



# A randomized, embedded trial of pre-notification of trial participation did not increase recruitment rates to a falls prevention trial

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## Keywords

embedded trial, leaflet, pre-notification, randomization, randomized controlled trial, recruitment

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## Abstract

**Objectives** To design and evaluate the effectiveness of a pre-notification leaflet about research to increase recruitment to a randomized controlled trial (RCT).

**Methods** A methodological, two-arm, RCT was conducted, embedded within an existing cohort RCT (REFORM). Participants were randomized for the embedded trial, using a 1:2 ratio (intervention : control) before being randomized for REFORM. Controls received a trial recruitment pack. The intervention group received an additional pre-notification leaflet 2–3 weeks before the recruitment pack. Primary and secondary analyses were conducted using relative risk, the Cox proportional hazards model and incremental cost-effectiveness ratios.

**Results** Of the 1436 intervention group participants, 73 (5.1%) were randomized into the REFORM trial compared with 126 (4.4%) of the 2878 control group participants. The associated relative risk (1.16) was not statistically significant [95% confidence interval (CI) 0.88–1.56]. Return rate was not significantly increased (relative risk 1.10, 95% CI 0.92–1.28) nor time to return decreased (hazard ratio: 1.11, 95% CI 0.93–1.33). Incremental cost-effectiveness ratios indicated the intervention may be cost-effective if the true estimate of effect was close to the upper bound of the associated 95% CI.

**Conclusion** Pre-notification for potential trial participants demonstrated a small difference to randomization (0.7% difference) and return rates (1.1% difference) in favour of the intervention. Results should however be interpreted with caution as CIs for these estimates cross the point of no effect. Nevertheless, this research enhances existing evidence for pre-notification to increase recruitment rates, with further development and assessment of this potentially cost-effective intervention being recommended.

## Introduction

Randomized controlled trials (RCTs) of health care interventions are often susceptible to recruitment difficulties [1] with a reported 45% of trials failing to recruit more than 80% of their intended sample size [2]. This poses a significant threat to the statistical power and validity of a trial and introduces potential for type II error (concluding there is no between group difference and so failing to reject the null hypothesis despite there being a real difference between the groups) [3] while impacting on associated trial costs and conclusions that can be drawn.

A number of randomized and quasi-RCTs have been conducted to assess the effectiveness of interventions to increase participant recruitment to RCTs. The evidence base is, however, sparse with only 45 of the 750 000 published RCTs recorded on the Cochrane Central Register of Controlled Trials [4] specifically focusing on improving trial recruitment and of these, 19 recruited patients to

‘hypothetical’ trials [5]. A Cochrane Review by Treweek *et al.* [5] has summarized and synthesized these trials enabling a variety of effective recruitment strategies to be identified (e.g. incentives or open trial designs). In reviews by Treweek *et al.* and Watson and Torgerson (2006) interventions exploring the use of different mailing strategies demonstrated mixed effectiveness [3,5] and despite the depth of information in both reviews, there is limited evidence of any use of pre-consent recruitment methods [3,5]. A literature search of pre-notification methods (undertaken by CA as part of this work) identified only one recorded instance of use of pre-notification in the context of recruitment. This single study [6] assessed the effectiveness of a postcard sent prior to approaching patients for consent, as part of the recruitment strategies for Carotene and Retinol Efficacy Trial [7]. The postcard increased recruitment pack return and completeness rates when compared with the control group, but the effect on the proportion of potentially eligible respondents was not statistically significant.

The intervention effectiveness assessment may however be limited by the use of multiple recruitment strategies without accounting for this through factorial trial design. Quality assessment of this trial indicated significant concerns regarding the methodological quality of the research. As a result, causal inferences could not be established and indicate a necessity for further, rigorous work to ascertain the effectiveness of this method.

Pre-notification has, however, indicated a statistically significant effect in the context of increasing questionnaire response rates [odds ratio 1.45, 95% confidence interval (CI) 1.29–1.68] [8]. It may therefore be appropriate to further investigate such interventions in a recruitment setting to see if similar results can be achieved in this context.

