

The effects of an open design on trial participant recruitment, compliance and retention – a randomized controlled trial comparison with a blinded, placebo-controlled design

Alison Avenell^a, Adrian M Grant^a, Maureen McGee^b, Gladys McPherson^a,
Marion K Campbell^a and Magnus A McGee^a for the RECORD Trial Management Group

Background In randomized trials there may be no overriding reason whether or not to have a placebo control.

Purpose We assessed the effects of an open trial design (no placebo and people know what tablets they are given) compared with a blinded, placebo-controlled design on recruitment, compliance and retention within a randomized trial of secondary osteoporotic fracture prevention.

Methods We undertook a randomized controlled comparison nested within a placebo-controlled trial of nutritional supplementation amongst people aged 70 years or over who had previously sustained a fracture, recruited in a UK teaching hospital. Randomization was 2:1 in favour of the blinded, placebo-controlled trial design.

Results From 180 eligible participants randomized to receive information based on the open trial design, 134 (74.4%) consented to take part, compared with 233 (65.1%) of 358 people randomized to the blinded, placebo-controlled design (difference 9.4%, 95% confidence interval 1.3–17.4%). Reluctance to take a placebo and the desire to know tablet allocation were reasons given for not taking part in the blinded, placebo-controlled design. There was no significant difference in tablet compliance. Open trial participants were more likely to remain in the trial for one year (difference 13.9%, 95% confidence interval 3.1–24.6%), mainly reflecting the high retention of the open trial no tablet group compared to the open trial tablet group (difference 23.6%, 95% confidence interval 11.9–35.2%). The odds ratio for reporting an adverse event in the open trial compared to the blinded, placebo-controlled design was 0.64 (95% confidence interval 0.28–1.49), and for reporting a fracture was 0.81 (0.36–1.85).

Conclusions We conclude that using an open trial design may enhance participant recruitment and retention and thus improve generalizability and statistical power, but withdrawal rates may differ between the study allocations and may threaten the internal validity of the trial. *Clinical Trials* 2004; 1: 490–498. www.SCTJournal.com

Introduction

Placebo controls are commonly used in randomized trials aiming to minimize bias; they are particularly encouraged in regulatory submissions of new clinical treatments such as drugs. A double-blind placebo-controlled design should

ensure that outcome assessment is unbiased and isolate any effects of the participant and/or caregiver knowing the type of treatment received (the placebo effect). There are, however, other ways to ensure unbiased outcome assessment, and keeping the recipient and caregiver ignorant of the nature of therapy does not mirror normal

^aHealth Services Research Unit, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK, ^bUniversity Department of Orthopaedic Surgery, Royal Infirmary of Edinburgh, Little France, Old Dalkeith Road, Edinburgh EH16 4SU, UK
Author for correspondence: Dr A Avenell. E-mail: a.avenell@abdn.ac.uk

health care. An open ("open-label") trial design where both the participant and caregiver know the therapy and where there is no placebo group (instead this group receives "no treatment") is closer to usual practice [1]. It might therefore give a better estimate of differential effects in normal care as this design would incorporate any effect modification such as enhanced motivation from knowing the treatment.

The choice between these designs carries other implications for a trial's validity and these may be important when there is no overriding reason to isolate or incorporate any placebo effect. Potential trial participants might be reluctant to accept the possibility that they will receive a placebo or not know the nature of their allocation and may therefore decline to take part. Thus, a blinded, placebo-controlled trial could lead to under recruitment and participation of people who are less representative of the population under investigation as a whole. On the other hand, later differential withdrawal from the trial groups might be more likely if participants know what they have been allocated, particularly if there is a "no treatment" group, thus potentially introducing attrition bias in an open design. The choice of design might also affect compliance. Participants may be more likely to adhere if they know what "active" treatment they are taking, whereas participants allocated open "no treatment", if disappointed, might be more likely to seek the intervention treatment outside the trial.

