Recruitment rate for a clinical trial was associated with particular operational procedures and clinician characteristics

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Abstract
Objective: Expenditure on research has grown substantially however, a major challenge for conducting successful clinical research is the efficient recruitment of participants. We investigated factors influencing the rate general practitioners (GP) recruit participants to a randomised controlled trial.

Study Design and Setting: We used data on 363 GPs recruiting participants for a randomised controlled trial of low back pain. Multivariate negative binomial regression was used to determine associations of characteristics of the GP and study operational aspects with recruitment rate.

Results: GPs recruited 1,195 participants at a rate of 0.013 participants per day. GPs located in a high socio-economic area recruited at half the rate as those located in a low socio-economic area (IRR 0.52, 95%CI 0.37-0.74). A follow up within two weeks of training the GP and a higher number of face-to-face visits were operational procedures associated with a higher rate of recruitment (IRR 2.15, 95% 1.58-2.94 and 1.17, 95%CI 1.11-1.24 respectively). Other contacts made with a GP were not associated with recruitment.

Conclusion: The results suggested that the type of operational procedures used in clinical trial recruitment strategies are important aspects to consider. The ability to predict which GPs will recruit based on GP characteristics seems limited.

Keywords: recruitment strategies, clinical trials, low back pain, primary care, research, feasibility

Running head: Recruitment features in a large clinical trial
What’s new?

Key findings:
- The number of face-to-face visits and a prompt follow up after the initial study training were associated with higher recruitment rate. Other methods of correspondence with recruiting clinicians had no association.
- One clinician characteristic (socioeconomic status of the clinic suburb) was associated with recruitment rate.

What this adds to what is known:
- The types of operational procedures are important considerations for improving the recruitment rate to a large clinical trial.
- The ability to predict which GPs will recruit based on GP characteristics seems limited.

What next:
- Understanding the effectiveness and costs effectiveness of manipulating these aspects.
Background
While one of the major challenges for health researchers has been how to successfully fund research, once funding has been obtained significant difficulties in the conduct of the research may arise. In 2009/10 Australia spent $121.4 billion on health, this representing 9.4% of GDP. Of this, the area of expenditure with the highest percentage growth was health research, which grew by 10.8% in real terms [1]. The substantial growth in research activity has meant there are now many researchers facing the challenges inherent in conducting clinical research. One of the greatest challenges is how to successfully recruit participants for large clinical trials.

Previous research has suggested that problems with recruitment are a major reason for the failure of clinical research leading to wasted research funding [2]. More than 50% of studies require a funding extension due to recruitment issues and more than a third do not achieve their original recruitment target [3]. Slow recruitment can lead to excessive costs to complete the study [4]. Inconsistent recruitment among study sites may lead to unrepresentative study samples being collected. Failure to recruit an adequate number of participants may deliver equivocal results because the study is underpowered [5,6]. Ultimately, any of these scenarios may limit the ability of clinical research to improve health outcomes. The potential consequences and costs of failed clinical research because of poor recruitment highlight the urgent need to identify strategies that will optimise recruitment.

Recruiting subjects to clinical trials in the primary care setting presents unique challenges because primary care studies frequently rely on practising clinicians to screen and enrol patients. While patient choice is a key driver of recruitment success, many other factors present significant barriers. Primary care clinicians are often time poor which significantly hinders their ability to recruit [7]. Inadequate training in the study protocol, loss of autonomy, concerns with the study methods (e.g. use of placebos, blind treatment allocation), issues gaining informed consent, and concerns that inviting patients to participate in research negatively affects the patient-doctor relationship have also been reported as recruitment barriers for clinicians [8]. The range of barriers that apply to different clinicians working in independently managed practices underpins the challenge of recruiting through primary care.
At present there is a paucity of useful research investigating strategies to overcome barriers and improve recruitment to clinical studies in primary care [9]. Many proposed strategies are not useful because they involve modifications to the study protocol which may negatively impact on trial quality [9,10]. Other strategies are only designed to address a specific barrier in a specific study and lack generalizability to other trials [11]. There is a need to develop and assess strategies that can be applied to different studies in order to improve the efficiency of participant recruitment for future research in primary care.

This study aimed to identify factors associated with general practitioners (GPs) recruiting patients with acute low back pain to a randomised controlled trial evaluating paracetamol. We investigated two different types of factors; characteristics of the GPs (e.g., demographic factors such as age, socioeconomic index of the suburb of practice, clinical experience), and operational aspects of the study (e.g., routine screening of patients by GPs, regular site visits by trial staff).

**Design and methods**

**Study design**
We studied GPs enrolling patients with acute low back pain to a double-blind randomised placebo controlled trial between November 2009 and June 2012. The trial methods and procedures for recruitment of patients have been published elsewhere [12]. Ethical approval for the trial was granted by the University of Sydney Human Research Ethics Committee. The trial was prospectively registered on the ANZ clinical trial registry (ACTN: 12609000966291).

