Recruitment to randomised studies

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MAINTAINING ADEQUATE and consistent accrual of patients is important for small clinical trials and crucial to large multicentre, multinational clinical trials, in which participants often number in the thousands. Trial recruitment that is slower than expected can result in prolonged trial durations, increased costs, uneven workload, and morale problems, both for trial participants and trialists.¹ Furthermore, when recruitment is so poor that it needs to be curtailed before the trial's target sample size is reached, study power is reduced and there may be a need to revise study endpoints.²

The CONSORT statement on recruitment (Box 1) requires that the dates of recruitment commencement and closure be delineated.³ These dates are influenced by a number of factors, described below.

Simplicity of study design and importance of the questions addressed

Study designs that are conceptually simple, and that address questions of clinical relevance where genuine uncertainty exists, are likely to facilitate the recruitment of both investigators and participants. Also, studies with uncomplicated entry criteria are usually more attractive to investigators; those with complex eligibility criteria make recruitment more difficult, are more difficult to explain to participants, and, ultimately, their findings may have limited generalisability. Further, the enthusiasm of investigators may wane if trial protocols require substantial efforts on their part.

The choice of an appropriate control arm can enhance investigator interest and comfort, particularly if the control arm reflects best clinical practice. Studies should permit changes to best clinical care during the course of study follow-up. This will maintain both the ethical integrity of the study and investigator interest, and protect participants while retaining scientific efficiency. For example, in a study examining the effects of a fibrate to prevent vascular disease in diabetes, a new indication for statin treatment, based on existing trial evidence, may emerge for some participants during follow-up. In this instance, it would be preferable to allow those participants to use statins while continuing their study medication, rather than requiring them to withdraw from the study or stop taking study medication, potentially increasing the risk of participants being lost to follow-up because statin therapy is prohibited in the study protocol.

1: CONSORT checklist of items to report when reporting a trial

Section and topic	Item no.	Descriptor
Recruitment	14	Dates defining the periods of recruitment and follow-up

This strategy also helps maintain the relevance of the study question.

Adequate planning and piloting of chosen recruitment strategies

Surveying potential clinical investigators about the current practice incidence of the condition under examination provides an estimate of the size of the population that might potentially be accrued into the study, and informs the geographical scope of the study requirements (eg, local, national, international recruitment).⁴⁻⁸ Such a survey also provides the opportunity to determine investigators' interest in the study question and their likely participation. Sources of information worth exploring for participants with the condition of interest include medical records, clinic data, occupational and other targeted data (eg, screening logs of patients attending specialised treatment centres), disease or patient support registries, and so on.

These sources of information make it possible to use direct mail (electronically or by post) to raise awareness of the study and the question being investigated among potential participants. Media coverage of the trial may also alert potential participants to the study's purpose and its possible clinical benefits.

While it is not uncommon for fewer than 10% of patients identified this way to be ultimately recruited into a clinical trial,⁹ careful strategies for priority questions that have been properly piloted in selected sites may increase the accrual rates to more than 50%.

Simplicity of trial procedures and data collection requirements

Sometimes a trial's inclusion criteria are broadened after the trial's commencement to improve recruitment or its generalisability. For example, in the West of Scotland Coronary Prevention Study, the eligible range of liver function tests were initially based on hospital normal ranges,¹⁰ and then revised to reflect the wider range seen in the community (Professor Ian Ford, Director, Robertson Centre for Biostatistics, University of Glasgow, UK, personal communication). However, if recruitment procedures are oversimplified, patients not likely to be compliant with the study treatment, or who may not have the disease under investiga-

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2: Checklist of successful strategies in recruiting centres and participants to clinical trials

Trial centres

- Develop a list of experienced investigators to invite to participate
- Formulate an important study question
- Develop an appropriate and ethical control treatment
- Devise a study design that is clear and simple
- Have informed consent that is clear and simple
- Conven meetings of investigators
- Provide an investigator's study manual
- Publish the study design, and information about treatment uncertainty in medical journals
- Use mass media
- Gain adequate funding
- Provide feedback on study progress

