PSI Scientific Meeting

Master Protocols: Industry, Academic, and Regulatory Perspectives

24th November 2023

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Venue

Venue

The event will be held at Johnson & Johnson's site in High Wycombe, located at:

Windsor Rooms, Johnson & Johnson, 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG

Hotels near the venue

There are several hotels located close to the venue in High Wycombe. Marlow, which is also well-linked to London, has a number of hotels. Alternatively, hotels in London can be reached easily (see below).

Getting to the venue

By car
Guest parking is available at the venue.

By train
High Wycombe is the closest station to the venue and is 30 mins away from London Marylebone. Alternatively, Marlow station is a 10 min taxi journey from the venue and is linked to London via Maidenhead station.

By plane
London Heathrow is approximately 90 mins away from High Wycombe by train, while London Gatwick is approximately 2 hours away.

Refreshments

Refreshments will be served as part of the morning and afternoon breaks, as well as during lunch. For any additional refreshment needs, there is a Costa Coffee at the venue open from 8am to 3pm.

Agenda

Time	Speaker/Title
09:15-09:50	**Registration**
09:50-10:00	**Opening remarks**
10:00-11:00	**Regulatory and practical considerations** Chair: Josephine Khan, *Johnson & Johnson*
10:00-10:20	Tobias Mielke, *Johnson & Johnson* *On the complexity of independent decision making in platform trials*
10:20-10:40	Julia Saperia, *MHRA* *Master protocols in the UK regulatory landscape*
10:40-11:00	Kim Lee, *King's College London* *The caveats in the analysis of platform trials*
11:00-11:30	**Break**
11:30-12:30	**Innovation in methodology and implementation** Chair: Thomas Burnett, *University of Bath*
11:30-11:50	David Robertson, *MRC BSU, Cambridge University* *Online error rate control for platform trials*
11:50-12:10	Luke Ouma, *AstraZeneca* *Bayesian modelling strategies for borrowing of information in randomised basket trials*
12:10-12:30	Elias Laurin Meyer, *Berry Consultants* *Using simulation for designing platform trials*
12:30-14:00	**Lunch and roundtable discussions**
14:00-15:40	**Reflections from case studies** Chair: Christine Baudelet, *Johnson & Johnson*
14:00-14:20	Max Parmar, *MRC CTU at UCL* *Multi-arm, multi-stage platform trials: Motivation, strategic and practical issues with an example of a trial run over 20 years*
14:20-14:40	Adrian Mander, *GSK* *Master protocols in the type 1 diabetes INNODIA consortium*
14:40-15:00	Vincent Haddad, *AstraZeneca* *Operational considerations of a ph1/2 basket study: Case study*
15:00-15:20	Cindy Billingham, *University of Birmingham* *Platform trials for rare cancers: Opportunities and challenges in the DETERMINE trial*
15:20-15:40	Willem Talloen, *Johnson & Johnson* *Lessons learned from a platform study for the treatment of Hepatitis B*
15:40-16:00	**Break**
16:00-16:50	**Panel discussion** Chair: Michael Grayling, *Johnson & Johnson,* Panelists: Cindy Billingham, *University of Birmingham;* Olivier Collignon, *GSK;* Tobias Mielke, *Johnson & Johnson;* Max Parmar, *MRC CTU at UCL*; Bernie Surujbally, *Roche*
16:50-17:00	**Close**

Presenter and panelist bios

Lucinda Billingham, *University of Birmingham*

Lucinda (Cindy) Billingham is Professor of Biostatistics within the Institute of Cancer and Genomic Sciences at the University of Birmingham. She has worked for almost thirty years as a Biostatistician at their Cancer Research UK Clinical Trials Unit and is now Director of Biostatistics for the Unit working with a large team of Biostatisticians on an extensive portfolio of early and late phase trials. Lucinda has a special interest in lung cancer research and is the Chief Biostatistician for the National Lung Matrix Trial. She has expertise in the design and analysis of trials in rare cancers and is the Lead Biostatistician for Cancer Research UK's DETERMINE trial and Director of the CAPTIVATE node within the MRC-NIHR UK Rare Disease Research Platform. Other key areas of expertise include statistical methods for the simultaneous analysis of quality of life and survival data, application of Bayesian methods in trials, early phase trial design and the evaluation of biomarkers in trials for stratified medicine. She is an invited member of the Cancer Research UK Clinical Expert Review Panel providing statistical advice for funding applications. She lectures on undergraduate and postgraduate courses at Birmingham, teaches widely on external courses and provides PhD supervision.

