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Trials

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P-1
Abstract omitted

P-2
Some practical considerations in the design of multi-arm multi-stage designs

Jerome Wulff, Nikolaos Demiris
Cambridge Clinical Trial Unit, Cambridge, United Kingdom
Trials 2019, **20(Suppl 1):**P-2

Introduction: In the design of cancer clinical trials, one is often concerned with a number of options in the event that several treatments are of interest.
Methods: We explore in this work the distinct possibilities when four treatments are available, one acting as control and three as potentially efficacious alternatives. This design may be embedded within the context of multi-arm multi-stage (MAMS) trials where one may select a two- or three-stage design.
Potential Results: We explore the application of such designs, including trade-offs between potential gains in the number of patients with additional stages contrasted with patients "lost" due to practical considerations such as patients randomised in dropped arms while waiting for interim analyses and inspection by an Independent Data and Safety Committee. In addition, in cancer studies one may focus on the primary end-point using a time-to-event analysis or a binary outcome by looking at the probability of (potentially progression-free) survival at a specific, clinically meaningful, time point. The effect of such choices is extensively investigated.
Potential Relevance & Impact: We conclude with a discussion of the available software for MAMS designs and their advantages and disadvantages in terms of accuracy.

P-3
The UK plasma based Molecular profiling of Advanced breast cancer to inform Therapeutic CHoices (plasmaMATCH) Trial: A multiple parallel-cohort, phase IIa platform trial aiming to provide proof of principle efficacy for designated targeted therapies in patient subgroups identified through ctDNA screening (CRUK/15/010)

Sarah Kernaghan[1], Laura Moretti[1], Lucy Kilburn[1], Katie Wilkinson[1], Claire Snowdon[1], James Morden[1], Iain Macpherson[2], Andrew Wardley[3], Rebecca Roylance[4], Richard Baird[5], Alistair Ring[6], Nicholas Turner[7], Judith M Bliss[1], on behalf of the plasmaMATCH Trial Management Group
[1]Clinical Trials and Statistics Unit at The Institute of Cancer Research (ICR-CTSU), United Kingdom; [2]The Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; [3]The Christie NHS Foundation Trust, Manchester, United Kingdom; [4]University College London Hospitals NHS Foundation Trust, London, United Kingdom; [5]Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; [6]The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; [7]The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, United Kingdom
Trials 2019, **20(Suppl 1):**P-3

Introduction: plasmaMATCH is a novel platform trial which assesses the potential of circulating tumour DNA (ctDNA) screening to direct targeted therapies in advanced breast cancer (ABC) patients. The trial recruited ahead of target and will report initial results within 3years of first patient first visit demonstrating efficiency of this design.
Methods: plasmaMATCH is an open-label, multi-centre phase IIa platform trial, consisting of a ctDNA screening component and five parallel treatment cohorts. Patients with an actionable mutation identified at ctDNA screening are invited to enter Cohorts A-D to receive a targeted treatment matched to the mutation identified (A: ESR1–extended-dose fulvestrant; B: HER2–neratinib+/-fulvestrant; C&D: AKT1 (or PTEN for Cohort D) –AZD5363+/-fulvestrant). Cohort E was added

later to recruit patients with triple negative BC with no actionable mutation identified by ctDNA screening to receive olaparib+AZD6738. ~1150 patients will be screened, with 195 evaluable patients entered into cohorts (A–78; B–16; C–16; D–16; E–maximum 69). Each cohort will be analysed independently. The primary endpoint for Cohorts A–E is confirmed objective response rate by RECIST v1.1. Secondary endpoints include clinical benefit rate, progression-free survival, safety and frequency of mutations identified in ctDNA screening.
Timing of potential results: Screening for Cohort A closed in March-2019 and for B-D in April-2019. ctDNA screening and Cohorts A-D results will be presented in Q4-2019.
Potential relevance & impact: plasmaMATCH is a successfully recruiting platform trial that seeks to determine the efficiency of the dynamic trial platform design in providing proof of principle efficacy for designated targeted therapies. plasmaMATCH also seeks to demonstrate utility of ctDNA as a screening tool for ABC patients, with the aim of future integration into routine clinical practice. Details of the novel trial design will be presented with illustrations of trial innovation and efficiencies. Clinical outcome data will not be presented.

