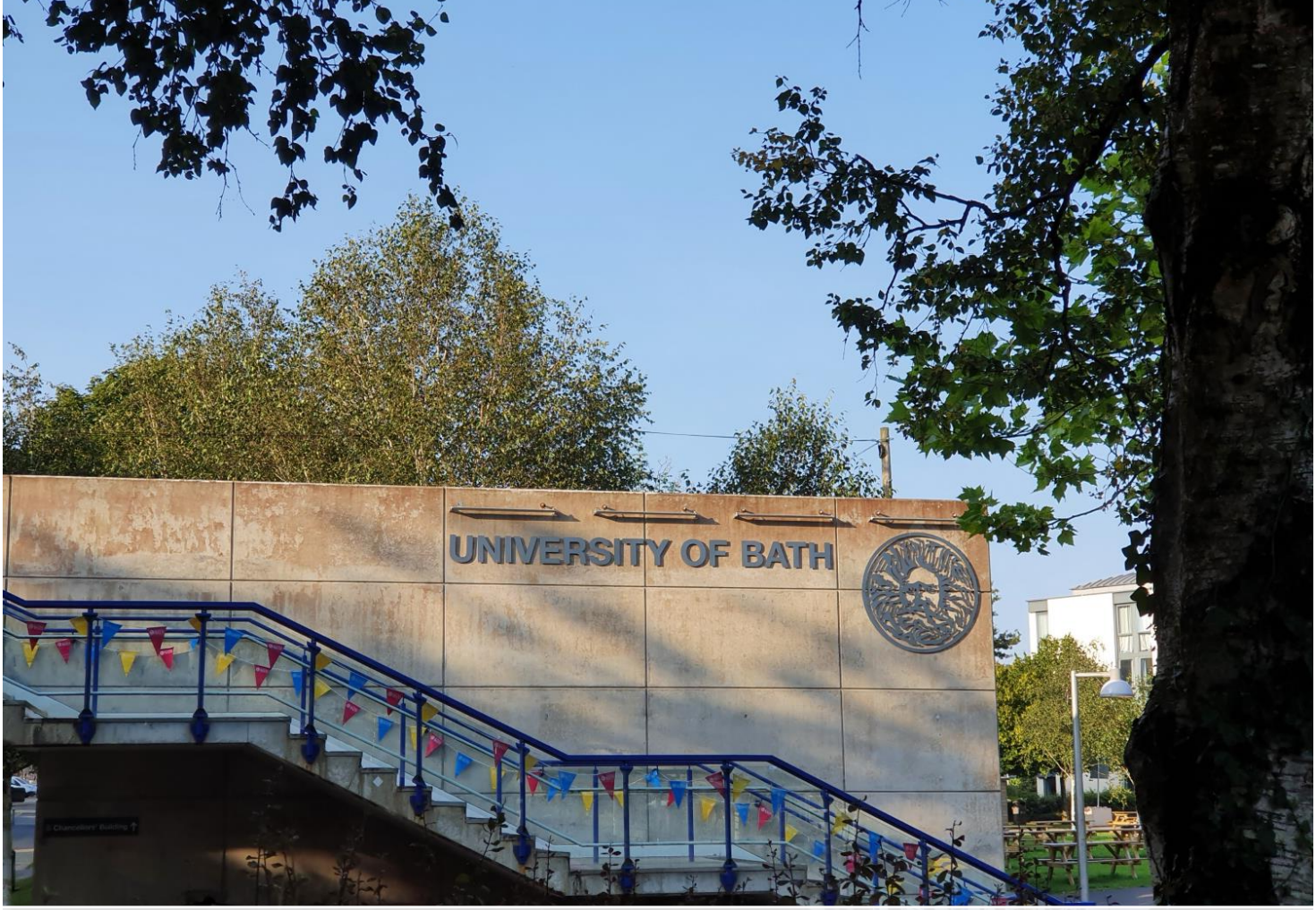

IDENT Research Dissemination Workshop

Advanced Statistical Designs to Empower Biomarker-driven Clinical Trials

Promoting the use of efficient statistical methods in practice·

30 April & 01 May 2024

16-18 Queen Square, Bath, BA1 2HN

Bath, UK

IDENT Research Dissemination Workshop, 29 April - 01 May 2024
Advanced Statistical Designs to Empower Biomarker-driven Clinical Trials
Promoting the use of efficient statistical methods in practice

Organising Committee:
Dr Haiyan Zheng, Dr Thomas Burnett, Kate Remington, Myla Watts
University of Bath, UK

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List of Abstracts – Talks

Tuesday 30 April

Session: Practical Implementation of Biomarker-driven Clinical Trials

Horses, Zebras and Unicorns

Juanita Lopez

IS

Drug Development Unit, The Institute of Cancer Research, UK

TBC.

