

Conducting randomized trials in general practice: methodological and practical issues

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SUMMARY

The evaluation of the outcome of health services technologies is a requirement for their efficient provision in clinical practice. The most reliable evidence for treatment efficacy comes from randomized trials. Randomized trials in general practice pose particular methodological and practical difficulties. In this paper, we discuss how best to plan and manage a clinical trial in this setting. We base our discussion on our experience of conducting randomized trials to evaluate the effectiveness of brief psychotherapy in general practice.

Keywords: randomized controlled trial; randomization; family practice; patient preference; recruitment; treatment.

Introduction

RESEARCH in general practice is expanding rapidly to meet the need for evidence-based health care. The results of randomized trials in secondary care settings may not be applicable to primary care. For example, while most antidepressants are prescribed in primary care, their efficacy has been assessed almost entirely within secondary care. The changes to research funding within the National Health Service (NHS) that stem from the recommendations of Culyer and Mant^{1,2} will increase pressure for the involvement of general practice, and currently primary care networks are being established to foster the development of research in this setting.² Randomized trials in general practice are used to evaluate a broad range of treatment, including musculoskeletal manipulation, psychotherapy, and self-help packages.³ In this article, we discuss the practicalities involved in conducting randomized trials in general practice. Although there has been considerable debate about the theory of randomized trials, we draw on our experiences of mental health research in this setting to suggest practical issues to consider in the planning stages. We aim this article at all practitioners involved in randomized trials in general practice, be they a part of the research or practice teams. We aim specifically to debate:

- methodological issues in trials in general practice,

- ethical and practical considerations in the evaluation of complex interventions,
- establishing and managing such trials,
- research collaboration in general practice, and
- funding issues.

Inevitably, much of our discussion focuses on the difficulties that may be encountered. This is not to suggest that running randomized trials in general practice is not worth attempting. In fact, we believe that general practice will take an increasing role in clinical trials in the United Kingdom (UK).

Methods: scientific issues versus patient autonomy

Randomization and patient choice

People are better informed than ever about medical research and clinical trials.⁴ They may not accept randomization when considerable differences exist between the arms of the trial, and therefore blindness cannot be maintained. This is particularly true of psychological interventions when patients must provide time, attention, and concentration, and disclose personal facts about themselves. People who refuse to participate in trials desire more participation in decision-making and cite aversion to randomization as the chief reason for their refusal.⁵ Patients may prefer one treatment arm of a trial. Their doctors will also have views and may influence their patients' decisions. Patients who do not receive the treatment arm of their choice may become resentful or drop out of the trial. Cooke and Campbell⁶ have described the 'resentful demoralization' that ensues when subjects are not randomized to their preferred treatment. Demoralization may reduce compliance with treatment, affect motivation, and influence outcome. For example, in a trial comparing brief psychotherapy with usual general practice care, patients may feel they can progress no further with their doctors and resent randomization back to their care. Disappointment with allocation may lead to a worsening of symptoms or objections to follow-up. Paradoxically, patients allocated to their less preferred option may make a special effort to get better, thus reducing the expected difference.⁶ Our experience provides some endorsement for this latter possibility. In a trial of brief psychotherapies compared with usual care, patients allocated back to their doctor for treatment complied as well with follow-up as those in the active treatment groups, but several admitted to feeling they had drawn the 'short straw' and so tried harder to overcome their problems themselves.

Patient preference trials

Trials with partial randomization or patient preference have developed as an attempt to cope with the difficulties posed by standard randomization.⁷ Only patients with no strong preference for a treatment arm are randomized. All patients (randomized or not) remain involved in the research assessments and doctors feel less concerned that patients will receive treatments they do not want or trust. External validity is ensured in that all eligible patients take part. Internal validity is maintained by the randomized group.

Although evidence suggests that results are little different in the randomized and non-randomized cohorts,⁸ there are statistical

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objections to including non-randomized patients in the analysis of data from such trials.⁹ Although there are a number of patient preference designs to choose from,¹⁰ the trials are more costly to run and it is difficult to elicit treatment preference without influencing participants. The proportion of participants agreeing to full randomization is often difficult to predict; which, in turn, affects power calculations and target recruitment. However, recruitment can be optimized by including a preference option in the study design.

Maximizing validity

Validity is important in any pragmatic or explanatory trial. In pragmatic trials in primary care, scientific rigour is balanced against the flexibility expected by professionals and participants in a naturalistic setting. Strict adherence to protocol and the use of standardized questionnaires will aid internal validity. External validity will be affected by the representativeness of participating sites and subjects. In addition, the doctor's approach to treatment, and consequently outcome, may be affected by participation in a trial that carries with it a confirmation of diagnosis.¹¹ External validity will also be affected if subjects who refuse or drop out are systematically different from those who complete the trial. It is unclear what effects it will have on representativeness if payments to patients in trials becomes commonplace in general practice research. In our experience, small payments to cover expenses are appreciated by participants and may increase compliance with follow-up assessments.