Olivier Collignon, *GSK*

Dr Olivier Collignon is Director of Statistics at GSK in the United Kingdom where he leads a team of statisticians who contribute to the development of various vaccines. He holds a PhD in Applied Mathematics and is especially interested in basket, umbrella and platform trials, use of historical controls and clinical prediction models. He previously worked as a biostatistician in France and Luxembourg for more than 15 years. During his mission at the Luxembourg Institute of Health he was seconded at the European Medicines Agency in London for 4 years, where he gained regulatory experience and participated to the scientific evaluation of the design and results of clinical trials to obtain marketing authorization of new drugs in Europe.

Vincent Haddad, *AstraZeneca*

Vincent graduated in France as a biostatistician & epidemiologist. He started his career as an academic in the epidemiology department of the Institute of Radioprotection and Nuclear Safety (France), and then as a biostatistician in the Institute Gustave Roussy (France) where he got his passion for oncology. He then joined the industry, Amgen (Cambridge, UK) for 8 years where he worked on various oncology programs and AstraZeneca (Cambridge, UK) since 2015. Vincent has been the lead statistician for the development of various molecules: ADC, next generation SERD, AKT inhibitor, MET inhibitor, EGFR TKI, etc.

Kim Lee, *King's College London*

I am a Research Fellow working on clinical trial methodology at the Institute of Psychiatry, Psychology & Neuroscience, King's College London. I obtained my PhD in statistics from the University of Southampton. Following my PhD, I worked with Prof. James Wason as a Research Associate at the MRC Biostatistics Unit, University of Cambridge on the topic of efficient trial approaches. I then did a one-year lectureship at the Pragmatic Clinical Trials Unit at Queen Mary University of London prior to joining the methodology research group lead by Prof. Richard Emsley at King's College London. My research interests include adaptive designs, Bayesian decision theoretic approach, missing data and mediation analysis.

Adrian Mander, *GSK*

Adrian started a post-doc in 1996 at the London School of Hygiene and Tropical Medicine working on longitudinal modelling of peak flow data collaborating with Astra. In 1998 he moved to the Medical Research Council (MRC) Biostatistics Unit to work with David Clayton on EM algorithms for haplotype analysis and multiple imputation methodology, focusing on the approximate Bayesian bootstrap. In 2001 Adrian then joined GSK, working initially in the Clinical Pharmacology group followed by statistical consulting role to the Worldwide Epidemiology group. He returned to academia in 2004 to become the head of statistics in the MRC Human Nutrition Research unit in Cambridge, working on dietary intervention trials and introducing Bayesian approaches to stable isotope modelling. Adrian then returned to the MRC Biostatistics Unit to create a new team in adaptive trial methodology. Over ten years the group grew developing new methodology/designs in dose-finding, dose-ranging, group sequential/MAMs and finally platform trials. Adrian then took a chair in Medical Statistics with Cardiff University's clinical trials unit, merging multiple statistics groups and creating a statistical reporting and methodology group. As post-lockdown working practices changed, Adrian moved back to GSK, in 2022, within the statistical data science innovation hub (SDS-IH) to head up a team of methodologists in statistical innovation.

Elias Laurin Meyer, *Berry Consultants*

Elias Laurin Meyer is a Statistical Scientist at Berry Consultants based in Vienna, Austria. Prior to joining Berry Consultants, he worked for several years with Franz König (his PhD supervisor) and Martin Posch at the Medical University of Vienna, where he (co-)authored around 40 peer-reviewed publications and where his tasks and interests ranged from statistical consulting, data analysis and writing study protocols to teaching, methodological research and statistical programming. He has gained industry experience while on secondments at Roche and Novartis. Prior to earning his PhD in 2022 while working on the EU-PEARL project, he received a BSc and MSc in Statistics from the University of Vienna and worked as an EMT and ambulance driver. Within the EU-PEARL project, he was co-lead contributor of a deliverable related to software implementation of statistical analysis and simulation procedures and first author of several papers related to the design and simulation of platform trials. Finally, he serves as an expert biostatistics reviewer for the Viennese Ethics Committee (IRB).

