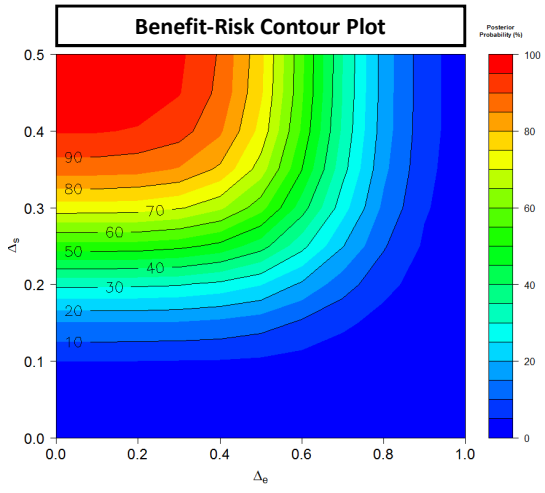
- Δ_e and Δ_s are **independent** and should be set by the project team - can be viewed as **clinical Go/No-go boundaries**
- **Trade-off** between efficacy and safety **represented by the joint probability statement**:

$$\text{Prob}\,(\mu_2 - \mu_1 > \Delta_e \text{ and } p_2 - p_1 < \Delta_s \mid \text{data, prior})$$

17

Joint Modelling, Benefit-Risk and Decision-Making



18

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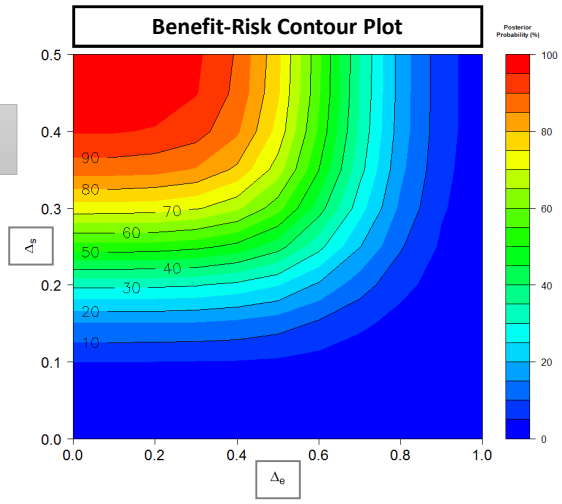
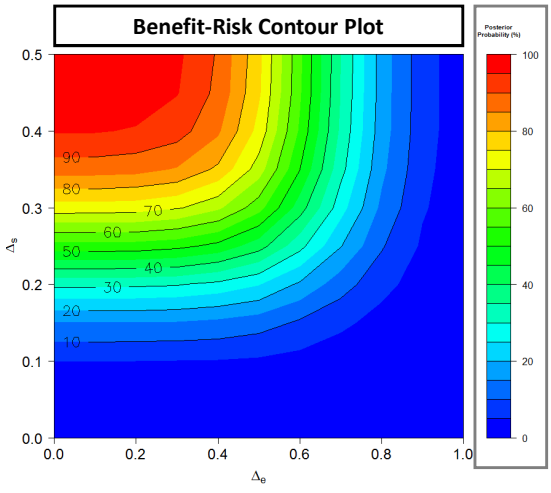


Δ_s = Theoretical treatment effect in safety endpoint, active - control

Δ_e = Theoretical treatment effect in efficacy endpoint, active - control

19

Joint Modelling, Benefit-Risk and Decision-Making

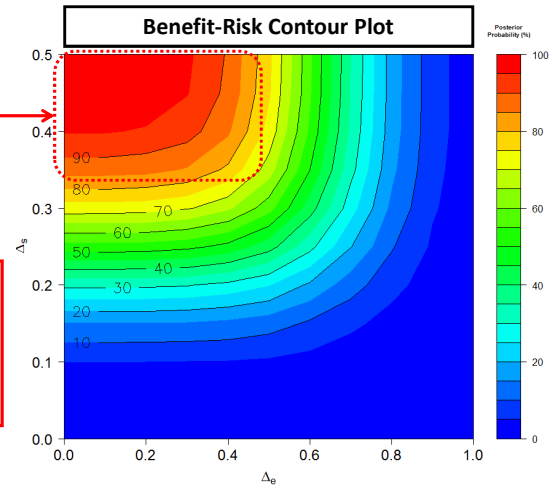


Trade-off between efficacy and safety **represented by the joint posterior probability statement**:

