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Improving recruitment of older people to clinical trials: use of the cohort multiple randomised controlled trial design

Abstract

There is widespread evidence of under-recruitment of older people to research studies, notably randomised controlled trials of interventions. Study exclusion criteria, ethical dilemmas, patient preference, risk of bias and challenges for treatment comparisons are particular problems faced by researchers. This article describes how more widespread use of the cohort multiple randomised controlled trial (cmRCT) design in ageing research may help address many of these problems. The original key features of the cmRCT design are a large observational cohort of people with the condition of interest (eg frailty) with regular measurement of outcomes for the whole cohort. For each RCT eligible patients are identified and a random selection offered the trial intervention; their outcomes are compared with those eligible patients not offered the intervention. Relevant assents are obtained at baseline to enable future involvement in a range of potential trials.

Where possible, the follow-up schedule is aligned with the key time points for assessment in future trials and includes the key baseline descriptors, and primary and secondary outcomes. The cmRCT approach also enables detailed observational and qualitative research for the chosen condition of interest, and might include the establishment of research biobanks to better align basic science, epidemiological, qualitative and clinical trial research.

Background

There is widespread evidence of under-recruitment of older people to research studies, notably randomised controlled trials (1). High participant exclusion and refusal rates are a major issue, and can be especially challenging in trials recruiting older people with frailty (1-3). Ethical decisions, particularly in the presence of co-existing cognitive impairment, add further complexity. Such problems can result in underpowered trial results and contribute to poor generalisability – an issue that has held up adoption of new interventions by clinicians caring for older people.

Concerns with information and consent are the most common reasons given for not participating in clinical trials (4). Understanding and weighing up the often complex information regarding randomisation and the possibility of entering a control group requires considerable cognitive and executive function abilities. Although trials can be designed to include older people with cognitive problems who lack capacity to consent, the presence of cognitive impairment and dementia can still be a barrier to participation, particularly if a consultee is not available (5).

An additional problem in trials of non-pharmacological interventions is that it can be difficult to achieve blinding of participants and assessors, particularly if a sham intervention is not included in the control arm. This can lead to performance and attrition bias for those randomised to the control group, and detection bias if the assessor is unblinded by the participant during follow-up visits (2).

A further challenge in clinical trials of common conditions in older age such as frailty, falls, and dementia, is that these conditions may have several potential treatments requiring investigation and evaluation. However, each treatment may be investigated separately in heterogeneous trial populations with a range of different outcome domains. This can mean that future pooling of evidence for meta-analysis, and generation of robust evidence statements, can be difficult, if not impossible. Furthermore, outcomes are typically collected in close proximity to the study intervention, and are often surrogate outcomes. Many studies are therefore underpowered to assess reliably clinically important events of interest to patients, clinicians and policymakers (e.g. hospitalisation, care home admission) that may require a longer duration of follow up. These events are particularly pertinent in older populations.

We describe how more widespread use of the cohort multiple randomised controlled trial (cmRCT) design in ageing research may help address many of the problems of recruitment, ethical dilemmas, patient preference, risk of bias and challenges for treatment comparisons outlined above. This approach could also enable detailed observational and qualitative research for the chosen condition of interest, and include the establishment of research biobanks to better align basic science, epidemiological, qualitative and clinical trial research.

The cohort multiple randomised controlled trial design

The cmRCT design has been proposed to address some of the shortcomings of existing clinical trial designs (6). The key features of the cmRCT design are:

1. A large observational cohort of people with the condition of interest (e.g. frailty), and where possible, a follow-up schedule aligned with the key time points for assessment in clinical trials. The cmRCT design might be applicable to existing cohorts, so does not necessarily require recruitment of a new cohort.
2. Regular measurement of outcomes for the whole cohort. These must include the key baseline descriptors, and where possible primary and secondary outcomes for the range of treatment options that might be considered for the condition of interest.
3. Gaining the relevant assents at baseline for future involvement in a range of potential future trials of treatment options.

Each randomised trial that is subsequently conducted requires:

1. Identification of all eligible participants in the whole cohort.
2. Random selection of some participants from all eligible participants in the cohort, who are then offered the trial intervention.
3. Comparison of outcomes with eligible patients who were not randomly selected.
4. "Intervention-centred" informed consent; that is, the process of providing patient information and obtaining consent aims to replicate that in real world routine health care.

In a conventional RCT design, participants give consent to join the trial prior to randomisation. The cmRCT design involves randomisation before offering treatment, so it is possible that a proportion of those who are offered treatment may decline. Statistical approaches such as a complier average causal effect (CACE) analysis (7) adjust for the possibility that significant numbers of participants may decline treatment following randomisation, so are recommended as part of a robust statistical analysis plan (6).

A cmRCT design is considered particularly relevant in situations in which 'usual treatment' is the comparator; where the aim is to inform healthcare decisions in routine practice; the clinical condition is chronic and several intervention studies are needed; and for studies where previous trials have struggled with recruitment (6). This approach may therefore be especially appealing in the many conditions associated with ageing, for example frailty, falls and dementia research. However, the cmRCT design does not allow for a placebo to be given to the comparator group and therefore many pharmacological trials are precluded.

An intervention-centred approach

A key feature of the cmRCT design is an intervention-centred approach to informed consent. Only those who are randomised to the intervention are offered treatment and the 'control' group is embedded within the cohort so is already receiving the planned follow-up schedule. This means that the process is aligned more closely with the method of offering and providing treatment in routine healthcare, and removes the need for detailed

understanding of the complex processes of randomisation and control group options that are hallmarks of the informed consent process in a conventional randomised controlled trial approach. This intervention-centred approach to gaining consent also has the added benefit that there is potentially greater generalisability of the trial results to the approach used in routine care. This is in part because of the previously discussed similarity between the process of care in the trial and the process of care in routine clinical practice, but also because the use of the cmRCT design should lead to a higher proportion of eligible patients agreeing to take part.

