

Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis

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ABSTRACT

Objective: To identify interventions designed to improve recruitment to randomised controlled trials, and to quantify their effect on trial participation.

Design: Systematic review.

Data sources: The Cochrane Methodology Review Group Specialised Register in the Cochrane Library, MEDLINE, EMBASE, ERIC, Science Citation Index, Social Sciences Citation Index, C2-SPECTR, the National Research Register and PubMed. Most searches were undertaken up to 2010; no language restrictions were applied.

Study selection: Randomised and quasi-randomised controlled trials, including those recruiting to hypothetical studies. Studies on retention strategies, examining ways to increase questionnaire response or evaluating the use of incentives for clinicians were excluded. The study population included any potential trial participant (eg, patient, clinician and member of the public), or individual or group of individuals responsible for trial recruitment (eg, clinicians, researchers and recruitment sites). Two authors independently screened identified studies for eligibility.

Results: 45 trials with over 43 000 participants were included. Some interventions were effective in increasing recruitment: telephone reminders to non-respondents (risk ratio (RR) 1.66, 95% CI 1.03 to 2.46; two studies, 1058 participants), use of opt-out rather than opt-in procedures for contacting potential participants (RR 1.39, 95% CI 1.06 to 1.84; one study, 152 participants) and open designs where participants know which treatment they are receiving in the trial (RR 1.22, 95% CI 1.09 to 1.36; two studies, 4833 participants). However, the effect of many other strategies is less clear, including the use of video to provide trial information and interventions aimed at recruiters.

Conclusions: There are promising strategies for increasing recruitment to trials, but some methods,

ARTICLE SUMMARY

Article focus

- Despite representing the gold standard in evaluating the effectiveness and safety of healthcare interventions, many randomised controlled trials do not meet their recruitment targets.
- Poor recruitment can lead to extended study duration, greater resource usage and findings that are not as statistically precise as intended; in the worst case, a trial may be stopped.
- A systematic review was carried out to identify methods used to improve recruitment to randomised controlled trials, and to quantify their effects on participation.

Key messages

- There are promising strategies for increasing recruitment to trials, most notably telephone reminders, open-trial designs, opt-out strategies and financial incentives.
- Many trials of recruitment methods involve hypothetical trials, and the applicability of their results to the real world is still unknown.
- There is a clear knowledge gap with regard to effective strategies aimed at those recruiting to trials.

Strengths and limitations of this study

- This Cochrane review utilised a comprehensive search and appraisal strategy, thereby ensuring that all relevant evidence was included.
- Many of the included studies were small, increasing the likelihood of their being underpowered, and resulting in CIs that included the possibility of substantial benefit.
- The interventions evaluated by included studies varied greatly, making it difficult to pool data for meta-analysis.

such as open-trial designs and opt-out strategies, must be considered carefully as their use may also present methodological or ethical challenges. Questions remain as to the applicability of results originating from hypothetical trials, including those relating to the use of monetary incentives, and there is a clear knowledge gap with regard to effective strategies aimed at recruiters.

INTRODUCTION

Randomised controlled trials represent the gold standard in evaluating the effectiveness and safety of health-care interventions, primarily because they help guard against selection bias.¹ Nonetheless, the recruitment of clinicians and patients to these studies can be extremely difficult.² While there are several possible consequences of poor recruitment, perhaps the most crucial is the potential for a trial to be underpowered.³ In such circumstances, clinically relevant differences may be reported as statistically non-significant, increasing the chance that an effective intervention will either be abandoned before its true value is established, or at the very least, delayed as further trials or meta-analyses are conducted. Similarly, while poor recruitment can be addressed by extending the length of a trial, this too can create delay in the roll-out of a potentially effective intervention, while increasing the cost and workload of the trial itself.

Several investigations of recruitment have attempted to quantify the extent of the problem, and while estimates differ, it is clear that many trials do not meet their recruitment targets.^{2 4-6} Of those that do, many achieve them only after extending the length of the trial. A recent cohort study of 114 multicentre trials, supported by two of the UK's largest research funding bodies (the Medical Research Council and the Health Technology Assessment Programme), found that less than a third achieved their original target (n=38; 31%), and more than half had to be extended (n=65; 53%).² In a similar study of 41 trials in the US National Institute of Health inventory, only 14 (34%) met or exceeded their planned recruitment, while a quarter (n=10; 24%) failed to recruit more than half.⁴ In many cases, trials may have to close prematurely due to recruitment problems.⁶

While trialists have used many interventions to improve recruitment, it has been difficult to predict the effect of these. The purpose of this review was to quantify the effects of specific methods used to improve recruitment of participants to randomised controlled trials, and where possible, to consider the effect of study setting on recruitment. Although there have been three previous systematic reviews on strategies to enhance recruitment to research, two do not include the most recent literature,^{7 8} while the third considers the combined effects of interventions across four strategic areas rather than the individual effects of specific interventions.⁹ Our synthesis builds on and updates an earlier Cochrane review,⁸ the protocol and full review are available from the Cochrane Library.¹⁰

METHODS

Criteria for inclusion

Study types and participant

We included randomised and quasi-randomised controlled trials, including those recruiting to hypothetical studies, that is, where potential participants are asked if

they would take part in a trial if it was run, but where no trial exists. Studies examining ways to increase questionnaire response rates, evaluating the use of incentives or disincentives to increase clinicians' recruitment of patients or studying strategies to improve retention were excluded as these are addressed by other Cochrane Methodology Reviews (CMR).¹¹⁻¹³ The study population included any potential trial participant (eg, patient, clinician and member of the public), or an individual or a group of individuals responsible for recruiting trial participants (eg, clinicians, researchers and recruitment sites).

Types of intervention

A recruitment intervention was defined as any method implemented to improve the number of participants recruited to a randomised controlled trial, whether this was directed at potential participants, at those responsible for recruiting participants or at trial design or co-ordination. Interventions used in any study setting were included.

Outcome measure

The outcome of interest was the proportion of eligible individuals or centres recruited.

Identification of studies

We searched the CMR Group Specialised Register 2010, Issue 2, part of *The Cochrane Library* (<http://www.thecochranelibrary.com>), ERIC (Educational Resources Information Centre), CSA (1966 to April 2010), Science Citation Index and Social Sciences Citation Index, ISI Web of Science (1975 to April 2010), National Research Register (online) (2007, Issue 3), The Campbell Collaboration Social, Psychological, Education and Criminological Trials Registry (C2-SPECTR) (up to April 2008), MEDLINE, Ovid (1950 to March week 5 2010) and EMBASE, Ovid (1980 to 2010 week 14). The UK Cochrane Centre previously ran a series of searches in MEDLINE (in 2000) and EMBASE (in 2004) to identify reports of methodological studies, with the resulting citations being subsequently entered into CMR. To increase the efficiency of our searches, we therefore restricted our searches of MEDLINE and EMBASE to records entered from 2001 and 2005, respectively. We searched PubMed to retrieve 'related articles' for 27 studies included in the previous version of this review. No language restrictions were imposed. A sample search is given in appendix 1; the complete strategy is available online from the Cochrane Library.¹⁰

Selection of studies

Titles and abstracts of identified studies were independently screened for eligibility by two reviewers. Full text versions of papers not excluded at this stage were obtained for detailed review. Potentially relevant studies were then independently assessed by two reviewers to determine if they met the inclusion criteria. Differences

of opinion were discussed until a consensus was reached; the opinion of a third reviewer was sought when necessary.

Data extraction and assessment of bias

Data extraction of included studies was carried out independently by two reviewers (ST with EM, PL or MP) using a pro-forma specifically designed for the purpose. Data were extracted on trial design, study setting, participants, inclusion and exclusion criteria, interventions and outcomes evaluated and results. In addition, data on the method of randomisation, allocation concealment (adequate, clear and inadequate), blinding (full, partial and none), adequacy (objective, unclear and subjective) and reporting of outcome measures and level of follow-up were collected to allow the risk of bias in each study to be determined.¹⁴ This was independently assessed by the same two reviewers, and summarised in line with Cochrane guidance (A, low risk; B, moderate risk and C, high risk).¹⁵ Studies at a high risk of bias were not excluded, but results were interpreted in light of this.

Data synthesis

Data were processed in accordance with the Cochrane handbook.¹⁵ Trials were grouped according to the type of intervention evaluated (eg, monetary incentives, alternative forms of consent, etc), with intervention groupings based on similarities in form and content. Where available, binary data were combined as risk ratios (RR) and the associated 95% CIs generated. Cluster randomised controlled trials were included only where there were sufficient data to allow analyses that adjusted for clustering. In such a case, an odds ratio (OR) was used as the summary effect in the meta-analysis, with the pooled result subsequently being converted to an RR using the average comparator group risk.

Heterogeneity was explored using the χ^2 test, and the degree of heterogeneity observed (ie, the percentage of

variation across studies due to heterogeneity rather than to chance) was quantified with the I^2 statistic. Where there was substantial heterogeneity, we informally investigated possible explanations and summarised data using a random-effects analysis if appropriate. Subgroup analyses were planned to explore key factors considered to be potential causes of heterogeneity, namely (1) trial design (randomised vs quasi-randomised); (2) concealment of allocation (adequate vs inadequate or unclear); (3) study setting (primary vs secondary care; healthcare vs non-healthcare); (4) study design (open vs blinded; placebo vs none); (5) target group (clinicians, patients and researchers) and (6) recruitment to hypothetical versus real trials. However, there were too few studies evaluating the same or similar interventions to allow these analyses to be conducted. Similarly, it was not possible to explore publication bias.

RESULTS

Description of studies

Search results

The search strategy identified 16 334 articles, of which 301 appeared to meet the inclusion criteria and were subject to detailed review (figure 1). We retrieved the full text of an additional 10 papers identified from the reference lists of previous reviews, and one article published out with the search period but which appeared relevant, giving a total of 312 potentially eligible studies. Forty-five papers, targeting more than 43 000 individuals, were included in the final analysis. Nineteen studies evaluated recruitment to hypothetical trials (table 1).

Study characteristics

Almost half of the studies were carried out in North America (n=21; 47%), with the remainder located in Europe (n=18; 40%) and Australia (n=5; 11%). One study involved centres in 19 countries worldwide. Studies were comparatively small in size, involving between 6 and 2561 participants (mean 493; median 79). It was

Figure 1 Flow of studies into the review.