Prob ($\mu_2 - \mu_1 > \Delta_e$ and $p_2 - p_1 < \Delta_s$ | data, prior)

20

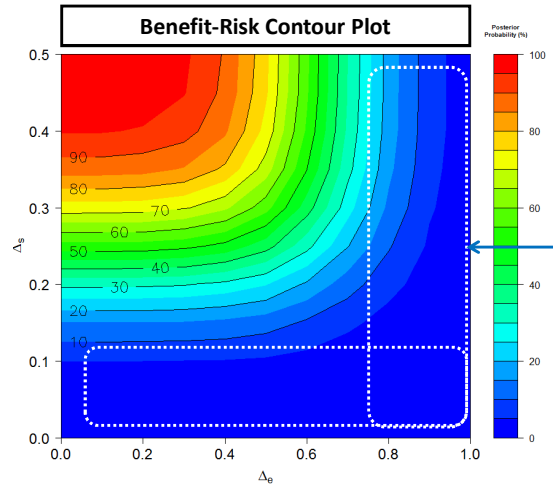
Joint Modelling, Benefit-Risk and Decision-Making



High (posterior) probability to increases in **risk (p_2 - p_1) > 0.4** with **active vs control,** for range of small to moderate efficacy effects (Δ_e < 0.5)

21

Joint Modelling, Benefit-Risk and Decision-Making



Low probability for scenarios with **increases in risk < Δ_s = 0.1 AND improvements in efficacy > Δ_e = 0.8** with **active vs control**

22

Simulation Study

- **Objective** of simulation study was 2-fold:
  - To **understand inference properties** with GLMM and Copulas
    - Bias, MSE, etc...
    - Impact of the characteristics of the marginal distributions on inference outcome
  - To **develop graphical approaches for decision-making**
    - For study design
    - For study data analysis
- All SAS and R code available!

23

Simulation Study – Set Up

- **Two treatment arms**: new active drug (treatment 2) vs control (treatment 1)
- Endpoints and parameters:

BR Endpoints	Endpoint Type	Parameter Values	Correlation between endpoints
Primary efficacy endpoint	Continuous, N (μ, σ^2)	μ_1 = -150, μ_2 = -50	ρ_1 = 0.1
Key AE endpoint (e.g AESI)	Binary, Bernoulli (p)	p_1 = 0.1, p_2 = 0.4	ρ_2 = 0.6

24

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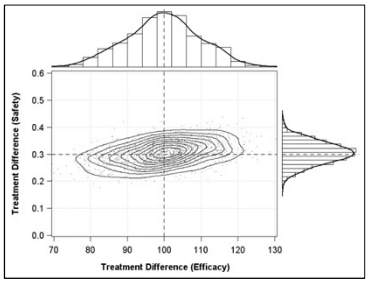
- **Joint distribution of interest**: $\mu_2 - \mu_1$ and $p_2 - p_1$
- 1000 simulated datasets generated, **n = 100** / **arm**
- **Non-informative priors** assumed for all model parameters
- **Bayesian inference** performed using MCMC

25

Simulation Study – Example Dataset

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



Elliptical shape of joint posterior reflects **correlation** between μ_2 and p_2

26

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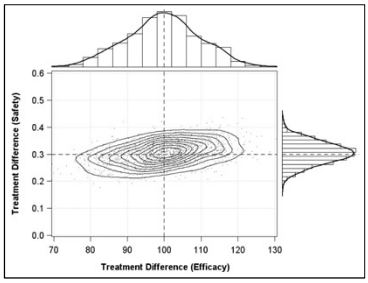
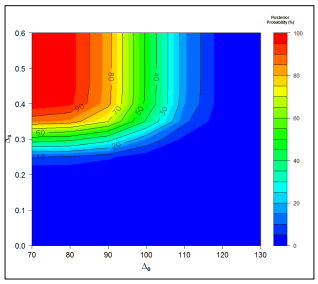