**Setting and Participants**
The clinical trial utilised practicing primary care clinicians (GPs and pharmacists) to recruit participants. All GPs practicing in the Sydney metropolitan area were invited to participate. GP contact information (phone, fax, postal) were obtained from internet sources and local GP divisions. Postal or electronic invitations were sent to GPs asking for expressions of interest in recruiting for the trial. Pharmacists attending a seminar series on managing low back pain hosted by the Faculty of Pharmacy, University of Sydney were also provided with written invitations to recruit patients for the trial. All clinicians who replied positively to invitations by fax were trained in the trial protocol. The current study provides descriptive information about the recruitment for the trial by all clinicians (GPs
and pharmacists) however modelling of factors associated with recruitment was restricted to GPs.

**Initial training of GPs and benefits for participating**

GPs received standardised training individually or in small groups. During training GPs were provided with a study manual, and educated on the study protocol and guideline recommendations for management of low back pain in primary care [13]. A GP was considered an active recruiting site and supplied with study materials (e.g. study treatment packs) after they had signed a clinical trial agreement and provided details about qualifications and work history. Each GP was asked to screen consecutive patients who presented with low back pain and to commit to attempting to recruit at least 2-5 patients.

For their active participation in the trial all GPs could register for mandatory Quality Improvement and Continuing Professional Development points (QICPD), which are essential for continued registration in Australia. GPs were reimbursed AU$187 for their time recruiting a participant included in the study to cover costs for the patients initial consultation and up to two clinical follow up visits. GPs were also reimbursed AU$11 per screened ineligible patient to cover administration costs.

**Patient screening and study conduct**

GPs were asked to screen consecutive patients who presented with low back pain. GPs provided eligible patients with guideline recommended advice and a sealed pre-randomised study pack containing the study medication and data collection forms. Research assistants confirmed eligibility and performed baseline assessment during a telephone interview scheduled for the patient later that day and before the patient started the study treatment. Researchers collected all subsequent data however GPs were asked to conduct up to two routine clinical follow ups as required for each patient they recruited.

**Operational aspects of the study**

Operational aspects including monitoring procedures were designed to support recruitment by study GPs. A research assistant responsible for individual GPs conducted these procedures. The operational plan was that all GPs were to be visited by a research assistant at least once every 3 months and were invoiced each month for reimbursement of recruitment activity. Research assistants were also encouraged to conduct additional
monitoring procedures with their allocated GPs. Additional monitoring procedures recommended to RAs included: an initial follow up within 2 weeks of the GPs training visit; regular site visits; telephone reminders to screen consecutive back pain patients; written correspondence (e.g. newsletters to provide updates about the progress of the trial and/or highlight recruitment activity of other GPs; personalised faxed or emailed recruitment reminders); contacting GPs who have failed to recruit a participant to identify and resolve any barriers to recruitment. The volume and type of these additional monitoring activities varied between study GPs.

**GP characteristics and data collection**

Data collected on recruiting GPs included years of practice, practice details (postcode) to determine suburb socioeconomic status (SES), the GP’s qualifications, gender, and whether the GP was a member of the Royal Australian College of General Practitioners (RACGP). Data on operational aspects conducted for each GP were prospectively collected by research assistants and entered into an electronic database. Operational procedures were coded as successful (or not) if the research assistant made contact directly with the GP. Contacts with GPs were categorised as a visit, phone call, or other (email, faxes or post). The date of the contact and any specific details were logged.

**Primary outcome and exposure variables**

The primary outcome for the current study was the rate of patients successfully recruited to the trial by each GP. The candidate exposure variables included GP characteristics and operational aspects. GP characteristics were: GP gender; the number of years the GP had practised; whether the GP was a fellow of the RACGP; the SES of the suburb in which the GPs clinic was located. SES was determined by comparing the clinic postcode to Australia Bureau of Statistics data on economic advantage and disadvantage by postcode. For interpretation, SES percentiles were trichotomised to three equal sized groups, high SES (100-95%), moderate (94-70%) and low (<70%). Operational aspects included whether the GP: received a follow up within two weeks from the initial training; received at least one follow up of any kind per month; screened consecutive patients; and remained contactable throughout their participation in the trial. Other operational aspects were the number of successful face-to-face visits, the number of phone calls and other contacts made with each GP. Consecutive patient screening was indicated by a GP routinely returning ineligible screening forms (at least one per month). A ‘contactable’ GP was one who was available.
to speak to research staff on more than half of the contact attempts made to the GP. As some GPs elected to withdraw from recruiting this was controlled for by coding a GP as currently enrolled to recruit or not.