We used the opportunity provided by the UK Medical Research Council sponsored RECORD trial to examine these issues further, specifically whether those eligible were: a) more likely to consent to take part; b) more likely to comply with treatment; and c) more likely to withdraw after entry in an open randomized trial design compared with a blinded, placebo-controlled randomized trial design. The standard RECORD trial is a randomized double-blind placebo-controlled, factorial design, evaluation of oral calcium (1 g daily) and/or vitamin D (800 IU/20 µg) supplementation in the secondary prevention of osteoporotic fractures [2]. We compared this with an open trial design, which was otherwise identical.

Methods

Ethical approval

The Multicentre Research Ethics Committee for Scotland and the Lothian Research Ethics Committee approved both the RECORD trial and the study reported here.

Study sample

Participants were recruited in the Edinburgh centre of the UK RECORD trial between July 2000 and July 2001. People eligible for the RECORD trial were identified from the hospital notes, and seen either in a fracture clinic or on an orthopaedic ward. Full details of the RECORD trial are available elsewhere [2]. Participants had had an osteoporotic fracture within the last 10 years, were aged 70 years or over, and had none of the prespecified exclusion criteria. Patients were also ineligible if they had daily oral treatment with more than 200 IU (5 µg) vitamin D or more than 500 mg calcium or other bone active medications.

Procedure

The study nurse approached people eligible for the RECORD trial and asked if they were interested in helping with a study looking at vitamin D and/or calcium for the prevention of another fracture. As far as possible all consecutive eligible people were approached. However, this was not always possible; for example, when two eligible patients were sitting next to each other in out-patients, there was a risk of group contamination. Potential participants were informed that they had a three out of four chance of getting real treatment and that the study would last until 2003, with questionnaires and tablets sent out by post every four months.

The study nurse then used a preprogrammed laptop computer to generate random allocation to either the open trial design or the blinded, placebo-controlled trial design in a 1:2 ratio. The unequal allocation was chosen so that the majority joined the standard RECORD trial. Randomization was minimized [3] by age (under 80 years or 80 years and over), sex, time since fracture (previous three months or longer) and type of enrolling fracture (proximal femur, distal forearm, clinical vertebral and other).

The study nurse gave a full explanation of the allocated study design: either the open randomized trial design (participants would be told to which compound they had been allocated, whether vitamin D, calcium, vitamin D and calcium, or no tablets) or the conventional RECORD trial (the randomized blinded, placebo-controlled trial of vitamin D, calcium, vitamin D and calcium, or placebo). The nurse described the study design with information leaflets, which were similar in appearance. The nurse had initial training and was regularly observed undertaking recruitment to ensure that information was consistent, well explained and as specified in the protocol.

Written consent was then collected. The nurse recorded the exact wording used by people to describe why they did not wish to take part. Reasons given for declining were coded into areas with common themes by one study investigator, who was blinded to group allocation.

Randomization within study design and follow-up

Tablets and questionnaires were subsequently sent by post from the trial co-ordinating centre. The covering letter and tablet bottles sent to participants in the open trial gave details of their study allocation. Participants' family doctors also received information about the open trial allocation. At subsequent four monthly intervals participants received further tablets as required by the trial design, and all participants received questionnaires identical in appearance to return by reply paid mail to the trial office. These questionnaires included questions on self-reported supplement consumption (trial tablets, purchases over the counter and prescriptions by family doctors), fractures and adverse events. With the mailing at eight months, all participants receiving tablets were asked to return unconsumed tablets in order to conduct a tablet count for compliance.

Outcome measures

The main outcome measures were: a) the proportions of eligible participants recruited under the two trial designs; b) the proportions compliant (taking tablets on more than 80% of days) on pill counts at eight months after randomisation; and c) the proportions of participants remaining in the study at one year (i.e., had not withdrawn). Secondary outcomes were reasons given for declining to take part and withdrawal, self-reported tablet consumption, and commencement of calcium and vitamin D supplements purchased over the counter and prescribed by the family doctor. Reported adverse events and fractures were also collected.

Sample size calculation

Initial work on the RECORD trial indicated that ~60% of eligible patients agreed to participate in the trial. Assuming a 1:2 randomization ratio, it was calculated that 540 people would be required to estimate a relative difference in recruitment of 20%, i.e., a difference from 60 to 72% (with 80% power, $2P < 0.05$) between the trial groups. This comparison of trial designs was not powered to

examine differences in reporting of adverse events or fractures.

