Pre-Clinical SIG Workshop 2025 - AGENDA

7-8 October | Verona, Italy

DAY 1

12:00 – 14:00 **Arrival and Lunch in La Ginestra**

14:00 – 14:15 **Welcome and Introductions**

Bernd-Wolfgang Igl (Boehringer Ingelheim)

14:15 – 15:15 **Session 1: Orientating in the Valley of Death**

Chair: Denise Federico (Aptuit (Verona) Srl, an Evotec company)

Navigating through reproducibility traps

A considerable number of promising results from preclinical research studies cannot be reproduced, which is a well-known but concerning issue. This phenomenon has various sources and many facets and in addition, severely influences the translation of animal findings to human studies.

In this presentation, common factors influencing reproducibility and usual decision strategies will be presented. The role of exploratory and confirmatory designs in animal experimental research will be discussed. Finally, further examples will be shown and initial ideas for solving the problem will be explained.

Bernd-Wolfgang Igl (Boehringer Ingelheim)

Lost in Translation?

The translation of preclinical findings to humans remains a cornerstone of drug development, yet it is characterized by complexity. Despite all challenges, animal studies form the essential foundation upon which all clinical strategies and development plans are initially built. Successful translation demands a nuanced approach and thoughtful planning that sets it up for best-possible predictive power and reproducibility of the preclinical finding in humans.

The presentation will discuss key aspects of the translational journey and offer considerations on measures to mitigate certain challenges.

Claudia Dallinger (Boehringer Ingelheim)

15:15 – 16:00 **Coffee and Check In**

16:00– 17:00 **Session 2: Experimental design**

Chair: Jan Serroyen (JnJ)

Improving Model Predictive Efficiency with Bayesian I-Optimal Design of Experiments and Machine Learning Algorithms

This presentation introduces an innovative approach to optimize modular NANOBODY® formatting by integrating Design of Experiments (DoE) with Machine Learning (ML). Our methodology strategically samples the design space through a Bayesian I-optimal DoE, enabling comprehensive exploration of formatting possibilities while minimizing experimental burden. The approach employs an application of self-validated ensemble models (SVEM) for cross-validation, preserving the DoE structure while maximizing predictive power.

The synergy between structured experimental design and ML creates an iterative optimization framework to efficiently identifying design areas of interest. Key benefits include broader design space coverage, rapid identification of high-potential regions, and accelerated development of therapeutical modular molecules. Through active learning in high-desirability regions, this method provides a robust platform for multispecific NANOBODY® format optimization.

Els Pattyn (Sanofi)

High dimensional experimentation in preclinical assay development

High Dimensional Experimentation (HDE) is an integrated strategy for in-vitro experimental plate design, lab automation, and data analysis. Historically, Design of Experiments (DoE) has focused on minimising costs by running smaller and sequential experiments. In contrast, HDE aims to accelerate delivery time by minimising the number of experimental rounds and maximising the information learnt from a single experiment, utilising the large experimental space afforded by 96 or 384-well microtiter plates. In this talk I will present the HDE process, some examples, and its impact on preclinical drug development.

Joff Jones (AstraZeneca)

17:00 – 18:00 Session 3: Statistical Software

Chair: Helena Geys (JnJ)

Same, same but different? - SAS vs. R in Mixed Model Repeated Measures (MMRM)

Over the past years, there has been a significant shift in the pharmaceutical industry from SAS to the open-source programming language R, with major pharma companies setting timelines for a complete migration. This transition is driven by R's cost-effectiveness, advanced statistical capabilities, flexibility, and vibrant community support, reflecting a broader trend towards open-source tools, fostering innovation, collaboration, and efficiency in pharmaceutical research.