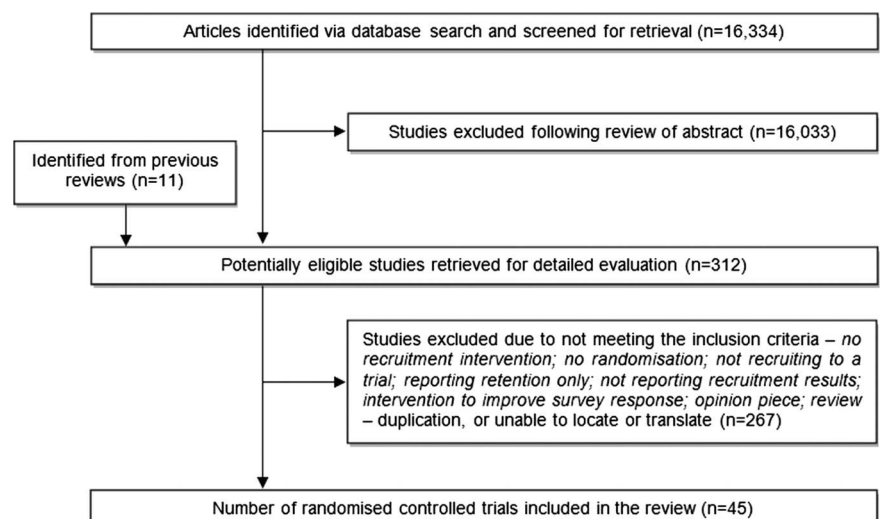


Table 1 Summary of included studies

| Authors (country) | RCT design | Setting | Intervention(s) | Comparator | Participants | Recruited to intervention(s) | Recruited to comparator | Risk of bias* | Comments† |
|---|----------------|------------------------------------|---|--|---|------------------------------|-------------------------|---------------|---|
| Avenell <i>et al</i> (UK) ¹⁶ | Parallel group | Secondary care | Open trial design comparing vitamin D, with calcium, with vitamin D and calcium, with no tablets | Conventional trial comparing vitamin D, with calcium, with vitamin D and calcium, with placebo | Patients aged ≥70 attending a fracture clinic or orthopaedic ward | 134/180 (74.4%) | 233/358 (65.1%) | A | Between-group difference was statistically significant (OR 1.56; 95% CI 1.05 to 2.33) |
| Bentley and Thacker (USA) ¹⁷ | Factorial | University (multicentre, n=5) | A: Info on a high-risk trial for a drug not yet tested on humans, pays \$1800 | Not applicable | Pharmacy students | Unclear | Not applicable | C | Assessed willingness to take part in hypothetical studies by risk and reward; did not differentiate recruitment rates between groups (270 participants); between-group differences were statistically significant for both risk level (p<0.0005) and level of payment (p=0.015) |
| | | | B: Info on a high-risk trial for a drug not yet tested on humans, pays \$800 | | | Unclear | | | |
| | | | C: Info on a high-risk trial for a drug not yet tested on humans, pays \$350 | | | Unclear | | | |
| | | | D: Info on a medium-risk study for a generic drug already on the market, pays \$1800 | | | Unclear | | | |
| | | | E: Info on a medium-risk study for a generic drug already on the market, pays \$800 | | | Unclear | | | |
| | | | F: Info on a medium-risk study for a generic drug already on the market, pays \$350 | | | Unclear | | | |
| | | | G: Info on a low-risk study measuring the salivary levels of stress hormones, pays \$1800 | | | Unclear | | | |
| | | | H: Info on a low-risk study measuring the salivary levels of stress hormones, pays \$800 | | | Unclear | | | |
| Cooper <i>et al</i> (UK) ¹⁸ | Parallel group | Secondary care | Partially randomised patient preference design allocating to medical management or transcervical resection of the endometrium or preferred option | Conventional RCT design allocating to medical management or transcervical resection of the endometrium | First time attendees at a gynaecological clinic | 90/135 (96.3%) | 97/138 (70.3%) | A | No information on statistical significance given |
| | | | | | | | | | |
| Coyne <i>et al</i> (USA) ¹⁹ | Cluster | Secondary care (multicentre, n=44) | Easy-to-read consent statements (altered text style, layout, font size, vocabulary; reading level 7th–8th grade) | Standard consent statements | Patients eligible for participation in a cancer treatment trial | 75/89 (84.3%) | 68/137 (49.6%) | C | Involved consent statements for three cancer treatment trials (one lung, two breast cancer); actual accrual to the parent studies was not significantly different (p=0.32) |

Continued

Table 1 Continued

| Authors (country) | RCT design | Setting | Intervention(s) | Comparator | Participants | Recruited to intervention(s) | Recruited to comparator | Risk of bias* | Comments† |
|--|----------------|---|--|---|--|--|---|---------------|---|
| DiGuseppi <i>et al</i> (USA) ²⁰ | Parallel group | Health Maintenance Organisation (HMO) (multicentre) | Telephone administered questionnaire on hazardous drinking and willingness to participate in lifestyle intervention | Face-to-face administered questionnaire on hazardous drinking and willingness to participate in lifestyle intervention | Patients aged ≥18 attending the HMO with an acute injury | 64/99 (64.6%) | 190/370 (51.4%) | C | Considered different methods of screening, which included willingness to participate in a hypothetical trial; the telephone group was somewhat more often associated with willingness to participate (OR 1.49; 95% CI 0.97 to 2.30) |
| Du <i>et al</i> (USA) ²¹ | Parallel group | Secondary care | 18 min educational video giving an overview of clinical trials and the importance of cancer clinical research to society | Standard care (ie, normal first visit to the oncologist) | Patients aged 21–80 attending a multidisciplinary lung clinic at a cancer centre | 11/63 (17.5%) to therapeutic trials; 16/63 (25.4%) to all trials | 7/63 (11.1%) to therapeutic trials; 10/63 (15.9%) to all trials | B | Considered recruitment to a range of cancer trials categorised into 'therapeutic', and 'therapeutic and non-therapeutic'; between-group difference was not statistically significant for therapeutic trials (p=0.308) or for all trials (p=0.187) |
| Du <i>et al</i> (USA) ²² | Parallel group | Secondary care | 18 min educational video giving an overview of clinical trials and the importance of cancer clinical research to society | Standard care (ie, normal visit to the oncologist) | Women aged 21–80 attending a breast cancer clinic at a cancer centre | 10/98 (10.4%) | 6/98 (6.1%) | C | Between-group difference was not statistically significant (p=0.277) |
| Ellis <i>et al</i> (Australia) ²³ | Parallel group | Secondary care | Information booklet explaining trials, how treatment is selected in an RCT, discussion of treatment options, advantages and disadvantages of participation, where to get more info plus usual discussion about treatment options from the clinician, inc. RCTs if appropriate (no standardisation of what is discussed) | Usual discussion about treatment options from the clinician, inc RCTs if appropriate (no standardisation of what is discussed) | Women undergoing definitive surgery for early stage breast cancer at a cancer institute | 12/30 (40.0%) at follow-up | 14/30 (46.7%) at follow-up | C | Studied willingness to participate in a hypothetical trial; between-group difference was statistically significant (p=0.05) |
| Ford <i>et al</i> (USA) ²⁴ | Parallel group | Community (multicentre, n=2) | A: Enhanced recruitment letter, phone screening by an African American interviewer, baseline questionnaire by mail, reminder calls/mailings for baseline info and consent B: Enhanced recruitment letter, phone screening by an African American interviewer, baseline questionnaire by phone, reminder calls/mailings for consent form | Standard recruitment letter, phone screening by an African American/ Caucasian interviewer, baseline questionnaire by mail, reminder calls/mailings for return of baseline info and consent | African American men aged 55–74, eligible for a prostate, lung and colorectal cancer screening trial | 78/3079 (2.5%) 87/3075 (2.8%) | 95/3297 (2.9%) | B | Between-group difference was statistically significant (p<0.01) |

Continued

Table 1 Continued

| Authors (country) | RCT design | Setting | Intervention(s) | Comparator | Participants | Recruited to intervention(s) | Recruited to comparator | Risk of bias* | Comments† |
|--|----------------------|---|---|--|---|--|--|---------------|--|
| | | | C: Enhanced recruitment letter, phone screening by an African American interviewer, reminder for project session held at church, baseline questionnaire at church session | | | 116/2949 (3.9%) | | | |
| Fowell <i>et al</i> (UK) ²⁵ | Clustered cross-over | Secondary care (multicentre, n=2) | Cluster randomisation | Zelen's design (only those randomised to intervention arm asked for consent) | Cancer inpatients receiving palliative care and starting on a syringe driver | 6/24 (25%) | 0/29 (0%) | C | Considered the effect of trial design on potential recruitment rate; aimed to explore the feasibility of the two designs for studies of dying patients; between-group difference was statistically significant (p=0.02) |
| Free <i>et al</i> (UK) ²⁶ | Parallel group | Community (multicentre, n=2) | A: A letter containing study and consent information, and a £5 note B: Four text messages over 1 week containing quotes from existing participants | Normal trial procedures (letter and patient information sheet) Normal trial procedures (letter and patient information sheet) | Members of the public who are aged ≥16, are daily smokers and willing to quit in the next month | 13/246 (5.3%) 17/405 (4.2%) | 1/245 (0.4%) 0/406 (0%) | A | Evaluated interventions in separate trials; between-groups differences were statistically significant for both the financial incentive (OR 4.9; 95% CI 2.0 to 7.7) and text messages (OR 4.2; 95% CI 2.2 to 6.1) |
| Freer <i>et al</i> (UK) ²⁷ | Parallel group | Tertiary neonatal intensive care unit | A: Five page US version of a study information leaflet (inc. more detail on study process, risks, benefits and patient rights) plus standard verbal explanation B: Less detailed single sheet UK version of a study information leaflet plus standard verbal explanation | US version of an information leaflet without verbal explanation UK version of an information leaflet without verbal explanation | Parents of immature infant(s) admitted to the NICU but not requiring intensive care | 5/9 (56%) 5/9 (56%) | 3/9 (33%) 4/10 (40%) | B | Considered the impact of information on parents' understanding of a research study and the validity of their consent to participation in a hypothetical trial; no information on statistical significance given |
| Fureman <i>et al</i> (USA) ²⁸ | Parallel group | Existing trial (university based) | Enhanced video on an HIV vaccine trial plus a 1 h pamphlet presentation (5 min pre-test, 26 min of video, 10 min to review pamphlet, RA initiated Q&A session, post-test questionnaire, survey at 1 month) | Standard half hour pamphlet-only presentation (5 min pre-test, 10 min to review a trial info pamphlet, RA initiated Q&A session, post-test questionnaire, survey at 1 month) | Participants in the Risk Assessment Project (injection drug users) | 1.84 (post-test 1); 1.69 (post-test 2) | 1.70 (post-test 1); 1.50 (post-test 2) | C | Studied recruitment to a hypothetical trial (targeted 98 individuals for intervention, 88 for comparator); results provided as mean willingness scores; between-group difference was not statistically significant (p>0.1) |
| Graham <i>et al</i> (USA) ²⁹ | Parallel group | Health Maintenance Organisation (multicentre) | A: Electronic questionnaire on hazardous drinking and willingness to participate in lifestyle intervention | Standard self-complete paper questionnaire | Patients aged ≥18 attending the HMO with an acute injury | 69/151 (45.7%) 42/78 (53.8%) | 76/141 (53.9%) | C | Considered different methods of screening, which included willingness to participate in a hypothetical |