PROFILE: a randomised, biomarker-stratified clinical trial of treatment strategies in newly-diagnosed Crohn's disease

Nurulamin Noor IS

Department of Medicine, University of Cambridge, UK

Background Management strategies and outcomes vary in patients newly-diagnosed with Crohn's disease. We evaluated the clinical utility of a biomarker in patients receiving "top-down" or "accelerated step-up" therapy in newly-diagnosed, active Crohn's disease.

Methods PROFILE (PRedicting Outcomes For Crohn's dIsease using a moLecular biomarker, ISRCTN 11808228) was an open-label, biomarker-stratified, randomised controlled trial of adults with newly-diagnosed Crohn's disease (Harvey Bradshaw Index >7 and C-reactive protein > upper limit of normal or fecal calprotectin >200 ug/g, with active inflammation at endoscopy). Patients were randomised to "top-down" (infliximab/immunomodulator) or "accelerated step-up" treatment stratified by: biomarker subgroup (termed IBDhi/IBDlo), endoscopic inflammation (mild/mod/severe) and extent (colonic/other). The primary endpoint was sustained steroid and surgery-free remission to week 48 and the key secondary endpoint was endoscopic remission (absence of ulcers) at week 48.

Results 386 patients were randomised from December 2017 to January 2022. Median time from diagnosis to trial enrolment was 12 days (0-191). Primary outcome data were available for 379 eligible participants, with sustained steroid and surgery-free remission being more frequent in "top-down" vs "accelerated step-up" (79% vs 15%, absolute difference 64%, 95% CI=57 to 72%, p<0.0001), and no biomarker-treatment interaction effect. Endoscopic remission at week 48 was greater in "top-down" compared to "accelerated step-up" (67% vs 44%, absolute difference 23%, 95% CI=11 to 36%, p-value <0.0001), with fewer urgent abdominal surgeries (1 vs 10, odds ratio=0.095, 95% CI=0.001-0.505).

Conclusion "Top-down" treatment with combination infliximab/immunomodulator achieved substantially better outcomes compared to "accelerated step-up" therapy. The biomarker did not show clinical utility in PROFILE. "Top-down" should now be considered standard-of-care for patients with newly-diagnosed active Crohn's disease.

Some examples of innovative trial design in real world practice

Alexander Ooms

IS

Centre for Statistics in Medicine, University of Oxford, UK

Precision medicine and biomarker-driven clinical trials have the potential to create targeted treatments based on a person's individual make-up, looking beyond average treatment effects in broad-based populations to inform treatment decisions. The use historical data to improve decision making, through Bayesian statistics, can lead to smaller, faster trials, making formal use of information already available to us. This talk will give an example of both a precision medicine and small Bayesian trial, making use of historical data in the form of an informative prior, that are currently being run in the real world.

The precision medicine trial focuses on patients with psoriatic arthritis (PsA) and asks if we can predict which patients will respond to certain biologic drugs using blood tests taken before starting treatment. If successful, this could ensure patients receive their best option first, ensuring their disease is controlled more quickly and quality of life improved, while avoiding unnecessary drug use.

The Bayesian trial explores the safety and tolerability of different doses of Radiotherapy (RT) delivered via machine called the MR Linac to treat pancreatic cancer. The MR Linac combines two technologies – an MRI scanner and a conventional radiotherapy treatment machine. This, in theory, allows higher more focused doses or RT to be given to the target tumour while reducing toxicities to the surrounding organs. Previous research into RT in Pancreatic cancer allowed us to have an informed idea of the prior toxicity profile. In this talk, I will present information on these trials.

Session: The Quest for Precision Medicine

Sample size re-estimation in a precision medicine trial

Chris Hurt IS

Southampton Clinical Trials Unit, University of Southampton, UK

Sample size calculation in precision medicine trials often involve more assumptions than other trials. As well as estimates of parameters such as control group event rates they also include estimates of proportions of patients going into different randomisations. Additionally, precision medicine trials are often longer than other trials due to the tighter definition of treatment groups and fewer available patients. This presents a problem in that initial estimates can change over time but also an opportunity for sample size re-estimation before recruitment ends.