Recruitment of patients

Explanations to patients

Even in randomized trials that take account of patient preference, it may be difficult to explain the nature of each treatment option to participants. Patients who are stressed or depressed only retain a limited amount of information. While it is crucial to avoid bias by providing a careful description of each treatment arm, explaining the differences between complex interventions, such as counselling or cognitive behaviour therapy, may be misleading. Who provides the information, at what point patients receive it, and how to avoid influencing their decisions are important strategies that must be planned before the trial begins.

General practitioners (GPs) may feel uncomfortable or lack the time needed to explain the treatments in the trial or to randomize patients. Trialists, who are independent of the doctor-patient relationship, can more readily carry out allocation to treatment. GPs may also bias allocation by implying the superiority of one or more treatment options.¹² This can be avoided by convincing them that genuine clinical equipoise exists and that there are ethical dangers in treating patients with unproven remedies in these situations. However, if family doctors lack confidence about the treatments under evaluation, they may not refer patients.^{13,14} One solution is to randomize only those patients in whom clinicians disagree on the most appropriate treatment.¹⁵ However, this introduces as many problems as it solves and raises the same statistical objections as in patient preference randomized trials. Alternatively, cluster randomization may be considered, where the unit of the randomization is the general practice. However, this also creates difficulties in that the unit of analysis in the trial becomes the practice rather than the patient. This has important knock-on effects in terms of the power of the study and the sample size required to show evidence of efficacy for the treatments under evaluation.

Provision of treatment

When evaluating services such as physiotherapy or practice nurse interventions, a choice may exist between using established providers or recruiting *de novo*. Using established providers means the trial may not have to fund the service. However, quality control of the service may be lost. For example, in a randomized trial of counselling versus GP management for patients with depression, it might seem pragmatic to use counsellors already attached to the practices. However, the trial team cannot control the quality of the intervention so easily and the doctors may question the advisability of *not* using their practice counsellor for patients randomized to usual care.¹²

Ethical issues

Participants must be informed of all aspects of a trial, be competent to give consent, and give it voluntarily. Another prerequisite is clinical equipoise.¹⁶ This means that doctors recruiting patients should be genuinely uncertain about the efficacy of the interventions. Doctors must act in patients' best interests by taking account of their values and preferences when deciding on their care. This can cause conflict if the doctor believes that one arm of the trial would be preferable. Equipoise would thus not exist, and entering that patient could be considered unethical. Doctors may simply be uninformed, and it is important that they understand the need for the trial in the first place. Doctors' concerns about equipoise do not arise in patient preference trials, or in trials where only patients for whom clinicians cannot agree on the best treatment are randomized. A further issue is who should obtain consent: patients may hesitate to refuse their doctor's request and it may be more appropriate for trialists to seek consent.

Managing the intervention under study in the trial

Providers of the intervention

Introducing a new service as part of the trial offers greater incentive to practices to take part and is easier for the research team to manage. However, the providers brought in for the trial may be less integrated into the practices and the costs for the research will be greater.¹⁷ When an established service is evaluated, the trial team will need to persuade the providers to take part. The providers of the intervention should be flexible to respond to the changing needs of the research, whether they are already practice-based or are brought in for the trial. It is essential to convey to them the benefits of participation. These include reports on their patients' progress, liaison with professional colleagues, and opportunities for professional development. Regular meetings provide team support, a forum for developing professional links, and time to discuss issues that arise during the research. Good morale in the providers reduces loss of staff from the study: a particular problem where a skill is in short supply, such as cognitive behaviour therapy or physiotherapy.

Financial issues

Where the intervention under study is financed by the research, a failure to predict service use can jeopardize the budget. In a multicentre trial, there may be geographical variations in cost. A patient preference design may produce greater demand for one treatment arm with a resultant increase in costs.

Whether payment for the intervention(s) is made to individuals or to a service provider, all parties must be clear about session payments, arrangements regarding non-attendance of patients, and travel and incidental costs.

Recruiting practices

General practitioners are likely to agree to a trial because of local contacts with the trialists and the attraction or relevance of the research. Practice staff may not wish, however, to remain in the background or merely refer patients. They may desire an active role; for example, as part of research networks of practices centred on academic departments of primary care (e.g. the North Central Thames Primary Care Research Network, NoCTeN). Besides trials funded by the pharmaceutical industry, payment to practices for their participation is unusual in the UK. Targeted financial incentives might, however, be an effective approach if other means of involving general practitioners fail.¹⁸ Redirection of the NHS levy for research and development from hospital and community trusts will also ease the underfunding of infrastructure for randomized trials in general practice.^{1,2}

Making the approach

Practices are most likely to be recruited if they lack the service that the trial will provide (such as counselling or physiotherapy). We introduce the trial in a letter, inviting the practice staff to meet with the research team to discuss it. Soon after sending the letter, it is advisable for the trialist to telephone the practice to gauge interest in the study and arrange a meeting. A GP who is associated with the research team should be present at this meeting. This is of obvious practical value and assists the credibility of the project. It is essential to prepare an attractive and accessible information pack that includes a summary of the study and a flowchart for the wall of each office in the practice. The meeting needs to include the practice manager and lead receptionist. It is helpful for the research team to allow practice staff several days after the meeting to decide whether they wish to participate.