Continued

Table 1 Continued

| Authors (country) | RCT design | Setting | Intervention(s) | Comparator | Participants | Recruited to intervention(s) | Recruited to comparator | Risk of bias* | Comments† |
|---|-----------------------|-----------------------------|---|---|---|--|-------------------------|---------------|--|
| Halpern <i>et al</i> (USA) ³⁰ | Within-subject design | Secondary care | B: Oral questionnaire read aloud to patients in the clinic, potential answers printed on cards and patients asked to point A: Variation in trial information on (1) the percentage of previous patients experiencing an adverse effect from the study drug (10%, 20%, 30%) and (2) payment participants would receive (\$100, \$1000, \$2000) B: Variation in trial information on (1) the percentage of patients who would be assigned to placebo (10%, 30%, 50%) and (2) the payment level (payment in range typically offered to participants in phase 3 trials of antihypertensive drugs) | Not applicable | Patients with mild to moderate hypertension attending an outpatient clinic | Unclear Unclear | Not applicable | C | trial; between-group difference was statistically significant (p=0.001) Assessed willingness to take part in hypothetical studies by risk and reward; did not provide recruitment rates (126 participants); there was a statistically significant increase in willingness to participate as risk of adverse effects reduced (p<0.001), payment level rose (p<0.001), and the risk of being assigned to placebo decreased (p=0.02) |
| Harris <i>et al</i> (UK) ³¹ | Factorial | Community | A: Personal recruitment letter and info plus telephone reminder (up to four) plus questionnaire on physical activity B: Personal recruitment letter and info plus telephone reminder (up to four) C: Personal recruitment letter and info plus questionnaire on physical activity D: Personal recruitment letter and info only | Not applicable | Households of older people aged ≥65, able to walk outside and registered with one GP practice | 69/140 (49.3%) 65/140 (46.4%) 47/140 (33.6%) 59/140 (42.1%) | Not applicable | A | Between-group difference was statistically significant for telephone reminders (OR 1.5; 95% CI 1.0 to 2.3), but not for the inclusion of a questionnaire (OR 0.9; 95% CI 0.6 to 1.3) |
| Hemminki <i>et al</i> (Estonia) ³² | Parallel group | Local clinics (multicentre) | Non-blinded allocation comparing active HRT treatment with no treatment | Traditional blinded allocation comparing active HRT treatment with placebo | Postmenopausal women aged 50–64 | 1027/2159 (47.6%) | 796/2136 (37.3%) | A | Between-group difference was statistically significant (p<0.001) |
| Hutchison <i>et al</i> (UK) ³³ | Parallel group | Secondary care | Video giving generic and site-specific trial info with a focus on randomisation, pictures of patients receiving care and a voiceover discussing uncertainty plus standard practice | Standard practice of clinician from tumour site team discussing trial and administering trial specific info sheet and consent form; at next visit patient sees a clinician from the same team to decide on treatment and whether it will be part of a trial | Patients with colorectal, breast or lung cancer, and eligible for a cancer treatment trial | 62/86 (72.1%) | 66/87 (75.9%) | A | Considered recruitment to a range of cancer trials; between-group difference was not statistically significant (p=0.661) |

Continued

Table 1 Continued

| Authors (country) | RCT design | Setting | Intervention(s) | Comparator | Participants | Recruited to intervention(s) | Recruited to comparator | Risk of bias* | Comments† |
|--|----------------|---|--|--|--|---|--|---------------|---|
| Ives <i>et al</i> (UK) ³⁴ | Parallel group | Secondary care | Standard trial information plus booklet entitled, "Clinical Trials in HIV and AIDS: Information for people who are thinking about joining a trial" | Standard trial information (information sheet specific to proposed trial plus discussion with trial doctor and research nurse) | Patients attending an HIV hospital clinic | 15/23 (65.2%) | 11/27 (40.7%) | C | Considered recruitment of patients eligible for participation in eight trials being carried out at the participating institution; no information on statistical significance given |
| Jeste <i>et al</i> (USA) ³⁵ | Parallel group | Secondary care | Multimedia consent with DVD presenting key information from consent form, including simultaneous narrative explanation; researcher also present to answer questions | Routine consent procedure plus 10 min control DVD giving general information about research; researcher also present to answer questions | Outpatients aged >40 with schizophrenia, and healthy comparison subjects | 41/62 (66.1%) patients with schizophrenia; 23/31 (74.2%) healthy comparisons | 44/66 (67.2%) patients with schizophrenia; 22/29 (75.9%) healthy comparisons | B | Studied agreement to participate in a hypothetical trial; between-group differences were not statistically significant (no p value provided) |
| Karunaratne <i>et al</i> (Australia) ³⁶ | Parallel group | Secondary care | Computer-based, interactive presentation of study information inc. diagrams, video clips, hyperlinks, quiz pages | Conventional paper-based study information | Patients aged 18–70 attending an outpatient diabetic clinic | 23/30 (76.7%) | 17/30 (56.7%) | C | Considered participant understanding of consent materials, including interest in participating in a hypothetical trial; between-group difference was statistically significant (p=0.01) |
| Kendrick <i>et al</i> (UK) ³⁷ | Parallel group | Primary care (multicentre) | Mailed invitation to participate in an injury prevention trial, including a home safety questionnaire | Mailed invitation to participate excluding home safety questionnaire | Families with children aged <5 years, living in deprived areas | 217/1203 (18.0%) | 157/1190 (13.2%) | A | Between-group difference was statistically significant (p=0.001) |
| Kerr <i>et al</i> (UK) ³⁸ | Parallel group | Further education colleges (multicentre, n=5) | A: Leaflet describing a trial of two treatments for arthritis, where A and B are described as standard treatments B: Leaflet describing a trial of two treatments for arthritis, where A is described as new treatment and B as standard treatment C: Leaflet describing a trial of two treatments for arthritis, where B is described as new treatment and A as standard treatment D: Leaflet describing a trial of two treatments for back pain, where A and B are described as standard treatments E: Leaflet describing a trial of two treatments for back pain, where A is described as new treatment and B as standard treatment | Not applicable | Students aged ≥18 enrolled on further education/leisure courses | 24/29 (82.8%) 10/17 (58.8%) 13/16 (81.3%) 26/31 (83.9%) 10/15 (66.7%) | Not applicable | C | Studied willingness to participate in a hypothetical trial; did not provide recruitment rates (130 participants); between-group difference was statistically significant (p<0.001), with those who had a preference for a standard treatment—available outside of the trial—less willing to participate than those with no preference |

Continued

Table 1 Continued

| Authors (country) | RCT design | Setting | Intervention(s) | Comparator | Participants | Recruited to intervention(s) | Recruited to comparator | Risk of bias* | Comments† |
|--|----------------|---|---|--|---|---|------------------------------|---------------|--|
| | | | F: Leaflet describing a trial of two treatments for back pain, where B is described as new treatment and A as standard treatment | | | 10/16 (62.5%) | | | |
| Kimmick <i>et al</i> (USA) ³⁹ | Cluster | Secondary care and academic institutions (multicentre, n=126) | Educational intervention of standard info plus an educational symposium, geriatric oncology educational materials, monthly mailings and emails for 1 year, lists of available protocols for use on patient charts, case discussion seminar | Standard information of periodic notification of all existing CALGB (Cancer and Leukaemia Group B) trials by the CALGB Central Office, and CALGB web site access | Practitioners and researchers from CALGB institutions | 36% in year 1; 31% in year 2 | 32% in year 1; 31% in year 2 | C | Considered recruitment of older people to existing CALGB treatment trials for a range of cancers; between-group difference was not statistically significant at year 1 (p=0.35) or at year 2 (p=0.83) |
| Larkey <i>et al</i> (USA) ⁴⁰ | Parallel group | Existing trial sites (multicentre, n=2) | A: Hispanic lay advocates; attended 6 h long training sessions, five quarterly meetings and received brochures with interest cards to distribute to other women B: Hispanic women controls, received quarterly 'phone calls and brochures with interest cards to distribute to other women | Anglo women controls, received quarterly 'phone calls and brochures with interest cards to distribute to other women | Participants in the Women's Health Initiative trial | 13/31 referrals (41.9%) 0/3 referrals (0.0%) | 2/19 referrals (10.5%) | B | Determined whether Hispanic women already enrolled in a study and trained as lay advocates would refer/enrol more participants than untrained Hispanic women and Anglo controls; between-group difference was statistically significant (p<0.01) |
| Liénard <i>et al</i> (France) ⁴¹ | Cluster | Secondary care (multicentre, n=135) | Site visits including an initiation visit to review trial protocol, inclusion/exclusion criteria, safety, randomisation, etc plus ongoing review visits | No site visits (unless requested) | Centres recruiting to an RCT for breast cancer | 302 | 271 | A | No denominator data provided; between-group difference was not statistically significant (no p value provided) |
| Litchfield <i>et al</i> (UK) ⁴² | Cluster | Primary care (multicentre, n=28) | Internet-based collection of trial data | Paper-based collection of trial data | 28 participating GP practices | 45/52 (86.5%) | 28/28 (100%) | B | Considered efficiency and ease of use of internet versus conventional paper-based data capture, and looked at recruitment incidentally; between-group difference was statistically significant (p=0.04) |
| Llewellyn-Thomas <i>et al</i> (Canada) ⁴³ | Parallel group | Secondary care | A: Booklet with negatively framed intervention about treatment side-effects and survival B: Booklet with positively framed intervention about treatment side-effects and survival | Booklet with neutrally framed intervention about treatment side-effects and survival | Colorectal cancer patients attending cancer hospital outpatients | 20/30 (66.7%) 18/30 (60.0%) | 23/30 (76.7%) | B | Determined the impact of probabilistic info on entry to a hypothetical trial; between-group difference was not statistically significant (p>0.40) |
| Llewellyn-Thomas <i>et al</i> (Canada) ⁴⁴ | Parallel group | Secondary care | Searchable computerised info on imaginary trial, including purpose, description of treatment arm and randomisation, possible benefits, side-effects, patients' rights | Tape-recorded info on imaginary trial, including purpose, description of treatment arm and | Patients attending the outpatient department of a cancer hospital | 31/50 (62.0%) | 21/50 (42.0%) | B | Studied recruitment to a hypothetical trial; between-group difference was statistically significant (p<0.05, unadjusted) |

Continued

Table 1 Continued

| Authors (country) | RCT design | Setting | Intervention(s) | Comparator | Participants | Recruited to intervention(s) | Recruited to comparator | Risk of bias* | Comments† |
|---|----------------|--|---|---|--|---|--|---------------|---|
| Mandelblatt <i>et al</i> (USA) ⁴⁵ | Parallel group | Community (multicentre, n=3) | 5–10 min educational counselling session about the trial delivered by non-physician study staff (inc benefits and risk of participation and need for minority participation) plus an informational brochure | randomisation, possible benefits, side-effects, patients' rights Informational brochure only | Spanish speaking women who were eligible for a trial on women at high risk of breast cancer | 178/232 (76.7%) general intent; 118/232 (50.9%) if mild side-effects mentioned; 108/232 (46.6%) if uterine cancer mentioned | 147/218 (67.4%) general intent; 118/218 (54.1%) if mild side-effects mentioned; 97/218 (44.5%) if uterine cancer mentioned | C | Results relate to intention to participate ('might, probably or definitely would'); between-group difference was statistically significant for general intention to participate (p=0.03) |
| Miller <i>et al</i> (USA) ⁴⁶ | Parallel group | Secondary care, primary care and community | Eligibility screening and recruitment by a senior investigator | Eligibility screening and recruitment by a Research Assistant | Patients aged 18–75, eligible for participation in two chronic depression treatment trials | 28/162 (17.3%) | 22/185 (11.9%) | C | Considered the relationship between interviewer experience and positive predictive value and cost of telephone screening, and looked at recruitment incidentally; between-group difference was not statistically significant (p=0.30) |
| Monaghan <i>et al</i> (Worldwide) ⁴⁷ | Cluster | Existing trial sites (multi-centre, n=167) | Additional communication—usual plus frequent emails, regular personalised mail-outs of league tables/graphs of performance against other sites, certificates of achievement for recruitment/other study items (1/month) | Usual communication (provided via the regional centre) plus occasional direct communications from the co-ordinating centre in the form of generic newsletters, emails and faxes | Clinical sites in 19 countries recruiting to a diabetes and vascular disease treatment trial | 37.5 (27.0–51.5) | 37.0 (21.0–54.5) | A | Result provided as median number of participants recruited; between-group difference was not statistically significant (p=0.68) |
| Myles <i>et al</i> (Australia) ⁴⁸ | Parallel group | Secondary care | A: Prerandomised to experimental drug and asked to provide consent; if no consent, standard treatment given B: Prerandomised to standard drug and asked to provide consent; if no consent, experimental treatment given C: Told that physician thinks experimental drug superior, if consent given, has 70% chance of receiving this; if no consent, standard treatment given | Standard randomisation method (equal chance of either drug) | Inpatients aged ≥18, scheduled for elective surgery | 90/169 (53.3%) 79/149 (53.0%) 91/150 (60.7%) | 84/151 (55.6%) | B | Considered recruitment to a hypothetical trial; between-group difference was not statistically significant (p=0.66) |