The relatively low cost and high potential benefits of database recruitment methods [1] for large cohort trials suggest that further research into the use of mailing strategies as a recruitment aid to RCTs is warranted. Given the limited number of pre-notification strategies and the differences in effect on response rate, investigation of pre-notification to increase recruitment to randomized trials is required. Understanding of the research process and the importance of trials by the general public is poor [9], with many people perceiving themselves to be more knowledgeable about research than they actually are [10]. A pre-notification leaflet detailing the importance of research participation may therefore help to improve understanding of and recruitment to RCTs. If proven effective, the intervention would provide researchers with a simple, low cost tool to improve RCT recruitment.

## Methods and materials

### Design

This was a two-arm, RCT embedded within the REFORM RCT [11]; a randomized cohort trial [12] whereby participants are initially recruited into an observational cohort and those that are (or later become) eligible for the intervention are subsequently randomized, evaluating the clinical and cost-effectiveness of a multifaceted podiatry intervention to prevent falls in patients aged 65 years and over. The REFORM trial recruited from nine National Health Service (NHS) Trusts in the UK and one site in the Republic of Ireland.

Herein, this paper will refer to the methods and results of the embedded trial evaluating the effectiveness of a pre-notification leaflet about research to increase recruitment to an RCT.

### Participants

The embedded trial was conducted in one NHS Trust based within the UK. Participants were allocated 1:2 to intervention and control groups within this embedded RCT.

Research podiatrists, from one NHS Trust in the UK, pre-screened routine podiatry clinic lists for the main REFORM trial and provided the York Trials Unit (University of York) with the total number of potentially eligible patients. As this embedded RCT was designed to conduct methodological research into trial recruitment methods, the inclusion and exclusion criteria for this embedded sub-study were the same as those detailed in the protocol for main REFORM study [11].

### Interventions

The two-page A4 leaflet intervention was based on Patient Information Sheet key themes, detailing the importance of research participation, and included frequently asked questions and contextualized local research to encourage participation. The readability of the leaflet was assessed using the 'Simplified Measure of Gobbledygook' assessment tool [13]. The leaflet also utilized gain framing to influence the choices made by the reader [14] as this method has been shown to be persuasive particularly when promoting behaviours that prevent onset of disease or that carry minimal risks [15].

The leaflet was piloted using a convenience sample (three women and two men), representing similar demographics as REFORM trial participants. This was discussed with the REFORM Patient and Public Involvement group to ascertain the readability and suitability of the language, design and information choices. Feedback from both groups was positive, and no changes to the leaflet were required.

The leaflet was sent to the intervention group participants 2–3 weeks before the REFORM recruitment pack. Participants allocated to the control group, did not receive a pre-notification leaflet and were mailed a REFORM recruitment pack as per protocol [11].

### Outcomes

The primary outcome measure was the proportion of participants randomized for the main REFORM trial. Secondary outcomes included recruitment to the trial cohort (proportion of people consenting to REFORM trial participation) and time taken to respond to the REFORM recruitment pack (days elapsed between recruitment pack mailing and return).

A cost-effectiveness analysis was also conducted for this intervention.

A further secondary analysis (rate of retention) was proposed as part of the protocol for this study; however, as the focus of this report is on recruitment, this has not been analysed and reported here.

### Sample size

The pilot phase of the REFORM trial indicated that 3% of participants approached were eligible for randomization into the trial. This embedded trial was therefore designed to investigate the effectiveness of pre-notification to increase randomization rates by 2%, from 3% as observed in the REFORM pilot to 5% – an appropriate increase in recruitment given the time and costs of completing this embedded trial. Embedded trials do not usually have a formal power calculation as they use all participants within the host trial. In this instance, because the host trial population was so large, it was not cost-effective to randomize all potential participants. A power calculation was therefore completed, based on 80% power 5% significance level, indicating a total sample size of 3300. As this trial had significant resource requirements in terms of intervention printing, postage and workforce costs, unequal allocation lessened the financial burden of the intervention. Participants were allocated 1:2 (intervention: control) resulting in a requirement for 2200 control group participants and 1100 intervention group participants.

