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Practical aspects of conducting a pragmatic randomised trial in primary care: patient recruitment and outcome assessment

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SUMMARY

Background. Conducting a pragmatic randomised trial in primary care is often accompanied by practical problems. Such problems are seldom reported and may constitute useful lessons for researchers planning future trials.

Aim. To address the difficulties involved in patient recruitment and to present measures to minimise bias during outcome assessment.

Method. A recently conducted trial comparing the effects of corticosteroid injections and physiotherapy for painful stiff shoulder was used to illustrate problems related to patient recruitment and outcome assessment.

Results. Recruitment of patients was not without difficulties despite careful preparation. Recruitment was discontinued after 20 months, when 109 of the intended 120 patients had been admitted to the trial. The shoulder trial mainly included patient-oriented subjective outcome measures. Subgroup analyses demonstrated that patient preferences might have had some influence on outcome.

Conclusions. General practitioners might be willing or unwilling to participate in research for many reasons. The researcher should take these motivations into account when inviting physicians to take part in research. Strategies to enhance enrolment should be prepared before the start of the trial. When blinding of patients is problematic, patient preferences should be assessed before randomisation and their influence on the outcome studied. Although involving a blinded independent observer enables a more objective assessment of outcome, the success of blinding should be clearly evaluated.

Keywords: patient recruitment; research; randomised trial; shoulder pain.

Introduction

EFFECTIVE patient recruitment is a prerequisite for the successful completion of any randomised clinical trial. Before

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the start of a trial researchers are often overly optimistic regarding the number of available and eligible patients but recruitment usually falls short of expectations once the trial has started. This phenomenon has been described as Lasagna's Law.^{1,2} When determining the required sample size and designing recruitment procedures, several factors should be taken into consideration, including the (lack of) appeal the trial may have for eligible patients, the relatively strict inclusion criteria, and the limited time or motivation of recruiting physicians. Trials may even have to be suspended or prematurely ended owing to unsuccessful recruitment.³ The first objective of this paper was to address the difficulties involved in patient recruitment when conducting a randomised trial in primary care. Such difficulties are seldom reported but may constitute useful lessons for researchers planning future trials.

This paper focuses on the design and execution of pragmatic trials⁴ only. Pragmatic trials compare the effects of interventions as they are being carried out in everyday clinical care. Placebo interventions are typically not included in the design, which limits the potentials for blinding. Inadequate blinding has been demonstrated to be associated with an increased risk of bias.⁵ Therefore, the second objective of this paper was to present measures that can be taken to minimise bias in the outcome assessment of pragmatic trials and to evaluate the influence of potential sources of bias on the results of a trial.

Method

In January 1995, data collection was started for a randomised trial in Dutch primary care, comparing the effects of corticosteroid injections and physiotherapy for painful stiff shoulder.⁶ Although the study has been completed successfully, a number of difficulties had to be overcome during data collection.

Patient recruitment

The intended study population was 120 patients. Sample-size calculations showed that approximately 60 patients in each intervention group would be needed to detect a difference in success rate of 25%, which was assumed to be clinically relevant. Patients who consulted their general practitioner (GP) for a painful stiff shoulder were considered for participation. The main selection criteria were painful restriction of the passive range of motion; unilateral symptoms; no treatment of the shoulder with injections or physiotherapy during the previous six months; and informed consent. Final selection was carried out at a research centre by an independent observer (trained physiotherapist).

The shoulder trial was preceded by an observational study on shoulder disorders.^{7,8} The results of this study enabled an estimation of the availability of eligible patients for the trial. New episodes of shoulder pain were recorded during a one-year period by 18 GPs. The incidence of shoulder disorders was estimated at 11.2/1000 registered patients per year,⁷ which was comparable to the results of a national survey (12.8/1000).⁹ The diagnosis 'painful stiff shoulder' (capsular syndrome or capsulitis) was made in 21% of all incident cases, implying that, on average,

about four new eligible cases are encountered each year. Sixty-one GPs agreed to participate in the trial. Allowing for patient refusals and dropouts owing to exclusion criteria, we estimated that the intended study population of 120 patients would be within easy reach, as 18 months were available for patient recruitment.

Outcome assessment

Participants were randomly allocated to either injection therapy (intra-articular corticosteroids) administered by the GP or six weeks of physiotherapy. Outcomes and adverse effects were assessed at three and seven weeks. Long-term follow-up assessments were scheduled at three, six, and 12 months after randomisation. The main outcome measures were general improvement according to the patient, severity of the main complaint, pain, and functional disability.

