



# Bayesian Methods in Adaptive Dose-Finding Trials

**Date:** April 13 2015, Time: 15.30-17.00

**Venue:** Roche IT Training Center Auditorium / Aeschentor, Aeschenvorstadt 56, 4051 Basel

The BBS is proud to invite to a seminar with focus on Bayesian methods in adaptive dose-finding trials with Speakers from MD Anderson Cancer Center (University of Texas), Roche and Novartis.

The early clinical stage of drug development is crucial to learn about key pharmacological, safety and activity characteristics of the drug under investigation, but also to identify an appropriate dose (appropriate doses) for use in future trials.

The three talks will focus on Bayesian approaches to dose-finding in early clinical stage, i.e. approaches to update prior information & knowledge with observed data to optimize dose selection and thus to set the foundation for the following clinical stages in the development process.

## Program:

15.30-16.00

Daniel Sabanes Bove, Roche *“Bayesian Learning in Early Phase Oncology, A Case Study”*

16.00-16.30

Ying Yuan, MD Anderson *“Bayesian Data Augmentation Continual Reassessment Method with Delayed Toxicity”*

16.30-17.00

Daniel Lorand, Novartis *“Bayesian Dose-Exposure Model for Oncology Phase I dose-escalation Combination Studies “*

**We look forward to your participation.**

**Kind Regards,  
Dominik Heinzmann, on behalf of the BBS**

*Remark: Abstracts included below*

## Abstracts

**Daniel Sabanes Bove, Roche**

***“Bayesian Learning in Early Phase Oncology, A Case Study”***

This case study on a new biologic from Oncology starts with the entry-into-human phase I dose escalation study. It is shown how the modified Continual Reassessment Method (CRM) design incorporated reasonable prior assumptions about the expected safety profile, and ensured maximum flexibility for study conduct. A separate dose escalation was then planned for the combination with another new drug, with the design building on the two compound's information. As during the phase I it became apparent that a large proportion of patients developed anti-drug antibodies against the biologic, a small proof-of-concept study with a pretreatment aiming to diminish the immune response against the biologic was designed. Finally, the information gathered so far can be used to setup the entry-into-human phase I study for another biologic from the same platform. The clinical development questions and Bayesian answers to them will be presented, with a focus on the decision making and practical considerations.

**Ying Yuan, MD Anderson**

***“Bayesian Data Augmentation Continual Reassessment Method with Delayed Toxicity”***

A major practical impediment when implementing adaptive dose-finding designs is that the toxicity outcome used by the decision rules may not be observed shortly after the initiation of the treatment. To address this issue, we propose the data augmentation continual reassessment method (DA-CRM) for dose finding. By naturally treating the unobserved toxicities as missing data, we show that such missing data are nonignorable in the sense that the missingness depends on the unobserved outcomes. The Bayesian data augmentation approach is used to sample both the missing data and model parameters from their posterior full conditional distributions. We evaluate the performance of the DA-CRM through extensive simulation studies, and also compare it with other existing methods. The results show that the proposed design satisfactorily resolves the issues related to late-onset toxicities and possesses desirable operating characteristics: treating patients more safely, and also selecting the maximum tolerated dose with a higher probability. The new DA-CRM is illustrated with two phase I cancer clinical trials.

**Daniel Lorand, Novartis**

***“Bayesian Dose-Exposure Model for Oncology Phase I dose-escalation Combination Studies “***

Statistical models such as BLRM (Bayesian Logistic Regression Model) is used in Oncology phase I trials to model relationship between binary toxicity data and dose of the trial drug(s). Additional data including Pharmacokinetic (PK) data are then used to select dose that is less than or equal to the statistical model recommendation for the next cohort of patients. The PK data is often limited and rarely modelled. In the combination setting, where two or more drugs are administered together, PK data from relevant single-agent trials are often available. Further physiologically based pharmacokinetic (PBPK) modeling informs about the risk of drug-drug interaction and the dose-exposure relationship for each component when given in combination. A Bayesian method can leverage this PK data from single agent studies and PB/PK modelling through prior. In this talk, we present how such a Bayesian method to model relationship between exposure and dose of the trial drug(s) is used jointly with the usual dose toxicity model to enhance dose-escalation decisions. We also discuss how in practice the posterior summaries from the dose-exposure model can be used to select the dose for the next cohort of patients. The method is illustrated through an example from Novartis trial.