## Randomization

Simple randomization, using a 1:2 intervention : control allocation ratio, was conducted using a secure, remote computer programme and was administered by a data manager, independent of the research team and study site, at York Trials Unit. The allocation was independent and concealed. Potential participants were allocated a participant identification number, who were then randomized prior to completing the leaflet, and subsequent recruitment pack, mailings.

## Blinding

It was not possible to blind podiatry clinic staff to the participant's embedded trial allocation as staff needed to handle patient identifiable data to facilitate the mail out to intervention participants. Research staff at York Trials Unit were however blinded to embedded trial allocation as they were not involved in the intervention implementation to protect participant confidentiality.

As participants were not informed of this 'embedded trial', they could not provide informed consent for their involvement and were therefore blinded to their sub-study allocation. Consent for the main REFORM trial was obtained when the participant returned the REFORM trial consent form, included in the recruitment pack, to the York Trials Unit. This occurred after the pre-notification leaflet had been sent out.

The leaflet was designed to be non-invasive and contained only generalized literature about research and RCTs; therefore, this was considered a low-risk trial. Both the leaflet and design of the embedded trial were granted ethical approval, by the REC East of England – Cambridge East (REC Reference 11/EE/0379).

## Statistical analysis

Analyses were conducted using SPSS Version 19 (IBM Corporation, Armonk, NY, USA) [16] on an intention-to-treat basis with two-sided significance at 0.05. The numbers and percentages of participants with data for both the primary outcome and the secondary outcome of recruitment to the cohort were compared using relative risk (RR) and associated 95% CI. The secondary outcome of time to return was analysed using Cox proportional hazards model.

All participants were included in the analyses with exception of time to return where exclusions were required because of incorrect recording of the consent return date ( $n=2$ ; intervention=0, control=2). Associated test assumptions were assessed, where applicable, and analysis methods were adapted when data did not fit a normal distribution.

## Economic analysis

Cost-effectiveness analyses were also conducted with incremental cost-effectiveness ratios (ICER) calculated, incorporating design, printing and postage costs associated with the intervention. Further cost-effectiveness sensitivity analyses were completed to include additional costs incurred to ensure the target sample size is met when recruitment and randomization rates are low. This included costs associated with the setup of one additional study site (specifically trial coordinator time) to give an additional cost per

participant randomized, on the basis of the additional site recruiting 50 participants. All participants were included in the analyses.

## Results

The embedded study mailings were completed between May and July 2013. A total of 1436 participants were randomized to receive a pre-notification leaflet (intervention group), and 2878 participants were randomized not to receive a pre-notification leaflet (control group) (Fig. 1). Seven participants were recorded as having crossed over from intervention to control due to errors in implementing the study allocations. There were no reported crossovers from control to intervention.

Of the participants returning a completed consent form, there was no between group difference in demographic factors or reported quality of health, measured using EQ-5D scores (Table 1).

Intention-to-treat analysis indicated that there was a positive but non-statistically significant difference in randomization rates between the intervention and control groups [intervention: 73 out of 1436 (5.1%) and control: 126 out of 2878 (4.4%)] (difference 0.7%, 95% CI  $-0.58$  to  $2.46$ ; RR 1.16; 95% CI 0.88–1.56).

For recruitment to the cohort, 186 (13.0%) of the intervention group (1436 participants) returned a consent form compared with 343 (11.9%) participants from the control group (2878 participants); however, this difference was not statistically significant (RR 1.10; 95% CI 0.92–1.28).