PATHOS is a Phase II/III non-inferiority trial of risk-stratified, reduced intensity adjuvant treatment in patients undergoing transoral surgery for HPV positive oropharyngeal cancer. A post operative pathological risk assessment classes patients into 3 groups: group A (low risk), group B (medium risk) and group C (high risk). Group B and Group C are randomised to different de-intensification strategies. At the design stage of the trial, assumptions were made about the proportion of all recruited patients who would go into each risk group and the event rate in the control groups.

The IDMC have been monitoring the estimates used in the initial sample size calculation and have recommended a sample size re-calculation as recruitment approaches completion. Changes in surgical technique during recruitment have dramatically changed the proportions of patients going into the different risk groups and event rates are also different to those used in the initial sample size calculation. The strategy that the IDMC proposed for dealing with this will be presented and lessons learned will be discussed.

Design and analysis of basket trials considering pairwise data commensurability

Haiyan Zheng

Department of Mathematical Sciences, University of Bath, UK

The paradigm of drug development has been revolutionised due to advances in genomic technology. Patients can now be stratified into small subgroups that may receive different benefits from a new treatment. This has brought a paradigm shift from one-size-fits-all approach towards precision medicine to deliver the right treatment to the right patients at the right time. One innovative approach to precision medicine is to conduct basket trials that simultaneously evaluate a new treatment in patients of various cancer types under an overarching protocol. Eligible patients nonetheless share a common feature (e.g., a genetic aberration, or mechanism of drug action), on which the new treatment may potentially improve patient outcomes. Sophisticated analysis models for basket trials, featuring borrowing of information between subgroups (strata), are preferred over the stand-alone analyses which regard the strata in isolation. Such joint analysis can generally yield higher power to detect a treatment benefit while accommodating patient's heterogeneity.

In this talk, I shall introduce an innovative Bayesian model [1] that characterise the complex data structure. More specifically, this model reflects the concern that the treatment effect in some strata may be more commensurate between themselves than with others. Closed-form sample size formulae can be derived to enable borrowing of information between commensurate strata [2,3]. Perspectives will be also given on the future methodology development for basket trial designs.

References

[1] Zheng H, Wason JMS. (2022) Borrowing of information across patient subgroups in a basket trial based on distributional discrepancy. Biostatistics, 23(1): 120-135.
[2] Zheng H, Jaki T, Wason JMS. (2023) Bayesian sample size determination using commensurate priors to leverage pre-experimental data. Biometrics (Biometric Methodology), 79(2): 669-683.
[3] Zheng H, Grayling MJ, Mozgunov P, Jaki T, Wason JMS. (2023) Bayesian sample size determination in basket trials borrowing information between subsets. Biostatistics, 24(4): 1000-1016.

Bayesian modelling strategies for borrowing of information in randomised basket trials

Luke Ouma IS

AstraZeneca, UK

Basket trials are an innovative precision medicine clinical trial design evaluating a single targeted therapy across multiple diseases that share a common characteristic. Today, several Bayesian methods permitting information sharing across subtrials have been proposed for their analysis, but mainly focusing on single-arm basket designs. In randomised basket trials, 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 different 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.

References

Ouma LO, Grayling MJ, Wason JMS, Zheng H. (2022) Bayesian modelling strategies for borrowing of information in randomised basket trials. Journal of the Royal Statistical Society: Series C, 71(5): 2014-2037.

Umbrella designs: Past, present and future implementations

Michael Grayling IS

Johnson & Johnson, UK

Using results from a recent review article [1], in this talk I will discuss all things umbrella trial related. This will include describing several examples of studies that have successfully leveraged this type of design, alongside discussion of some core design issues like multiplicity control and handling patient eligibility for multiple sub-studies. I will also talk about the potential of umbrella designs outside of oncology, and the barriers to this potential being realised. To conclude, I will describe where I think umbrella designs hold most promise for future trials.

References

[1] Ouma LO, Wason JMS, Zheng H, Wilson N, Grayling MJ. (2022) Design and analysis of umbrella trials: Where do we stand? Frontiers in Medicine, 9: 1037439.

Session: Dose-finding Trials Using Biomarker Information

Using ctDNA as a novel biomarker of efficacy for dose-finding designs in oncology

Pavel Mozgunov IS

MRC Biostatistics Unit, University of Cambridge, UK

Dose-finding trials are designed to identify a safe and potentially effective drug dose and schedule during the early phase of clinical trials. Historically, Bayesian adaptive dose-escalation methods in Phase I trials in cancer have mainly focused on toxicity endpoints rather than efficacy endpoints. This is partly because efficacy readouts are often not available soon enough for dose escalation decisions. In the last decade, 'liquid biopsy' technologies have been developed, which may provide a readout of treatment response much earlier than conventional endpoints.