Benefit-Risk Contour
Prob ($\mu_2 - \mu_1 > \Delta_e$ and $p_2 - p_1 < \Delta_s$|data, prior)



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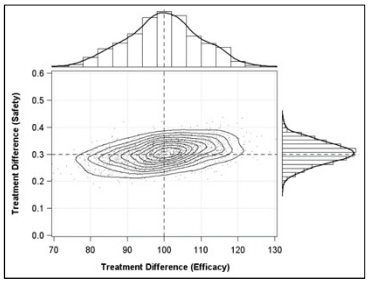

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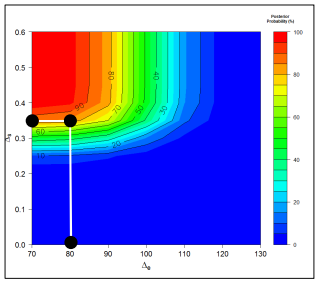

Elliptical shape of joint posterior reflects **correlation** between μ_2 and p_2

Example: 84% posterior probability that difference active vs control in risk of an AE is *at most* 0.35 ($\Delta_s = 0.35$) AND in efficacy *at least* 80 units ($\Delta_e = 80$)

28

Simulation Study – Results

Model	Parameter	Mean	SD	2.5%	50%	97.5%	Bias	MSE
GLMM	μ_1	−150.27	10.10	−170.04	−150.27	−130.49	0.27	105.78
	μ_2	−50.14	10.11	−69.93	−50.14	−30.35	0.14	109.52
	p_1	0.10	0.03	0.05	0.10	0.16	<0.01	<0.01
	p_2	0.40	0.05	0.31	0.40	0.49	<0.01	<0.01
	ρ_1	0.08	0.07	<0.01	0.07	0.22	0.02	<0.01
	ρ_2	0.59	0.05	0.49	0.60	0.68	0.01	<0.01
Gaussian copula model	μ_1	−150.27	10.13	−170.10	−150.28	−130.44	0.27	105.71
	μ_2	−50.13	10.04	−69.77	−50.13	−30.50	0.13	109.37
	p_1	0.10	0.03	0.05	0.10	0.16	<0.01	<0.01
	p_2	0.40	0.05	0.31	0.40	0.49	<0.01	<0.01
	ρ_1	0.09	0.09	−0.09	0.09	0.27	0.01	0.01
	ρ_2	0.58	0.05	0.47	0.58	0.68	0.02	<0.01
	θ_1	0.15	0.16	−0.16	0.16	0.46	0.02	0.02
	θ_2	0.74	0.07	0.60	0.74	0.86	0.03	0.01

29

Simulation Study – Results

Posterior median estimates close to true parameter values with **minimal bias**

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	θ_2	0.74	0.07	0.60	0.74	0.86	0.03	0.01

30

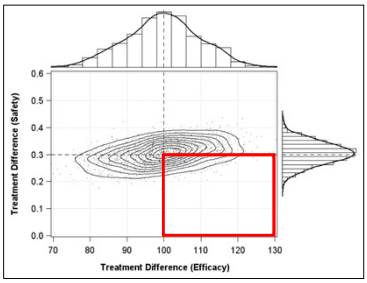
Simulation Study – Correlation

- What is the **impact of correlation ρ_2** on Prob ($\mu_2 - \mu_1 > \Delta_e$ and $p_2 - p_1 < \Delta_s$ | data, prior) ?

