

Adaptive Designs & Multiple Testing Procedures

Workshop 19th- 21st April, 2023

🏰 Basel, Switzerland 🇨🇭



Pixabay images

Organising Committee:

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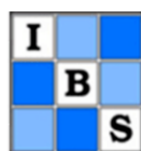
Workshop webpage:

<https://admt2023.github.io/>

Sponsored by:



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Deutsche Region



WORKSHOP VENUE

Location:

The workshop "Adaptive Designs and Multiple Testing Procedures 2023" will take place at Fabrikstrasse 6, Novartis Campus, Basel.

Address:

Fabrikstrasse 6,
Novartis Campus,
CH-4056 Basel

How to find Novartis Campus:

How to find us

By public transport

From EuroAirport Basel (15 min travel time)

Either take a taxi to Novartis Campus or take the Airport Express Bus PTT 50 to Kannenfeldplatz. Change to Tram 1 (direction Dreirosenbrücke) to the Novartis Campus stop. Across the street you find the main entrance to the Novartis Campus.

By train from Bahnhof Basel SBB (15 min travel time)

Take a taxi to Novartis Campus or take the Tram 1 (direction Dreirosenbrücke) in front of the main station to the Novartis Campus stop. Across the street you find the main entrance to the Novartis Campus.

By train from Basel Badischer Bahnhof (10 min travel time)

Take a taxi to Novartis Campus or take either Tram 6 (direction Allschwil) or Tram 2 (direction Binningen) to the Messeplatz stop. Change to Tram 14* (direction Dreirosenbrücke) to the Novartis Campus stop. Across the street you find the main entrance to the Novartis Campus. Tram 21 operates directly via Messe to the Novartis Campus stop during morning and evening rush ours.

(*At the stop Dreirosenbrücke the tram changes its number sign from 14 to 1, you can continue your trip in the same vehicle.)

By car

The first basement of our parking is exclusively reserved for visitors. The access is very easy and there is no registration required to enter.

From France

Motorway A35/E60 direction Basel, after customs St. Louis take first exit and turn left, follow sign direction St. Johann. At the end of the street turn right into Schlachthofstrasse and follow sign direction St. Johann/Novartis Campus. After 700 m turn right into Elsässerstrasse and follow to Voltaplatz, then turn left into Voltastrasse, after approx. 200 m turn left into Fabrikstrasse/Novartis Campus.

From Germany

Motorway A5/E35 direction Basel, after customs take exit Basel-Nord/Kleinhünigen/St. Johann/Mulhouse/France, enter the tunnel and follow the signs to Basel St. Johann/Novartis Campus.

From Switzerland

Motorway A2 direction Basel, exit at Basel Nord/Kleinhünigen/St. Johann/Mulhouse/France, enter the tunnel and follow the signs to Basel St. Johann/Novartis Campus.

How to find the workshop from Novartis Campus Entrance:



Break out room:

If you need to take a call during the workshop, we have a break out room available throughout the workshop in Fabrikstrasse 6. Please reach out to Eliane Imfeld (eliane.imfeld@novartis.com) to book a slot.

How to connect to Novartis Guest Wi-Fi during the workshop:

How to connect and approve access to the Guest_Multi-Day network

🌐 English (Original)

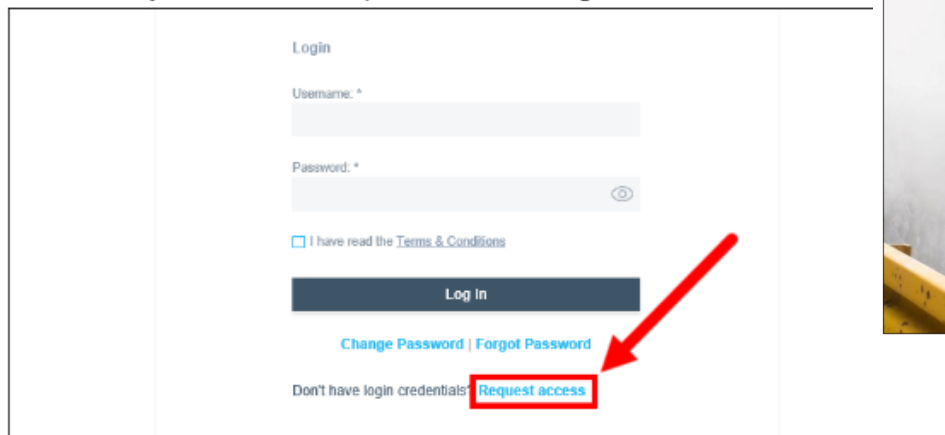
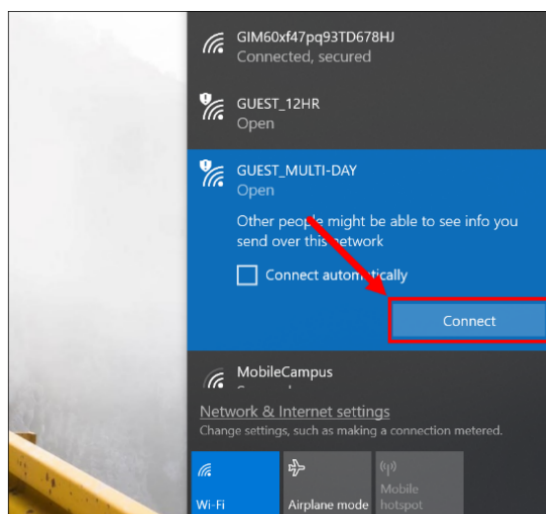
Introduction

This article explains how to connect and approve access to the Guest_Multi-Day wireless network. The Guest_Multi-Day network allows a guest to use the Guest Wi-Fi for up to 180 days. This information is applicable to all users who wish to connect to Guest Wi-Fi and their Novartis sponsor.