Statistical methods

The proportions of the two groups recruited were compared by multivariate logistic regression, adjusting for the minimization variables age, sex, type of fracture and time since fracture [4].

The proportions of participants remaining in the trial after 12 months were compared using the log-rank test within a multidecrement life table approach, where participants who died were censored at the date of death. The confidence interval for the difference in proportions were based on the life table estimates.

Differences between groups for compliance, adverse events and fractures were examined by Newcombe's method [5].

Results

Table 1 shows the baseline characteristics of the various groups compared and Figure 1 summarizes the participants' flow through the study.

Recruitment under the two trial designs

Five hundred and thirty-eight participants took part; 180 were allocated to the open design and 358 to the placebo design. The groups were well balanced; their mean ages were 77 and 78 years, 83% were women, the preceding fracture was proximal femur or distal forearm for 50% of people, and 93% of the participants had had their fracture within the previous three months.

Of the 180 people given information about the open trial design, 134 (74.4%) consented, compared with 233 (65.1%) of 358 given information about the blinded, placebo-controlled design [difference 9.4%, 95% confidence interval (CI) 1.3–17.4%; odds ratio 1.56, 95% CI 1.05–2.33]. The odds ratio was not materially influenced by adjusting for age, sex, type of fracture and time since fracture (OR 1.58, 95% CI 1.06–2.36).

Table 2 describes the reasons given for declining to take part (some people gave more than one reason). The larger proportion of people declining to take part in the blinded, placebo-controlled design reflected not wanting to take more tablets, wanting a named medication, or wanting to see their GP, as well as not wanting to take a placebo and wanting to know what was in the tablets.

Table 1 Characteristics of groups randomized to information about open or blinded, placebo-controlled designs and subsequent participants

Given information	Randomized to information on open trial design (N = 180)		Randomized to information on blinded, placebo-controlled trial design (N = 358)		Open trial design participants			Blinded, placebo-controlled trial design participants		
	All (N = 180)	Active (N = 99)	All (N = 358)	Active (N = 172)	No tablets (N = 35)	All (N = 233)	Active (N = 172)	Placebo (N = 61)		
Age (years)	77 (5)	76.7 (4.7)	78 (6)	77.0 (4.9)	75.6 (3.8)	77.4 (5.6)	77.2 (5.5)	78.0 (5.7)		
Mean (SD)	149 (82.8)	111 (82.3%)	297 (83.0)	81 (81.8%)	30 (85.7%)	196 (84.1%)	146 (84.9%)	50 (82.0%)		
Sex	13 (7.2)	9 (6.7%)	23 (6.4)	8 (8.1%)	1 (2.9%)	13 (5.6%)	9 (5.2%)	4 (6.6%)		
Type of fracture	77 (42.8)	57 (42.5%)	157 (43.9)	41 (41.4%)	16 (45.7%)	95 (40.8%)	69 (40.1%)	26 (42.6%)		
Proximal femur, number (%)	90 (50.0)	68 (50.7%)	178 (49.7)	50 (50.5%)	18 (51.4%)	125 (53.6%)	94 (54.7%)	31 (50.8%)		
Distal forearm, number (%)	167 (92.8)	124 (92.5%)	334 (93.3)	92 (92.9%)	32 (91.4%)	217 (93.1%)	160 (93.0%)	57 (93.4%)		
Other, number (%)										
Time since fracture										
Within previous three months, number (%)										

Characteristics of participants taking part in the two trial designs

Table 1 also gives details of those who were recruited to the designs, overall and according to their actual allocations. The groups compared were similar at baseline, despite differences in the proportions recruited to the two study designs.

Tablet compliance

Compliance amongst those who returned their tablet containers was similar (overall 85 versus 84.5% of tablet takers took their tablets on more than 80% of days; Table 3). The same pattern was observed for self-reported tablet consumption at four, eight or 12 months during the study (data not shown).