This paper develops a novel design that uses a biomarker, circulating tumor DNA (ctDNA), with toxicity and activity outcomes in dose-finding studies. We compare the proposed approach based on repeated ctDNA measurement with an existing Bayesian adaptive approach under various scenarios of dose-toxicity, dose-efficacy relationship, and trajectories of regular ctDNA values over time. Simulation results show that the proposed approach can yield significantly shorter trial duration, and may improve identification of the target dose. In addition, this approach has the potential to minimise the time individual patients spend on potentially inactive trial therapies.

Optimizing NK cell doses for heterogeneous cancer patients based on multiple event times

Peter F. Thall IS

MD Anderson Cancer Center, The University of Texas, US

A sequentially adaptive Bayesian design is presented for a clinical trial of umbilical cord blood-derived natural killer cells to treat severe haematologic malignancies. Six prognostic subgroups are defined by disease type and severity. The goal is to optimize cell dose within each subgroup, based on five co-primary outcomes, the times to severe toxicity, cytokine release syndrome, disease progression, response, and death. A multivariate Weibull regression model is assumed, with marginals depending on dose, subgroup, and patient frailties that induce association among the event times. Utilities of all possible outcome combinations over the first 100 days following cell infusion are elicited, and posterior mean utility is used as a criterion to optimize dose. For each subgroup, the design stops accrual to doses having an unacceptably high death rate, and selects an optimal safe dose at the end of the trial. A simulation study is presented to validate the design's safety and ability to identify optimal doses.

References

Lee J, Thall PF, Rezvani K. Optimizing natural killer cell doses for heterogeneous cancer patients on the basis of multiple event times. JRSS-C 68: 461–474, 2019.

DEMO: Dose Exploration, Monitoring, and Optimization using a biological mediator for toxicity, response, and survival

Ruitao Lin IS

MD Anderson Cancer Center, The University of Texas, US

While phase 1-2 designs provide a methodological advance over phase 1 designs for dose finding by using both clinical response and toxicity, a phase 1-2 trial still may fail to select a truly optimal dose. This is because early response is not a perfect surrogate for long term therapeutic success. To address this problem, a generalized phase 1-2 design first uses a phase 1-2 design's components to identify a set of candidate doses, adaptively randomizes patients among the candidates, and after longer follow up selects a dose to maximize long-term success rate. In this paper, we extend this paradigm by proposing a design that exploits an early treatment-related, real-valued biological outcome, such as pharmacodynamic activity or an immunological effect, that may act as a mediator between dose and the clinical outcomes including tumor response, toxicity, and survival time. We assume multivariate doseoutcome models that include effects appearing in causal pathways from dose to the clinical outcomes. Bayesian model selection is used to identify and eliminate biologically inactive doses. At the end of the trial, a therapeutically optimal dose is chosen from the set of doses that are acceptably safe, clinically effective, and biologically active to maximize restricted mean survival time. Results of a simulation study show that the proposed design may provide substantial improvements over designs that ignore the biological variable.

Keynote Speech

Overview of augmenting randomized-controlled trials by incorporating information across multiple external sources of the control arm

J. Jack Lee KL

MD Anderson Cancer Center, The University of Texas, US

Interest in augmenting randomized controlled trials by supplementing the concurrent control arm with external data sources in drug development has been rapidly growing. The work includes hybrid control and synthetic control studies. Bayesian hierarchical models with informative priors are used as a common platform for information borrowing. Several methods have been proposed including the power prior, commensurate prior, meta-analytic predictive prior, multi-source exchangeable model, and self-adaptive mixture (SAM) prior, etc. However, external data may lack between-population exchangeability due to varying eligibility criteria, different distributions of confounding covariates, and other factors. Despite these challenges, to further facilitate proper information borrowing, we propose approaches with stratified propensity score and data-driven mixture prior. We stratify patients in both concurrent and external controls based on their propensity scores to address the effect of heterogeneity and mitigate observed confounding. To reduce unobserved confounding and address prior data conflict at the outcome level, we construct self-adaptive mixture prior and calibrated elastic mixture prior to form, the stratified propensity score self-adaptive mixture (SPS-SAM) prior and the stratified propensity score calibrated elastic mixture (SPS-CEM) prior, respectively. The mixture prior is composed of an MAP prior and a vague prior. Simulations show that, under various data heterogeneity scenarios, SPS-SAM prior and SPS-CEM prior can obtain accurate, efficient, and robust estimations of both stratum-specific and overall treatment effects.