How to apply for Guest_Multi-Day access (Guest)

1. Click the Wi-Fi icon to view available networks.
2. Locate and click **GUEST_MULTI-DAY**, then click **Connect**. The Guest Wi-Fi Registration page opens in your browser.

3. Click **Request access** to open the Guest Registration form.

A screenshot of the Guest Registration form. It features a 'Login' section with fields for 'Username: *' and 'Password: *'. Below these is a checkbox for 'I have read the Terms & Conditions' and a 'Log In' button. At the bottom, there are links for 'Change Password' and 'Forgot Password', and a 'Request access' link highlighted with a red box and a red arrow pointing to it from the right.

4. Complete all required fields then click **Request Access**.

Important: The **Password** that you enter in the **Guest Registration** form is the one you will need when using the **GUEST_Multi-Day Network** Wi-Fi. The username is the email ID you provided during registration

5. The person (Novartis sponsor) whose email you entered into **Contact Person Corporate Email** field receives an email with a link to approve or deny your request and specify the duration of internet access.

Conclusion: If your request is approved, to use the **GUEST_Multi-Day Network** Wi-Fi, enter the username and **Password** - one that you entered in the **Guest Registration** form.

Important note:

- Novartis sponsor email: bibiana.blatna@novartis.com
- The username is your email address
- Choose your own password

WORKSHOP DINNER

The workshop dinner can be attended on Wednesday 19th April at 19:30. Payment is the responsibility of participants. The dinner will take place in the Basel [Restaurant Zur Mägd.](#)



Address:

St. Johannis-Vorstadt 29,
CH-4056 Basel



SCIENTIFIC PROGRAM – OVERVIEW

Wednesday, 19th April

12:30 – 13:00	Registration
13:00 – 13:15	Welcome Addresses
13:15 – 14:15	Invited Session 1
14:15 – 15:15	Session I: Platform trials
15:15 – 15:45	Coffee Break
15:45 – 17:45	Invited Session II: Platform trials – findings from the EU-PEARL initiative
19:00	Workshop Dinner

Thursday, 20th April




09:00 – 11:00	Session II: Adaptive designs and multiple testing in a confirmatory setting
11:00 – 11:30	Coffee break
11:30 – 13:00	Session III: Adaptive designs for clinical trials with time-to-event endpoints
13:00 – 14:00	Lunch break
14:00 – 15:30	Session IV: Group sequential and adaptive designs
15:30 – 16:00	Coffee Break
16:00 – 17:30	Session V: Multiple Testing Procedures

Friday, 21st April



09:00 – 10:00	Session VI: Adaptive designs permitting sample size re-estimation
10:00 – 11:00	Invited Session III
11:00 – 11:30	Coffee Break and Workshop Photo
11:30 – 12:00	Session VII: History of the IBS-DR and ROeS ADMTP working group
12:00 – 12:30	Meeting of the IBS-DR / ROeS Working Group on ADMTP
12:30 – 12:40	Close of workshop

SCIENTIFIC PROGRAM – DETAILED TIME SCHEDULE


Wednesday 19th April

12:30-13:00 	Registration
13:00- 13:15	<p>Welcome</p> <ul style="list-style-type: none"> • Lisa Hampson (Chair of local organizing committee) • Thomas Asendorf (Chair of IBS-DR and ROeS ADMTP working group) • Marisa Bacchi (Basel Biometric Society)
13:15-14:15	<p>Invited Session I</p> <p>Chair: Marisa Bacchi</p> <p>Tobias Mielke: <i>Adaptive platform trials: complex and innovative – but how useful?</i></p>
14:15-15:15	<p>Session I: Platform trials</p> <p>Chair: Marta Bofill Roig</p> <ol style="list-style-type: none"> 1. Peter Greenstreet, Thomas Jaki, Alun Bedding, Pavel Mozgunov: Why keeping previous data can be detrimental in platform trials with a change in standard of care 2. Michaela Maria Freitag, Dario Zocholl, Stefan Gold, Martin Posch, Franz König: Early stopping, allocation ratios and power: how to tailor design options for a platform trial in Major Depressive Disorder
15:15-15:45 	Coffee Break
15:45-17:45	<p>Invited Session II: Platform trials – findings from the EU-PEARL initiative</p> <p>Chair: Ekkehard Glimm</p> <ol style="list-style-type: none"> 1. Pavla Krotka, Katharina Hees, Peter Jacko, Dominic Magirr, Martin Posch, Marta Bofill Roig: NCC: An R-package for analysis and simulation of platform trials with non-concurrent controls 2. Quynh Nguyen, Hue Kästel, Katharina Hees, Benjamin Hofner: The use of complex clinical trials: A regulatory review 3. Marta Bofill Roig, Ekkehard Glimm, Tobias Mielke and Martin Posch: Optimal allocation strategies for platform trials 4. Sonja Zehetmayer: Looking forward and benefiting from the past: Sample size estimation for new arms in platform trials <p>Discussion panel: Benjamin Hofner, Tobias Mielke, Tom Parke, and presenters 30 minutes</p> <p>Audience Q&A: 10 minutes</p>
19:30 	Workshop Dinner (Restaurant Zur Mägd)

