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Sample size of four clusters-per-arm as a rule of thumb for pilot cluster-randomised controlled trials

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Introduction: There currently exists little guidance on sample size for pilot cluster-randomised controlled trials (cRCTs). Previous work shows that parameter estimates from such studies, particularly the ICC, are imprecise and problematic to use in subsequent sample size calculations. We performed a systematic review to describe trends in pilot cRCT sample size and illustrate the typical imprecision in ICC estimation. We also aimed to explore the changing precision of ICC estimates with increasing sample size, and establish the impact on main trial power when imprecise ICC estimates are used to design a main trial.
Methods: We searched PubMed and Web of Science for papers published between 2010-2017 with the terms 'pilot' or 'feasibility' in the title or topic, supplemented with terms to identify CRTs. We extracted sample sizes and other key information including estimation of the ICC. Swiger's formula was utilised to explore the precision and impact of ICC estimates generated from different pilot sample sizes.
Results: 574 studies were returned. 81 studies were included in the final review. These had a median of 4 planned clusters per-arm (IQR: 3,7) and 77 planned participants per-arm (IQR: 40, 240). The precision of ICC estimates was highly varied with 95% CIs ranging from less than 0.1 to more than 1. Analysis showed minimal gains in precision when using more than 8 total clusters. However, inaccurate ICC estimates can yield power of over 50% in a main trial when used in a sample size calculation.
Discussion: The trend of 4 clusters-per-arm is consistent with the minimum number of clusters suggested for pilot cRCTs in previous work. We have shown this sample size to be a reasonable minimum for such studies. Understanding the impact on power of utilising imprecise ICC estimates in sample size calculations will assist researchers in designing main trials.

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Exploring challenges in trials with surgical versus non-surgical intervention comparators: a qualitative evidence synthesis

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Introduction: Randomised controlled trials in surgery can be difficult to design and conduct, especially when including a non-surgical comparison. Only around half of initiated surgical trials reach their recruitment target, and failure to recruit is cited as the most frequent reason for premature closure of surgical RCTs.
The aim of this qualitative evidence synthesis was to identify, and synthesise findings from qualitative studies exploring the challenges in the design and conduct of trials directly comparing surgical and non-surgical interventions.
Methods: A qualitative evidence synthesis using meta-ethnography was conducted. Six electronic bibliographic databases were searched up to the end of February, 2018. Studies that explored patients' and health care professionals' experiences regarding participating in RCTs with a surgical and non-surgical comparison were included. The GRADE-CERQual framework was used to rate confidence in review findings.
Results: 3,697 abstracts and 49 full texts were screened and 26 published studies reporting experiences of patients and healthcare professionals were included. Five themes related to challenges to these types of trials were identified: 1. Radical choice between treatments; 2. Patients' discomfort with randomisation: best treatment for me as an individual; 3. Achieving balance: challenge of exploring patients' a priori preferences for treatment.4. Clinicians' conflict with equipoise: strong speciality convictions and 5. Imbalanced presentation of interventions and 'buy-in' of clinical specialities.
Discussion: The marked dichotomy between the surgical and non-surgical interventions was identified in this review as making the conduct of these types of trials particularly challenging. Consideration of these five specific challenges should be made in the planning and design of future studies of this type of comparison to optimise the delivery of these particular trials.

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Systematic review of prospective studies comparing different monitoring strategies in clinical intervention studies

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Introduction: Trial monitoring is requested by Good Clinical Practice (GCP) guidelines to ensure safety and rights of study participants as well as data quality. Recent developments at international bodies and regulatory agencies have supported the need for risk-based and centralised approaches to trial monitoring. Several studies have empirically assessed the effectiveness of such alternative monitoring approaches with discrepant findings. The objective of the present systematic review is to comprehensively summarise the benefits and disadvantages of different monitoring strategy for prospective intervention studies.
Methods: We submitted a protocol to the Cochrane Methodology Review Group and are currently systematically searching MEDLINE, EMBASE, and CENTRAL from their inception to May 3, 2019, for all prospective studies comparing different monitoring strategies in intervention studies. Two authors will independently assess the methodological quality of eligible studies using the Cochrane Risk of Bias tool and extract information on a number of key study characteristics using pre-piloted data collection forms. The primary outcome will be the number of critical and major monitoring findings as defined by the European Medical Association. Secondary outcomes will include patient recruitment and retention rates, and resource use. We will quantitatively pool results if appropriate.
Timing of Potential Results: Our electronic search yielded 3497 hits. Title and abstract screening is currently ongoing. There are at least five eligible studies evaluating different monitoring strategies (ADAMON, OPTIMON, TEMPER, START, MONITORING). At the time of the conference we will be able to present comprehensive results from this systematic review.
Potential Relevance & Impact: Given the large heterogeneity of monitoring practices among research institutions, a guideline for