31

Simulation Study – Correlation

- What is the **impact of correlation ρ_2** on Prob ($\mu_2 - \mu_1 > \Delta_e$ and $p_2 - p_1 < \Delta_s$ | data, prior) ?
- Given Δ_e = 100 and Δ_s = 0.3, **simulations were repeated** for **different values of ρ_2**



32

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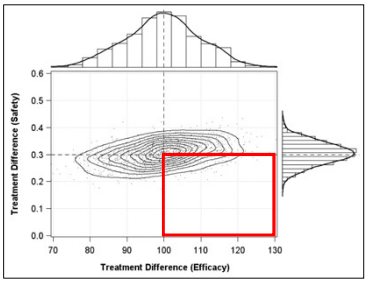

ρ_2	GLMM Model	Gaussian Copula Model
0	25.19%	25.48%
0.2	23.28%	23.26%
0.4	21.06%	21.29%
0.6	19.02%	19.48%
0.75	17.00%	17.60%

33

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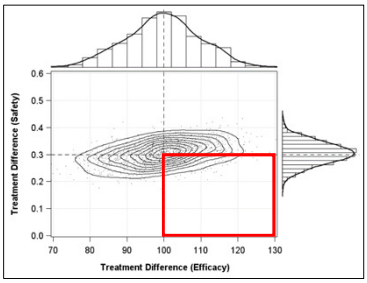

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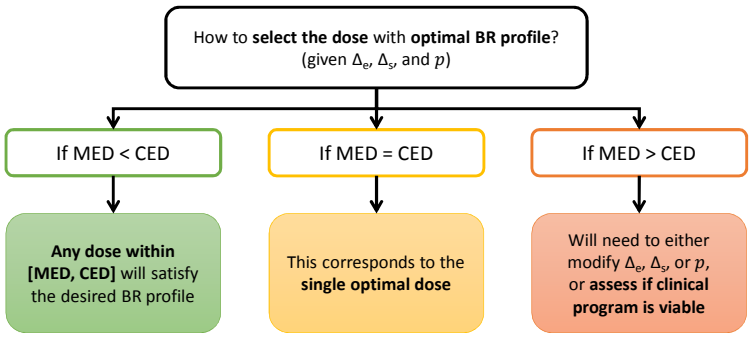
0.6	19.02%	19.48%
0.75	17.00%	17.60%

Increasing value of ρ_2 leads to **lower posterior probability** for the **BR profile** defined by $\Delta_e = 100$ and $\Delta_s = 0.3$

34

Simulation Study – Dose-Response

- Define the following quantities:
  - **Minimum Effective Dose** (MED) = the **smallest dose** d that produces an **improvement in efficacy of at least** Δ_e 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%



35

Simulation Study – Dose-Response

- Assume ρ_2 **increases with dose** of active drug
- **Emax model** for efficacy endpoint, **probit linear regression** for safety endpoint of interest

36

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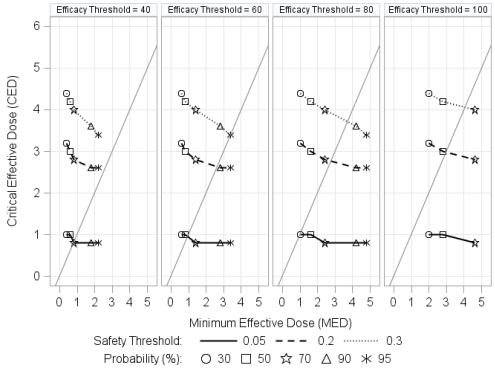

37

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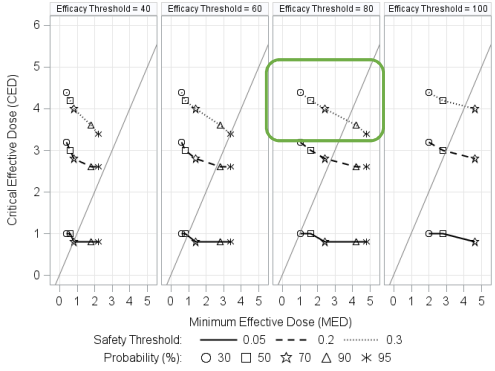