Thursday 20th April

09:00- 11:00	<p>Session II: Adaptive designs and multiple testing in a confirmatory setting Chair: Ekkehard Glimm</p> <ol style="list-style-type: none"> 1. Frank Bretz, Uli Burger: Principles of adaptive clinical trials - a personal view 2. Marie Louise Østerdal, Kyle Raymond, Christian Bressen Pipper: Properties of a confirmatory two-stage adaptive procedure for assessing average bioequivalence 3. Leonhard Held: Sequential alternatives to the two-trials rule 4. Akshay Patil: Checklist and reporting guidelines for estimands in adaptive or innovative clinical trial designs
11:00- 11:30 	Coffee Break
11:30-13:00	<p>Session III: Adaptive designs for clinical trials with time-to-event endpoints Chair: Dominic Magirr</p> <ol style="list-style-type: none"> 1. Moritz Fabian Danzer, Andreas Faldum, Rene Schmidt: Adaptive designs for multiple time-to-event outcomes in Markovian multi-state models 2. Pantelis Vlachos: A new approach to trial design and probabilistic risk assessment for trials with dual survival endpoints 3. Deepak Parashar: A predictive biomarker enrichment design for Phase II oncology trials
13:00-14:00 	Lunch
14:00- 15:30	<p>Session IV: Group sequential and adaptive designs Chair: Anh Nguyen Duc</p> <ol style="list-style-type: none"> 1. Kelly Van Lancker, Josh Betz, and Michael Rosenblum: Combining Covariate Adjustment with Group Sequential, Information Adaptive Designs to Improve Randomized Trial Efficiency 2. Cornelia Ursula Kunz, Shannon Amy Zellner, Sonja Drescher, Johannes Krisam: An adaptive balance-ensuring big stick randomization procedure for equal and unequal allocation ratios 3. Maria Vittoria Chiaruttini, Jacopo Gallochio, Alessandro Desideri, Danila Azzolina, Dario Gregori: Resampling algorithm for calculation of sample size of two-stage and three-arm sequential non-inferiority clinical trials when applied to skewed outcome: a simulation study
15:30- 16:00 	Coffee Break
16:00- 17:30	<p>Session V: Multiple Testing Procedures Chair: Tobias Mielke</p> <ol style="list-style-type: none"> 1. Jixian Wang, Ram Tiwari: Toward optimal graphic tests 2. Lasse Fischer, Marta Bofill Roig and Werner Brannath: Online closed procedures 3. Remi Luschei: The effect of estimating prevalences on the population-wise error rate

Friday 21th April

09:00- 10:00	<p>Session VI: Adaptive designs permitting sample size re-estimation Chair: Lisa Hampson</p> <ol style="list-style-type: none">1. Arunava Chakravartty, Xiaodong Li, Shoubhik Mondal, Pabak Mukhopadhyay: Sample size re-estimation for long term time to event trials- A case study and practical considerations2. Lara Vankelecom, Tom Loeys & Beatrijs Moerkerke: How to safely re-assess variability and adapt sample size? A primer for the two-sample the t-test
10:00- 11:00	<p>Invited Session III Chair: Robbie Peck</p> <p>Chris Jennison: Optimising sequential and adaptive designs: the power of dynamic programming</p>
11:00- 11:30 	Coffee Break and Workshop Photo
11:30- 12:00	<p>Session VII: History of the IBS-DR and ROeS ADMTP working group Chair: Thomas Asendorf</p> <p>Gerhard Hommel, Gernot Wassmer: Adaptive Designs and Multiple Testing Procedures Before the ADMTP Working Group</p>
12:00- 12:30	<p>Meeting of the IBS-DR / ROeS Working Group on ADMTP Chairs: Thomas Asendorf and Marta Bofill Roig</p>
12:30- 12:40	<p>Close of workshop Lisa Hampson and Marta Bofill Roig</p>

ABSTRACTS

INVITED SESSION I

WEDNESDAY 19TH APRIL, 13:15-14:15

Tobias Mielke

Adaptive platform trials: complex and innovative – but how useful?

Platform trials have received considerable attention over the past years, due to their successful contributions in fighting Covid-19 and due to numerous success stories in Oncology, including trials such as STAMPEDE or I-SPY-2. The central idea of platform trials is the shift in focus from a “compound perspective” to an “indication perspective”. Platform trials eventually serve as research hubs for the targeted indications and allow testing of multiple interventions against a common control arm under the common master protocol. This multi-armed nature of platform trials introduces multiplicity concerns, as well as opportunities for efficiency through a smaller total sample size (vs. separate trials), which may result in accelerated development. Platform trials allow for introduction of novel interventions as the trial progresses, since not all candidate interventions may be ready to start testing at the same time and since resource constraints may limit concurrent evaluation of too many interventions. This flexibility of adding and dropping arms during the trial introduces additional multiplicity concerns, in addition to inferential and practical complications. Platform trials are useful, as demonstrated during the Covid-19 pandemic. However, the utility of platform trials is highly dependent on stakeholder requirements, considered design elements and finally the actual real-life trial situation, which will not be fully known during the planning stage of the trial. Target of this presentation is to share experiences and lessons learned on the process of designing platform trials to ensure that the designs are fit for the purpose - instead of fitting the purpose to the design.