Panel Discussion: Borrowing of Information & Statistical Tools

Discussants:
Dr Ruitao Lin, Dr Michael Grayling, Professor Nigel Stallard, Professor Lucinda Billingham

End of Workshop Day 1.

Speakers' Dinner - start from 6pm

Wednesday 01 May

Session: Statistical Analysis of Basket, Umbrella, and Platform Trials

Dealing with challenges emerging during recruitment in the umbrella-basket DETERMINE trial

Lucinda Billingham IS

CRUK Clinical Trials Unit, University of Birmingham, UK

TBC.

Frequentist analysis of basket trials with one-sample Mantel-Haenszel procedures

Satoshi Hattori IS

Department of Biomedical Statistics, Osaka University, Japan

Recent substantial advances of molecular targeted oncology drug development are requiring new paradigms for early-phase clinical trial methodologies to enable us to evaluate efficacy of several subtypes simultaneously and efficiently. The concept of the basket trial is getting of much attention to realize this requirement borrowing information across subtypes, which are called baskets. Bayesian approach is a natural approach to this end and indeed the majority of the existing proposals relies on it. On the other hand, it required complicated modelling and may not necessarily control the type 1 error probabilities at the nominal level. In this talk, we discuss a purely frequentist approach for basket trials based on one-sample Mantel-Haenszel procedure relying on a very simple idea for borrowing information under the common treatment effect assumption over baskets. We show that the proposed Mantel-Haenszel estimator for the treatment effect is consistent under two limiting models of the large strata and sparse data limiting models (dually consistent) and propose dually consistent variance estimators. The proposed estimators are interpretable even if the common treatment effect assumptions are violated. Then, we can design basket trials in a confirmatory matter. We propose this confirmatory part is followed by exploratory analyses to identify effective baskets with a newly developed information criterion. Further extension to incorporate external information within frequentist framework is also discussed to improve the exploratory basket-identification.

Online error rate control for platform trials

David Robertson

IS

MRC Biostatistics Unit, University of Cambridge, UK

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 (FWER). In this article, 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 show that the algorithms for online error rate control can have a substantially lower FWER than uncorrected testing, while still achieving noticeable gains in power when compared with the use of a Bonferroni correction. We also illustrate how online error rate control would have impacted a currently ongoing platform trial.

Session: Practice and Perspectives on Innovative Trial Designs

Venturing into non-cancer territory: a tale of two baskets

Philip Pallmann IS

Centre for Trials Research, Cardiff University, UK

When the 'Decision on Optimal Combinatorial Therapies in IMIDs Using Systems Approaches' (DocTIS) trial was first proposed in 2018, it was one of the first non-cancer studies to use an adaptive basket design. The EU Horizon 2020 funded DocTIS project aimed to identify an optimal combinatorial therapy of repurposed drugs and test its efficacy across six different immune-mediated inflammatory diseases (IMIDs): 1) systemic lupus erythematosus, 2) ulcerative colitis, 3) Crohn's disease, 4) rheumatoid arthritis, 5) psoriasis, and 6) psoriatic arthritis. Despite being a clinically heterogeneous group of autoimmune conditions, these IMIDs share key features at the molecular and cellular levels, thus making a treatment with a common molecular target, identified via a positive biomarker profile, suitable for joint cross-disease evaluation in a basket trial.

DocTIS was designed as an adaptive basket trial, consisting of one single-arm study using Simon's two-stage design per IMID, allowing for early 'pruning' of IMIDs for which the combinatorial treatment is not showing sufficient response, and 'pooling' of results across multiple IMIDs at the end, with opportunities to borrow information across conditions. The primary endpoint was chosen to be the proportion of participants who achieve disease remission at 24 weeks based on condition-specific criteria. The sample size was specified as 80 adults with active disease, a positive biomarker profile, and refractory to conventional therapy. This was based on the assumption that 24-week remission rates of at least 30-35% would be required for combinatorial therapy to be viewed as sufficiently promising.

Enhancing Bayesian two-endpoints adaptive design with semiparametric priors

Paola Berchialla IS

Department of Clinical and Biological Sciences, University of Torino, Italy

Clinical trial designs often fall short in the pediatric context due to assumptions that may not hold for children. For instance, the linear dose-response relationship assumed in adult trials may not apply to pediatric populations, where developmental stages significantly impact treatment efficacy and safety. Moreover, minimizing burden and ethical placebo concerns necessitate conclusive results from smaller samples and shorter duration. Another critical, overlooked aspect is incorporating secondary endpoints, particularly discontinuation rates, which can provide crucial insights into tolerability and long-term feasibility.