Reluctance to be involved

Practices may not wish to participate for the following reasons:

- They perceive they are already over-committed to research or feel pressurized by time. The constant bombardment with postal questionnaires experienced by most GPs may create this impression, rather than actual research that is underway. Payments for practice staff time^{1,2} may alleviate this difficulty.
- Staff are concerned about lack of space, particularly if this involves treatments taking place on the premises. Payments for research infrastructure that will allow practices to create space may help to ameliorate this difficulty in future.^{1,2}
- Doctors may not see how their working practices can accommodate the study. Although this is a common objection,¹⁹ it usually stems from a misunderstanding of what the trial involves. Trials that depend on lengthy participation by clinicians will founder in any setting.
- Practices may be undergoing structural or personnel change.

Advantages for the practices

There may be competition to recruit general practices into trials. Thus, the potential benefits of participation must be highlighted. These might include:

- ready access to a new treatment under evaluation;
- a free, or highly professional, service;
- a reduced patient load;
- closer links with a university department;
- feedback about their own practice;
- acquisition of new knowledge about the treatments being tested; and

- an opportunity for practice staff to participate and learn about research.

The research team should emphasize how benefits can offset the costs of participation, such as time or space, in the practice. Even if one of the doctors is a member of the trial team, the research needs to appeal to the remainder of the practice staff.

Role of the researcher

Coordination of practices

One GP or practice manager needs to coordinate the study within each practice; the practice manager usually assumes this role. Linking research assistants to specific general practices helps them to develop relationships with the practice staff. The same applies to the providers of services under evaluation. Maintaining a good relationship between the research and practice teams requires effective channels of communication. Poor communication may have led to the collapse of at least one large multicentre trial.²⁰

Keeping in touch

Regular contact with practices serves to detect problems and check that the presence of the study personnel is acceptable. It is not clear whether it boosts referrals but it does have the effect of enhancing relations as well as monitoring actual participation and referrals to the study. We have rarely found that regular telephone calls or informal visits are unwelcome. The research team can become aware of obstacles in advance and decide whether to withdraw from a practice at any time. This can occur, for example, when building works threaten the availability of space.

Providing regular, one-page 'news flashes' will remind practice staff about the project, update them on the progress of all the practices involved, make them feel part of the study, and remind them of the inclusion and exclusion criteria. News flashes can display the recruitment rates of all practices in the trial and introduce a competitive element. Most practitioners value the updates as useful reminders to avoid protocol deviations and maintain recruitment.

Maintaining momentum

Even enthusiastic practitioners become fatigued after recruiting for many months, and staff may wish to phase their involvement. We find it helpful to suggest that practices recruit for one month at a time. This on-off approach is welcome where participation of a doctor or practice nurse is required in one treatment arm. However, it may have cost implications when the trialists provide the intervention.

Recruitment early in the trial predicts the pattern for the practice. Once the protocol is fully understood, it is rare that slow practices can be encouraged to recruit greater numbers. Persistently low recruiting practices may have to leave the study. It usually proves cost-effective to limit the number of practices and maximize cooperation from each of them. Withdrawal may, however, jeopardize randomization if this is by practice or by therapist. Once decided upon, it requires diplomacy if practice staff are to avoid regarding it as a failure. Withdrawal is even more sensitive if one of the GPs is a member of the trial team. A reserve list of interested general practices is necessary for replacements. Equally, it is vital to have alternative service providers available if the need arises. This is indispensable where a service is limited in supply, as with cognitive behaviour therapists or community pharmacists.

Funding arrangements

Multicentre trials

Randomized trials in more than one general practice are, by definition, multicentre. When the trial involves multiple academic centres, however, the difficulties compound. It is important to build in flexible funding that is not centralized but can follow high recruiting academic centres. Research staff will have contracts that provide them with job security during the study. However, in multi-centre trials, they may need to move the base in response to fluctuating recruitment. This can pose logistical problems if the centres are dispersed, and requires forward planning.

Payment of practice staff is likely to expand with the establishment of general practice research networks. Just as academic institutions and some hospital trusts receive overheads for the infrastructural costs of research, so should participating general practices receive funding for the cost the research entails. This cost must ultimately be borne by the organizations funding the trial, or by the NHS funding levy for research and development.¹

Discussion

In this paper, we have discussed a number of methodological and practical ideas, many of which stem from our own experience. In order to run a successful randomized controlled trial to evaluate a complex intervention in primary care, it is vital to use effective and practical research strategies. This type of project requires a tailored, workable design. Success is likely as a result of prudent planning and depends on cooperative, well-informed health professionals. It can be achieved by addressing factors likely to affect recruitment and follow-up, by sensitive management, and by payments to practices for the use of their time and infrastructure as required by the project.

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