SESSION I: PLATFORM TRIALS

WEDNESDAY 19TH APRIL, 14:15-15:15

Peter Greenstreet, Thomas Jaki, Alun Bedding, Pavel Mozgunov

Why keeping previous data can be detrimental in platform trials with a change in standard of care

Platform trials are often seen as a more efficient way of testing multiple treatments compared to running separate trials. In this presentation we consider platform trials, where if a treatment is found to be superior to the control then it will become the new standard of care (and the control in this platform trial). The remaining treatments continue to be tested against this new control. One can either keep

the information on both the new standard of care and the other active treatments before the control is changed or one could discard this information. We will show analytically and numerically that retaining the old information can be detrimental to the power of the study. Specifically, we consider the overall power, the probability that at the end of the trial the standard of care is the active treatment with the greatest treatment effect. We also consider the conditional power of the active treatments, the probability a given treatment can be found superior against the current control. We begin by proving that in a multi-arm multi-stage trial where no arms are added during the trial, retaining the information is detrimental to the conditional power of the remaining treatments. Finally, we discuss some situations, including when arms are added later, where one may find benefit in keeping the information before the control is changed. Therefore, conclude with some ideas to consider when deciding whether to run a continuous platform trial or not.

Michaela Maria Freitag, Dario Zocholl, Stefan Gold, Martin Posch, Franz König:

Early stopping, allocation ratios and power: how to tailor design options for a platform trial in Major Depressive Disorder

Major Depressive Disorder (MDD) is one of the most common causes of disability worldwide and the leading cause of death by suicide. Even though many treatments are available for MDD, about 50% of patients do not benefit sufficiently from first-line treatment and the majority of those do not benefit from second-line treatment as well. Therefore, it is important to investigate new treatments for MDD.

Platform trials provide a new approach for clinical study designs that, compared to separate clinical trials, allows more compounds to be tested in a shorter period of time by, e.g., sharing controls, reducing clinical trial activation times, as well as recruitment times. As part of the Innovative Medicines Initiative (IMI) project EU PEARL we developed a phase II platform trial design in the field of MDD. We discuss the design process and the selection of important design elements like allocation ratios, early stopping and number of concurrently active arms. We compare different design options and present results of an extensive simulation study to investigate the operating characteristics under a range of scenarios, e.g., with regard to time trends and the availability of new compounds. Furthermore, we compare the platform trial to classical two armed randomized clinical trials to demonstrate the advantages of platform trials in terms of power and average number of compounds tested.

INVITED SESSION II: PLATFORM TRIALS – FINDINGS FROM THE EU-PEARL INITIATIVE

WEDNESDAY 19TH APRIL, 15:45-17:45

Pavla Krotka, Katharina Hees, Peter Jacko, Dominic Magirr, Martin Posch, Marta Bofill Roig

NCC: An R-package for analysis and simulation of platform trials with non-concurrent controls

"Platform trials aim at evaluating the efficacy of multiple treatments, allowing for late entry of the experimental arms and enabling efficiency gains by sharing controls. For arms that join the trial later, the control data is divided into concurrent (CC) and non-concurrent controls (NCC). Using NCC for treatment-control comparisons can improve the power but might cause biased estimates if there are time trends. Aiming at utilizing NCC while leading to valid inference, several analysis approaches have been proposed. Frequentist model-based approaches adjust for potential bias by adding time as a covariate to the regression model. The Time Machine considers a Bayesian generalized linear model that smooths the control response over time. The Meta-Analytic-Predictive prior approach estimates the control response by combining the CC data with a prior distribution derived from the NCC data.

We present the R-package "NCC" for the design and analysis of platform trials. "NCC" allows for simulating platform trials and evaluating the properties of analysis methods that use NCC in a variety of settings. In this talk, we illustrate the use of the above-mentioned approaches and show how to perform simulations through the "NCC" package. We investigate the operating characteristics of the considered approaches by means of a simulation study, focusing on assessing the impact of the overlap between treatment arms and the strength of the time trend on the performance of the evaluated models."

Quynh Nguyen, Hue Kästel, Katharina Hees, Benjamin Hofner

The use of complex clinical trials: A regulatory review

In platform trials, multiple treatments are evaluated with the possibility to add or drop treatments during the trial. Several reviews have been performed to identify complex trials including platform trials to analyse the use of these trials and the corresponding design aspects. However, literature or guidance on regulatory acceptance of specific design aspects in complex trials are still limited. Thus, we performed a review of scientific advice (ScA) procedures of products in the remit of the PEI such as mAbs, vaccines or ATMPs. The database includes more than 50000 documents covering around 2500 ScA procedures. We identified more than 140 documents representing around 20 trials. We present preliminary results on design components of proposed complex trials and the corresponding regulatory opinion. General aspects such as the study phase or the number of treatment and control arms will be described. Aspects frequently discussed for complex trials such as the use of a common control, the

use of non-concurrent controls or the need for multiplicity control were also evaluated. The latter is an ongoing discussion and guidance from regulators are limited. Thus, we performed simulations on the impact of a common control with and without multiplicity control in platform trials on error rates and the power (arXiv:2302.04713). We will complement our findings from the review with key results from our simulation to aid further discussions on the use or need for multiplicity control.