Trial participants

- Adopt strategies proven in previous studies
- Plan early for recruitment
- Ensure strong leadership at all levels
- Obtain interested and keen investigators
- Recruit skilled and dedicated study staff
- Gain informed cooperation of primary carers
- Pilot-test planned recruitment strategies
- Coordinate multiple strategies
- Use logs of subjects with the condition of interest
- Use referrals from physicians
- Use referrals from laboratories
- Use mass media
- Provide feedback on recruitment progress

tion, may be recruited. For example, recruiting patients presenting with fever and acute respiratory symptoms into a study of treatments for severe acute respiratory syndrome (SARS), in which some may turn out to have negative tests for coronavirus, would result in a study with reduced efficiency (statistical power).² In this example, a brief run-in period or delayed randomisation may provide an opportunity for patients still uncertain about a commitment to participate, or those who don't actually have SARS, to be identified and not randomly allocated to a study group.

The amount of data collected at registration and subsequently throughout the trial can have a negative impact on the enthusiasm of both participants and investigators. Onerous clinical tests and data requirements at registration to determine eligibility can deter participants from entering trials, while complicated or tedious protocols can dissuade clinical staff from identifying and recruiting subjects. Because of this, each proposed data item to be collected should be carefully justified for inclusion in the trial protocol.

Adequate resources and site facilities

Recruiting a large number of participants usually requires a considerable number of centres to be involved. However, all centres need to have a patient pool of adequate size, and the infrastructure and resources to recruit and manage the projected number of patients efficiently. Centres interested in participating in the study should identify through their screening logs (or equivalents) their potential participant

numbers. However, only a proportion of these would eventually be recruited into the study. Research clinics should ideally be geographically accessible to the targeted patient group, and reimbursement of patient's expenses, as well as their transport and parking arrangements, should be considered. Payments to participating clinics for study costs are usually on a pro-rata basis, with funds matched to the number of participants recruited at each location.

Participating research clinics need to be easy to find, well organised, and efficient in scheduling tests, drug dispensing and so on. They should offer flexible appointment times, and sufficient time with the clinical trial staff for participants to adequately understand the study's rationale, its requirements and risks, and have all their questions answered. Employing an experienced and dedicated research coordinator at each participating trial centre is a key to successful recruitment, and reduces the time demanded of investigators. In the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study,¹¹ experience during the recruitment phase suggested that staff became better at identifying patients who would be poor long-term compliers, and were able to exclude more of such patients in the later stages of recruitment. Centres should plan to recruit steadily over the recruitment period to ensure an even workload during study follow-up.

Some strategies identified in the literature to facilitate recruitment of investigators and participants are shown in Box 2.

Options to consider when planned recruitment to a study looks unachievable

A low accrual rate can undermine the viability of the study plan. Strategies to overcome this require a detailed understanding of the reasons for the slow accrual, so these can be addressed. This might involve adding more clinical centres, revising the study eligibility criteria or other trial requirements, or re-assessing resources.

As recruitment to trials may occur over several years, clinical changes may influence the continuing importance of the study question. Further recruitment may not be appropriate as another trial may have satisfactorily answered the same question, or a better treatment alternative may have become available. In this case, the study management committee should review the situation to determine whether the study should continue in its current form, whether a revised study (with a smaller sample size or modified endpoints) could still be ethical and scientifically valuable, or whether the study should be abandoned.

Conclusions

Successful recruitment into clinical trials is best achieved by having a feasible recruitment plan, together with dedicated trial staff and adequate resources. The plan should be based on well-piloted recruitment strategies, involving clinical centres with demonstrated commitment to the proposed study and adequate numbers of patients for recruitment. Sites with previous clinical research experience can help

newer sites to be successful. Central monitoring of recruitment and feedback to participating centres on the trial's progress, by means of email, newsletters, or meetings, will foster continued interest and participation, and will enable the effectiveness of different recruitment methods to be evaluated. Further, adequate resources and incentives for trial staff and potential participants are key requirements for success. A question worth answering and an uncomplicated design are more likely to attract investigators and participants.

Competing interests

None identified.

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