If $\Delta_e = 80$ $\Delta_s = 0.3$ and $p = 70\%$ then MED = 2.5 and CED = 4.0

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

38

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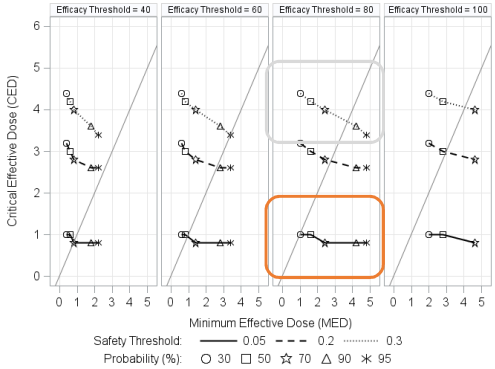

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Any dose in the range [2.5, 4.0] can be considered "**optimal**"

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

There is **more uncertainty** with this more stringent BR profile

39

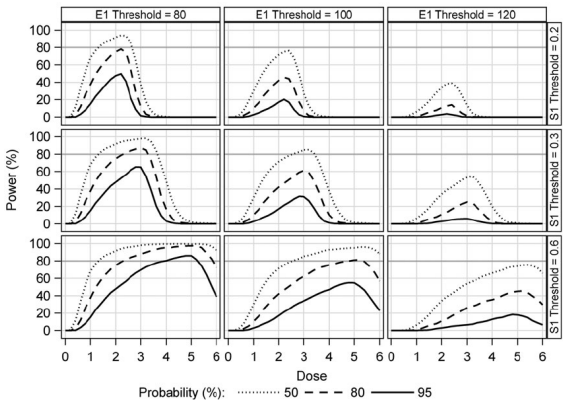
Simulation Study – Dose-Response

- How to assess the **Power** of a chosen study design to **deliver a dose with the BR profile of interest?**
- Define **Success =** Prob ($\mu_2 - \mu_1 > \Delta_e$ and $p_2 - p_1 < \Delta_s$ | data, prior) ≥ p

40

Simulation Study – Dose-Response

- How to assess the **Power** of a chosen study design to **deliver a dose with the BR profile of interest?**
- Define **Success =** Prob (μ_2 - μ_1 > Δ_e and p_2 - p_1 < Δ_s | data, prior) ≥ p



41

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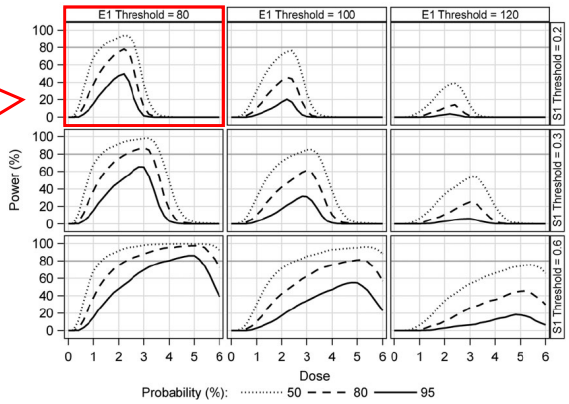
Given design assumptions, there is **80% power** that at least **one dose satisfies study success** if success is defined using Δ_e = 80, Δ_s= 0.2, and p = 80%



42

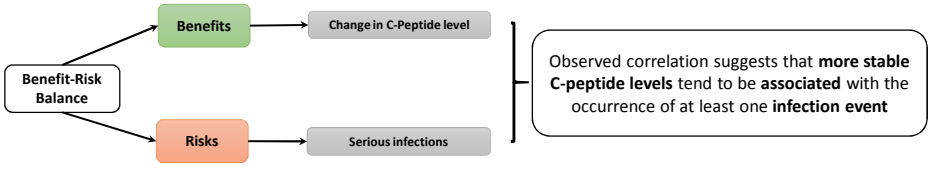
Case Study in Type 1 Diabetes

- The **monoclonal antibody X** targeting CD3 receptors was being developed as a potential **treatment for new-onset** (<3 months) **Type 1 diabetes mellitus**
- A **PoC** was designed to **assess the efficacy and safety of X** over an 18 month period in patients with new-onset Type 1 DM
  - **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)