Tobias Mielke, *Johnson & Johnson Innovative Medicine*

Tobias works as Senior Scientific Director in J&J's internal statistical consulting group. Tobias joined J&J in 2018 to support the planning and implementation of adaptive and complex innovative designs in J&J across therapeutic areas. Tobias contributed as J&J representative to the statistical methodology work-package of the IMI Project EU PEARL. Prior to joining J&J, Tobias worked at ICON Clinical Research as statistical consultant and had the chance to gather through numerous consulting projects experience on late-phase adaptive study designs, dose-response modeling and multiplicity problems. Tobias was one of the architects of ADDPLAN DF, a software for the design, simulation and analysis of adaptive dose-finding studies using MCPMod. Within this role at ICON, Tobias particularly enjoyed to implement his (at that time) fresh learnings from his PhD into some adaptive dose-finding methods. Tobias has a PhD from University of Magdeburg (Germany) on the topic of model-based design of experiments for nonlinear mixed effects models.

Luke Ouma, *AstraZeneca*

Luke Ouma is a Senior statistician at AstraZeneca, within the Late phase Oncology team. Previously he completed a PhD, and worked as a research associate (Biostatistics) at Newcastle University where he focused on developing improved methods for the design and analysis of innovative trial designs in precision medicine. His main research interests are in Master protocols, particularly the use of Bayesian approaches for the design and analysis of Umbrella, basket and platform trials.

Max Parmar, *MRC CTU at UCL*

Mahesh (Max) Parmar is a Professor of Medical Statistics and Epidemiology and Director of both the MRC Clinical Trials Unit at UCL and the Institute of Clinical Trials and Methodology at University College London. He was for over 10 years an Associate Director of the National Cancer Research Network since its inception in 2001, an organisation which more than doubled the number of patients going into cancer studies in England. Max joined the MRC in 1987. He has more than 400 publications in peer-reviewed journals, many of which have had a direct impact on policy, clinical practice, and improving outcomes for patients. The MRC Clinical Trials Unit he directs is at the forefront of resolving internationally important questions, particularly in infectious diseases and cancer, and also aims to deliver swifter and more effective translation of scientific research into patient benefits. It does this by carrying out challenging and innovative studies and by developing and implementing methodological advances in study design, conduct, and analysis. In 2019, Professor Parmar was awarded the Officer of the Order of the British Empire (OBE).

David Robertson, *MRC BSU, University of Cambridge*

David Robertson is a Senior Research Associate at the MRC Biostatistics Unit, University of Cambridge, where he has been based since 2013. His research focuses on the development of novel methodology for the design and analysis of adaptive clinical trials. From 2018 - 2021, David held a Biometrika Trust Research Fellowship, which explored questions around error rate control for clinical trial designs that test multiple hypotheses simultaneously. His current main areas of research include estimation after adaptive designs, response-adaptive randomisation in clinical trials and multiple hypothesis testing.

Julia Saperia, *MHRA*

Julia Saperia is a statistical assessor at the MHRA (Medicines and Healthcare products Regulatory Agency, UK) and has been for the last 11 years. She has also worked at the EMA (European Medicines Agency) and also as a systematic reviewer, writing clinical guidance for NICE.

Bernie Surujbally, *Roche*

Bernie is a senior principal statistician at Roche and has been there since 2013, working across infectious disease areas both in early and late phase, building on experiences she had gained from her years before that spent in the stats department at Pfizer. In the last few years, Bernie has been focusing on early phase development and through this had the opportunity to co-lead the study design, set-up and execution of a platform Proof of Concept study in Infectious Diseases. Bernie has an MSc in Mathematics, Statistics and Computing from the University of Ulster, Jordanstown, Northern Ireland. Outside of work, Bernie likes to run (well, maybe like is too strong a word!) and has recently taken up yoga.

Willem Talloen, *Johnson & Johnson Innovative Medicine*

Willem Talloen is head of Early Development Statistics in Infectious Diseases at J&J. He has 18 years of experience in both discovery and early development. Before joining J&J in 2005, he worked for the Belgian Public Institute of Health as a statistical consultant. Willem authored more than 100 biological and/or statistical publications, edited a book on biclustering and wrote a book on gene expression studies. He co-invented two patents in the field of biomarkers.