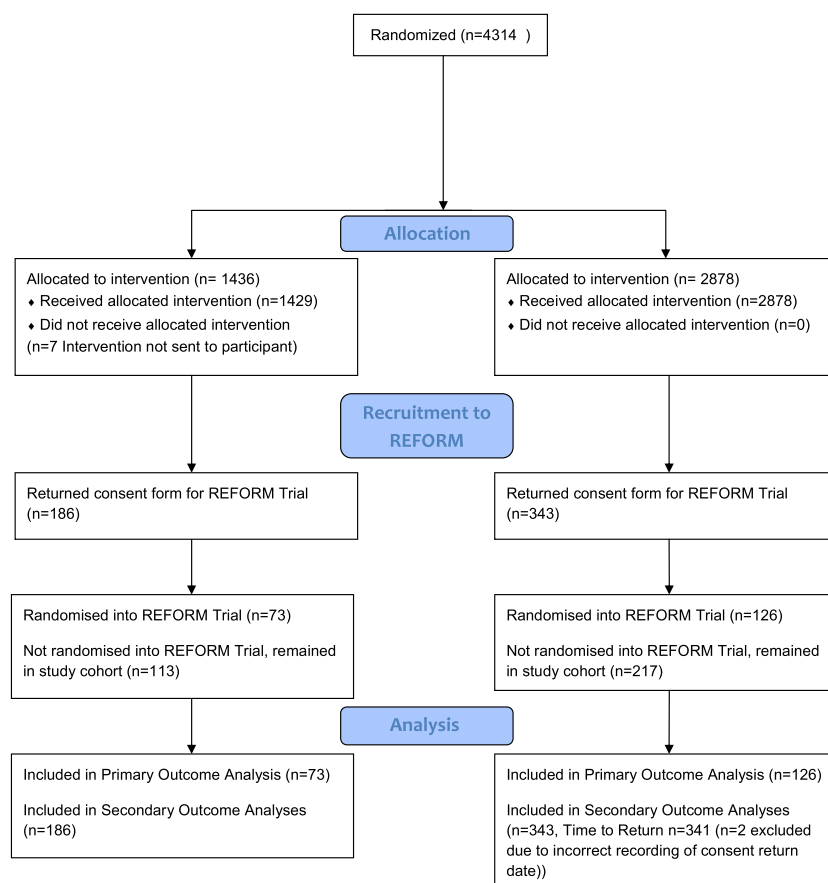
The mean time to return was 15.44 days (standard deviation: 11.83) and 17.46 days (standard deviation: 20.08) for the intervention and control groups, respectively. Cox proportional hazard regression indicated a positive effect in reducing time to return; however, this result was not statistically significant (hazard ratio: 1.11; 95% CI 0.93–1.33).

## Results – economics

The costs used to estimate the intervention cost per participant are detailed in Table 2.

Per participant, intervention group costs were £4.36, while control group costs were £2.79, giving an incremental cost of £1.57. The average cost per recruited participant was £63 in the control group (i.e.  $£2.79 \times 100/4.4$ ) and £85.50 in the intervention group. The important difference is however the ICER of the intervention. The extra cost per mailed participant was £1.57, and the incremental effectiveness was 0.7%, giving an ICER of £224.29 per additional participant randomized into REFORM. Compared with the cost of randomizing an additional control group participant into REFORM (£63), the intervention was three and a half times more expensive than the control, per additional randomization obtained. Therefore, the intervention is not cost-effective at the point estimate difference, and for the intervention to be cost-effective, it would need to increase the recruitment rate by nearly 2.5% (i.e.  $£1.57/£63 \times 100$ ), a value similar to the upper 95% CI of the difference observed.

Sensitivity analyses were conducted to identify the difference required to demonstrate cost-effectiveness. The upper 95% CI of the primary outcome was applied to the observed recruitment rates

**Figure 1** Study flow diagram.**Table 1** Baseline characteristics of participants returning a completed consent form

	Intervention group		Control group	
	Number of participants (n)		Number of participants (n)	
Age mean (SD)	186	76.72 (7.21)	343	76.95 (6.98)
Gender (n, %)	186	Male: 81 (43.5%)	343	Male: 145 (42.3%)
		Female: 105 (56.5%)		Female: 198 (57.7%)
		White 182 (99.5%)		White 339 (99.1%)
Ethnicity (n, %)	183	Asian 1 (0.5%)	342	Asian 1 (0.3%)
EQ5D score (mean, SD)	127	0.79 (0.19)	240	0.80 (0.15)
EQ5D line (mean, SD)	125	70.82 (19.6)	235	74.31 (16.63)

SD, standard deviation.

of the control group and of REFORM. The intervention was potentially cost-effective because the values generated met but did not exceed the threshold increases required for cost-effectiveness. When additional costs incurred when compensating for under recruitment were incorporated, the values exceeded the thresholds for all observed recruitment rates. The intervention is therefore potentially cost-effective at 6.86%, as the value exceeds the percentage difference required (4.77%) to offset the cost of additional sites, if the true value falls close to the upper 95% CI.