Continued

Table 1 Continued

| Authors (country) | RCT design | Setting | Intervention(s) | Comparator | Participants | Recruited to intervention(s) | Recruited to comparator | Risk of bias* | Comments† |
|--|----------------|------------------------------|--|---|---|--|----------------------------------|---------------|---|
| | | | <i>D</i> : Allowed to increase or decrease chance of receiving experimental drug if consent given, and if no preference, 50% chance of receiving it; if no consent, standard treatment given | | | 85/150 (56.7%) | | | |
| Nystuen and Hagen (Norway) ⁴⁹ | Parallel group | Community (multicentre, n=6) | Written invitation to participate in a community-based trial followed by a 'phone reminder if no response within 2 weeks; guide used for discussion | Written invitation to participate in a community-based trial followed by no reminder if no response within 2 weeks | Sick-listed employees attending a participating social security office | 31/256 (12.1%) | 11/242 (4.5%) | A | Between-group difference was statistically significant (p=0.003) |
| Perrone <i>et al</i> (Italy) ⁵⁰ | Parallel group | Community | <i>A</i> : randomised consent to new treatment; if no consent given standard treatment <i>B</i> : randomised consent to standard treatment; if no consent given new treatment <i>C</i> : if consents to participate, standard or new treatment assigned at random; if no consent, can choose standard or new treatment | On consent to participate, standard or new treatment assigned at random; if no consent, given standard treatment | Members of the general public aged 16–80, attending a scientific exhibition | 997/1151 (86.6%) 246/474 (51.9%) 482/607 (79.4%) | 836/985 (84.9%) | C | Studied recruitment to a hypothetical trial; between-group difference was significant for both the single (p=0.08) and double consent scenarios (p<0.0001) |
| Pighills <i>et al</i> (UK) ⁵¹ | Parallel group | Primary care (multicentre) | <i>A</i> : Newspaper article about the trial included with recruitment materials <i>B</i> : Inclusion of a more 'upbeat' newspaper article about the trial | Usual recruitment materials only Inclusion of the <i>Intervention A</i> newspaper article | Men and women aged ≥70 who had at least one fall in the previous 12 months | 73/2243 (3.3%) 57/1374 (4.1%) | 71/2245 (3.2%) 54/1371 (3.9%) | B | Evaluated interventions in separate trials; between-group differences were not statistically significant (p=0.80; p=0.62) |
| Simel and Feussner (USA) ⁵² | Parallel group | Secondary care | Consent form including a statement that the new treatment may work twice as fast as usual treatment | Consent form including a statement that the new treatment may work half as fast as usual treatment | Patients attending an ambulatory care clinic | 35/52 (67.3) | 20/48 (41.7%) | B | Considered recruitment to a hypothetical trial; between-group difference was statistically significant (p<0.01) |
| Simes <i>et al</i> (Australia) ⁵³ | Parallel group | Secondary care | Individual approach to consent—patients given info about aims, expected results, potential toxicities of treatment; details of treatment left to discretion of consultant; patients given opportunity to ask questions, verbal consent obtained | Total disclosure approach—patients fully informed about all trial aspects by consultant: patients given opportunity to ask questions, also given a consent form outlining the info; this was kept overnight and written consent obtained next day | Patients attending an oncology unit | 27/29 (93.1%) | 23/28 (82.1%) | A | Considered recruitment of patients eligible for 16 trials being carried out at the participating institution; between-group difference was statistically significant (p=0.01) |

Continued

Table 1 Continued

| Authors (country) | RCT design | Setting | Intervention(s) | Comparator | Participants | Recruited to intervention(s) | Recruited to comparator | Risk of bias* | Comments† |
|--|------------------|----------------|--|---|--|--------------------------------------|-------------------------|---------------|--|
| Treschan <i>et al</i> (Austria) ⁵⁴ | Parallel group | Secondary care | A: Info on study of wound healing said to have no risk but involving additional procedures described as provoking considerable pain and discomfort B: Info on study of wound healing said to have no pain but involving additional procedures described as inducing risk of injury | Info on study of wound healing described as posing essentially no risk and producing no significant pain | Patients aged 19–80, and scheduled for minor surgery with general anaesthesia | 18/51 (35%) 13/50 (26%) | 30/47 (64%) | B | Studied willingness to participate in a hypothetical trial, although patients were not aware of this until after the decision to take part; between-group difference was statistically significant ($p < 0.001$) |
| Trevena <i>et al</i> (Australia) ⁵⁵ | Sequential start | Primary care | Opt-out recruitment; letter from doctor advising that practice taking part in screening trial; would be contacted unless practice advised to withhold contact details | Opt-in recruitment; letter from doctor advising that practice taking part in screening trial; would only be contacted if contact details returned | Patients aged 50–74 eligible for a colorectal cancer screening trial | 40/60 (66.7%) | 44/92 (47.8%) | A | Compared the effect of opt-in requirements in new privacy laws with an opt-out approach that was previously permissible; no information on statistical significance given |
| Wadland <i>et al</i> (USA) ⁵⁶ | Parallel group | Primary care | Consent form read out to potential participants by study co-ordinator | Consent form read by potential participants | Current smokers aged ≥ 18 | 27/51 (53%) | 25/53 (47%) | C | Smoking cessation study carried out in two practices, with the intervention evaluated in one; between-group differences were not statistically significant (no p value provided) |
| Weinfurt <i>et al</i> (USA) ⁵⁷ | Parallel group | Secondary care | A: Consent documents containing a disclosure indicating that the clinic received per capita payments covering the costs of the research (including investigator's salary) B: Consent documents containing a disclosure describing an investment by the investigator in the company sponsoring the research ('equity') | Consent documents containing no financial disclosure | Patients of a cardiovascular outpatient clinic aged ≥ 18 , and diagnosed with coronary artery disease | 3.51 (SD 1.30) 3.20 (SD 1.32) | 3.50 (SD 1.29) | C | Studied willingness to participate in a hypothetical trial; did not provide recruitment rates (470 participants); results provided as mean willingness scores; between-group difference was statistically significant ($p = 0.02$); patients in the equity group were also less willing to participate than those in the per capita ($p = 0.01$) and no disclosure groups ($p = 0.03$) |
| Weinfurt <i>et al</i> (USA) ⁵⁸ | Parallel group | Community | A: Info inc a general disclosure that the investigator may gain financially from the study plus a statement that ethics committee does not think this affects patient safety or study quality B: Info inc a disclosure that the drug company pays running costs to the investigator plus a statement that | Not applicable | Aged ≥ 18 with asthma or diabetes and a member of a panel of adults who agreed to be contacted about research opportunities | 3.28 (SD 0.04) 3.46 (SD 0.04) | Not applicable | C | Studied willingness to participate in a hypothetical trial; did not provide recruitment rates (3623 participants); results provided as mean willingness scores; between-group difference |

Continued

Table 1 Continued

| Authors (country) | RCT design | Setting | Intervention(s) | Comparator | Participants | Recruited to intervention(s) | Recruited to comparator | Risk of bias* | Comments† |
|--|----------------|----------------------------------|--|--|---|---|---|---------------|--|
| | | | ethics committee does not think this affects safety or quality C: Info inc a disclosure that the drug company pays monies out with the study to the investigator plus a statement that ethics committee does not think this affects safety or quality D: Info inc a disclosure that the investigator has an investment in the drug company plus a statement that ethics committee does not think this affects safety or quality E: Info inc a disclosure that the investigator's institution has an investment in the drug company plus a statement that ethics committee does not think this affects safety or quality | | | 3.22 (SD 0.04) | | | was statistically significant (p<0.001) |
| | | | | | | 3.16 (SD 0.04) | | | |
| | | | | | | 3.28 (SD 0.04) | | | |
| Welton <i>et al</i> (UK) ⁵⁹ | Parallel group | Primary care (multicentre, n=10) | Verbal info about a trial of HRT, comparing oestrogen only, with combined oestrogen and progestogen, with placebo | Verbal info about a trial of HRT, comparing oestrogen only with combined oestrogen and progestogen | Women aged 45–64 who had not had a hysterectomy | 65/218 (29.8%) | 85/218 (39.0%) | C | Considered willingness to take part in a hypothetical trial; between-group difference was not statistically significant (p=0.06) |
| Weston <i>et al</i> (Canada) ⁶⁰ | Parallel group | Secondary care (multicentre) | Written study information followed by viewing of Term Prelabour Rupture of the Membranes (Term PROM) video | Written study information only | Women attending for antenatal visits | 26/42 (61.9%) initially; 23/41 (56.1%) at 2–4 weeks | 17/48 (35.4%) initially; 17/44 (38.6%) at 2–4 weeks | B | Between-group difference was statistically significant (p=0.01) |

*Risk of bias: A, low; B, moderate; C, high.

†Includes difference in outcomes as reported by the authors.
RCT, randomised controlled trial.

not possible to determine actual participant numbers for two studies aimed at recruiters. In a further six studies evaluating recruitment to hypothetical trials, the number willing to participate was unclear, or was reported as a mean score. In more than half of the studies, participants were recruited from secondary care (n=23), or from secondary care in combination with another setting (n=2). Trials based in the community (n=8) or in primary care (n=6) were also common (table 1).

Risk of bias within studies

All of the studies were described by their authors as being either randomised (n=41) or quasi-randomised (n=4), but more than a third failed to provide details of the method used to achieve this. Similarly, while allocation concealment was adequate in half of the studies, details were poorly reported in many others. This was also true in relation to the procedures used to blind participants, which was often missing or not fully reported. All studies provided details on the outcome measures used, many of which were subjective (eg, willingness or intention to consent). When considered across the domains, 12 studies had a low risk of bias, 13 had moderate risk and 20 had a high risk (table 1).

Effects of interventions on recruitment

The 45 included studies evaluated 46 interventions across six main categories: trial design, obtaining consent, approach to participants, financial incentives, training for recruiters and trial co-ordination (table 2). As might be expected, the majority of studies were aimed directly at trial participants (n=40), with few studies targeting those responsible for recruitment. Although some of the categories incorporate several studies, we considered the majority of interventions to be sufficiently different to make pooling them inappropriate. Where reported data did not allow for calculation of an estimate of effect based on our outcome measure, the results from the paper have been presented. Effects of the interventions studied are presented in table 3 and figures 2–7; only those figures relating to pooled estimates have been presented.

Trial design

Six studies (5675 participants; one study also recruited 28 general practices) considered the effect of trial design changes on recruitment.

