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- O4 Investigating the application of a multi-arm, multi-stage (MAMS) design to compare optimal treatment duration of Herceptin in a non-inferior setting in treating early breast cancer patients

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Introduction: Implementing multi-arm, multi-stage (MAMS) designs have proven to be efficient and effective for assessing new treatments with survival outcomes. MAMS designs are yet to be applied in studies assessing different durations of treatment. This simulation study aimed to evaluate the efficiency and effectiveness of a MAMS design for testing the optimal duration of Herceptin in treating early breast cancer.
Methods: Non-inferiority (NI) properties were explored in six Herceptin duration trials. Simulations were used to assess performance of implementing a four arm three stage MAMS NI trial with 12 months of Herceptin as the control arm (standard care) versus experimental arms of six months, three months and nine weeks of Herceptin. Intermediate and primary outcomes, ranges of NI margins and survival outcome rates based on trials were investigated.
Results: Simulations showed that implementation of a four arm three stage MAMS design is more efficient than performing each trial separately as the required sample size and duration of the study was reduced. The most efficient and effective MAMS design proved to be when five year disease-free survival of 81% was used as the intermediate and primary outcome with a 3% NI margin. Emphasis was placed on ensuring that the family-wise error rate (FWER) remained below 5%.
Conclusion: A MAMS design should be considered when implementing a new therapy into a disease area as it allows different treatment duration to be explored as well as the efficacy of the treatment. Simulations showed that a MAMS design for the Herceptin duration question in early breast cancer would have identified the optimal treatment duration quicker.
Implementation of MAMS designs in practice requires input from clinical stakeholders to determine the appropriate timing for randomisation and the minimum amount of follow-up required once patients have completed the course of treatment before performing an interim analysis.

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- O5 Experiences of setting up Trials within Cohort Studies: Overcoming challenges and maximising efficiency – a case study

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Background: The Trials within Cohorts (TWiCs) recruit trial participants from an existing cohort. This pragmatic design allows robust generalizability to routine healthcare, avoids disappointment bias, aids recruitment and assessment of longer-term outcomes.
Despite their theoretical advantages, implementation and conduct can be demanding. Here, we share our experiences of setting up our first TWICs.
Methods: MONITOR is a multicentre TWiCs cohort assessing the effectiveness of a treat-to-target approach in psoriatic arthritis. Currently, two RCTs are set up within our cohort study.
Results: Detailed explanations of methodology were essential for approvals by funders, sponsors and regulators unfamiliar with this novel design. Separate protocols were required for the cohort and each RCT. While this resulted in duplication, increased administration and additional approval processes, it allows for set-up and amendment of individual trials while the cohort continues.
The use of routinely collected data ensures the efficient collection of high-quality data. However, it necessitated the use of separate databases, resulting in additional programming to collate data, and more complex data checks.
Our TWICS design required a two-stage eligibility check for randomisation, and additional safety reviews for the interventional arms only. Close collaboration with our programming team allowed us to adapt existing systems and minimise patient burden.
Safety reports are identical for all included RCTs, and can therefore automated easily and will be presented to a joint committee, reducing workload and the number of independent oversight committee members required.
Statistical considerations include the potential for differential take-up of the intervention between the trial arms, and the potential for differential missing data rates.
Discussion: TWICS can be challenging to set-up, and require careful planning involving all trial team members and relevant external agencies. When implemented successfully, they are a very efficient design to facilitate a multitude of trials in a specific patient population.

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PS7C

- O1 Outcome assessment by central adjudicators versus site investigators in randomised stroke trials: A systematic review and meta-analysis

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Background: In randomised stroke trials, central adjudication of a trial's primary outcome is regularly implemented. However, recent evidence questions the importance of central adjudication in randomised trials. The aim of this review was to compare outcomes assessed by central adjudicators with outcomes assessed by site investigators.
Methods: We included randomised stroke trials where the primary outcome had undergone assessment by site investigators and central adjudicators. We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Web of Science, PsycINFO and Google Scholar for eligible studies. We extracted information about the adjudication process as well as the treatment effect for the primary outcome, assessed both by central adjudicators and by site investigators. We calculated the ratio of these treatment effects (RTE) so that an RTE > 1 indicated that central adjudication resulted in a more beneficial treatment effect than assessment by site investigator. A random-effects meta-analysis model was fitted to estimate a pooled effect.
Results: Fifteen trials including 69,560 participants were included. The primary outcomes included were stroke (8/15, 53%), a composite event including stroke (6/15, 40%) and functional outcome after stroke measured on the modified Rankin Scale (1/15, 7%). The majority of site investigators were blind to treatment allocation (9/15, 60%). On average, there was no difference in treatment effect estimates based on data from central adjudicators and site investigators (pooled RTE=1.02, 95% C.I: [0.95, 1.09]).
Discussion: We found no evidence that central adjudication of the primary outcome in stroke trials had any impact on trial conclusions. This suggests that potential advantages of central adjudication may not outweigh cost and time disadvantages in stroke studies if the primary purpose of adjudication is to ensure validity of trial findings.