P-4
Abstract omitted

P-5
Optimising hypothesis tests of efficacy in external pilot trials using Bayesian statistical decision theory
Duncan T. Wilson, Rebecca E. A. Walwyn, Julia Brown, Amanda J. Farrin
Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK
Trials 2019, **20(Suppl 1):**P-5

Introduction: External pilot trials of complex interventions are often conducted in advance of a definitive trial to assess feasibility and to inform its design. The efficacy of the intervention is rarely assessed using a formal hypothesis test since it would have low power, given the small sample size of a pilot and assuming a conventional type I error rate (e.g. 0.05). An external pilot not testing efficacy will effectively have a type I error rate of 1, suggesting an infinite preference for type I errors over type II errors. As such a preference will never occur in practice, we consider methods for finding the optimal balance of type I and II error rates in external pilots.
Methods: We consider the problem of determining the sample size and type I error rate which maximise the expected utility of an external pilot trial testing intervention efficacy. We introduce a utility function which accounts for improvement in primary outcome, the cost of sampling, treatment costs, and the decision-maker's attitude to risk. We apply the method to the re-design of a pilot trial with a continuous primary outcome with known standard deviation and where uncertainty in the treatment effect is quantified using a normal prior distribution.
Timing of potential results: A study of the proposed method's properties under a range of values for the utility function and prior distribution parameters is to be completed by August 2019.
Potential relevance and impact: By viewing external pilot trial design from a Bayesian decision-theoretic viewpoint, we will provide a method for finding the optimal balance of type I and II error rates in external pilots. In particular, we will identify in which (if any) settings the current approach of not assessing efficacy is the optimal course of action.

P-6
Rare Disease Clinical Trials: Using a continuous covariate to allocate patients in a response-adaptive clinical trial
Holly Jackson
Lancaster University, United Kingdom
Trials 2019, **20(Suppl 1):**P-6

Introduction: The randomised controlled trial (RCT) is the conventional method used in a clinical trial, as it produces large power. However, the RCT gives no opportunity to change the treatment allocation probability within the trial. In many rare disease clinical trials, a large proportion of the patient population is entered into the trial. Hence, a response-adaptive design can change the probability of each patient receiving a treatment, to prioritise the health of those patients within the trial. The aim of these trials is not just to determine if a new treatment is safe and effective, but also, to treat as many patients as successfully as possible. Response-adaptive designs are not often used as they produce a low power and many of them do not consider the patient's covariates.
Method: We present a response-adaptive method, using a continuous covariate and a non-parametric regression procedure to allocate patients to the best treatment for them with varying probability. This method starts with 0.5 allocation probability to their estimated best treatment, but increases to 0.9 for the last patient who enters the trial. We evaluated the method against an RCT using simulations.
Results: This method produces more patient successes than the RCT in all scenarios. A number of these scenarios involved the best treatment changing depending on the patient's covariate. In these scenarios, we split the trial depending on the patient's covariate and calculated the power. The power of this method is at least 82.7% of the power of the RCT for all scenarios.
Discussion: Future work will include testing this method for many more scenarios to see in which situations it works best. We would also like to extend this method to involving multiple covariates (including both continuous and binary) to make its use in clinical trials more realistic.