**Statistical analysis**

Descriptive statistics were carried out to describe recruitment rate for the study, using data from all clinicians (GPs and pharmacists). Descriptive statistics were also performed for characteristics and operational aspects applied to all GPs who participated in the study.

The primary analysis assessed the effect of the candidate variables on the rate of patients recruited by a GP. A rate is defined as the number of events per time. Since each GP commenced the study on different dates this was accounted for in the analysis by including the number of days a GP was active on the trial as an offset variable in the model. As we expected the outcome data (number of patients recruited by a GP) to be overdispersed counts we used a negative binomial regression to determine the effect of candidate variables on GP recruitment rate. We tested data overdispersion by comparing the variance of the data to the mean patient count recruited by GPs with the likelihood ratio test. A small (significant) p value suggests the dispersion parameter is different from zero and overdispersion is likely.

**Modelling procedure and interpretation**

Univariate analyses were used to determine the unadjusted effect of each candidate exposure variable on the recruitment rate. Candidate variables with a p value of less than 0.20 were then entered into a multivariate model. The current status of the GP (whether the GP was still enrolled to recruit for the study or had previously withdrawn at the time of analysis) was forced into the model. A manual backward stepwise procedure was undertaken. Non-significant variables, at the 0.05 level, were subsequently removed to determine independent associations with recruitment rate.

The difference in parameter estimates and their standard error in each model were compared to consider the effect of suspected highly collinear variables where correlation coefficients indicated this. Incident rate ratios and their 95% confidence intervals were constructed for variables retained in the final model. Incident rate ratios were obtained by exponentiating the regression coefficient. For continuous variables the incident rate ratio
can be interpreted as the rate ratio in which the total number of participants is expected to change with a one unit increase in the exposure variable. For binary variables, the incident rate ratio indicates the expected change in rate of patient recruitment when the variable is positive.

Internal validation of the final model was undertaken by bootstrapping. Average performance measures were calculated from 100 bootstrap sample sets. A comparison was made between the measures derived from the original sample and bootstrapped samples. All analyses were conducted using STATA version 12 [14].

**Results**

**Descriptive results:**
From 3,912 patients screened by 363 GPs and 125 Pharmacists between November 2009 and June 2012, there were 1,312 patients randomised into the trial. This was an overall recruitment yield of 34%, however, the average rate of recruitment for clinicians was low (0.005 patients per day of participation). Of the 2,600 patients not taking part 1785 (68.7%) did not meet the eligibility criteria and 815 (31.3%) declined to participate. GPs recruited the majority of participants (90.5%) to the study however more than 57% of GPs did not recruit any participants. Most of these GPs (87.6%) neither screened a single patient. The average recruitment rate for GPs alone was 0.013 patients per day of participation. Data on frequency of GPs achieving different recruitment levels are provided in Table 1.

(Table 1)

Descriptive data and univariate analyses are displayed in Table 2. The majority of GPs were male (60.5%) and the average of clinical experience was 21.7 years. Most GPs were not fellows of the RACGP (57.6%). Nine of the 11 candidate variables revealed an unadjusted association with recruitment.

(Table 2)

**Multivariate analyses:**
The outcome data were overdispersed (P<0.0001). After the stepwise selection six variables were independently associated with recruitment rate. High correlation coefficients between the variable ‘number of calls’ and two other variables (the number of visits, r = 0.66 and whether a GP was contactable r = 0.45) prompted investigation into collinearity and subsequent removal of the variable ‘number of calls’ (indicated by large change in the standard error and direction change of point estimates). The five remaining variables are presented in Table 3 with incident rate ratios. Of the GP characteristics, only SES was associated with recruitment. GPs in areas of lower SES appeared to recruit more than those in high or moderate SES areas (P<0.0001 and P=0.04) and GPs in moderate SES areas appeared to recruit more than those in high SES areas (P=0.02). The remaining factors were operational aspects, which revealed strong associations with recruitment. GPs that received an initial follow up within two weeks of the initial training had a recruitment rate 2.2 times greater (95%CI 1.6 to 2.9; P<0.0001) than those that did not receive this follow up. GPs that routinely returned ineligible screening forms had a recruitment rate of 2.1 times greater (95%CI 1.5 to 2.8; P<0.0001) than those who did not. Bootstrapped estimates were not substantially different from those estimated by the final model.

(Table 3)

**Discussion**

**Summary of findings:**
Our study found five variables that were statistically associated with the rate at which GPs recruited patients to the study. Of these only one GP characteristic (SES) was significant, indicating that identifying GPs likely to recruit at faster rates is difficult. Some simple operational procedures were associated with increased recruitment and these provide potential strategies to optimise recruitment. GPs who had a follow up visit within 2 weeks recruited at a rate 2.2 times greater than those who did not, suggesting this is an important and relatively easy strategy to improve recruitment rate. Other operational aspects were also associated with increased recruitment rate (a greater number of visits and identifying GPs that routinely screen patients and are readily contactable); however determining the merit of these aspects is complex because they are also associated with high costs.

