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# New investigations regarding improved assessment of Treatment Effect Heterogeneity in clinical trials; Bayesian Shrinkage and Enrichment strategies.

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**Björn Bornkamp**
**Please provide a brief biography for the Presenting author(s)**
Björn works in the Statistical Methodology Group at Novartis in Basel,
where he provides consulting to statisticians and clinical teams on topics related to dose-finding studies, treatment effect heterogeneity,
Bayesian statistics and causal inference.

**Marie-Karelle Riviere**
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Marie-Karelle Riviere is Director Statistical Methodologist at Saryga, a company dedicated to support innovation in statistics and decision-making in healthcare. Jointly with her colleagues, she assists pharmaceutical companies, biotechnology companies and hospitals on developing and using advanced statistical methodologies to optimize drug development plans and clinical trials. With an active collaboration with academia, Saryga also contributes to the research and the publication of novel approaches.Before joining Saryga, Marie-Karelle was in the Statistical Methodology Group at Sanofi in France where she provided support on complex innovative methodologies across all therapeutic areas and all development phases, but more specifically in early phases oncology. Marie-Karelle holds a PhD in Biostatistics from Paris-Diderot University on adaptive dose-finding designs in oncology. During her post-doc in pharmacometrics, she worked on the estimation of the Fisher information matrix for non-linear mixed effect models

**Wilmar Igl**
**Please provide a brief biography for the Presenting author(s)**
Wilmar Igl, PhD, is a statistician, psychologist and former researcher at the interface between statistics and data science with over 20 years of experience in biomedicine. He has been working as a Biostatistics Consulting Director at ICON, Sweden, since November 2022. Here, he provides biostatistical consulting services to biotech and pharma companies. Before he started this role, he served as a statistical assessor at the Swedish Medical Products Agency between 2018 and 2022. He collected experience in the pharma industry between 2010 and 2012 at Bayer Pharma (Berlin, Germany) and at AstraZeneca (Cambridge, UK) between 2015 and 2017.
His main interests include clinical trial designs (including adaptive designs), Bayesian statistics, patient-reported outcomes, open-source software, and statistical programming.

**David Svensson**
**Please provide a brief biography for the Presenting author(s)**
MODERATOR OF THE SESSION.

Ph.D, Senior Statistical Science Director at Astraeneca R&D, and Subgroup SIG lead since 2018.

**Single topic, multi-speaker session, Workshop or Single presentation submission**

A single topic, mutli-speaker session/workshop

**Single presentation or poster submission**

**Single topic session or workshop abstracts**

NOTE: this is intended as a Subgroup SIG session, please see further below for the details: 3 SPEAKERS,  ALL PRESENTING!!! (THIS SYSTEM DOES NOT LET ME SELECT THE "PRESENTING" BOX!!!)

SHORT **SESSION ABSTRACT**: The assessment of subgroups is a key regulatory requirement and the basis for precision medicine initiatives, but also notoriously hard from theoretical perspectives. This SIG session with reflect activities withing the Subgroup SIG, focusing on consistency assessments using novel Bayesian shrinkage approaches and aspects on study design.

## TALK1: Bayesian shrinkage estimation for subgroup analysis in clinical trials: Examining the critical aspects (Björn Bornkamp)

This talk will compare different ways of implementing Bayesian shrinkage estimation for subgroup analysis in clinical trials. Traditionally Bayesian shrinkage is applied to non-overlapping subgroups using hierarchical models. This implies that several models need to be fitted when several subgroup defining variables are of interest. Recently Wolbers et al (2024) propose to use a single global regression model using priors such as horseshoe priors to induce shrinkage for the used model. This method has the benefit that there is no need to create a disjoint space of subgroups. Thus, overlapping subgroups can be investigated with a single model. We will compare the performance of different shrinkage approaches (including no and full-shrinkage towards the overall treatment effect) based on real data.

## TALK2: A simulation study to compare Group Sequential Designs for subpopulation testing and enrichment procedure. (Marie-Karelle Riviere)

An important component of clinical trials in drug development is the analysis of treatment efficacy in patient subgroups. When designing such trials, it may be unclear for the clinical team which strategy is preferred: test the different subpopulations throughout the trial, adaptively enrich the patients most likely to benefit from the experimental treatment, or possibly both. Our work was motivated by an actual Phase 3 clinical trial in non-small cell lung cancer with a survival endpoint. Two subpopulations are defined based on tumor proportion score (TPS), resulting in two nested subpopulations of interest: the full population and the subgroup with high TPS. One interim analysis (IA) for futility and multiple IAs for efficacy were planned. Multiplicity issues arising from the numerous questions involved make the design and statistical analyses of these trials challenging.  We proposed an extensive simulation study where different designs were explored: (1) subgroup testing at different IAs with either (a) Bonferroni, (b) Holm procedures proposed by Ye et. al (2012), or (c) a hierarchical procedure; (2) enrichment with two different criteria to make the decision to enrich or not, and (3) both subgroup testing and enrichment in the

same design. The control of the type I error for subgroup selection and multiple analyses was analytically proven and the simulation study provides satisfactory operating characteristics in terms of power and detection of subgroup-specific effects.

**TALK3: Improving Outlier Detection in Subgroup Analysis using Bayesian Predictive Cross-validation Models (Wilmar Igl).**

The estimation of differential treatment effects between subgroups in clinical trials remains a challenging statistical problem in drug development. To overcome the lack of information in subgroups, which are usually not powered for the evaluation of treatment effects, Bayesian Hierarchical Models (BHM) have been proposed. Here, Bayesian Predictive Cross-Validation Models (BPCM) are presented as a superior, yet underused approach. The question in this context is whether one or more subgroups show a differential treatment effect relative to other subgroups. If so, the assumption of an overall treatment effect may not be appropriate. Shrinkage of the treatment effects towards the overall mean may make it harder to detect subgroup outliers. Moreover, the overall mean and its credible interval is less relevant here. However, BPCMs do not assume an overall treatment effect but predict the treatment effect in a subgroup of interest based on the heterogeneity of the treatment effects in all other subgroups. In addition, these models calculate the prediction interval for the subgroup of interest, which considers its sample size. The differences between a BHM and a BPCM for the identification of differential treatment effects are illustrated using a meta-analysis of 16 studies (incl. the ISIS-4 ‘mega-trial’) comparing treatments in patients with acute myocardial infarction. While the BHM results indicate that the ISIS-4 ‘mega-trial’ is an outlier, the BPCM results does not show a relevant differential treatment effect. BPCM models are a methodologically sound approach to evaluate differential treatment effects in subgroups, which should be preferred over standard BHM models.