Nonetheless, the shift to R comes with challenges. Many organizations have developed extensive libraries of SAS code over decades, and migrating this code to R can be both time-consuming and error-prone, particularly for complex macros or proprietary SAS procedures. Additionally, certain SAS functionalities lack direct equivalents in R, necessitating custom solutions or workarounds. Furthermore, for some statistical approaches, subtle differences in underlying algorithms and assumptions between the two languages can result in discrepancies in outputs, which may cause concern or might even remain undetected without rigorous comparisons.

This workshop session aims to present and discuss the pitfalls, challenges, and lessons learned from reproducing results from SAS code in R, using the example of MMRM models for different covariance structures and degrees of freedom approximations.

Inka Rösel (Boehringer Ingelheim)

Navigating the Mixed Model Minefield: SAS vs. R

This presentation will consist of a lessons learned when trying to translate certain hierarchical models implemented in SAS to R, such as linear mixed-effects models with spatial correlation. The pros and cons/limitations of the most commonly used R packages for mixed models will be covered, and well as our attempts of finding a solution for these limitations.

Jan Serroyen (JnJ)

19:00 – 21:00 Dinner at the hotel restaurant, La Ginestra

DAY 2

09:00 – 10:30 Session 4: Virtual Control Groups

Chair: Bernd-Wolfgang Igl (Boehringer Ingelheim)

Selection of virtual control groups from historical data, comparison of methods

Generation of a sufficient virtual control group (VCG) from historical control data (HCD) using baseline covariate balancing techniques to approximate the conditions of a randomized design. A simulation framework is employed to compare various methods for covariate balancing, with a focus on achieving baseline comparability between the VCG and treatment groups. The findings offer insights into the performance and suitability of different selection strategies for constructing robust virtual control groups.

Andreas Schulz (Sanofi, Vict3r Package)

Identification of Key Covariates Using Statistical Analysis of the Microscopical Domain in the VICT3R Project

The VICT3R project has been launched to advance the field of toxicology research by developing Virtual Control Groups (VCGs), with the objective of achieving a substantial reduction in the utilisation of animals in such research. The VICT3R data builds on earlier work from the eTRANSAFE initiative, leveraging extensive historical control data from animal toxicity studies to create VCGs that can substitute for concurrent control groups. The necessity for regulatory acceptance is addressed by the establishment of a comprehensive database of high-quality control data, supported by advanced statistical and artificial intelligence methodologies. In one domain, the microscopic findings from the SEND (Standard for the Exchange of Nonclinical Data) format include standardised descriptions of histopathological findings. The purpose of this is to ensure consistent data transfer from pharmaceutical companies to the FDA (US Food and Drug Administration) and this format is used to compile data from different institutions. The findings encompass specific details regarding cell types, tissue changes, and pathological lesions identified in the examined samples. Statistical analysis in this context involves the application of various methods to evaluate and interpret data, with the aim of identifying significant relationships and patterns among variables. It is imperative to comprehend the explanatory variance, as it quantifies the proportion of variability in the response variable that can be attributed to the explanatory variables. This, in turn, provides insights into the underlying factors influencing the observed outcomes

Timur Tug (Fraunhofer ITEM)

Developing Virtual Control Groups in preclinical toxicology: Database, Statistical Methods, and Impact in Safety Assessments

VICT3R will be presented as large European consortium working on a project that aims to substantially decrease animal use in nonclinical safety assessments by replacing concurrent control groups (CCGs) with Virtual Control Groups (VCGs). The project is focused on developing an extensive, high-quality database of curated and analyzed control animal data, together with the development of the statistical methodology to use to generate the VCG and assess their impact in safety studies. This presentation outlines the project's work plan, challenges and accomplishments.

Guillemette Duchateau-Nguyen (Roche) / Paolo Piraino (Organon)

10:30 – 10:45 Coffee

10:45 – 12:15	**Round Table Discussion**
12:15 – 12:30	**Wrap-up and closing remarks** ***Chair: Bernd-Wolfgang Igl (Boehringer Ingelheim)***
12:30 – 14:00	**Lunch in La Ginestra**
14:00	**Close and departure**