Two trials^{16 32} compared an open design (where participants know what treatment they are receiving) with a blinded, placebo-controlled design, and found that an open design improved trial recruitment (RR 1.22, 95% CI 1.09 to 1.36; figure 2). A study investigating the impact of a placebo group on women's willingness to participate in a hypothetical hormone replacement trial⁵⁹ suggests that the number likely to take part may be less when a non-active comparator is included (RR 0.76, 95% CI 0.59 to 0.99). A trial of menorrhagia

management compared conventional randomisation with a patient preference design, where those with a preference for a specific treatment receive it, while the remainder are randomised.¹⁸ Although this made little or no difference to the number who agreed to be recruited to the trial, women were more likely to participate in the study overall (96% vs 70%).

In a crossover trial for palliative care, cluster randomisation was compared with consenting individuals after randomisation if they were assigned to experimental treatment (Zelen design).²⁵ Only two sites with few participants were included (6/24 recruited in the cluster arm vs 0/29 in the Zelen arm; p=0.02). The final study involved 28 general practices in a trial of two delivery methods for insulin, and compared internet-based data capture with paper-based collection, reporting higher recruitment with the paper-based method (45/52 vs 28/28; p=0.04).⁴²

Obtaining consent

Five studies (4468 participants) considered modifications either to the consent process (including timing) or to the format of the consent form.

Consent process

In a trial on decision aids for colorectal cancer screening,⁵⁵ the use of opt-out (potential participants were contacted unless they withdrew their details) was found to improve recruitment when compared with an opt-in approach to contact (RR 1.39, 95% CI 1.06 to 1.84). Two studies recruiting to hypothetical trials (one on a new drug and one on anaesthesia) evaluated various combinations of prerandomisation and consent.^{48 50} Both evaluated consenting specifically for the experimental or standard treatment, but there was considerable heterogeneity for the latter ($I^2=93\%$), and under a random-effects model, neither form of consent may lead to any difference in recruitment (figure 3). Three other variants of consent were also considered: (1) consent allowing those refusing participation to choose between the treatments,⁵⁰ (2) consent to a 70% chance of receiving the experimental treatment because the clinician believes it is better⁴⁸ and (3) consent to a participant-modified chance of receiving the experimental treatment (60%, 70% and 80%).⁴⁸ All three appear to have had little effect on recruitment compared with usual consent.

Consent format

Two trials dealt with how the consent form was presented to potential participants. Researchers in a smoking cessation trial⁵⁶ compared the effect of the consent form being read aloud by the researcher with it being read by participants, while a cluster trial recruiting to oncology studies evaluated an easy-to-read version of the consent form.¹⁹ Neither study found that the intervention improved recruitment.

Table 2 Recruitment intervention and effect on participation

| Recruitment intervention ^{Reference ID} | Increases | Decreases | Little impact | Inconclusive |
|--|-----------|-----------|---------------|--------------|
| Trial design | | | | |
| Open design ^{16 32} | ● | | | |
| Placebo* ⁵⁹ | | ○ | | |
| Patient preference design ¹⁸ | | | ○ | |
| Zelen design† ²⁵ | | ○ | | |
| Internet-based data capture† ⁴² | | ○ | | |
| Obtaining consent | | | | |
| Process—opt-out approach ⁵⁵ | ○ | | | |
| Process—consent to experimental treatment* ^{48 50} | | | ● | |
| Process—consent to standard treatment* ^{48 50} | | | ● | |
| Process—refuser chooses treatment option* ⁵⁰ | | | ○ | |
| Process—physician modified chance of experimental* ⁴⁸ | | | ○ | |
| Process—participant modified chance of experimental* ⁴⁸ | | | ○ | |
| Form—researcher read aloud ⁵⁶ | | | ○ | |
| Form—altered readability level† ¹⁹ | | | ○ | |
| Approach to participants | | | | |
| Delivery—video presentation*† ^{28 35} | | | ● | |
| Delivery—video presentation plus written information ⁶⁰ | ○ | | | |
| Delivery—audiovisual overview of trials ^{21 22 33} | | | ● | |
| Delivery—interactive computer presentation* ^{36 44} | | | | ● |
| Delivery—verbal education session ⁴⁵ | ○ | | | |
| Supplementing info—booklet on clinical trials* ^{23 34} | | | ● | |
| Supplementing info—study-relevant questionnaire ^{31 37} | | | ● | |
| Supplementing info—newspaper article ⁵¹ | | | ○ | |
| Framing—treatment as faster* ⁵² | ○ | | | |
| Framing—treatment as new* ³⁸ | | ○ | | |
| Framing—emphasis on pain or risk* ⁵⁴ | | ○ | | |
| Framing—positively or negatively* ⁴³ | | | ○ | |
| Content—more detailed info (inc. total disclosure)* ^{27 53} | | | ● | |
| Content—financial disclosure of investigator interest*† ^{57 58} | | ● | | |
| Telephone reminders ^{31 49} | ● | | | |
| SMS messages ²⁶ | ○ | | | |
| Eligibility screening—face-to-face* ^{24 29} | | | | ● |
| Eligibility screening—telephone* ²⁰ | ○ | | | |
| Eligibility screening—electronic self-complete* ²⁹ | | | ○ | |
| Screening personnel ⁴⁶ | | | ○ | |
| Financial incentives | | | | |
| Cash incentive with invitation ²⁶ | ○ | | | |
| Paid participation*† ^{17 30} | ● | | | |
| Level of trial risk*† ^{17 30} | | | | ● |
| Training for recruiters | | | | |
| Training lay advocates† ⁴⁰ | ○ | | | |
| Education sessions† ³⁹ | | | ○ | |
| Trial co-ordination | | | | |
| On-site visits† ⁴¹ | | | ○ | |
| Additional communication† ⁴⁷ | | | ○ | |

●, Multiple studies; ○, single study.

*Includes recruitment to hypothetical trial(s).

†Includes result reported by study authors only (effect size not calculated).

Approach to participants

Twenty-eight studies (31 910 participants) evaluated the effect of modifying trial information or the way it was delivered.

Delivery of trial information

Nine studies considered various ways of providing potential participants with information about the trial. Studies

using video or other audiovisual materials had mixed results. A study evaluating the effect of providing a 10 min video alongside written information in a trial of pregnant women with prelabour rupture of membranes⁶⁰ found that this most likely improved willingness to participate compared with written information alone (RR 1.75, 95% CI 1.11 to 2.74). There were three studies presenting audiovisual overviews of clinical

Table 3 Effects of interventions to improve recruitment

| Intervention | Reference ID | Participants recruited | | Risk ratio (95% CI) | Absolute difference (%) [*] | Heterogeneity | | | Risk of bias [†] (studies) |
|---|--------------|------------------------|------------|------------------------|---|---------------|---------|--------------------|--|
| | | Intervention | Comparator | | | χ^2 | p Value | I ² (%) | |
| Trial design | | | | | | | | | |
| Open vs blind design ^{16 32} | | 1161/2339 | 1029/2494 | 1.22 (1.09 to 1.36) | 9 | 2.74 | 0.10 | 64 | A A (2) |
| Active comparator vs placebo ^{59‡} | | 65/218 | 85/218 | 0.76 (0.59 to 0.99) | −9 | — | — | — | C (1) |
| Patient preference vs conventional RCT ¹⁸ | | 90/135 | 97/138 | 0.95 (0.81 to 1.11) | −4 | — | — | — | A (1) |
| Obtaining consent | | | | | | | | | |
| <i>Consent process</i> Opt-out vs opt-in ⁵⁵ | | 40/60 | 44/92 | 1.39 (1.06 to 1.84) | 19 | — | — | — | A (1) |
| Consent to experimental vs usual ^{48‡, 50‡} | | 1087/1320 | 920/1136 | 1.01 (0.98 to 1.05) | 1 | 0.42 | 0.51 | 0 | B C (2) |
| Consent to standard vs usual ^{48‡, 50‡} | | 325/623 | 920/1136 | 0.76 (0.49 to 1.17) | −19 | 14.74 | <0.001 | 93 | B C (2) |
| Refusers choose treatment vs usual ^{50‡} | | 482/607 | 836/985 | 0.94 (0.89 to 0.98) | −5 | — | — | — | C (1) |
| Physician modified consent vs usual ^{48‡} | | 91/150 | 84/151 | 1.09 (0.90 to 1.32) | 5 | — | — | — | B (1) |
| Participant modified consent vs usual ^{48‡} | | 85/150 | 84/151 | 1.02 (0.83 to 1.24) | 1 | — | — | — | B (1) |
| <i>Consent form</i> Researcher read vs participant read ⁵⁶ | | 27/51 | 25/53 | 1.12 (0.76 to 1.65) | 6 | — | — | — | C (1) |
| Approach to participants | | | | | | | | | |
| <i>Delivery of information</i> Full video presentation+Q&A vs standard info+brief video+Q&A ^{35‡} | | 64/93 | 66/95 | 0.99 (0.82 to 1.20) | −1 | — | — | — | B (1) |
| Video presentation+written information vs written only ⁶⁰ | | 26/42 | 17/48 | 1.75 (1.11 to 2.74) | 26 | — | — | — | B (1) |
| Audiovisual information on trials vs standard ^{21 22 33} | | 88/247 | 82/248 | 1.20 (0.75 to 1.91) | 7 | 4.00 | 0.14 | 50 | B C A (3) |
| Interactive computer presentation vs paper-based information ^{36‡} | | 23/30 | 17/30 | 1.35 (0.93 to 1.96) | 20 | — | — | — | C (1) |
| Interactive computer presentation vs audio-taped information ^{44‡} | | 31/50 | 21/50 | 1.48 (1.00 to 2.18) | 20 | — | — | — | B (1) |
| Verbal educational session+information brochure vs brochure only ⁴⁵ | | 178/232 | 147/218 | 1.14 (1.01 to 1.28) | 9 | — | — | — | C (1) |
| <i>Supplementing information</i> Booklet on trials+standard information vs standard information only ^{23‡, 34} | | 27/53 | 25/57 | 1.18 (0.64 to 2.18) | 8 | 2.38 | 0.12 | 58 | C C (2) |
| Study questionnaire with invitation vs invitation only ^{31 37} | | 333/1483 | 281/1470 | 1.14 (0.77 to 1.64)§ | 3 | 4.41 | 0.04 | 77 | A A (2) |