Gajewski's Bayesian two-endpoint sequential design is based on interim assessments of treatment effect estimation and a secondary endpoint evaluation. The original parametric framework assumed a normal prior for both. However, for the pediatric-specific challenges, a semiparametric prior elicitation approach could be a proficient strategy, especially when defining priors is uncertain, or prior-data conflicts arise. The semiparametric flexibility suits pediatric populations, where treatment responses can be highly variable, and diverse expert opinions may arise.

This study incorporated semiparametric priors for expert opinion into the Bayesian two-endpoint sequential design. Simulation experiments evaluated the design's operating characteristics across uninformative, weakly informative, and informative prior scenarios.

A phase II trial evaluating oral dexamethasone for reducing kidney scarring in infants with febrile urinary tract infections served as an example. The trial assessed adding oral steroids to antibiotics to prevent scarring versus antibiotics alone. The primary endpoint was the difference in scarring rates between treatment groups. The secondary outcome focused on the acceptability of adjunct steroid treatment, evaluated by discontinuation rates and reported side effects.

Use of short-term outcomes in adaptive seamless designs with treatment or subgroup selection

Tim Friede IS

Department of Medical Statistics, University Medical Center Göttingen, Germany

The landscape of clinical research is rapidly changing with boundaries between development phases dissolving, master protocols facilitating broader developments focussing not only on a single treatment or single disease, and study designs becoming more flexible through applications of adaptive designs. Adaptive seamless designs combine aspects of learning and confirming, which are associated with phases 2 and 3 of clinical development programmes, in a single trial. These include treatment or dose selection as well as subgroup selection (also known as enrichment). In practical applications adaptations are often informed by short-term outcomes, since no or insufficient information on the longer-term primary outcome is available at the time of the interim analysis. In this presentation, we present adaptive seamless designs with treatment or subgroup selection. Specifically, we will comment on a framework for optimal designs and will comment on computational aspects included efficient simulations. The approaches will be motivated and illustrated by clinical trials in a variety of disease areas.

Complex trial designs at the MHRA

Julia Saperia IS

Medicines and Healthcare products Regulatory Agency, UK

TBC.

Session: Confirmatory Adaptive Designs with Multiple Comparisons

Designing a multi-test multi-stage clinical trial

Chris Jennison IS

Department of Mathematical Sciences, University of Bath, UK

Multiple hypothesis testing arises in clinical trials that compare more than one treatment against a control, have multiple patient subgroups, or have more than one endpoint. Examples include: basket and umbrella trials, phase 3 trials comparing 2 versions of a new treatment against control, seamless phase 2/3 designs, enrichment designs, and group sequential trials with a secondary endpoint. It is common to use adaptation in such trials to shift the focus onto specific questions in response to interim data. I shall describe a general framework that facilitates the design of multi-test multi-stage trials which protect the family-wise error rate. The building blocks for these designs are a closed testing procedure (to guarantee the family-wise error rate) and combination tests (to merge data across stages). I shall offer guidance on how to define the ingredients of these procedures in order to meet a trial's objectives in an efficient manner, illustrating this with an example of a multi-arm multi-stage trial.

Optimising subgroup selection in two-stage adaptive enrichment and umbrella designs

Thomas Burnett IS

Department of Mathematical Sciences, University of Bath, UK

TBC.

Confirmatory adaptive enrichment designs with a continuous biomarker

Nigel Stallard IS

Division of Health Sciences, University of Warwick, UK

TBC.

Session: Talks by Student Award Winners

Bayesian sample size determination using robust commensurate priors with interpretable discrepancy weights

Lou E. Whitehead IS

Newcastle University, UK

Randomized controlled clinical trials provide the gold standard for evidence generation in relation to the effectiveness of a new treatment in medical research. Relevant information from previous studies may be desirable to incorporate in the design (and analysis) of a new trial, with the Bayesian paradigm providing a coherent framework to formally incorporate prior knowledge. Many established methods involve the use of a discounting factor, sometimes related to a measure of 'similarity' between historical sources and the new trial. However, it is often the case that the sample size is highly nonlinear in those discounting factors. This hinders communication with subject-matter experts to elicit sensible values for borrowing strength at the trial design stage. Focusing on a commensurate predictive prior method that can incorporate historical data from multiple sources, we highlight a particular issue of nonmonotonicity and explain why this causes issues with interpretability of the discounting factors (hereafter referred to as 'weights'). We propose a solution and further derive an analytical sample size formula. We then propose a linearization technique such that the sample size changes uniformly over the weights. Our approach leads to interpretable weights that represent the probability that historical data are (ir)relevant to the new trial, and could therefore facilitate easier elicitation of expert opinion on their values.