The patients in the shoulder trial could not be blinded for the allocated intervention. A preference for one of the interventions under study could influence their response to treatment and their scores on subjective outcome measures. If many patients indicate a preference and the preferences are unequally distributed among intervention groups there is an increased risk of obtaining a biased estimate of outcome. Therefore, before randomisation all patients were asked to state any preferences. After the conclusion of data collection their influence on the results of the trial was evaluated in exploratory subgroup analyses.

In order to enable a partly-blinded assessment of outcome, the independent observer, who measured range of motion and gave a judgement of the overall severity of the disorder, was not informed about the allocated treatment. Before each follow-up examination, the patients were instructed by a research assistant not to mention their allocated treatment. Furthermore, the (potential) injection site was covered with gauze in each patient. In order to evaluate the success of blinding, the independent observer was asked to guess the allocated treatment after each examination and to state reasons for any assumptions.

Results

Patient recruitment

A total of 203 patients were referred to the research centres but 94 could not be admitted to the trial. In most cases the diagnosis could not be confirmed by the independent observer ($n = 73$). Findings from our observational study had indeed indicated that, in many cases, the diagnosis of shoulder pain was not unequivocal. Inter-observer agreement between GPs and physiotherapists was only fair ($K = 0.31$).¹⁰ Nevertheless, exclusion for this reason was more frequent than we had anticipated. The GPs were also asked to refer patients for whom they were uncertain about the diagnosis. This probably increased the sensitivity of our search for eligible patients but simultaneously decreased its specificity. Recruitment was discontinued after 20 months, when 109 patients had been admitted to the trial.

All participants were enrolled by 40 of the 61 GPs (Table 1). Eleven GPs recruited at least four participants each, together enrolling more than half of the study population (57 patients). There were more male physicians than female among the more successful recruiters but it was a female practitioner who recruited the largest number of participants ($n = 12$). The proportion of referrals that were actually enrolled in the trial was more or less similar for most GPs (60% to 67%), which may indicate that the majority of GPs were not discouraged by exclusion of patients by the independent observer. Other variables, such as the size or location of the practice, did not appear to have a large influence on recruitment rate.

When asked, the GPs indicated that the main reasons for not referring eligible patients to the research centre were busy

surgery hours, forgetfulness, or the conviction that a patient would benefit more from a specific intervention. Several measures were taken to encourage participation. Monthly newsletters were distributed, reminders were sent, and practices were visited at six-month intervals. Any questions regarding trial procedures received prompt and adequate feedback, implying easy accessibility during office hours. When a patient was excluded from the trial, the GP received a copy of the results of the examination at the research centre, including reasons for exclusion. The flexibility of trial procedures was increased by assessing patients at home if they were unable to visit the research centre or by enabling assessments after office hours.

After an extension of the recruitment period of two months, we decided to settle for a slightly smaller study size. As the dropout rate was very low, there was very little compromise of the statistical power because of this decision.

Outcome assessment

The results of subgroup analyses on patient preferences seem to indicate that being allocated to the preferred intervention had some influence on success rate but only for patients allocated to injection therapy (Table 2). Success rate (complete recovery or considerable improvement) was 85% for patients who received their preferred intervention (injections), compared with an overall success rate of 77% and only 64% for those who had received injections but preferred physiotherapy. It should be noted that the number of patients in the subgroups is small, which has probably resulted in unstable subgroup effects.

Blinding of the independent observers was partially successful. At the seven-week follow-up, the observers correctly guessed the allocated intervention for 65 patients and incorrectly guessed for 19 patients. For 24 patients the observers had no idea about the allocated intervention. A 'slip of the tongue' by the patient or one of the co-workers of the study was the reason for unmasking in 13 cases. In most other patients the guess was based on the clinical course of symptoms. A fast recovery, particularly from pain, was often correctly ascribed to injection therapy.

Discussion

Patient recruitment

Although a considerable number of GPs agreed to take part in the shoulder trial, not all turned out to be effective and successful recruiters. We are not sure about the main reasons for the difficulties during recruitment but they could be manifold: busy surgery hours may have interfered with selection of patients, trial procedures may have been too restrictive, or maybe there was simply a lack of eligible patients.

When GPs are asked to participate in patient recruitment, attention should be paid to the many reasons why they might be either willing or unwilling to participate in a trial (Box 1).^{2,3,11-13} The trial should address a relevant research question, the outcome of which is applicable to general practice. It is of no use if research questions are 'merely the products of scientific advertising, however attractive'.³ A smooth organisation is important, with adequate support from researchers, clear guidelines, and short questionnaires that impose minimal demands on time. We share the opinion of other authors that reimbursement should not be used as a coercive tactic.^{2,3,14} Nevertheless, a reasonable compensation can be offered for the time invested during surgery hours. Extra training or postgraduate education is often appreciated, such as the instruction on the physical examination of the shoulder joint and injection technique that preceded our trial.