Continued

Table 3 Continued

| Intervention | Reference ID | Participants recruited | | Risk ratio (95% CI) | Absolute difference (%)* | Heterogeneity | | | Risk of bias† (studies) |
|--|--------------|------------------------|------------|------------------------|-----------------------------|---------------|---------|--------------------|----------------------------|
| | | Intervention | Comparator | | | χ^2 | p Value | I ² (%) | |
| Newspaper article+study information vs study information only ⁵¹ | | 73/2243 | 71/2245 | 1.03 (0.75 to 1.42) | 0 | – | – | – | B (1) |
| Favourable article+information vs standard article+information ⁵¹ | | 57/1374 | 54/1371 | 1.05 (0.73 to 1.52) | 0 | – | – | – | B (1) |
| <i>Framing and content</i> Treatment described as working 'twice as fast' vs 'half as fast' ⁵² ‡ | | 35/52 | 20/48 | 1.62 (1.10 to 2.37) | 26 | – | – | – | B (1) |
| Trial of treatment described as new vs treatment described as standard ³⁸ ‡ | | 43/64 | 50/60 | 0.81 (0.66 to 0.99) | –16 | – | – | – | C (1) |
| Information emphasising pain involved vs standard information ⁵⁴ ‡ | | 18/51 | 30/47 | 0.55 (0.36 to 0.85) | –29 | – | – | – | B (1) |
| Information emphasising risk involved vs standard information ⁵⁴ ‡ | | 13/50 | 30/47 | 0.41 (0.24 to 0.68) | –38 | – | – | – | B (1) |
| Negative framing vs neutral framing of side-effects/survival ⁴³ ‡ | | 20/30 | 23/30 | 0.87 (0.63 to 1.20) | –10 | – | – | – | B (1) |
| Positive framing vs neutral framing of side-effects/survival ⁴³ ‡ | | 18/30 | 23/30 | 0.78 (0.55 to 1.11) | –17 | – | – | – | B (1) |
| Total information disclosure vs standard disclosure ⁵³ | | 27/29 | 23/28 | 1.13 (0.93 to 1.38) | 11 | – | – | – | A (1) |
| Less detailed information on risk and benefits vs more detailed information ²⁷ ‡ | | 4/10 | 3/9 | 1.20 (0.36 to 3.97) | 7 | – | – | – | B (1) |
| Information leaflet+verbal explanation vs information leaflet only ²⁷ ‡ | | 10/18 | 7/19 | 1.51 (0.73 to 3.10) | 19 | – | – | – | B (1) |
| <i>Telephone contact</i> Telephone reminder vs no reminder ^{31 49} | | 165/536 | 117/522 | 1.66 (1.03 to 2.46)§ | 15 | 2.44 | 0.12 | 59 | A A (2) |
| SMS messages (inc quotes) vs no SMS messages ²⁶ | | 17/405 | 0/406 | 35.09 (2.12 to 581.48) | 4 | – | – | – | A (1) |
| <i>Eligibility screening</i> Enhanced recruitment (inc African American interviewer) vs standard ²⁴ | | 78/3079 | 95/3297 | 0.88 (0.65 to 1.18) | 0 | – | – | – | B (1) |
| Enhanced recruitment+baseline data by telephone vs standard ²⁴ | | 87/3075 | 95/3297 | 0.98 (0.74 to 1.31) | 0 | – | – | – | B (1) |
| Enhanced recruitment+baseline data face-to-face vs standard ²⁴ | | 116/2949 | 95/3297 | 1.37 (1.05 to 1.78) | 1 | – | – | – | B (1) |
| Researcher-administered screening questionnaire vs standard paper based ²⁹ ‡ | | 42/78 | 76/141 | 1.00 (0.77 to 1.29) | 0 | – | – | – | C (1) |

Continued

Table 3 Continued

| Intervention | Reference ID | Participants recruited | | Risk ratio (95% CI) | Absolute difference (%) [*] | Heterogeneity | | Risk of bias† (studies) |
|---|--------------|------------------------|------------|------------------------|---|---------------|---------|----------------------------|
| | | Intervention | Comparator | | | χ^2 | p Value | |
| Electronic screening questionnaire vs standard paper based ^{29,†} | | 69/151 | 76/141 | 0.85 (0.67 to 1.07) | -8 | - | - | C (1) |
| Telephone screening vs face-to-face screening ^{20,‡} | | 64/99 | 190/370 | 1.26 (1.06 to 1.50) | 13 | - | - | C (1) |
| Eligibility screening by senior investigator vs screening by research assistant ⁴⁶ | | 28/162 | 22/185 | 1.45 (0.87 to 2.44) | 5 | - | - | C (1) |
| Financial incentives | | | | | | | | |
| Cash incentive+study information vs information only ²⁶ | | 13/246 | 1/245 | 12.95 (1.71 to 98.21) | 5 | - | - | A (1) |

‡Recruitment to a hypothetical trial.

*Absolute difference between the intervention and comparator groups (for multistudy interventions, this was calculated using the risk ratio and average comparator group risk).

†Risk of bias: A, low; B, moderate; C, high.

§Analysed as an OR and converted to a risk ratio using the average comparator group risk.

trials (including risks and benefits, randomisation and value to society) for a range of cancer studies (figure 4),^{21 22 33} one using interactive computer information in a hypothetical trial on managing complications after heart attack³⁶ and another using video plus a pamphlet for a hypothetical HIV vaccine trial,²⁸ but all found little or no difference in recruitment.

Interactive computer presentation compared with audio-taped presentation in a hypothetical cancer trial⁴⁴ slightly improved recruitment (RR 1.48, CI 95% 1.00 to 2.18), while showing a multimedia presentation of key trial information while a research assistant was available to answer questions, appears to have had little impact compared with just the research assistant in a hypothetical drug trial for schizophrenia.³⁵ Finally, a study using a brief verbal education session for Spanish-speaking women eligible for a trial on high breast cancer risk⁴⁵ found slightly improved recruitment compared with print materials alone (RR 1.14, 95% CI 1.01 to 1.28).

Supplementing trial information

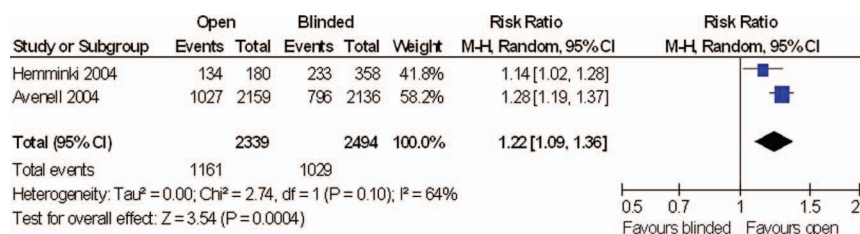
Five studies considered the effect of supplementing usual trial information with additional materials. Two studies evaluated the inclusion of a booklet on clinical trials, one in a hypothetical breast cancer trial,²³ the other in a real trial for HIV patients,³⁴ while two trials on physical activity³¹ and injury prevention³⁷ included study-relevant questionnaires with the invitation letters to potential participants. All four interventions made little or no difference to recruitment (figures 5 and 6). In the final study, the authors investigated the effect of including a newspaper article publicising the trial.⁵¹ This led to little or no difference in recruitment, even when the article was replaced with one that was more favourable to the trial.

Framing and content of trial information

Eight studies evaluated modifications to the way study information was presented, seven of them for hypothetical trials. The only study to evaluate an intervention for a real trial compared total disclosure of information relevant to a cancer trial with a more limited individual approach, where the level of detail was at the clinician's discretion.⁵³ This found that providing more information led to little or no difference in recruitment. Similarly, a study comparing a more detailed information leaflet with a less detailed one in a hypothetical cancer trial also found that this made little or no difference.²⁷

A consent form describing a new medication that 'may work twice as fast as usual treatment' most likely increased recruitment compared with one describing it as working 'half as fast' (RR 1.62, 95% CI 1.10 to 2.37),⁵² while describing treatment as 'new' rather than 'standard' may have slightly decreased recruitment (RR 0.81, 95% CI 0.66 to 0.99).³⁸ Similarly, emphasising the pain or risk involved in a trial most likely decreased recruitment (RR 0.55, 95% CI 0.36 to 0.85 and RR 0.41,

Figure 2 Recruitment with open and blinded trial design.



95% CI 0.24 to 0.68, respectively).⁵⁴ Neutrally framed information about side effects and survival compared with negatively or positively framed information⁴³ appears to have led to little or no difference in recruitment.

Two studies investigated the effects of disclosing the financial interests of those involved in the trial. In the first, a hypothetical heart disease trial, three scenarios outlining the investigators' interests were presented.⁵⁷ Willingness to participate reduced when the investigator had an investment in the drug company, compared with no disclosure ($p=0.03$) or per capita research payments to the investigating institution ($p=0.01$). In the second study, five scenarios were presented to research-interested adults with asthma or diabetes.⁵⁸ Again, willingness to participate was lowest when the investigator had an investment in the drug company, and highest when the company paid the running costs ($p<0.001$).

Telephone contact

Three studies used telephones as a means of contacting potential participants. Two trials (on returning sick-listed people to work⁴⁹ and activity in older people³¹) found that using telephone reminders to follow-up written invitations improved recruitment (OR 1.95 95% CI 1.04 to 3.66; figure 7), although there was moderate heterogeneity related to the magnitude of effect ($I^2=59\%$). In the third study, a series of SMS messages containing quotes from existing recruits were texted to potential participants of a smoking cessation trial.²⁶ This improved recruitment compared with the standard written invitation (RR 35.09, 95% CI 2.12 to 581.48), although small numbers overall led to a wide CI.

Figure 3 Recruitment with consent to experimental, standard and usual consent procedure.

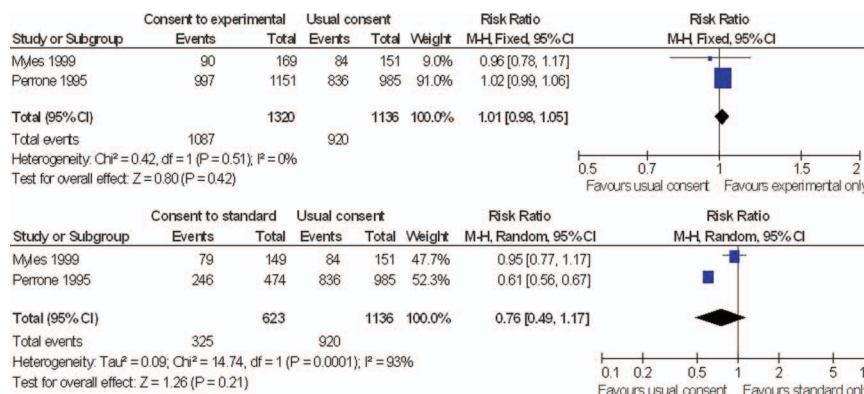
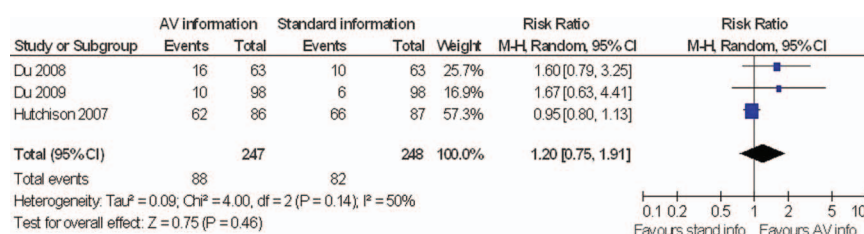


Figure 4 Recruitment with audiovisual and standard trial information.



involved. One study combined three levels of trial risk (high, medium and low) with three levels of payment (\$1800, \$800 and \$350),¹⁷ while the other varied the payment levels (\$2000, \$1000 and \$100) and the risk of adverse drug effects or of receiving placebo in a hypothetical antihypertensive drug trial.³⁰ Both studies found that willingness to participate increased with payment ($p=0.015$, $p<0.001$, respectively) in one case, regardless of the associated risk.¹⁷

Training for recruiters

Two studies, one with 98 recruiters and the other with 126 recruiting centres, considered interventions aimed at those recruiting, both involving educational packages.^{39 40} One study evaluated training Hispanic participants in a prevention trial as lay advocates—*Embajadoras*—to refer other Latinas to the study.⁴⁰ Data analysis did not correct for clustering and no ICC was provided, but the authors reported that more *Embajadoras* recruited to the trial than either untrained Hispanic or Anglo controls (8/28 vs 0/26 and 2/42, respectively). The second study, a cluster trial involving 126 centres in a cancer and leukaemia research network, compared the standard input for recruiters with an educational package (including a symposium and monthly mailings) aimed at improving recruitment of older participants.³⁹ Although centre-level data and ICC were not provided, clustering was considered in the analysis, and the authors found that additional education did not significantly influence recruitment (31% vs 31%, $p=0.83$).