Marta Bofill Roig, Ekkehard Glimm, Tobias Mielke and Martin Posch

Optimal allocation strategies for platform trials

"Platform trials are randomized clinical trials that allow simultaneous comparison of multiple interventions, usually against a common control. Arms to test experimental interventions may enter and leave the platform over time. Therefore, the number of experimental intervention arms in the trial can change over time. Determining optimal allocation rates to allocate patients to the treatment and control arms in platform trials is challenging because the change in treatment arms implies that also the optimal allocation rates will change when treatments enter or leave the platform. In addition, the optimal allocation depends on the analysis strategy used.

In this talk, we describe optimal treatment allocation rates for platform trials with shared controls, assuming that a stratified estimation and testing procedure based on a regression model is used to adjust for time trends. We consider analysis methods using concurrent controls only as well as methods based on also non-concurrent controls. Assuming that the objective function to be minimized is the maximum of the variances of the effect estimators, we show that the optimal solution depends on the entry time of the arms in the trial and, in general, does not correspond to the square root of k allocation rule used in the classical multi-arm trials. We illustrate the optimal allocation and evaluate the power and type 1 error rate compared to trials using one-to-one and square root of k allocations by means of a case study."

Sonja Zehetmayer

Looking forward and benefiting from the past: Sample size estimation for new arms in platform trials

Platform trials have been proposed where several randomized clinical trials with related objectives are combined to a single trial with a joint master protocol to improve efficiency by reducing costs and saving time. Treatment arms can enter and leave the study at different times during its conduct, possibly depending on previous results or available resources and the total number of treatment arms in a platform trial is not fixed in advance. One big advantage of platform trials is the sharing of one or several control arms.

We optimise platform trials and give special focus on the planning stage for adding new treatment arms. This includes development of strategies for the sample size calculation for a new arm depending on the nominal level dedicated to this treatment when entering the trial. To determine the sample size

of a new treatment, also data already collected within the platform trial might be utilized, e.g., to get better estimates for nuisance parameter. The question is how to combine a priori information with the observed estimate(s) for the sample size calculation and how to address the uncertainty of the estimates. Furthermore, only part of the data might be used, e.g., data from the control arm only instead of unblinding all active treatment arms as well. We compare the impact on sample sizes needed and power also depending on which error rate should be controlled, e.g., the experiment-wise error rate or control of the False Discovery Rate with online methods.

SESSION II: ADAPTIVE DESIGNS AND MULTIPLE TESTING IN A CONFIRMATORY

THURSDAY 20TH APRIL, 09:00-11:00

Frank Bretz, Uli Burger

Principles of adaptive clinical trials - a personal view

Adaptive designs are becoming increasingly popular, with many applications in exploratory and confirmatory clinical trials. This is also reflected by the existing regulatory guidelines from EMA, FDA and NMPA, and the ongoing efforts by ICH to develop a harmonized set of principles for the regulatory review of these studies. Principles are important to provide the flexibility for the evaluation and discussion of innovative approaches to clinical trial design throughout the development process. In this presentation we review such principles for the planning, design, conduct, and analysis of trials with an adaptive design that are intended to confirm the effectiveness and safety of a treatment.

Marie Louise Østerdal, Kyle Raymond, **Christian Bressen Pipper**

Properties of a confirmatory two-stage adaptive procedure for assessing average bioequivalence

We investigate a confirmatory two stage adaptive procedure for assessing average bioequivalence and provide some insights to its theoretical properties. Effectively, we perform Two One-Sided Tests (TOST) to reach overall decision about each of the two traditional null-hypotheses involved in declaring average bioequivalence. The tests are performed as combination tests separately for each hypothesis based on the corresponding pair of stagewise p-values. Features of the procedure include a built in futility, sample size reassessment, and the ability to simultaneously assess average bioequivalence with respect to multiple endpoints while controlling the familywise error rate. To facilitate inference at the end of a trial we consider confidence limits that match the decision reached on each one sided hypothesis and provide theory ensuring their appropriateness. The performance is

assessed by simulation in the context of planning a study to compare two different administrations of an antibody treatment.

Leonhard Held

Sequential alternatives to the two-trials rule

The two-trials rule for drug approval requires "at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness". This is usually employed by requiring two significant pivotal trials and is the standard requirement by regulators before new drugs are approved. However, drug applications are often based on more than two trials and some alternatives and generalizations have been recently proposed to properly deal with this case, among them the harmonic mean chi-squared test (Held, 2020, doi: 10.1111/rssc.12410) and the 2-of-3 rule (Rosenkranz, 2022, doi: 10.1007/s43441-022-00471-4). I will show that the former has an in-built stopping rule for futility and can be extended to a sequential assessment of success while controlling the overall Type I error rate at the Type I error rate from the two-trials rule. I will compare it to the 2-of-3 rule in terms of project power and the expected number of studies required.