U-PRO-CRM: Designing patient-centred dose-finding trials with patient-reported outcomes

Emily Alger IS

The Institute of Cancer Research, UK

Background Determining the Maximum Tolerated Dose (MTD) remains the primary objective for the majority of dose-finding oncology trials. Whilst MTD determination often relies upon clinicians to identify dose-limiting toxicities (DLTs) experienced by patients during the trial, research suggests that clinicians may underreport patient's adverse events. Therefore, contemporary practice may be exposed to recommending intolerable doses to patients for further investigation in subsequent trials. There is increasing interest in patients self-assessing their own symptoms using Patient-reported Outcomes (PROs) in dose-finding trials.

Design We present Utility-PRO-Continual Reassessment Method (U-PRO-CRM), a novel trial design which simultaneously uses clinician-rated and patient-rated DLTs (Clinician-DLTs and Patient-DLTs respectively) to make dose (de-) escalation decisions and to recommend a MTD. U-PRO-CRM contains the published PRO-CRM as a special case and provides greater flexibility to trade-off the rate of Patient-DLTs and Clinician-DLTs to find an optimal dose. We present simulation results for U-PRO-CRM.

Results For specified trade-offs between Clinician-DLT and Patient-DLT rate, U-PRO-CRM outperforms the PRO-CRM design by identifying the true MTD more often. In the special case where U-PRO-CRM generalises to PRO-CRM, U-PRO-CRM performs as well as its published counterpart. U-PRO-CRM minimises the number of patients overdosed whilst maintaining a similar proportion of patients allocated to the true MTD.

Conclusion By employing a utility-based dose selection approach, U-PRO-CRM offers the flexibility to define a trade-off between the risk of patient-rated and clinician-rated DLTs for an optimal dose. Patient-centric dose-finding strategies, which integrate PROs, are poised to assume an ever more pivotal role in significantly advancing our understanding of treatment tolerability. This bears significant implications in shaping the future landscape of early phase trials.

Panel Discussion: Master Protocols for Precision Oncology and Beyond

Discussants:
Professor Chris Jennison, Dr Philip Pallmann, Julia Saperia, Professor J. Jack Lee

End of Workshop Day 2.

Useful Information

Workshop **talks** will be held at the **Elwin Room** of BRLSI. It is situated on the 1st floor.

Coffee, tea, biscuits, luncheons will be offered according to the schedule available at `https://www.zhengh-stats.co.uk/projects/ident/workshop`.

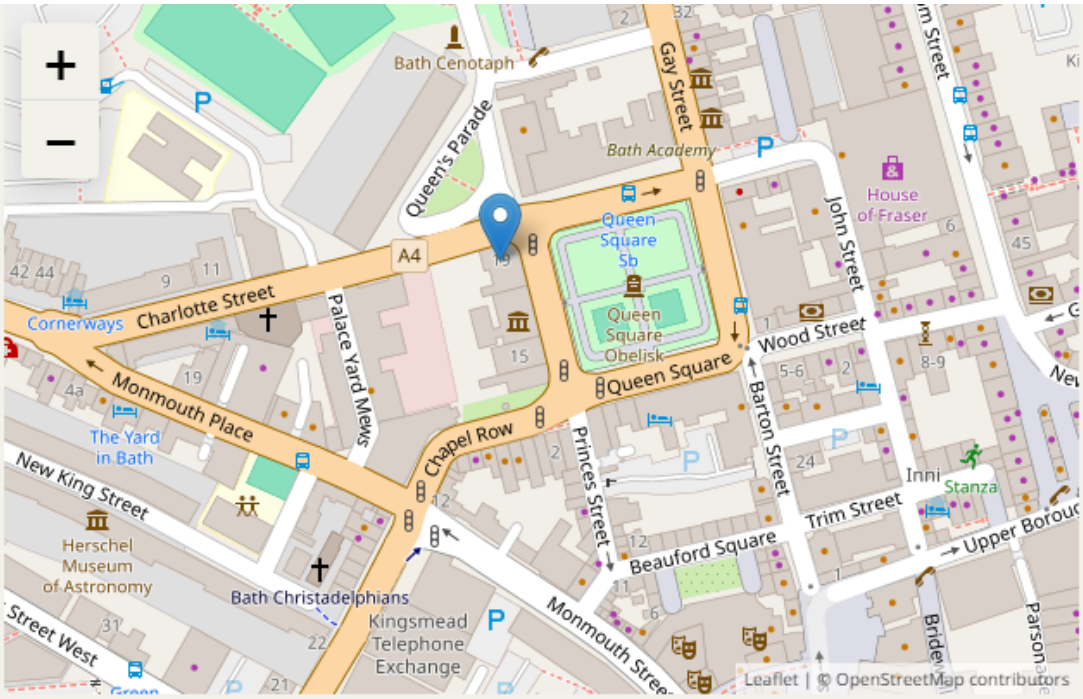
Wi-Fi will be available during the conference. The BRLSI also provides access to an eduroam network.