Withdrawals

Figure 2 presents the percentage of total participants still taking part in the trial designs during the year. Open trial design participants as a group were more likely to remain in the trial for longer (difference 13.9%, 95% CI 3.1–24.6%). This difference was mainly due to more people remaining in the trial in the open trial design no tablet group compared to the open trial tablet group (difference 23.6%, 95% CI 11.9–35.2%) (Figure 3). There was no apparent difference in those remaining in the trial between the placebo and active groups in the blinded design group (difference -0.6%, 95% CI -17.9–16.7%). There was, however, a tendency for the open trial design tablet group to be less likely to withdraw than the active tablet group in the blinded, placebo-controlled design group (difference 7.5%, 95% CI -5.9–20.9%). There was no statistically significant difference in gender, age, type of fracture, or time since fracture in those who dropped out in the two trial designs.

The overall difference was explained by fewer participants in the open trial design changing their minds about participation, or having difficulties with taking tablets or taking too many tablets as reasons for withdrawal (Table 4). No participant gave unhappiness with blinding or the possibility of taking a placebo as a reason for withdrawal.

Reported adverse events and fractures

Reported adverse events and fractures are given in Table 5. There were no statistically significant differences between the groups. The odds ratio for reporting an adverse event in the open trial

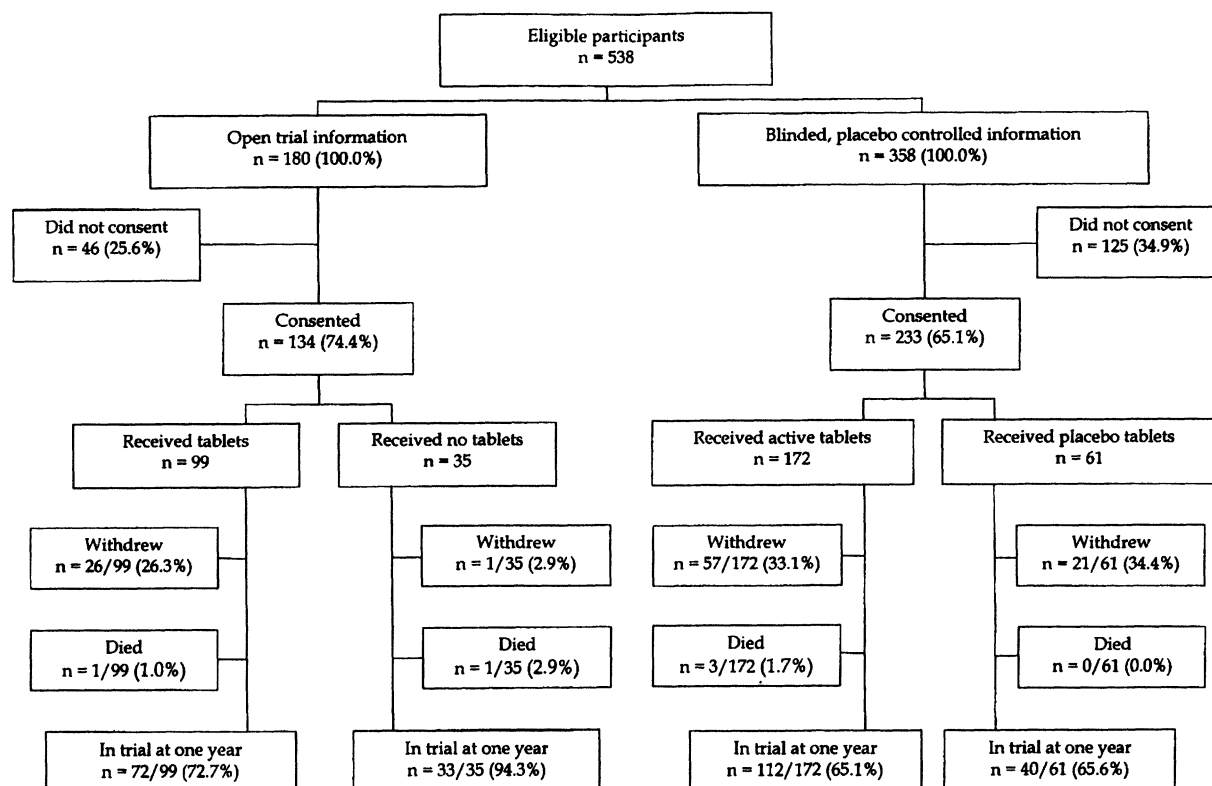


Figure 1 Participant flow through the trial

compared to the blinded, placebo-controlled design was 0.64 (95% CI 0.28–1.49). The odds ratio for reporting a fracture in the open trial compared to the blinded, placebo-controlled design was 0.81 (95% CI 0.36–1.85).