Akshay Patil

Checklist and reporting guidelines for estimands in adaptive or innovative clinical trial designs

Introduction and Objective(s): The systematic review & JM method interview with consensus round will aim to develop Checklist and reporting guidelines for estimand in adaptive or Innovative clinical trial Designs. There is no existing reporting guidance or related guidance under development on estimand in adaptive designs.

Method(s) and Results: We will adhere to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines and the Cochrane Collaboration Handbook. We will perform a literature search through MEDLINE (PubMed), EMBASE and CENTRAL, clinicaltrial.gov a detailed data extraction of trial characteristics and a narrative synthesis of the data.

Phases of development of checklist and reporting guidelines.

- Phase I: Systematic review of estimand in adaptive clinical trials (Literature based dataset)
- Phase II: Collect responses from stakeholders from pharmaceutical lead statistical experts (Interview based dataset)
- Phase III: Combine responses from stakeholders and systematic review (Increase validity of surveys)
- Phase IV: Development of checklist
- Phase V: Validation of checklist from pharmaceutical lead statistical experts and stakeholder.

Conclusions:

- We also address the potentially data-driven, adaptive selection of estimands in an ongoing trial and disentangle certain statistical issues that pertain to estimation.

- This guideline development work may contribute to extension of CONSORT and SPIRIT guidelines.

SESSION III: ADAPTIVE DESIGNS FOR CLINICAL TRIALS WITH TIME-TO-EVENT ENDPOINTS

THURSDAY 20TH APRIL, 11:30-13:00

Moritz Fabian Danzer, Andreas Faldum, Rene Schmidt

Adaptive designs for multiple time-to-event outcomes in Markovian multi-state models

Adaptive designs for the assessment of a single time-to-event outcome are well established. However, caution should be exercised when using interim data from secondary endpoints to make data-dependent design changes (e.g., sample size recalculation). It is particularly problematic to base design changes on interim data from an additional endpoint that may serve as a surrogate for the chosen primary endpoint.

Similar problems arise when multiple time-to-event endpoints are assessed simultaneously, as one of these variables may be used to make predictions about another variable for patients who enter the trial before an interim analysis and remain event-free beyond the interim analysis. Existing sequential group designs for multivariate survival trials cannot be extended to adaptive designs because they do not take this additional information into account.

We provide adaptive group sequential designs for testing hypotheses about the joint distribution of multiple time-to-event endpoints. Our approach allows data-dependent design modifications based on information from all involved time-to-event endpoints. To enable this, some distributional assumptions must be made. More specifically, we assume that the underlying multistate model is Markovian. Asymptotic properties of the test procedure are derived using counting process approaches. The small sample properties and the behaviour under deviations from the above conditions are studied by simulation.

Pantelis Vlachos

A new approach to trial design and probabilistic risk assessment for trials with dual survival endpoints

The advent of complex clinical trials that require Monte Carlo simulations to understand their operating characteristics has challenged the traditional process of study design. In addition to the technical challenge of exploring the design/scenario space, the process of alignment and communication of tradeoff between power, duration and cost for the clinical development team can be challenging.

Leveraging the immense power of cloud computing, the former issue is becoming quickly moot. The problem shifts from exploring the large space of possible designs and potential outcomes to how we can quickly summarize and draw conclusions from the vast amount of data at our disposal.

In this talk, we will discuss novel approaches and technologies to design trials with dual Time-to-Event(TTE) or mixtures of TTE and Binary endpoints. We arrive at optimal designs by simulating trials at scale and sort through the simulated data to surface trade-offs when selecting designs with good operating characteristics and decision-making properties. We will also showcase how probabilistic risk assessments can be visualized to strengthen exchanges with clinical, regulatory, and operational stakeholders

Deepak Parashar

A predictive biomarker enrichment design for Phase II oncology trials

In biomarker-driven trial designs patients are stratified by their biomarker signature, and one tests the null hypothesis of no treatment effect in either the full population or the targeted subgroup. However, in order to verify the predictability of a biomarker, it is essential that hypothesis be tested in the non-targeted subgroup too. I shall discuss a novel two-stage Phase II adaptive enrichment trial design in oncology that sequentially tests hypotheses in both subgroups. The data obtained can inform the Phase III design whether to restrict recruitment to just the targeted subgroup or not. For a time-to-event endpoint of progression-free survival, it is assumed that the hazard ratio of the targeted subgroup is much less than that of non-targeted such that the design reflects predictive enrichment. Results from simulations for an example trial in non-small cell lung cancer illustrate the efficiency achieved. Our adaptive design serves as an example of 'empirical enrichment' by establishing proof of the biomarker's predictability during the trial.

SESSION IV: ADAPTIVE DESIGNS FOR CLINICAL TRIALS WITH TIME-TO-EVENT ENDPOINTS

THURSDAY 20TH APRIL, 14:00-15:30

Kelly Van Lancker, Josh Betz, and Michael Rosenblum

Combining Covariate Adjustment with Group Sequential, Information Adaptive Designs to Improve Randomized Trial Efficiency

In clinical trials, there is potential to improve precision and reduce the required sample size by appropriately adjusting for baseline variables in the statistical analysis. This is called covariate

adjustment. Despite recommendations by regulatory agencies in favor of covariate adjustment, it remains underutilized leading to inefficient trials. We address two obstacles that make it challenging to use covariate adjustment. A first obstacle is the incompatibility of many covariate adjusted estimators with commonly used boundaries in group sequential designs (GSDs). A second obstacle is the uncertainty at the design stage about how much precision gain will result from covariate adjustment.