43

Case Study in Type 1 Diabetes

- For safety, focus initially on **risk of infection**



- **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

44

Case Study in Type 1 Diabetes

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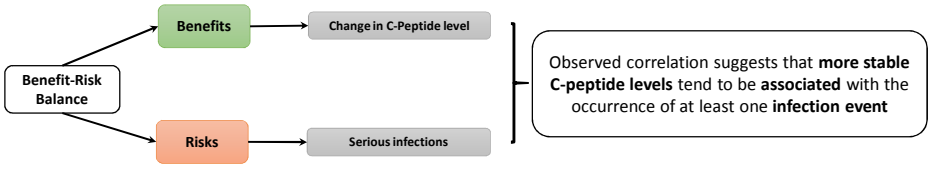

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Patients receiving X have more stable levels of C-Peptide

45

Case Study in Type 1 Diabetes

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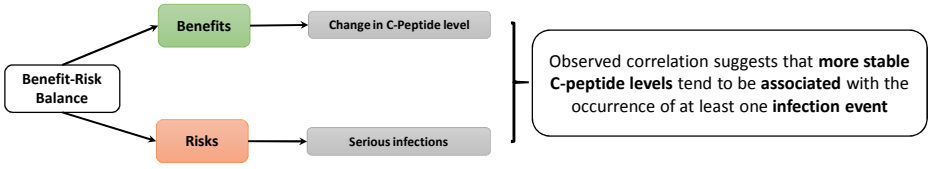

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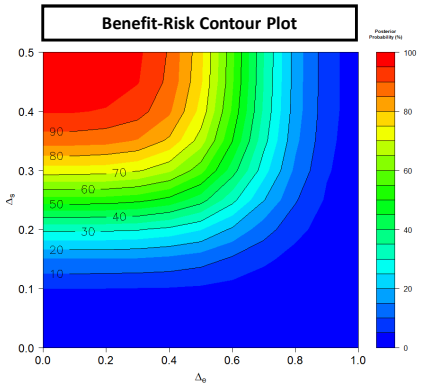
CFB = Change from baseline at 6 months

Patients receiving X have more stable levels of C-Peptide

Patients receiving X have higher risk of serious infection

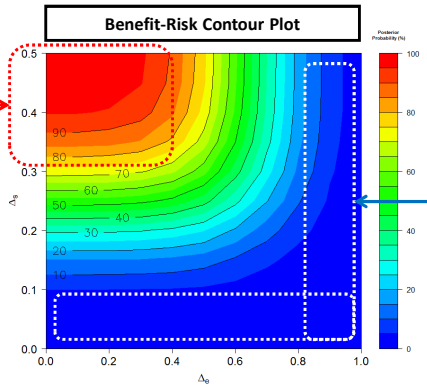
46

Case Study in Type 1 Diabetes



47

Case Study in Type 1 Diabetes



High (posterior) probability to increases in **risk of infection > 40% AND differences in C-peptide levels < 0.4** nmol/L with **drug X vs placebo,**

The data **does not support** difference in **C-peptide levels > 0.8 nmol/L** in drug X vs placebo AND difference in **risk infection with drug X vs placebo < 0.1**

48

Case Study in Type 1 Diabetes

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

49

Case Study in Type 1 Diabetes

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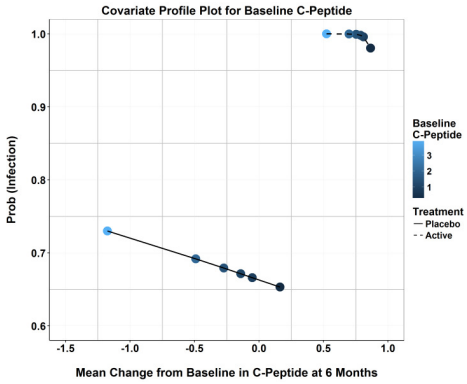