Requesting informed consent can be difficult, as it may not be easy to forsake the role of the confident prescriber and adopt the attitude of the researcher who is uncertain about the most effective

Table 1. Recruitment of patients by general practitioners (n = 61) for the shoulder trial.

Success of recruitment	n	Male (%)	Median number of referrals (range)	Median number of patients enrolled (range)	Median proportion enrolled (range)
0 enrolled	21	67	0 (0–2)	0	0%
1–3 enrolled	29	79	3 (1–8)	2 (1–3)	60% (20–100)
×4 enrolled	11	91	7 (4–12)	4 (2–12)	67% (35–100)
Total	61	77	203	109	54%

Table 2. Overall success rates after seven weeks and for subgroups with and without a treatment preference.

	Success rates (%)		Group sizes (n)	
	Injections	Physiotherapy	Injections	Physiotherapy
Overall	77	46	52 ^a	56
No preference subgroup	80	47	25	34
Allocated to preferred intervention	85	43	13	14
Not allocated to preferred intervention	64	50	14	8

^aOne withdrawal (refused injections).

- Relevant research question
- Interest in and knowledge of research methods
- Adequate support by researchers
- Minimal investment of time, the study does not disrupt everyday practice, fool-proof organisation
- Adequate financial reimbursement
- Postgraduate training (credited)
- Not too much of a burden on the patient, no additional costs for the patient
- No interference with patient–physician relationship
- No clear preference in favour of one of the interventions in the trial
- Not too much involvement in other studies

Box 1. Reasons why general practitioners may participate in a randomised trial.

tive treatment available.³ Taylor and Kelnor designed a questionnaire (Physician Orientation Profile) giving physicians a score along the continuum of attitude towards treatment, ranging from purely experimental to purely therapeutic.¹⁵ Although it will not be necessary to use such a questionnaire, it may be worthwhile to specifically aim for the participation of GPs who are interested in research and are acquainted with research methods, rather than to take a random sample or simply recruit as many practitioners as possible.

A strategy for approaching primary care settings has been proposed by Murphy *et al.*¹⁶ They recommend identifying all people who may have an interest in the study (stakeholders), finding a 'local champion' to assist in approaching primary care settings (care providers of some standing or influence in the community), and supplying adequate, but concise, information. Half-hearted or ill-informed consent may guarantee the successful start of a trial but practitioners may soon withdraw once the implications of participation become clear.

Even if many GPs have consented to participate, actual patient recruitment may fall short of expectations. A prolonged and laborious recruitment procedure may result in changes in the implementation or interpretation of selection criteria, outcome measures, and other procedures. A 'rescue plan' developed prior to the trial, including a series of alternative strategies to increase enrolment, will enable prompt actions to be taken.² Measures to enhance recruitment during a study may include enhancing the

motivation of all co-workers by writing newsletters, paying regular visits to the practice, providing consistent feedback, and increasing the flexibility of trial procedures.^{14,17,18} Disagreeable tests or questionnaires may be eliminated from the protocol. Finally, researchers may decide to approach patients by advertising in the local media or weakening selection criteria. However, as adjustment of selection criteria may result in the enrolment of patients with a potentially different prognosis, it should not be used without careful consideration.

Outcome assessment

Obtaining an unbiased estimate of outcome can be quite difficult when different types of interventions are compared, and blinding is difficult to implement. When subjective outcome measures are used, patient preferences should be assessed before randomisation. Our results demonstrate that subgroup analyses can be helpful to determine whether the results of the trial are liable to be influenced by preferences for one of the interventions under study.

One way to prevent bias owing to patient preferences is to include only 'naïve' patients¹⁹ — patients who have never been treated with either intervention — or to include only those who do not indicate a preference. We decided to allow participation of patients with a preference, provided they were willing to take the 50% risk of receiving the other treatment. Exclusion of all patients indicating a preference would have resulted in an unacceptable reduction in the number of eligible patients.

Involving an independent observer can enable a more objective assessment of outcome. In this case the design of the trial should incorporate methods to evaluate the success of blinding. Frequent unmasking, or hypotheses made by the observers regarding the expected results of the trial, may imply an increased risk of bias. In the shoulder trial the blinding of independent observers was partially successful. The observers apparently had a presupposition about the results of the trial and their hypothesis was confirmed in many cases. This does not necessarily mean that outcome assessment was biased. The frequency of unmasking was similar in both intervention groups. Furthermore, the clues for guessing the assigned treatment were the results of the follow-up examination, which might indicate that the assessment of outcome measures (as part of the examination) was not influenced. Rabkin *et al.*²⁰ have also shown that clinical outcome can be the major predictor of accuracy in unmasking treatment

allocation. They too believe that this may not necessarily harm the internal validity of a trial, as long as assessment of clinical status precedes the awareness of treatment condition.

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