## Discussion

This 'embedded trial' provides a significant contribution to the limited literature on the development and effectiveness of pre-notification methods to improve randomization and recruitment to RCTs and specifically adds additional information regarding the cost implications of utilizing such interventions. Although the differences observed in this trial were not statistically significant, this intervention did demonstrate a positive effect on the rates

**Table 2** Intervention costs incorporated into economic assessment

Cost type	Associated rate	Time associated with task (hours)	Overall cost (£)
Design	Researcher salary (including superannuation and NI contribution): £16 per hour	30	480.00
Printing	A4 Landscape, double sided, 135gsm gloss art paper. Printing of 1436 leaflets		376.95 (0.26 per leaflet)
Postage	Packing – Researcher Salary (including superannuation and NI contribution): £16 per hour	8	128.00
	Supplies – 1436 C5 manila non-windowed, peel and seal envelopes (£238.35) and small second-class stamps (£718.00)		956.35
	Labelling by podiatry clinic – Research Podiatrist salary (including superannuation and NI): £19.38 per hour	16	310.00
Total			2251.30

NI, National Insurance.

of randomization and consent form return. Despite the wide CIs associated with the estimates of effect, results from cost-effectiveness analysis suggest that similar pre-notification interventions could provide a cost-effective strategy for implementation in future RCTs.

The outcomes of this trial correspond to the findings of Valanis *et al.* [5] who also found no statistically significant increase in the proportions of eligible or randomized participants when pre-notification was used. While pre-notification appears to increase response rates in the context of both recruitment and questionnaire returns, our trial and others [6,8] differ in terms of the statistical significance of the effect, and further investigation is required to make firm conclusions before applying this intervention to future RCTs.

Strengths of this trial include the large sample size that ensured there was power to detect relatively small differences, albeit failing to completely exclude a 'cost-effective' difference. Demographic analysis of the participants indicated that both groups were comparable across all criteria. The results are therefore applicable to the participant population the sub-study sample represented (i.e. White British, NHS patients in a predominantly high socio-economic area of the UK, aged 65 years or older and reporting good health at the time of consent). Subsequent studies may wish to explore the use of pre-notification in different population groups to demonstrate wider generalizability beyond the population of this trial and the population used by Valanis *et al.* [6] (American smokers and asbestos exposed workers aged 45–69 years).

### Limitations

This study has some limitations. Difficulties in blinding research staff to treatment allocation limited this trial because of podiatry staff needing to access patient identifiable details to facilitate intervention dissemination. It is however unlikely that this resulted in

differential treatment as clinic staff are unlikely to have contacted potential participants in either group.

There were seven recorded participant crossovers from intervention to control due to errors in implementation of the intervention. In addition, as the intervention was delivered by postal methods, it is possible that some participants may have inadvertently crossed from control to intervention by virtue of residing with an intervention participant. The level to which this occurred is difficult to quantify; however, no crossovers were reported to the study site. As a result, estimates of effect should be viewed with caution.

For further development of this recruitment method, in-depth qualitative work may be beneficial. Although work was conducted in this trial to elicit participant's views to inform intervention design, the pre-notification leaflet could be further enhanced by through patient user interviews.

In addition, future studies may wish to evaluate the most appropriate gap between pre-notification and recruitment mailings. This trial incorporated a 2- to 3-week gap between pre-notification and REFORM recruitment pack mailings, similar to the time period used by Valanis *et al.* (1 week gap) [6]. As both studies found a non-significant increase in randomization rates, this may however not be the most appropriate timeframe between pre-notification and recruitment pack mailings, and so further work is warranted.

### Conclusion

Recruitment to RCTs remains a significant issue with a lack of reported research of interventions to improve trial recruitment. This trial therefore represents a significant contribution to the limited evidence base. The findings of this trial indicated a small difference in randomization rates to REFORM (0.7%) in favour of the leaflet intervention. However, as the CIs for this estimate cross 0 (associated with no intervention effect), the results should be interpreted with caution. Consideration should be given to further

development and research into the effectiveness of pre-notification methods on RCT randomization and recruitment rates.

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