We propose a method that modifies the original estimator so that it becomes compatible with GSDs, while increasing or leaving unchanged the estimator's precision. Our approach allows the use of any asymptotically linear estimator, which covers many estimators used in randomized trials. Building on this, we propose using an information adaptive design, that is, continuing the trial until the required information level is achieved. Such a design adapts to the amount of precision gain and can lead to faster, more efficient trials, without sacrificing validity or power.

We evaluate estimator performance in simulations that mimic features of a completed stroke trial.

Cornelia Ursula Kunz, Shannon Amy Zellner, Sonja Drescher, Johannes Krisam

An adaptive balance-ensuring big stick randomization procedure for equal and unequal allocation ratios

Randomization is a key element of clinical trials reducing possible systematic bias of the treatment effect from confounding variables. The simplest complete randomization method is tossing a coin, which has the advantage that treatment assignment is unpredictable. The disadvantage of this method is that the resulting group sizes can be very different, which can noticeably affect the power. Hence, restricted randomization procedures have been proposed in which the current treatment assignment depends on the history of previously assigned treatments yielding more balanced groups.

Within the big stick design (BSD), patients are randomized equally to two groups until the observed difference between the group sizes crosses the predefined, fixed maximum tolerated imbalance (MTI). Once the MTI is reached, the next patient is assigned with probability 1 to the smaller group, forcing the groups to be more equal. Then, the procedure switches back to equal randomization probabilities until the observed difference crosses the MTI again.

While the BSD ensures that the observed difference between the sample sizes is at most equal to the MTI, there are some limitations. E.g., for trials with interim analyses, the MTI is a fixed number not considering that acceptable imbalances of group sizes are sample size dependent. We therefore extend the BSD so that the MTI adapts to the realized sample size. The new design is compared to existing methods with respect to the operating characteristics.

Maria Vittoria Chiaruttini, Jacopo Gallochio, Alessandro Desideri, Danila Azzolina, Dario Gregori

Resampling algorithm for calculation of sample size of two-stage and three-arm sequential non-inferiority clinical trials when applied to skewed outcome: a simulation study

The three-arm gold-standard design for noninferiority studies is recommended by regulatory authorities. Three-arm non-inferiority trials are challenging for the hypothesis formulation, and their design is often characterized by uncertainty in estimating the experimental treatment effect. Some methods have been proposed for the recalculation of the sample size at interim analysis but none for continuous skew outcome. The present study focuses on properly calculating the sample size of two-stage, three-arm sequential non-inferiority clinical trials with skewed endpoint, considering the benefits from the economic and ethical point of view. We questioned the homoskedasticity in the case of asymmetrical outcomes simulated as gamma variables. We provided a resampling algorithm that accounts for different standard deviations to be set across the three arms. We found that if the discrepancy between variances is considered, we can estimate an adequate initial sample size to achieve the desired power, avoiding the risk of overestimation (saving patients) or underestimation (saving power), even in case of deviation from normality. Lastly, we developed a Web application for the sample size estimation for both Gaussian and gamma populations. The tool helps to keep track of the properties of the design, as it provides an estimate of the probability of success/failure of the study, giving us the possibility to choose the best set of parameters to optimize the resources for the trial.

SESSION V: MULTIPLE TESTING PROCEDURES

THURSDAY 20TH APRIL, 16:00-17:30

Jixian Wang, Ram Tiwari

Toward optimal graphic tests

Graphic tests have been widely used in drug development. A graphic test is intuitive and flexible as it can be adapted for specific scenarios by choosing design parameters such as the relative weight of alpha (type I error) for each hypothesis and the transit matrix for alpha re-distribution after a hypothesis is rejected. In practice, a key step is to determine the design parameters based on prior information such as clinical importance and power of individual hypotheses. Although a decision analytic approach that maximizes expected average power (EAP), the task of finding optimal design parameters is very complex. We take a practical approach to consider 1) optimization approaches such as that alternating between the weights and transition matrix optimizations and/or using an optimal subgraph as initial design; 2) characters of optimal designs that may guide practical consideration, 3) sensitivity analysis that explore the impact of prior information change on EAP as well as the design parameters. We show that for many practical tasks, the abovementioned optimization approaches with derivative-free optimizers often work well. The design parameters are often more sensitive than EAP to the change of prior information. We use some well-known graphic

test examples to compare with the optimal tests we found. We argue that it is important to compare different graphic tests in practice and finding optimal tests is useful as a reference, even it is not necessarily used.

Lasse Fischer, Marta Bofill Roig and Werner Brannath

Online closed procedures

The closure principle is fundamental in multiple testing and has been used to derive many efficient procedures with familywise error rate control. However, it is often not suitable for modern research, as more flexible multiple testing settings are considered where not all hypotheses are known at the beginning of the evaluation. In this presentation, we focus on online multiple testing where a possibly infinite sequence of hypotheses is tested over time. At each step, it must be decided on the current hypothesis without having any information about the hypotheses that have not been tested yet. Our main contribution is a new online closure principle which ensures that the resulting closed procedure can be applied in the online setting. We demonstrate how short-cuts of these online closed procedures can be obtained under a suitable consonance property and apply the results in order to construct new online multiple testing methods. In particular, we illustrate the usage of the online closure principle by deriving an online version of the graphical procedure by Bretz et al. (2009).