Trial co-ordination

Two studies involving a total of 302 trial sites looked at the effect of greater contact from the trial co-ordinators. In the first, a breast cancer trial, 68 of the 135 recruiting centres received on-site visits (including an initiation visit to review the trial protocol, etc), while the remainder received none.⁴¹ In the second, an international diabetes trial, additional communication from the co-ordinating centre (frequent emails, individually

tailored feedback on recruitment, etc) was compared with usual communication.⁴⁷ Neither study presented the proportion of eligible participants, but both reported finding little difference in recruitment when site visits were made (302 with visits vs 271 with no visits), or when communication was increased (median number of recruits 37.5 vs 37.0 for standard communication).

DISCUSSION

Principal findings

In this systematic review, we assessed the evidence from 45 trials evaluating the effect of intervention strategies designed to improve recruitment to randomised controlled trials. We found that a number of interventions do appear to be effective, although the evidence base related to some is still limited. Telephone reminders to non-responders,^{31 49} opt-out procedures requiring potential participants to contact the research team if they do not want to be contacted about a trial,⁵⁵ including a financial incentive with the trial invitation,²⁶ and making the trial open rather than blinded^{16 32} all improved recruitment in high-quality studies involving real trials. The effect of other strategies to improve recruitment, however, remains less clear.

Although partial preference designs may improve participation in a study as a whole, they appear to have little impact on recruitment to randomisation,¹⁸ and with the exception of the opt-out approach already mentioned, a variety of strategies involving changes to consent procedures failed to produce any increase in recruitment. Similarly, modifications to the method or quantity of information presented to potential participants—either about trials in general or about a specific trial—did not provide clear evidence of the benefit of this approach to improving recruitment. Providing information to prospective participants in the form of quotes from existing participants via SMS shows potential, but it was evaluated in a single study,²⁶ and requires further evaluation. Few studies looked at interventions aimed not at potential participants

Figure 5 Recruitment with clinical trials booklet and standard trial information.

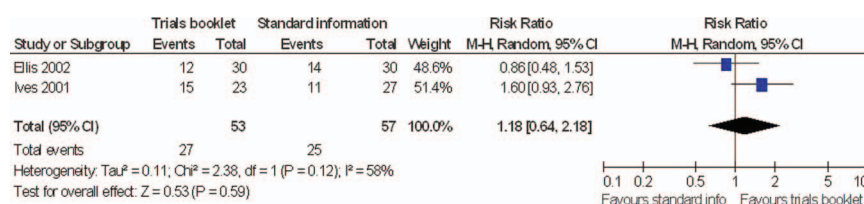
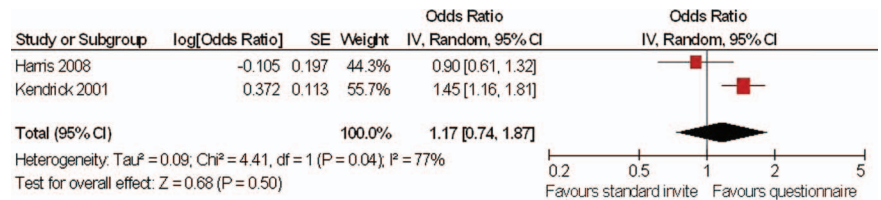


Figure 6 Recruitment with invitation including study questionnaire and standard invitation.



but at those recruiting them,^{39–41 47} and none presented clear evidence in favour of the strategies used.

While several of the interventions studied show promise, there are some caveats. Pooled analysis for telephone reminders had moderate heterogeneity ($I^2 = 59\%$), although it would appear that it is the magnitude of effect rather than the benefit of the intervention that is in doubt. Similarly, while the inclusion of a financial incentive as used by Free *et al*²⁶ did improve recruitment, the number of participants recruited was small, leading to uncertainty about the magnitude of effect. Two additional studies involving financial incentives found that increasing payment led to increased recruitment,^{17 30} but these involved hypothetical trials as well as sums of money that might not be feasible when recruiting to real studies. In addition, ethical concerns have been raised about the use of some of these strategies. Telephone reminders and financial incentives have both been used and accepted by many as a legitimate recruitment tool, but they may be considered by some to be a form of coercion. Opt-out procedures have previously been proposed as a way of improving recruitment to health research,⁶¹ but this approach remains controversial, as ethics committees generally require that research participants provide express approval for research participation, including being contacted about the study by researchers. However, it is worth noting that the trial included in this review⁵⁵ studied opting-out of being contacted about a trial rather than opting-out of consenting to trial participation. This may be viewed as being less controversial, and as such, ethics committees may be more willing to accept it as part of a recruitment strategy. Finally, while it may be easier to recruit to an open trial rather than a blinded trial, there is clearly a greater risk of bias involved, and it is therefore an approach that requires careful consideration before being implemented.

Limitations of the review

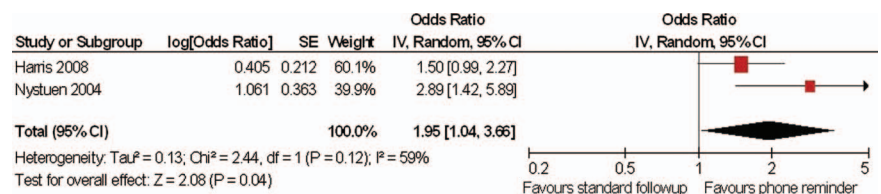
Many of the studies included in this review were small, likely to be underpowered and with CIs including the

possibility of substantial benefit. This is particularly true of interventions that modified the approach made to potential participants. In addition, 19 studies involved hypothetical trials, and the implications of their results for real trials are still unclear.

The interventions used by studies varied significantly, making it difficult to pool data. Even those studies adopting the same basic approach, such as altering the consent process, were generally sufficiently different to make pooling inappropriate.⁶² For example, while there were five studies of seven interventions looking at changes to consent procedures, only two interventions were comparable enough to be pooled. Similarly, video presentations were used in six studies but generally delivered different information, or were used in combination with other interventions that differed between studies. Consequently, only three could be combined in the same analysis. At the outset of the review, we had planned to undertake a number of subgroup analyses of the key factors considered relevant to heterogeneity, but variations in the interventions themselves would have made these comparisons meaningless. One such subgroup related to the impact of recruiting to a hypothetical trial versus a real trial. There was, however, only one comparison where there was at least one of each type of trial, and we were therefore unable to assess this factor. Only one of the cluster trials³¹ provided sufficient data to allow an appropriate analysis to be incorporated in the review. In addition, there were a number of studies which potentially had data clustered by the study the participant was invited to join, even though participants were individually randomised. As such, estimates from these studies may be overly precise.

Potential bias was also a problem in many of the studies, often linked to hypothetical trials. Although allocation concealment was considered high quality for 22 of the 45 trials (it was unclear for 16 and poor for 7), the overall assessment of the risk of bias was considered as low for only 12 studies. Twenty trials were considered to be at a high risk of bias. It was not possible to predict the direction of effect that any bias may have had on

Figure 7 Recruitment with telephone reminder and standard follow-up.



study outcomes. In addition, we were unable to make statistical judgements about the likelihood of publication and related biases due to the relatively small number of included studies per comparison, and the wide variation in the recruitment strategies being evaluated.

However, this review provides an update to previous reviews in the field, identifying a greater number of relevant studies and presenting new evidence relating to trial design (the potentially negative impact of using a Zelen design), the approach to participants (the benefits of using SMS messages, framing of trial information, financial disclosure) and financial incentives (including a cash incentive with the trial invitation). In addition, it has generated further evidence to support the broad conclusions from earlier work, namely that opt-out procedures, open rather than blinded trials, paid participation and telephone reminders to non-responders improve recruitment, while various methods of consent and the provision of supplementary information appear to have little effect.

Implications for research

The findings from this review would suggest that there are two key areas within recruitment-related research where activity could be focused. First, despite the failure of many trials to meet their recruitment targets, and the significant implications of this both practically and in relation to the delayed application of effective interventions,^{2–6} few strategies designed to improve trial participation have been rigorously evaluated in the context of a real trial. Almost half of the trials in this review involved hypothetical studies, including many of those evaluating changes to the consent process, and all but one of those looked at the use of financial incentives. In some of these studies, there was evidence of benefit. In others, the intervention demonstrated little impact. But what is true for all is that their effect in a real setting is unknown. Given that, we would argue that while the use of hypothetical trials to study recruitment interventions has its place, trialists should include evaluations of their recruitment strategies within their trials, and research funding bodies should support this as part of future trial methodologies. Where uncertainty exists around two or more strategies, an evaluation could actually help trialists to focus their efforts on the most effective strategy (or strategies) while at the same time adding to the methodological literature. If recruitment is carried out in phases, evaluation could be used in the early phases with later phases employing the most effective strategies identified.⁶³ Since everyone receiving a recruitment intervention ‘counts’ for the evaluation—the study is simply counting the number of yes and no responses—statistical power is generally not a problem. Graffy *et al*⁶⁴ have discussed nested trials of recruitment interventions in more detail.

Second, previous research on potential barriers to trial participation has suggested that there are various factors that may provide the means by which recruitment can

be increased, many of them related to trial recruiters. These include evaluating a clinically important question, minimising the workload of participating clinicians, removing responsibility for consent away from clinicians and involving research networks.^{65–67} Only 4 of the 45 studies included in this review evaluated interventions specifically designed for recruiters, and of those, only one reported an improvement in recruitment (although the data analysis did not adjust for clustering).⁴⁰ There is clearly a gap in knowledge with regard to effective strategies targeting this group, and additional research aimed at how to increase recruitment by individuals or sites participating in trials would be beneficial. Other authors have used multivariable regression to look for factors that influence recruitment, although there were few insights gained from this.^{2 67} However, this approach may be worth revisiting as more evaluations of recruitment interventions are published.

Evidence from this review has demonstrated that there are promising strategies for increasing recruitment to trials, including telephone reminders to non-responders and requiring potential participants to opt-out of being contacted by the trial team. Some of these strategies, such as open trial designs, need to be considered carefully as their use also has disadvantages. Many, however, require further rigorous evaluation to conclusively determine their impact.