Abstracts

10:00-10:20 **On the complexity of independent decision making in platform trials**

Tobias Mielke, *Johnson & Johnson Innovative Medicine*

Platform trials offer multiple opportunities to increase efficiency in research through shared concurrent and non-concurrent control data, adaptive decision making, quicker site-start up and potentially larger awareness within the patient community. Some of those opportunities to increase efficiency come at the cost of increased complexity. Besides obvious operational complexity, dependency structures of decisions pose a particular complexity for the interpretation of the results of platform trial designs. Decisions on any substudy within a platform trial may involuntarily impact other substudies through some indirect design adjustments, even if decisions were meant to be implemented independently. For example, addition of a new intervention to a platform trial may result in an adjustment to the allocation ratio, thereby changing possibly the shared control group size available for testing any ongoing intervention. Similarly, an early futility or success declaration for one intervention could result in an adjusted data-driven control group allocation for other ongoing interventions. In this presentation, we will have a closer look at such design adjustments, how those may affect power and type-1 error rate and how one could mitigate such complexities using conventional adaptive design methodology.

10:40-11:00 **The caveats in the analysis of platform trials**

Kim Lee, *King's College London*

Platform trial designs offer an innovative approach to increase the efficiency of intervention development process. This approach allows adding and dropping research arms throughout the course of a study via protocol amendments. It can be considered as an extension of a multi-arm multi-stage adaptive design that adds arms at different stages of the study. For this reason, the statistical challenges met in the topic of adaptive designs remain in platform trials. Moreover, there are other issues which are unique or more common to platform trials. For example, recent work explored how to utilise all control data in the study analysis in the presence/ absence of time trends, as some of the control data are not concurrent to interventions that are added after the onset of the trial.

In this talk, I will give a brief overview on the statistical challenges in platform trials. I will then focus on the inference of interventions when there is heterogeneity across stages of a platform study. Example of reasons include modification of eligibility criteria as arms are dropped or added; there exist patients who respond differently to the same treatment across stages in the presence/absence of other intervention arms. I will illustrate the impact of heterogeneity on the interpretation of study results with a simulation study.

11:30-11:50 **Online error rate control for platform trials**
David Robertson, *MRC BSU, Cambridge University*

Platform trials evaluate multiple experimental treatments under a single master protocol, where new treatment arms are added to the trial over time. Given the multiple treatment comparisons, there is the potential for inflation of the overall type I error rate, which is complicated by the fact that the hypotheses are tested at different times and are not necessarily pre-specified. Online error rate control methodology provides a possible solution to the problem of multiplicity for platform trials where a relatively large number of hypotheses are expected to be tested over time. In the online multiple hypothesis testing framework, hypotheses are tested one-by-one over time, where at each time-step an analyst decides whether to reject the current null hypothesis without knowledge of future tests but based solely on past decisions. Methodology has recently been developed for online control of the false discovery rate as well as the familywise error rate. In this talk, we describe how to apply online error rate control to the platform trial setting, present extensive simulation results, and give some recommendations for the use of this new methodology in practice. We also illustrate how online error rate control would have impacted a currently ongoing platform trial.

11:50-12:10 **Bayesian modelling strategies for borrowing of information in randomised basket trials**
Luke Ouma, *AstraZeneca*

Basket trials are an innovative precision medicine clinical trial design evaluating a single targeted therapy across multiple diseases that share a common characteristic. Several precision medicine trials of this type are designed as single-arm trials and are now common in early-phase oncology settings, for which several Bayesian methods permitting information sharing across subtrials have been proposed. With the increasing need for randomised evidence in precision medicine, randomised basket trials have gained popularity. Here, the advantages of borrowing information using Bayesian methods could be exploited in two ways; considering the commensurability of either the treatment effects or the outcomes specific to each of the treatment groups between the subtrials. In this work we propose an approach to borrowing over the subtrial groupwise responses ('treatment response borrowing', TRB) based on distributional discrepancy. We contrast the performance of TRB to the widely adopted approach for borrowing over the subtrial treatment effects ('treatment effect borrowing', TEB). Simulation results demonstrate that both modelling strategies provide substantial gains over an approach with no borrowing. TRB outperforms TEB especially when subtrial sample sizes are small, while the latter has considerable gains in performance over TRB when subtrial sample sizes are large, or the treatment effects and groupwise mean responses are noticeably heterogeneous across subtrials. Further, we observe that TRB, and TEB can potentially lead to

conclusions when applied to the analysis of real basket trial data. Our findings suggest the need for careful consideration of the approach to borrowing in randomised basket trials, and to consider TRB when trial sample is small as it confers higher power and better coverage probability of treatment effect estimates over TEB.