Table 2 Reasons given for declining to take part

	Open trial design	Blinded, placebo-controlled design
Allocated	180 (100%)	358 (100%)
Number declining to take part	46 (25.6%)	125 (34.9%)
Didn't want (more) tablets/supplements	31 (17.2%)	73 (20.4%)
Didn't believe needs tablets/supplements	11 (6.1%)	22 (6.1%)
Wanted named medicine and gives name, or wants to speak to GP or get tablets/supplements from GP	4 (2.2%)	17 (4.7%)
Worried about side effects	3 (1.7%)	5 (1.4%)
Didn't want to take placebo	N/A	8 (2.2%)
Wanted to know what was in tablets given	N/A	8 (2.2%)
Other	13 (7.2%)	27 (7.5%)

Multiple responses were possible.
N/A = not applicable.

Calcium and vitamin D purchases over the counter and prescription by family doctors

No participant in either trial design reported purchasing calcium or vitamin D supplements over the counter. One participant in the open trial design and one participant in the placebo-controlled design were prescribed vitamin D supplements by their family doctor. No calcium supplements were prescribed in the placebo-controlled design, and three participants in the open trial design were prescribed calcium.

Discussion

This is the first study to use an experimental design to assess the impact of an open rather than placebo-controlled design on recruitment, compliance and retention. Selection bias was avoided in the comparison of recruitment by randomly allocating eligible people to the designs, and the trial was large enough to identify a plausible difference. We recognize, however, that this is a single case study in a specific group of people and acknowledge that at least some of the differential effects will be different in other trial settings.

Table 3 Drug count at eight months

	Open trial design		Blinded, placebo-controlled design	
	Active n/N (%)	All n/N (%)	Active n/N (%)	Placebo n/N (%)
Total participants	78	173	127	46
Total participants returning drugs for count	60/78	116/173	87/127	29/46
Participants taking tablets >80% of days	51/60 (85.0%)	98/116 (84.5%)	70/87 (80.5%)	28/29 (96.6%)
Participants taking tablets 50–80% of days	7/60 (11.7%)	12/116 (10.3%)	12/87 (13.8%)	0/29 (0%)
Participants taking tablets <50% of days	2/60 (3.3%)	6/116 (5.2%)	5/87 (5.7%)	1/29 (3.4%)

Difference in proportion in those taking tablets >80% of days: open trial design (active) versus blinded, placebo-controlled design (all) test on 1 degree of freedom: 0.5% (95% CI 11.9% to -10.8%).

We found that these older people with a history of osteoporotic fracture were less likely to consent to join a randomized trial with a blinded, placebo-controlled design. Unwillingness to take a placebo and the desire to know the tablet allocation were reasons mentioned when declining. Others have found that having a placebo group may reduce the proportion of patients willing to take part in clinical trials of treatments for cancer and schizophrenia [6–9]. However, these studies did not investigate specifically whether it was the chance of not receiving the “active” treatment, the possibility of taking a dummy tablet, or the blinding to allocation that influenced patients. Welton *et al.* [10] examined whether willingness to take part in a hypothetical randomized controlled trial of hormone

replacement therapy might be influenced by a placebo arm in the trial. In this quasi-randomized study, women received information about one of two trial scenarios: with three groups including one placebo arm, or with only the two treatment arms. Women were blinded in both trial designs. Women were 9% more likely to indicate a willingness to take part if there was no placebo, a result of borderline significance (95% CI 0–18%) but similar to the difference in recruitment found here.