The **Speaker's Dinner** will be held at the Boho Marché, 6 Queen Square Bath, Bath and North East Somerset BA1 2HH. TEL: 01225473351

How to get to the BRLSI?

Founded in 1824, the Bath Royal Literary and Scientific Institution (BRLSI) is an educational charity based in Bath, England. The address is16-18 Queen Square Bath BA1 2HN. It can be reached by:

- **Rail:** Bath Spa railway station is 10-15 minutes walk away. Taxis are available from the railway station at most times.
- **Coach:** Bath's new coach station is next door to the railway station.
- **Car:** BRLSI is on the A4 as it goes through the centre of Bath. We are five minutes from the Charlotte Street long-stay car park (10 mins if you park at the far end!) - drive past BRLSI, turn left at the top of the square, then first right (it's the empty space below 'Royal Ave' on the map, right). There is also limited on-street parking in Queen Square.



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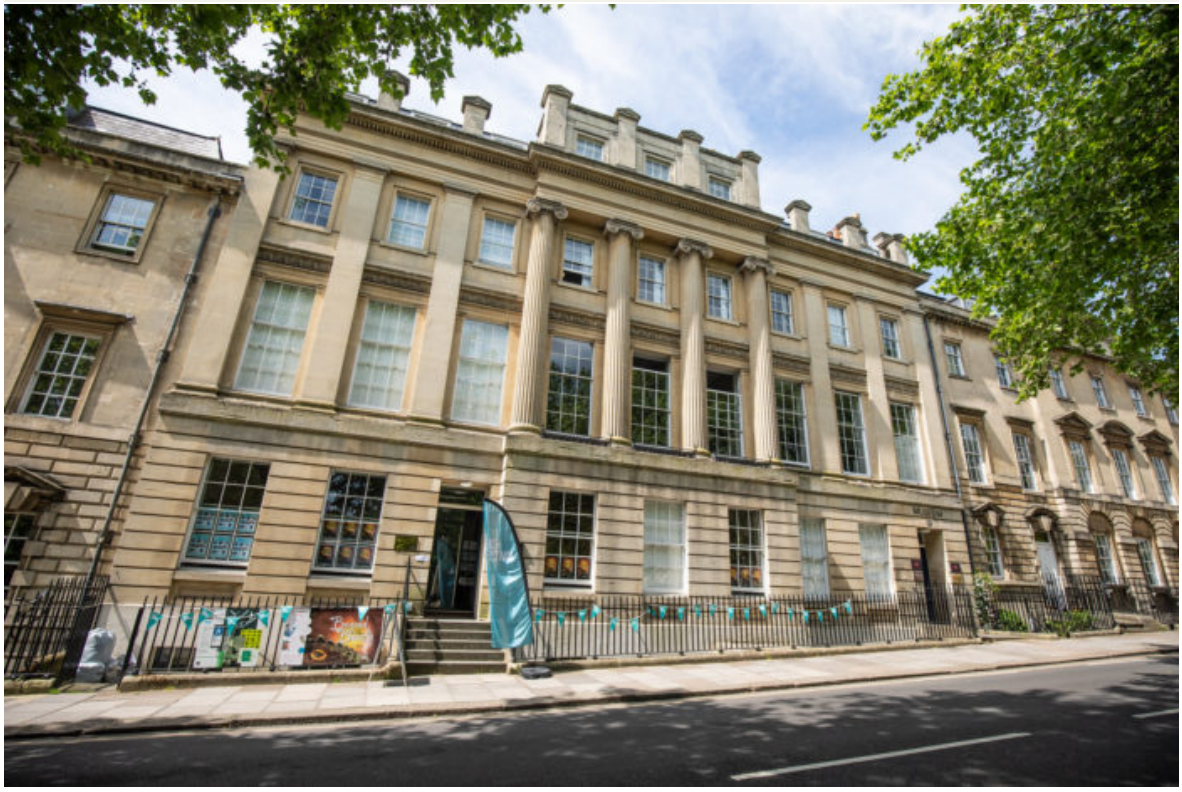

Host Institution and Sponsors

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