
Proceedings Paper:
Totton, N., Julious, S., Hughes, D. et al. (1 more author) (2019) MRC-NIHR methodology guideline development on utilising benefit-risk assessments within clinical trials. In: Trials. 5th International Clinical Trials Methodology Conference (ICTMC 2019), 06-09 Oct 2019, Brighton, UK. BioMed Central , p. 93.

https://doi.org/10.1186/s13063-019-3688-6

Trials 2019, **20**(Suppl 1):579
https://doi.org/10.1186/s13063-019-3688-6

Trials

MEETING ABSTRACTS Open Access

Meeting abstracts from the 5th International Clinical Trials Methodology Conference (ICTMC 2019)

Brighton, UK. 06-09 October 2019

Published: 22 October 2019

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

Introduction: Clinical trials often assess effectiveness of interventions through the use of responder-based endpoints. These classify patients based on whether they meet a number of criteria; some of these criteria are whether or not continuous variables take values above or below a threshold. Traditional analyses estimate the proportion of patients who are responders and test for differences between arms.
An alternative method called the augmented binary method utilises information contained within the continuous component(s) to increase the power considerably (equivalent to increasing the sample size by >30%). This method has been proposed in several methodological papers as being useful in solid-tumour oncology and rheumatoid arthritis. However, it could be potentially useful in a much wider variety of disorders.
In this talk we aim to summarise the method and provide results from a review identifying new clinical conditions where it could be used
Methods: We reviewed a database from the COMET initiative of physiological and mortality trial endpoints recommended for collection in clinical trials of different disorders. We identified responder-based endpoints where the augmented binary method would be useful for increasing power.
Results: We identified 68 new clinical areas where endpoints were used that would be more efficiently analysed using the augmented binary method.
D**iscussion**: The augmented binary method can potentially provide large benefits in a vast array of clinical areas. Further methodological development is needed to account for some types of endpoint.

PS1B

- O5 Exploring the Hawthorne effect using a balanced incomplete block design in the aspire cluster randomised controlled trials

Michelle Collinson[1], Thomas Willis[2], Robbie Foy[2], Liz Glidewell[3], Suzanne Hartley[1], Paul Carder[4], Stella Johnson[4], Michael Holland[1], Amanda Farrin[1]
[1]Clinical Trials Research Unit, University of Leeds, Leeds, United Kingdom; [2]Leeds Institute of Health Sciences, University of Leeds, Leeds, United Kingdom; [3]Hull York Medical School, University of York, Leeds, United Kingdom; [4]NHS Bradford Districts Clinical Commissioning Group, Bradford, United Kingdom
Trials 2019, **20(Suppl 1):**PS1B

Introduction: The Hawthorne effect is a non-specific treatment effect: an alteration in behaviour resulting from observation /assessment, leading to an overestimate of intervention effectiveness. If this effect is unbalanced across trial arms, treatment estimates may be biased.
ASPIRE is a NIHR-funded programme evaluating interventions to promote adherence to quality indicators in general practice (GP). Implementation packages were evaluated using electronic health records in two parallel cluster-randomised controlled trials in West Yorkshire GPs.
Methods: Balanced incomplete block designs, were chosen to equalise Hawthorne effects whilst maximising power and efficiency. Trial 1 examined the effect of an intervention on adherence to diabetes control and risky prescribing whilst Trial 2 examined blood pressure control and anticoagulation in atrial fibrillation. Within trials, GPs randomised to the intervention for one indicator, acted as control practices for the other intervention and vice versa.
A non-intervention control group was included to allow exploration of Hawthorne effects: GPs randomised to this group received none of the adapted interventions.
If a Hawthorne effect is present, the non-random aspect of differences in intervention effects is attributed to the fact that GPs were aware of being observed and is not attributable to the intervention. We expect the intervention effect in the primary analysis will be smaller than in the secondary analysis utilising the non-intervention control practices.
Results: ASPIRE randomised 178 GPs using opt-out recruitment; trial 1=80; trial 2=64; non-intervention control=34. The intervention reduced risky prescribing (OR=0.82, 97.5% CI (0.67–0.99)) but had no statistically significant effect on other primary endpoints. Secondary analysis showed evidence of a Hawthorne effect; OR=0.76, 97.5% CI (0.63-0.92).
Discussion: Balanced incomplete block designs incorporating randomised non-intervention controls could inform the interpretation of RCTs, particularly those utilising routinely collected data in implementation research.

PS1C

- O1 MRC-NIHR Methodology Guideline Development on Utilising Benefit-Risk Assessments within Clinical Trials

Nikki Totton[1], Steven Julious[1], Dyfrig Hughes[2], Jonathan Cook[3]
[1]University Of Sheffield, Sheffield, United Kingdom; [2]Bangor University, Bangor, United Kingdom; [3]University of Oxford, Oxford, United Kingdom
Trials 2019, **20(Suppl 1):**PS1C

Introduction: The Medical Research Council (MRC) and the National Institute for Health Research (NIHR) fund randomised controlled trials to provide evidence to inform national policy decisions. Currently, these trials have a primary focus, which dictates the choice of primary outcome. However, there are commonly multiple outcomes of importance to evaluate. Benefit-risk methodology can be included in trials to simultaneously evaluate multiple outcomes by assessing the trade-off and allowing decisions on the most overall beneficial treatment.
Benefit-risk methodology is commonly used within the regulatory setting with much of the available information and guidance relating to regulatory drug trials conducted by innovator pharmaceutical companies. In the context of MRC/NIHR trials, the studies are of health technologies (not just drugs) and often of therapies that are already licensed. To utilise benefit-risk in the MRC/NIHR context requires consideration additionally of economic outcomes, the selection of core outcome measures and trial design features.
The MRC have funded this project as part of their Methodology State-of-the-Art Workshops series with an aim of developing guidance to include benefit-risk within MRC/NIHR funded trials. This aim will be achieved by completing the following objectives:
1.Review current practice of benefit-risk methodology
2.Review available benefit-risk methodologies
3.Achieve expert consensus on the recommended benefit-risk methodologies
Methods: The three objectives will be met using the following methods:
1.Web-based survey of current practice,
2.Rapid methodological review,
3.Two-day expert consensus workshop using nominal group technique.
Timing of Potential Results: Results from the survey and rapid review plus preliminary headline results from the workshop (held early September 2019) will be available for the ICTMC conference in October.
Potential Relevance & Impact: This research will provide guidance for researchers applying to MRC/NIHR funding streams to ensure research is appropriate to support NHS policy decisions.

PS1C

- O2 Essential items for a Health Economics Analysis Plan (HEAP): expert Delphi consensus survey

Joanna Thorn[1], Charlotte F Davies[1], Sara T Brookes[1], Melina Dritsaki[2], Ewan Gray[3], Dyfrig Hughes[4], Sian M Noble[1], Stavros Petrou[5], Colin Ridyard[4], Tracey Sach[6], Ed Wilson[6], Borislava Mihaylova[2], Sarah Wordsworth[2], William Hollingworth[1]
[1]University of Bristol, United Kingdom; [2]University of Oxford, United Kingdom; [3]University of Edinburgh, United Kingdom; [4]Bangor University, United Kingdom; [5]University of Warwick, United Kingdom; [6]University of East Anglia, United Kingdom
Trials 2019, **20(Suppl 1):**PS1C

Introduction: Health Economics Analysis Plans (HEAPs) setting out the proposed analysis in a randomised controlled trial (RCT) currently