In the present study, participants had an equal chance of not receiving the “active” treatment, irrespective of the trial design. The lower recruitment rate in the blinded, placebo-controlled design seems, therefore, to relate to the wish to avoid taking unnecessary, unspecified tablets

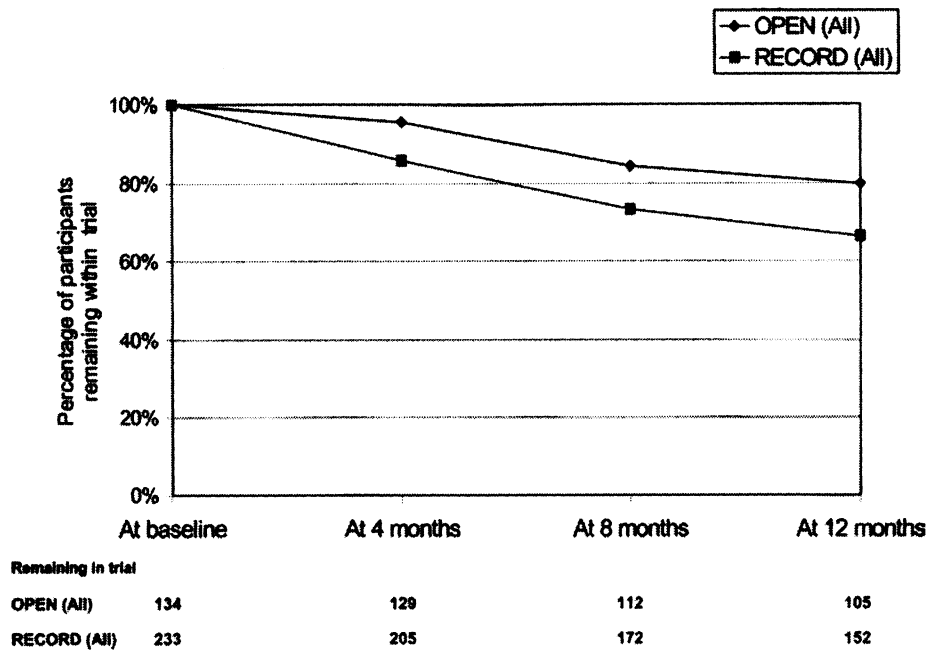


Figure 2 Graph of participants remaining in the open trial and the blinded, placebo-controlled trial (RECORD)

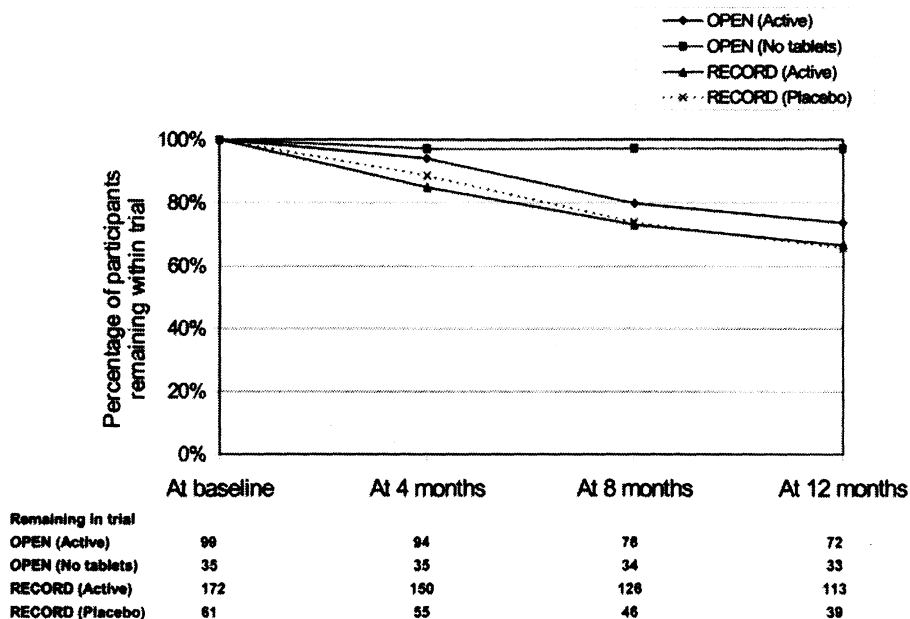


Figure 3 Graph of participants remaining in the open trial and the blinded, placebo-controlled trial (RECORD) according to allocation

or to know what the tablets were, rather than to circumvent the chance of allocation to a no active treatment group. On this basis, an open randomized trial design could produce results that are more generalizable (and also statistically more powerful), by increasing the proportion of eligible patients recruited.

