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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

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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)

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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

Methods: Many pilot trials adopt a 'traffic light' system for evaluating progression to the main trial determined by a set of criteria set up a priori. We can set up a hypothesis-testing approach focused around this system that tests against being in the RED zone (unacceptable outcome) based on an expectation of being in the GREEN zone (acceptable outcome).
Results. For example, in relation to treatment fidelity, if we assume the upper boundary of the RED zone is 40% and the lower bound of the GREEN zone is 70% (designating unacceptable/acceptable treatment fidelity, respectively), the sample size required for analysis given 90% power and one-sided 5% alpha would be n=22 (intervention group alone). A larger sample size would increase the power to reject the RED signal in favour of potential progression.
Discussion: In general, more than one key process outcomes are assessed for progression to a main trial; a composite approach would be to appraise the rules of progression across all these key outcomes. This methodology begins to provide a formal framework for hypothesis-testing and sample size indication around process outcome evaluation for pilot RCTs.

PS4B

- O1 Considerations concerning the use of health economics in the design and analysis of adaptive clinical trials – a qualitative study

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Trials 2019, **20(Suppl 1):**PS4B

Introduction: Both adaptive designs and health economics offer innovative approaches to efficient research and decision making. Adaptive designs allow data to be examined as a trial progresses to inform changes to that trial. The methods of health economics aim to maximise the health gained for the money spent. Methods for evaluating cost-effectiveness could be incorporated into the design and analysis of adaptive clinical trials, to give innovative and efficient trials.
Methods: A qualitative study explored the attitudes of key stakeholders – including researchers, decision makers and members of the public - towards the use of health economics in the design, monitoring and analysis of adaptive clinical trials. Data were collected using interviews and focus groups. Framework analysis was used to analyse the data and identify themes.
Results: Twenty-nine participants took part in the study. Participants considered that answering the clinical research question should be the priority in a clinical trial, despite their awareness that cost-effectiveness was important for decision making. Concerns raised by participants included: handling the volatile nature of cost data at interim cost-effectiveness analyses; implementing this approach in global trials; resourcing the development of adaptive trial designs that use health economics in their design and analysis and training stakeholders in these methods so that they can be implemented by researchers and appropriately interpreted by decision makers.
Conclusion: The use of health economics in the design and analysis of adaptive clinical trials has the potential to increase the efficiency of health technology assessments worldwide. However, careful consideration is needed to ensure the statistical methods reflect the importance of clinical effectiveness and adequate training and resources are provided to facilitate the implementation of this approach.

PS4B

- O2 Stopping a clinical trial early based on the probability that cost-effectiveness is unlikely: An extension of conditional power computations to economic evaluation

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Trials 2019, **20(Suppl 1):**PS4B

Introduction: Conditional power (CP) is a well-established method for conducting futility analyses in clinical trials to stop a trial early for lack of efficacy using observed data at some interim point. However, despite futility criteria not being met, a trial may continue with modest efficacy gains that are unlikely to be cost-effective. Treatment effects from such trials may not offer value for money to tax payers because the cost per quality adjusted life year (QALY) can be much higher than acceptable thresholds. Stopping a trial based on the joint criteria of efficacy and costs have not been examined in detail.
Objectives: We extend the conditional power computations and examine the probability of cost-effectiveness conditional on the data observed at some interim point when applied in practice.
Methods: Expressions for the conditional power based on efficacy for the two sample case (1:1 allocation) are extended to cost-effectiveness. The incremental net benefit (INB), willingness to pay (WTP) threshold, interim and final sample sizes, variabilities and correlations between costs and effects are examined. Data from several clinical trials are used to examine the operating characteristics of the conditional power of cost-effectiveness (CPCE).
Results (TBC): Both CP and CPCE agree in general, about 70% of the time for a CP threshold of 80%. CPCE conclusions will differ and can be much lower 30% of the time, depending on the WTP. Hence, trials may continue based on clinical efficacy, despite interventions being unlikely to be cost-effective. Value of information methods (VOI) and Bayesian predictive power results provide consistent conclusions with CPCE.
Conclusions: CP based on cost-effectiveness is feasible and a useful tool during IDMC meetings (where health economists are increasingly involved) for decision making, especially where clinical effects are modest or small. CPCE uses more information than standard CP methods and is more informative.

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- O3 Cost-Effective Clinical Trial Design: Application of a Bayesian Sequential Stopping Rule to the ProfHER Pragmatic Trial

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Introduction: We investigate value-based, sequential, clinical trial design by applying a Bayesian decision-theoretic model of a sequential experiment to data from the ProfHER pragmatic trial. The work represents the first applied analysis of this value-based, sequential, design to retrospective data from a completed clinical trial.
Methods: We take information on the research cost profile from the trial and incorporate information on the accumulation of evidence on cost-effectiveness to obtain a stopping boundary. We compare this with the accumulation of data in the trial itself and use a bootstrap analysis to study the stopping rule's operating characteristics.
Results: We show that the model's stopping policy would have stopped the trial early, saving about 5% of the research budget