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REFERENCES

1. Odgaard-Jensen J, Vist GE, Timmer A, *et al.* Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev* 2011;4:MR000012.
2. McDonald AM, Knight RC, Campbell MK, *et al.* What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. *Trials* 2006;7:9.
3. Altman DG. Statistics and ethics in medical research III. How large a sample? *BMJ* 1980;281:1336–8.
4. Charlson ME, Horwitz RI. Applying results of randomised trials to clinical practice: impact of losses before randomisation. *BMJ* 1984;289:1281–4.
5. Haidich AB, Ioannidis JPA. Patterns of patient enrollment in randomized controlled trials. *J Clin Epidemiol* 2001;54:877–83.
6. Foy R, Parry J, Duggan A, *et al.* How evidence based are recruitment strategies to randomized controlled trials in primary care? Experience from seven studies. *Fam Pract* 2003;20:83–92.
7. Watson JM, Torgerson DJ. Increasing recruitment to randomised trials: a review of randomised controlled trials. *BMC Med Res Methodol* 2006;6:34.
8. Mapstone J, Elbourne D, Roberts I. Strategies to improve recruitment to research studies. *Cochrane Database Syst Rev* 2007;2:MR000013.
9. Caldwell PHY, Hamilton S, Tan A, *et al.* Strategies for increasing recruitment to randomised controlled trials: systematic review. *PLoS Med* 2010;7:e1000368.
10. Treweek S, Mitchell E, Pitkethly M, *et al.* Strategies to improve recruitment to randomised controlled trials. *Cochrane Database Syst Rev* 2010;4:MR000013.
11. Edwards PJ, Roberts I, Clarke MJ, *et al.* Methods to increase response to postal and electronic questionnaires. *Cochrane Database Syst Rev* 2009;3:MR000008.
12. Rendell JM, Merritt RK, Geddes J. Incentives and disincentives to participation by clinicians in randomised controlled trials. *Cochrane Database Syst Rev* 2007;2:MR000021.
13. Brueton VC, Rait G, Tierney J, *et al.* Strategies to reduce attrition in randomised trials (protocol). *Cochrane Database Syst Rev* 2011;2:MR000032.
14. Schulz KF, Chalmers I, Hayes RJ, *et al.* Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408–12.
15. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.0.1. Cochrane Collaboration, 2008. <http://www.cochrane-handbook.org> (accessed 7 Jan 2013).
16. Avenell A, Grant AM, McGee M, *et al.* The effects of an open design on trial participant recruitment, compliance and retention—a randomized controlled trial comparison with a blinded, placebo-controlled design. *Clin Trials* 2004;1:490–8.
17. Bentley JP, Thacker PG. The influence of risk and monetary payment on the research participation decision making process. *J Med Ethics* 2004;30:293–8.
18. Cooper KG, Grant AM, Garratt AM. The impact of using a partially randomised patient preference design when evaluating alternative managements for heavy menstrual bleeding. *Br J Obstet Gynaecol* 1997;104:1367–73.
19. Coyne CA, Xu R, Raich P, *et al.* Randomized, controlled trial of an easy-to-read informed consent statement for clinical trial participation: a study of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2003;21:836–42.
20. DiGiuseppi C, Goss C, Xu S, *et al.* Telephone screening for hazardous drinking among injured patients seen in acute care clinics: feasibility study. *Alcohol Alcohol* 2006;41:438–45.
21. Du W, Mood D, Gadgeel S, *et al.* An educational video to increase clinical trials enrollment among lung cancer patients. *J Thorac Oncol* 2008;3:23–9.
22. Du W, Mood M, Gadgeel S, *et al.* An educational video to increase clinical trials enrollment among breast cancer patients. *Breast Cancer Res Treat* 2009;117:339–47.
23. Ellis PM, Butow PN, Tattersall MHN. Informing breast cancer patients about clinical trials: a randomized clinical trial of an educational booklet. *Ann Oncol* 2002;13:1414–23.
24. Ford ME, Havstad SL, Davis SD. A randomized trial of recruitment methods for older African American men in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. *Clin Trials* 2004;1:343–51.
25. Fowell A, Johnstone R, Finlay IG, *et al.* Design of trials with dying patients: a feasibility study of cluster randomisation versus randomised consent. *Palliat Med* 2006;20:799–804.
26. Free C, Hoile E, Robertson S, *et al.* Three controlled trials of interventions to increase recruitment to a randomized controlled trial of mobile phone based smoking cessation support. *Clin Trials* 2010;7:265–73.
27. Freer Y, McIntosh N, Teunisse S, *et al.* More Information, less understanding: a randomized study on consent issues in neonatal research. *Pediatrics* 2009;123:1301–5.
28. Fureman I, Meyers K, McLellan AT, *et al.* Evaluation of a video-supplement to informed consent: injection drug users and preventive HIV vaccine efficacy trials. *AIDS Educ Prev* 1997;9:330–41.
29. Graham A, Goss C, Xu S, *et al.* Effect of using different modes to administer the AUDIT-C on identification of hazardous drinking and acquiescence to trial participation among injured patients. *Alcohol Alcohol* 2007;42:423–9.
30. Halpern SD, Karlawish JHT, Casarett D, *et al.* Empirical assessment of whether moderate payments are undue or unjust inducements for participation in clinical trials. *Arch Intern Med* 2004;164:801–3.
31. Harris TJ, Carey IM, Victor CR, *et al.* Optimising recruitment into a study of physical activity in older people: a randomised controlled trial of different approaches. *Age Ageing* 2008;37:659–65.
32. Hemminki E, Hovi SL, Veerus P, *et al.* Blinding decreased recruitment in a prevention trial of postmenopausal hormone therapy. *J Clin Epidemiol* 2004;57:1237–43.
33. Hutchison C, Cowan C, McMahon T, *et al.* A randomised controlled study of an audiovisual patient information intervention on informed consent and recruitment to cancer clinical trials. *Br J Cancer* 2007;97:705–11.
34. Ives NJ, Troop M, Waters A, *et al.* Does an HIV clinical trial information booklet improve patient knowledge and understanding of HIV clinical trials? *HIV Med* 2001;2:241–9.
35. Jeste DV, Palmer BW, Golshan S, *et al.* Multimedia consent for research in people with schizophrenia and normal subjects: a randomized controlled trial. *Schizophr Bull* 2009;35:719–29.
36. Karunaratne AS, Korenman SG, Thomas SL, *et al.* Improving communication when seeking informed consent: a randomised controlled study of a computer-based method for providing information to prospective clinical trial participants. *Med J Aust* 2010;192:388–92.
37. Kendrick D, Watson M, Dewey M, *et al.* Does sending a home safety questionnaire increase recruitment to an injury prevention trial? A randomised controlled trial. *J Epidemiol Community Health* 2001;55:845–6.
38. Kerr CEP, Robinson EJ, Lilford RJ, *et al.* The impact of describing clinical trial treatments as new or standard. *Patient Educ Couns* 2004;53:107–13.
39. Kimmick GG, Peterson BL, Kornblith AB, *et al.* Improving accrual of older persons to cancer treatment trials: a randomized trial comparing an educational intervention with standard information: CALGB 360001. *J Clin Oncol* 2005;23:2201–7.
40. Larkey LK, Staten LK, Ritenbaugh C, *et al.* Recruitment of Hispanic women to the Women's Health Initiative: the case of Embajadoras in Arizona. *Control Clin Trials* 2002;23:289–98.
41. Liénard J-L, Quinaux E, Fabre-Guillevin E, *et al.* Impact of on-site initiation visits on patient recruitment and data quality in a randomized trial of adjuvant chemotherapy for breast cancer. *Clin Trials* 2006;3:486–92.
42. Litchfield J, Freeman J, Schou H, *et al.* Is the future for clinical trials internet-based? A cluster randomized clinical trial. *Clin Trials* 2005;2:72–9.
43. Llewellyn-Thomas HA, McGreal MJ, Thiel EC. Cancer patients' decision making and trial-entry preferences: the effects of "framing" information about short-term toxicity and long-term survival. *Med Decis Making* 1995;15:4–12.
44. Llewellyn-Thomas HA, Thiel EC, Sem FWC, *et al.* Presenting clinical trial information: a comparison of methods. *Patient Educ Couns* 1995;25:97–107.
45. Mandelblatt J, Kaufman E, Sheppard VB, *et al.* Breast cancer prevention in community clinics: will low-income Latina patients participate in clinical trials? *Prev Med* 2005;40:611–18.
46. Miller NL, Markowitz JC, Kocsis JH, *et al.* Cost effectiveness of screening for clinical trials by research assistants versus senior investigators. *J Psychiatr Res* 1999;33:81–5.

47. Monaghan H, Richens A, Colman S, *et al.* A randomised trial of the effects of an additional communication strategy on recruitment into a large-scale, multi-centre trial. *Contemp Clin Trials* 2007;28:1–5.
48. Myles PS, Fletcher HE, Cairo S, *et al.* Randomized trial of informed consent and recruitment for clinical trials in the immediate preoperative period. *Anesthesiology* 1999;91:969–78.
49. Nystuen P, Hagen KB. Telephone reminders are effective in recruiting nonresponding patients to randomized controlled trials. *J Clin Epidemiol* 2004;57:773–6.
50. Perrone F, De Placido S, Giusti C, *et al.* The request for consent in clinical research: a randomised study in healthy subjects. *Epidemiol Prev* 1995;19:282–90.
51. Pighills A, Torgerson DJ, Sheldon T. Publicity does not increase recruitment to falls prevention trials: the results of two quasi-randomized trials. *J Clin Epidemiol* 2009;62:1332–5.
52. Simel DL, Feussner JR. A randomized controlled trial comparing quantitative informed consent formats. *J Clin Epidemiol* 1991;44:771–7.
53. Simes RJ, Tattersall MHN, Coates AS, *et al.* Randomised comparison of procedures for obtaining informed consent in clinical trials of treatment for cancer. *BMJ* 1986;293:1065–8.
54. Treschan TA, Scheck T, Kober A, *et al.* The influence of protocol pain and risk on patients' willingness to consent for clinical studies: a randomized trial. *Anesth Analg* 2003;96:498–506.
55. Trevena L, Irwig L, Barratt A. Impact of privacy legislation on the number and characteristics of people who are recruited for research: a randomised controlled trial. *J Med Ethics* 2006;32:473–7.
56. Wadland WC, Hughes JR, Secker-Walker RH, *et al.* Recruitment in a primary care trial on smoking cessation. *Fam Med* 1990;22:201–4.
57. Weinfurt KP, Hall MA, Dinan MA, *et al.* Effects of disclosing financial interests on attitudes toward clinical research. *J Gen Intern Med* 2008;23:860–6.
58. Weinfurt KP, Hall MA, Friedman JY, *et al.* Effects of disclosing financial interests on participation in medical research: a randomized vignette trial. *Am Heart J* 2008;156:689–97.
59. Welton AJ, Vickers MR, Cooper JA, *et al.* Is recruitment more difficult with a placebo arm in randomised controlled trials? A quasirandomised, interview based study. *BMJ* 1999;318:1114–17.
60. Weston J, Hannah M, Downes J. Evaluating the benefits of a patient information video during the informed consent process. *Patient Educ Couns* 1997;30:239–45.
61. Hewison J, Haines A. Overcoming barriers to recruitment in health research. *BMJ* 2006;333:300–2.
62. Engels EA, Schmid CH, Terrin N, *et al.* Heterogeneity and statistical significance in meta-analyses: an empirical study of 125 meta-analyses. *Stat Med* 2000;19:1707–28.
63. Treweek S, Barnett K, MacLennan G, *et al.* E-mail invitations to general practitioners were as effective as postal invitations and were more efficient. *J Clin Epidemiol* 2012;65:793–7.
64. Graffy J, Bower P, Ward E, *et al.* Trials within trials? Researcher, funder and ethical perspectives on the practicality and acceptability of nesting trials of recruitment methods in existing primary care trials. *BMC Med Res Methodol* 2010;10:38.
65. McKinstry B, Hammersley V, Daly F, *et al.* Recruitment and retention in a multicentre randomised controlled trial in Bell's palsy: a case study. *BMC Med Res Methodol* 2007;7:15.
66. van der Wouden JC, Blankenstein AH, Huibers MJH, *et al.* Survey among 78 studies showed that Lasagna's law holds in Dutch primary care research. *J Clin Epidemiol* 2007;60:819–24.
67. Prescott RJ, Counsell CE, Gillespie WJ, *et al.* Factors that limit the quality, number and progress of randomised controlled trials. *Health Technol Assess* 1999;3:1–143.