Once recruited, knowledge that a tablet was “active” and knowing what it actually was did not appear to have an effect on compliance amongst those allocated tablets. This should be interpreted cautiously however. The estimates are imprecise and this also assumes that those who did not return their containers were similar to those who did.

Those in the open design were more likely to still be in the trial at one year. In principle, it might be expected that those allocated no treatment in an open design might be most likely to withdraw. In the event, they proved least likely to in this study. The extra withdrawals in the placebo design were due to changing minds, difficulty taking the tablets, or complaining of taking too many tablets. Nevertheless, the differential withdrawal rates in the open group could still introduce more bias; this may offset the advantages of having larger numbers in the analysis.

The people studied were all over 70 years, mostly women, with recent osteoporotic fractures.

Table 4 Reasons for withdrawing

	Open trial design			Blinded, placebo-controlled design		
	All (N = 134)	Active (N = 99)	No tablets (N = 35)	All (N = 233)	Active (N = 172)	Placebo (N = 61)
Total who withdrew, number (%)	27 (20.1)	26 (26.3)	1 (2.9)	78 (33.5)	57 (33.1)	21 (34.4)
Changed mind, difficulty taking tablets or taking too many tablets	4 (3.0)	4 (4.0)	0	35 (15.0)	26 (15.1)	9 (14.8)
Thinks may get or have side-effects	8 (6.0)	8 (8.1)	0	19 (8.2)	11 (6.4)	8 (13.1)
Withdrawn by family or doctor	3 (2.2)	3 (3.0)	0	7 (3.0)	7 (4.1)	0
Too unwell to continue	6 (4.5)	6 (6.1)	0	10 (4.3)	7 (4.1)	3 (4.9)
Doesn't like placebo or blinding	0	0	0	0	0	0
Other reasons	2 (1.5)	1 (1.0)	1 (2.9)	5 (2.1)	4 (2.3)	1 (1.6)
Unknown	4 (3.0)	4 (4.0)	0	2 (0.9)	2 (0.9)	0

One reason for withdrawal was given by each participant.

Table 5 Reported adverse events and fractures

	Open trial design			Blinded, placebo-controlled design		
	All (N = 134)	Active (N = 99)	No tablets (N = 35)	All (N = 233)	Active (N = 172)	Placebo (N = 61)
Participants with reported adverse events, number (%)	8 (6.0)	7 (7.1)	1 (2.9)	21 (9.0)	14 (8.1)	7 (11.5)
Participants with fractures, number (%)	9 (6.7)	6 (6.1)	3 (8.6)	19 (8.2)	13 (7.6)	6 (9.8)

Odds ratio for reporting adverse event, all in open trial design versus all in blinded, placebo-controlled design 0.64 (95% CI 0.28–1.49).

Odds ratio for reporting fracture, all in open trial design versus all in blinded, placebo-controlled design 0.81 (95% CI 0.36–1.85).

Common reasons for declining or withdrawing, irrespective of study design, were the wish not to take tablets or not to take more tablets. As older people often already take many medications, the desire to avoid further, unspecified medicines may be particularly strong. This clearly had a major impact on the ways in which they responded.

Nevertheless, this study has illustrated the complex and potentially competing implications of choosing between open or placebo-controlled designs. In some circumstances, there will be no option but to perform an open trial because the use of a placebo is impossible, impractical or unethical. In other circumstances, placebos will continue to be used where there are likely strong placebo effects and it is judged important to isolate them. The choice may also depend on whether or not unbiased assessment of outcome is possible without a placebo. Trials are less likely to require a placebo where there are objective trial endpoints, such as mortality or myocardial infarction [11], which are unlikely to be influenced by participant, investigator and outcome assessor preferences.

In many trials, like the one considered here, there will be no overriding reason for or against a placebo to eliminate a placebo effect. This study suggests that each design has advantages and disadvantages. The decision can introduce (or avoid) performance, attrition and detection bias, decrease (or enhance) generalizability, and influence statistical power. This suggests that these competing considerations should be weighed up on a case by case basis before a decision is taken about blinding and placebo use. Contexts will differ and further research is needed to clarify the advantages and disadvantages in other patient groups and settings.

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