12:10-12:30 Using simulation for designing platform trials
Elias Laurin Meyer, *Berry Consultants*

Platform trials are becoming increasingly popular within drug development, attracting interest by patients, clinicians, regulatory agencies and certainly also statisticians. More often than not, these platform trial designs are highly complex and involve too many weakly predictable events (e.g. number of investigational treatments that will enter over time) to determine the impact of relevant design parameters (e.g. decision rules, sharing of information across cohorts and allocation ratios) on the operating characteristics with high confidence. Simulations may address these uncertainties at the design stage. However, the number and combination of design elements for implementation in real platform trials is close to infinite. As a result, simulation software which is developed based on specific project needs is typically limited in the variety of available design options for comparison, as such software is developed for a particular need, not for researching all potential new approaches to clinical research and statistical science. On the other hand, software solutions which allow for a wide range of design options may easily overload the user with requirements for design specifications or lack proper documentation and validation. We will give an overview of different software packages useful for simulating platform trials and explain their advantages and limitations.

14:20-14:40 Master protocols in the type 1 diabetes INNODIA consortium
Adrian Mander, *GSK*

This talk will introduce the INNODIA consortium's work of building a European network of clinical trials units to run phase 2 trials under a common master protocol. The consortium has been running 7 years and has several trials that are ongoing or planned. One of these sub-trials is a dose-ranging trial called MELD-ATG that is trying to replicate the findings of an earlier trial that showed the benefits of a 2.5mg/kg dose Antithymocyte Globlin (ATG), in terms of C-peptide preservation. This trial also sought to include a younger group of participants and to investigate lower doses that may give benefit with lower toxicities. This sub-trial used a Bayesian predictive model to guide seven interim analyses that determined which doses are selected in subsequent cohorts, whilst maintaining the standard frequentist analyses at the end of the trial. The difficulties of designing this trial and running a complex multi-centre trial are discussed.

15:20-15:40 **Lessons learned from a platform study for the treatment of Hepatitis B**

Willem Talloen on behalf of the Wings Platform core team, *Johnson & Johnson Innovative Medicine*

The 'Wings' Platform study, conceived in 2018, was designed to assess multiple innovative therapies and combination regimens targeting Chronic Hepatitis B treatment. To date, the platform has seen the planning of 8 interventions, with 2 having reached completion, 3 still active, and 3 cancelled.

During this presentation, we will provide an overview of our journey, spanning from Senior Leadership endorsement through regulatory consultations, to the launch and subsequent expansion of the platform trial. We will talk about insights gained from regulatory, clinical, statistical, and operational perspectives. Key topics will include the modular Master protocol approach, the strategic planning required both initially and throughout the trial, and we will conclude by shedding light on the advantages and challenges we encountered during our platform study.

Future PSI events

PSI Medical Statistics Careers Event

Date: 29 Nov 2023 **Time:** 12:00-17:00 GMT
Location: Cutlers' Hall, Sheffield

This event is aimed at students with an interest in the field of Medical Statistics, for example within pharmaceuticals, healthcare and/or medical research.

PSI Career Young Virtual Meet (Q4 2023)

When: 05 Dec 2023 **Time:** 12:00-13:00 GMT
Where: Online

This networking event is aimed at statisticians that are new to the pharmaceutical industry who wish to meet colleagues from different companies and backgrounds. During this session there will be an activity to be completed in small groups allowing for connections to develop.

PSI Webinar(s): Causal inference in Clinical Trials

When: 06 Dec 2023 & 14 Dec 3023
Time: 13:30-16:00 GMT (both days) **Where:** Online

The event will be structured as two webinars in consecutive weeks. The first webinar will introduce causal inference ideas and methods and how these relate to the estimand framework in both the setting of RCTs or real world data. The second webinar is aimed at illustrating real practical applications in drug development using case studies.

*To learn more about future PSI events, visit **psiweb.org***