P-7
Introducing the Adaptive designs CONSORT Extension (ACE) Statement to improve reporting of randomised trials that use an adaptive design
Munya Dimairo[1], Philip Pallmann[2], James Wason[3,4], Susan Todd[5], Thomas Jaki[6], Steven A. Julious[1], Adrian P. Mander[3], Christopher J. Weir[7], Franz Koenig[8], Marc K. Walton[9], Jon P. Nicholl[1], Elizabeth Coates[1], Katie Biggs[1], Toshimitsu Hamasaki[10], Michael A. Proschan[11], John A. Scott[12], Yuki Ando[13], Daniel Hind[1], Douglas G. Altman[14]
[1]School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom; [2]Centre for Trials Research, Cardiff University, Cardiff, United Kingdom; [3]MRC Biostatistics Unit, University of Cambridge, Cambridge, United Kingdom; [4]Institute of Health and Society, Newcastle University, Newcastle upon Tyne, United Kingdom; [5]Department of Mathematics and Statistics, University of Reading, Reading, United Kingdom; [6]Department of Mathematics and Statistics, Lancaster University , Lancaster, United Kingdom; [7]Edinburgh Clinical Trials Unit, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, United Kingdom; [8]Centre for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Austria; [9]Janssen Pharmaceuticals, United States of America; [10]National Cerebral and Cardiovascular Center, Japan; [11]National Institute of Allergy and Infectious Diseases, National Institutes of Health, United States of America; [12]Division of Biostatistics in the Center for Biologics Evaluation and Research, Food and Drug Administration, United States of America; [13]Pharmaceuticals and Medical Devices Agency, Japan; [14]Centre for Statistics in Medicine, University of Oxford, United Kingdom
Trials 2019, **20(Suppl 1):**P-7

Background: The reporting of adaptive designs (ADs) in randomised trials is inconsistent and needs improving [1]. Incompletely reported AD randomised trials are difficult to reproduce and are hard to interpret and synthesise. This consequently hampers their ability to inform practice as well as future research and contributes to research waste. Better transparency and adequate reporting will enable the potential benefits of ADs to be realised.
Methods: We developed an Adaptive designs CONSORT Extension (ACE) guideline through a two-stage Delphi process with input from

multidisciplinary key stakeholders in clinical trials research in the public and private sectors from 21 countries, followed by a consensus meeting [1]. Delphi survey response rates were 94/143 (66%), 114/156 (73%), and 79/143 (55%) in round one, two and across both rounds, respectively. Members of the CONSORT Group were involved during the development process.
Results: The resultant ACE checklist is comprised of seven new items, nine modified items, six unchanged items for which additional explanatory text clarifies further considerations for ADs, and 20 unchanged items not requiring further explanatory text. The ACE abstract checklist has one new item, one modified item, one unchanged item with additional explanatory text for ADs, and 15 unchanged items not requiring further explanatory text. The ACE guideline contains minimum essential reporting requirements and it applies to both frequentist and Bayesian ADs in randomised trials.
Discussion: The intention is to enhance transparency and improve reporting of AD randomised trials to improve the interpretability of their results and reproducibility of their methods, results and inference. We also hope indirectly to facilitate the much-needed knowledge transfer of innovative trial designs to maximise their potential benefits.

Reference

[1] Dimairo et al. Development process of a consensus-driven CONSORT extension for randomised trials using an adaptive design. BMC Med. 2018;16(1):210

P-8

The PITHIA trial: a stepped wedge, cluster randomised, registry based national trial with economic evaluation

Laura A Pankhurst[1], Emma Laing[1], Helen L Thomas[1], Alison J Deary[1], Karla Hemming[2], Dominic M Summers[3], John OO Ayorinde[3], Edward CF Wilson[4], Victoria Bardsley[5], Desley A H Neil[6], Gavin J Pettigrew[3]
[1]Clinical Trials Unit, NHS Blood and Transplant , Cambridge and Bristol, United Kingdom; [2]Department of Public Health, University of Birmingham, Birmingham, United Kingdom; [3]Department of Surgery, University of Cambridge, Cambridge, United Kingdom; [4]Health Economics Group, Norwich Medical School, University of East Anglia, Norwich, United Kingdom; [5]Cambridge University Hospitals NHS Foundation Trust, United Kingdom; [6]Department of Histopathology, University Hospitals Birmingham NHS Foundation Trust, United Kingdom
Trials 2019, **20(Suppl 1):**P-8