**Strengths and limitations:**
There are a number of strengths to this study. Firstly, the data used are high quality. Data were routinely captured prospectively and are likely to provide representative and precise
estimates. We used a large dataset of nearly 1,200 cases of recruitment and data from 363 GPs. Secondly, we tested the internal validity of the results with resampling methods and this showed the results were reproducible. Finally, the findings of the study can be easily applied in future research because we used variables that are generic to many studies and settings.

We cannot rule out the possibility of confounding in the current study design. The variables found to be associated with recruitment rate may be proxies for other factors. For example the number of follow up visits, including one performed within the first 2 weeks, could have been influenced by prior recruitment activity. For instance, a research assistant maybe more inclined to visit a GP who has just recruited a patient or who has a proven record of recruitment. Another limitation is that the data did not allow us to make any judgement on the importance of patient centred influences on recruitment rate.

Comparison to other research and interpretation:
Several strategies designed to improve recruitment in randomised controlled trials have been proposed previously. Many of these were included in our protocol, for example adequately reimbursing clinicians for their time, minimising time required to recruit subjects, and educational incentives for clinical staff. A recent Cochrane review however found that many such strategies have little or no impact on actual recruitment [9]. While we did not assess these strategies specifically, the findings of the Cochrane review are consistent with observations from our trial. For instance, despite the availability of research staff to facilitate the screening and consent process and the provision of CME points, reimbursement and extra education to all GPs, the majority of GPs did not recruit any patients.

Our finding that GP contact increased recruitment rate is consistent with findings from a previous randomised trial, which found additional communication (e.g. personalised newsletters, email, and recruitment feedback) with trial sites compared to usual communication (e.g. generic newsletter, emails or faxes; telephone calls and personal contact to support recruitment) resulted in a slightly faster recruitment [15]. Unlike our study, the volume of communication was not assessed and the effect of different types of communication (e.g. face-to-face contact versus email) was not considered. This is
important because our results suggested a potential link between recruitment rate and the type and volume of contacts per site.

Our study demonstrates two main additional communication approaches were potentially important to influence recruitment rate; a prompt follow up after training and the number of face-to-face visits a clinician received from the research team. A follow up within two weeks of the initial training aims to reinforce critical information about the study protocol and encourage early recruitment. This was associated with more than double the rate of recruitment. Likewise, face-to-face visits appear to be a meaningful contributor. Given that other contact types (e.g. emails, phone calls) were not associated with recruitment rate it would seem that face-to-face visits allow for a more meaningful exchange of communication and development of stronger relationships. Visits to a clinician from one of the research team may demonstrate to the clinician they are a significant partner in the project as well as aid the identification of modifiable barriers to recruitment. Such factors have previously been proposed as important moderators for recruitment [16].

We found practices in areas of lower SES were associated with a greater recruitment rate. To our knowledge this has not been previously reported. Previous literature suggests the number of people presenting to general practice for back pain do not typically vary across SES [17] so other factors may explain our findings. Patients presenting to care in areas of lower SES may be less inclined to undertake treatments supplied by other allied health services at a relatively high out-of-pocket cost. Similarly, the financial reimbursement for a bulk billing GP in lower SES areas may have provided more incentive to recruit than a private billing GP located in an area with a higher SES.

**Future directions:**

There are three important directions for future research into recruitment strategies. Firstly, while our study provides evidence of features associated with the rate a GP recruits patients, it is important to determine whether manipulating these factors results in increased recruitment rates. Future studies could randomly allocate recruiting GPs to groups that receive different types and numbers of follow up contact. This would provide strong evidence for which strategies (e.g. types and/or number of contact) are important to recruitment rates. Secondly, an important aspect to this work would be to investigate the cost effectiveness of providing additional follow up support to GPs as many of these
operational procedures involve substantial costs. Finally, other potentially important
influences on recruitment need to be considered. Integrating strategies into our model that
aim to overcome barriers to participation from a patients perspective is one such
possibility.

**Conclusion**
This study identified that certain operational procedures such as prompt follow-up of
clinicians following initial training, and the number of face-to-face visits provided to
clinicians are more strongly associated with increasing recruitment rate than clinician
characteristics such as clinician age and experience. Clinicians with practices in areas of
lower SES have higher recruitment rates. These results suggest that operational aspects
employed in a study are a critical consideration when designing recruitment procedures for
a randomised controlled trial in primary care. Further testing of the effectiveness of
manipulating these variables is required.
References