50

Case Study in Type 1 Diabetes

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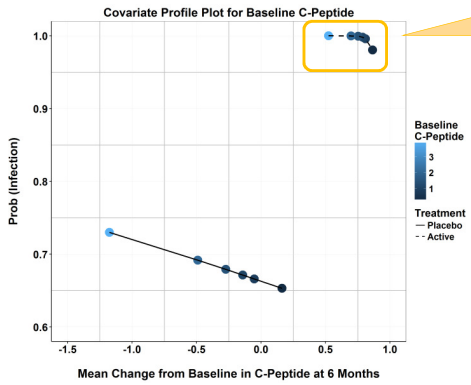


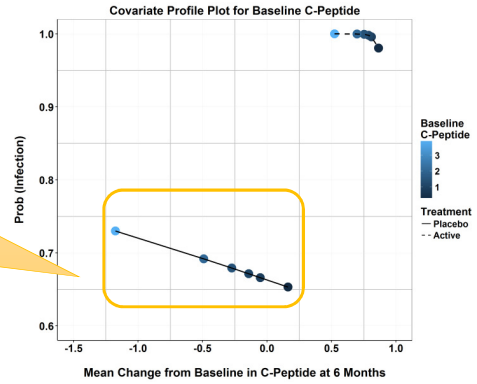
The BR profile of drug X is **robust** to a patient's baseline C-Peptide level

51

Case Study in Type 1 Diabetes

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

In the placebo group, subjects with **lower baseline C-Peptide** levels have a **more favourable BR profile**



52

Case Study in Type 1 Diabetes

- Does the **joint modelling assessment** of this PoC for drug X **support further development**?
  - The analysis suggests that simultaneous **high efficacy levels** AND **small increases in risk** are **unlikely** (< 10% probability)

53

Case Study in Type 1 Diabetes

- Does the **joint modelling assessment** of this PoC for drug X **support further development**?
  - The analysis suggests that simultaneous **high efficacy levels** AND **small increases in risk** are **unlikely** (< 10% probability)
- A **phase 3 program** was run with a **lower dose** of drug X – **both studies failed** to achieve their primary endpoint, although **risk profile improved**
  - This is **coherent** with outcome of **joint modelling analysis** conducted on POC data

54

Bayesian Joint Modelling of Benefit and Risk in Drug Development – Summary

- **Bayesian inference** coupled with **joint models of mixed outcomes** is a **powerful tool for Benefit-Risk** assessment
  - Can explore **dependency** between **benefit** and **risk** using clinical thresholds for **decision-making**
  - Build joint (and conditional) probabilistic statements that **help quantify risk in development programs**
  - **Predict responses** for a new subject conditional on learnings from clinical trial data
- Benefit-Risk profile is a **combination of two aspects**:
  - 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 **applied to 3-dim** setting (mixture of continuous, binary and count endpoints)
  - Beyond 3 dimensions it may be difficult to interpret and visualise quantitative BR assessments
- Models and visualisations **can be adapted to other settings** beyond BR, e.g., co-primary endpoints

55

Bayesian Joint Modelling of Benefit and Risk in Drug Development – Outlook

- Joint modelling of BR can be used to **gain insight** into outcomes from **Multi-criteria decision analysis** (MCDA)
  - E.g., consider top influencing attributes/endpoints on MCDA outcome and estimate their joint posterior distribution
- **Impact of estimands** on benefit-risk assessments?
  - E.g., variable of interest may include key safety event leading to use of rescue medication
- Can **clinical thresholds** be used to convey **Patient Preference**?

56

EFSPI/PSI Benefit-Risk SIG

- If you want to **learn more about benefit-risk** in drug development...
  - Check out the EFSPI/PSI Benefit-Risk Special Interest Group (SIG): **please reach out to me!**
  - The SIG has created the **benefit-risk blog**: www.benefit-risk-assessment.com
    - Upcoming seminars and recent publications
    - Trainings and workshops
    - ...
- Watch out for the **half-day course on preference elicitation** at **PSI 2019**!

57

Thank you!

maria_j.costa@novartis.com

58