Introduction: The Pre-Implantation Trial of Histopathology In renal Allografts (PITHIA) will assess whether a national, 24-hour, digital histopathology service increases the number, and improves outcomes, of kidneys transplanted in the UK from older deceased donors.
Methods: PITHIA is a stepped-wedge cluster randomised study, involving all UK adult kidney transplant centres. At 4-monthly intervals, a group of randomly selected centres will be given access to urgent histopathology: centres can request biopsies of kidneys from donors aged over 60, as required. Biopsies are reviewed by specialist renal histopathologists, who provide a Remuzzi score showing the extent of chronic damage. The score provided may be used by centres to decide whether and how the kidney may be used. The trial is open, and it is anticipated that over 2000 kidneys will be eligible during the 24-month trial duration.
Results: The trial has two primary end points: proportion of primary kidney offers transplanted and kidney function 12 months post-transplant. The trial will be analysed using mixed effects models allowing for clustering within centres and adjusting for secular trends. Results will inform a decision-model based economic evaluation to determine whether it is cost-effective.
The trial is registry based; hence the majority of the data can be drawn from the UK Transplant Registry (UKTR) held by NHS Blood and Transplant. The UKTR collects survival and covariate data on all patients undergoing transplantation. The design allows patients to be followed up using only data that is collected routinely. Only one additional data collection form is required, to record and report the histopathology information to the requesting centre.
Conclusion: The PITHIA trial is using a stepped-wedge design to include all centres in an evaluation of a new service. The registry based design is novel in transplantation, and is low cost to implement with high levels of data completeness.

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Issues in the design, analysis, and reporting of factorial trials: a review

Diana Elbourne[1], Brennan C Kahan[2], Elaine M Beller[3], Michael Tsui[4], Vipul Jairath[5], Douglas Altman[6]
[1]LSHTM, London, United Kingdom; [2]Queen Mary University of London, London, United Kingdom; [3]Bond University, New South Wales, Australia; [4]Schulich School of Medicine and Dentistry, Ontario, Canada; [5]University of Western Ontario, Ontario, Canada; [6]Centre for Statistics in Medicine, Oxford, United Kingdom
Trials 2019, **20(Suppl 1):**P-9

Introduction: Factorial designs can allow efficient evaluation of multiple treatments within a single trial. We report the quality of the design, analysis, and reporting in a sample of factorial trials.
Methods: A 6-person team from the UK, Australia and Canada reviewed 2x2 factorial trials evaluating health-related interventions and outcomes in humans. Using MEDLINE, we identified articles published between January 2015 and March 2018. We randomly selected 100 articles for inclusion.
Results: Few trials (22%) provided a rationale for using a factorial design. Only 63 trials assessed interaction for the primary outcome, and only 39/63 (62%) made a further assessment for at least one secondary outcome. 12/63 trials (19%) identified a significant interaction for the primary outcome, and 16/39 trials (41%) identified a significant interaction for at least one secondary outcome. Inappropriate methods of analysis to protect against potential negative interaction effects were common, with 18 (18%) of trials choosing an analysis method based on a preliminary test for interaction, and 13% (n=10/75) of authors conducting a factorial analysis including an interaction term in the model.
Conclusions: Reporting of factorial trials was often suboptimal, and assessment of interactions was poor. Investigators often used inappropriate methods of analysis to try to protect against adverse effects of interactions. The CONSORT Group (Consolidated Standards of Reporting Trials) has developed guidelines to alleviate problems arising from inadequate reporting of RCTs. The results of this review suggest items of the CONSORT statement that can be extended for factorial trials.

P-10

Designing a multi-arm multi-stage trial in progressive multiple sclerosis

Baptiste Leurent[1], Frederik Barkhof[2], Olga Ciccarelli[2], Arman Eshaghi[2], Emma Gray[6], Vivien Li[5], Jennifer Nicholas[1], Nigel Stallard[3], James Wason[4], Fay Cafferty, Jeremy Chataway[2,5]
[1]London School of Hygiene and Tropical Medicine; [2]University College London; [3]University of Warwick; [4]Newcastle University; [5]University College London Hospitals; [6]MS Society
Trials 2019, **20(Suppl 1):**P-10

Introduction: Multiple sclerosis affects more than 100,000 people in the UK, with few effective treatments for the progressive stage of the disease (PMS). Multi-Arm Multi-Stage (MAMS) trials may accelerate treatment discovery in PMS, as done with success in other disease areas. MAMS are adaptive trials characterised by multiple experimental arms, and multiple interim analyses, where treatments with insufficient indication of efficacy are discontinued. MAMS designs can provide efficiencies, particularly in terms of duration and sample size, but their preparation is more complex.
The aim of this research was to explore designs for a feasible and efficient MAMS trial in PMS.