Additional benefits

Recruitment rates for clinical trials of interventions for common conditions in older age have frequently been low. Although there is evidence that participation in observational studies may be declining (8) recruitment to ageing and dementia cohort studies has remained relatively high. For example, as a percentage of those eligible, the Newcastle 85+ and Leiden 85+ studies reported recruitment rates of 72% and 87% respectively (9, 10). A recruitment rate of 56% was reported for the second wave of the UK Medical Research Council Cognitive Function and Ageing Study (MRC CFAS II) (11) which, although lower than the 80% rate reported in the first wave of the study (MRC CFAS I), remains encouraging. However, the potential effect of including the option of assent for future involvement in trials on overall study recruitment and retention is not currently known.

Possible limitations

A cmRCT design is best suited to situations in which the health and wellbeing of the participant population is relatively stable as this limits attrition rates. This may not be the case in, for example, severe frailty or advanced dementia. Additionally, relatively high rates of attrition due to mortality may be anticipated in these situations. Purposeful recruitment of populations across the spectrum of condition severity, and inclusion of plans for ongoing cohort recruitment to match anticipated attrition rates, may be strategies to reduce the possible impact of participants with unstable disease at greater risk of adverse events that include hospitalisation and death.

However, very large cohorts may be needed to ensure that a series of trials can be embedded, and large-scale, constant refreshment of the cohort has considerable implications for funding. Additionally, the skill-set required for running a clinical trial is not the same as that required for observational research. Robust cmRCT design requires expertise to be blended, potentially increasing cost and complexity. However, there is the possibility of longer-term gain through more effective and efficient clinical trials. Greater use of routine data linkage may help improve cohort sustainability and reduce loss to follow-up. Incorporation of measures that have been validated for self-report might be another strategy to help sustain the cohort, but would require careful piloting to establish feasibility.

The cmRCT approach is likely to work best for topics where agreement exists on the minimum dataset, intervention duration and assessment interval for a condition. Although this may be relatively well established in certain

conditions, for example dementia, this is not necessarily the case in others, for example sarcopenia. Additionally, there is a lack of international consensus on the minimum dataset and assessment schedule for nutrition and physical activity interventions, which are potential treatments across a range of conditions associated with ageing. In many trials in older people, the assessment schedule is much more frequent than is typically the case in large cohort studies, particularly in trials to establish efficacy, and in pilot trials. There is often a trade-off between detail and frequency of measures versus size of trial, and infrequent measurements may lead to a requirement for larger trials, partially negating the benefit of the cmRCT approach. Establishing consensus on the minimum dataset and assessment schedule prior to commencement of a cmRCT is especially important as trials represent wasted effort if the chosen comparisons and outcomes are clinically irrelevant (12).

Four examples of cmRCT studies with older people

1. **The Yorkshire and Humber Community Ageing Research (CARE) study (13)**

   The CARE study is using a cmRCT design to recruit a large cohort of older people (aged 75 and over) with frailty for clinical trials, observational and basic science research (target n=1,000). Participants are assessed for frailty at baseline and re-assessed at six, 12, 24 and 48 months. Additional measures include demographic details, basic and instrumental activities of daily living, cognition, health related quality of life, loneliness, pain and depression.

2. **The Yorkshire Health Study (14)**

   The Yorkshire Health Study has used a cmRCT design and has recruited a total of 27,802 adults of whom 2752 are people aged 76 and over. Participants of all ages are being followed up using questionnaires and data linkage, and a proportion are randomly selected to the intervention arms of RCTs, for example the Depression in South Yorkshire (DEPSY) trial (15).

3. **The Reducing Falls with Orthoses and a Multifaceted Podiatry Intervention (REFORM) trial (16)**

   The REFORM trial is using a cmRCT design to recruit 1,700 participants over the age of 65 who have attended a podiatry clinic to evaluate the clinical and cost-effectiveness of an orthotic, foot and ankle exercise and footwear advice intervention for the prevention of falls.

4. **The Comprehensive Longitudinal Assessment of Salford Integrated Care (CLASSIC) study (17)**

   The CLASSIC study is investigating the implementation and effectiveness of a new model of care for older people with long-term conditions using a cmRCT design, routine data linkage and self-report measures, with a target sample size of 4,000.

Conclusion

The cmRCT design has considerable potential to improve the recruitment of older people with a range of long-term conditions to clinical trials. However, there are potential limitations that require further consideration, potentially by

first testing the cmRCT design in existing cohorts, or establishing cmRCT pilot studies to test feasibility. Pilot work would include establishing consensus regarding the minimum dataset, intervention duration and assessment schedule for the condition of interest prior to cohort recruitment.

This novel design is likely to have additional benefits, including enabling the investigation of less common outcomes that require longer term follow-up with particular relevance in older age, such as care home admission or hospitalisation. Additionally, trial populations are more likely to be representative and methods of consent are better aligned with routine healthcare practice, so results are more likely to be generalisable to the wider older population. Finally, this approach could help align basic science, observational, qualitative and clinical trial research for a range of common conditions in older age that have major impact on health and social care systems internationally.

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Conflict of interest

AC is principal investigator for the Yorkshire & Humber Community Ageing Research (CARE) study. JY is co-investigator for the CARE study. CR is principal investigator for the Yorkshire Health Study. MW has no conflicts of interest.

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