Remi Luschei

The effect of estimating prevalences on the population-wise error rate

The population-wise error rate (PWER, Brannath et al., 2022) is a type I error rate for clinical trials with multiple target populations. It is defined as the average probability that a randomly selected, future patient will be exposed to an inefficient treatment based on the study results. By only considering type I errors that are relevant in this setting, the PWER is less conservative than the family-wise error rate. In practice, however, the relative prevalences of the patient populations needed to compute the PWER are often not known and must be estimated from the study sample. In this talk, I will examine the impact of estimating the prevalences on the true PWER. I will present results of simulations where they are estimated by the maximum-likelihood estimator from a multinomial distribution. Because of the consistency of this estimator, this leads to asymptotic PWER-control. The simulation results show that adequate control is also reached for realistic sample sizes. Finally, I will also consider the maximum family-wise error rate for the disjoint population strata that result from PWER-control in realistic situations.

Brannath et al. (2022). The population-wise error rate for clinical trials with overlapping populations. *Statistical Methods in Medical Research*. Vol. 32 (2) 334–352

SESSION VI: MULTIPLE TESTING PROCEDURES

FRIDAY 21ST APRIL, 09:00-10:00

Arunava Chakravartty, Xiaodong Li, Shoubhik Mondal, Pabak Mukhopadhyay

Sample size re-estimation for long term time to event trials- A case study and practical considerations

Sample size estimation is an important step in the design of a clinical trial. It is usually determined by statistical power requirements, a pre-specified treatment difference under the alternative hypothesis and any other nuisance parameters. However in some situations these pre-specified assumptions may be inadequate and may need to be revised based on emerging data from the ongoing trial and/or additional external information available. Adaptive methods such as sample size re-estimation can be useful to re-assess the sample size of a trial in order to ensure adequate power in such scenarios.

In this talk we present a case study with a long term time-to-event endpoint in which an unblinded sample size re-estimation is incorporated into the trial design based on health authority feedback. Using this example, the performance of the Cui, Huang and Wang method and the Promising Zone method are assessed under different assumptions of the hazard function and different adaptation strategies with regard to timing and size of the adaptation. In addition, operational perspectives such as enrollment of new patients, duration of follow-up and trial integrity implications will also be discussed.

Lara Vankelecom, Tom Loeys & Beatrijs Moerkerke

How to safely re-assess variability and adapt sample size? A primer for the two-sample the t-test

Properly powered research is crucial to ensure that published findings in the literature are reliable. Without a priori good knowledge about the population effect size and variability of the data, power analyses may underestimate the true required sample size. A specific type of a two-stage adaptive design where the sample size can be re-estimated during the data collection might partially mitigate the problem. In the design proposed in this paper, the variability of the data collected at the first stage is estimated and then used to re-assess the originally planned sample size of the study, while the raw effect size (i.e. difference in means) is fixed at a good potential estimate or at a smallest effect size of interest. We investigate through simulation the implications on the type I error rate of the final independent-samples t-test, when this re-assessment is ignored. Inflation can be substantial when the interim variance estimate is based on a small sample, but approaches the nominal level when more first stage data are collected. An R-function is provided that enables researchers to calculate for their specific study 1) the maximum type I error rate inflation and 2) the adjusted alpha-level to be used in the final t-test to correct for this inflation. Finally, the desired property of this design to better guarantee the power of the study is verified.

INVITED SESSION III

FRIDAY 21ST APRIL, 10:00-11:00

Chris Jennison

Optimising sequential and adaptive designs: the power of dynamic programming

Dynamic programming is a method for computing an optimal strategy in a sequential decision problem. It is computationally efficient since the computational demand increases linearly with the number of stages, even though the number of sample paths grows exponentially. The design of a group sequential or adaptive trials poses a sequential decision problem and thus may be amenable to dynamic programming techniques. I shall describe a number of applications of dynamic programming to clinical trial design. In particular, I shall explain how to derive optimal group sequential tests for Phase 3 confirmatory trials and how to develop an optimal treatment allocation scheme in a Phase 1, First in Human trial.

SESSION VII: HISTORY OF THE IBS-DR AND ROES ADMTP WORKING GROUP

FRIDAY 21ST APRIL, 11:30-12:00

Gerhard Hommel, Gernot Wassmer

Adaptive Designs and Multiple Testing Procedures Before the ADMTP Working Group

Long time ago, it was recognized that multiple comparisons can lead to interpretatory problems, and solutions were developed. In contrast, the consideration of (scientifically correct) adaptive designs started much later, and was initiated by Peter Bauer at the beginning of the nineties.

We start with a short overview of the history of multiple comparison procedures (MCPs) and adaptive designs (ADs) worldwide. Since the beginning of the eighties, in the German speaking countries a more intensive research on MCPs was started. In consequence, the research results were presented in some specific conferences on MCPs. In 1997, a working group of the German Region of the IBS about „Multiple Methods“ was initiated by Ludwig Hothorn. In 1999, a first kind of workshops on ADs took place, and was perpetuated in the following years. We describe the development of these working groups up to their unification forth to the ADMTP WG.