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Review Article **14-00240R1**

A Systematic Review of Strategies Used to Increase Recruitment of People with Cancer or Organ Failure into Clinical Trials: Implications for Palliative Care Research

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Abstract

Context. The challenges of palliative care clinical trial recruitment are well documented.

Objectives. To review tested strategies to improve recruitment to trials of people with a range of conditions who may access palliative care services but are not explicitly stated to be "palliative."

Methods. This was a systematic review with narrative description. The Cochrane, Embase, PubMed, PsycINFO and CINAHL electronic databases were searched (English; Jan. 2002-Feb. 2014) for quasi-experimental and randomized controlled trials (RCTs) testing the effect of recruitment strategies on accrual to clinical trials of people with organ failure and cancer. Titles, abstracts and retrieved papers were screened by two researchers and categorized by recruitment challenge:1) patients with reduced cognition, 2) those requiring emergency treatment, and 3) willingness of patients and clinical staff to contribute to trials.

Results. Of 549 papers identified, 15 were included. Thirteen reported RCTs and two papers reported three quasi-experimental studies. Five were cluster RCTs of recruiting sites/institutions. One was a randomized cluster crossover feasibility study. Seven studies recruited patients with cancer. Others included patients with dementia, stroke, cardiovascular disease, diabetes, frail elderly and bereaved carers. Some interventions improved recruitment: memory aid, contact prior to arrival, cluster consent, "opt out" consent. Others either reduced recruitment (formal mental capacity assessment; a variety of educational, supportive and advertising interventions) or made no difference (advance research directive).

Conclusion. Successful strategies from other disciplines could be considered by palliative care researchers. Tailored, efficient, evidence-based strategies must be developed, acknowledging that strategies with face validity are not necessarily the most effective.

Key Words: Patient selection, clinical trials, disease progression, palliative care, research subject recruitment

Running head: Review of Trials of Rcruitment Srategies

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Introduction

The challenges faced when recruiting participants into palliative care trials are cited as the reason for poor accrual, resulting in abandoned or underpowered studies (1-4). This represents a poor return for the time and effort of the participants and the funding bodies, and fails to address the need for interventions to have high-level evidence to support their use in the palliative care population, with regard to efficacy, safety and tolerability (5, 6).

The difficulties of recruitment to clinical trials in palliative care have been well documented (1-3, 7, 8). Mostly these center on ethical and logistical issues. Ethical issues relate to the burden and intrusiveness of study measures on the participants, concerns regarding randomization, and gate-keeping by clinicians, carers and Ethics Committees. Logistical issues include lack of research infrastructure such as trials unit support, research funding, collaborative centers, sponsorship, indemnity and research time, particularly for clinicians. Further, palliative care patients have an expected trajectory of deterioration and death that may complicate the ethical issues in this population, and increases the risk of underpowered trials (9).

The remit of palliative care is evolving to include people with non-cancer conditions. Despite similar recruitment challenges, clinical trials have been successfully completed in this population even with advanced disease (10). Indeed, some recruitment strategies (Table 1) have already been successfully applied in palliative care trials, increasing the number of adequately powered clinical trials of palliative care interventions (8, 11-14).

As people with a range of conditions are increasingly cared for by palliative care services, recruitment strategies tested in such populations, which may not be explicitly named as "palliative care," may provide useful information for palliative care researchers. Previous reviews have restricted the search to studies in explicitly palliative care populations or

conversely have reviewed an extensive range of conditions and study interventions, including public health interventions (1, 10, 15). For this review a "palliative care patient" is defined in terms of the health status (progressive, incurable illness) and the care given (multidisciplinary, holistic approach) (1, 16).

The aims of this study were: 1) to identify, assess and summarize the findings of randomized or quasi-experimental trials of strategies designed to optimize trial recruitment of people with cancer or organ failure (including cognitive failure) compared with usual methods with regard to effect on trial accrual; and 2) to identify those strategies applicable to palliative care clinical studies.

Methods

Cochrane, Embase, PubMed, PsycINFO and CINAHL electronic databases were searched using terms developed from those used by Wohleber (7), Lovato (10), Rinck (15) and Sladek (17) (Table 2). These were extended to include other conditions mapped to medical subject heading (MeSH) terms. Search #17 had titles and abstracts reviewed for inclusion; eligibility criteria are shown in Table 3. Reference lists from identified reviews were hand-searched. An initial search was performed in November 2012 and updated in February 2014.

Inclusion Criteria

Types of Participants. Studies of patients with cancer, or conditions affecting vital organ(s) including dementia, delirium and stroke were included.

Types of Studies. Studies that tested the effect of a recruitment strategy on recruitment to a clinical study as a primary outcome *a priori* using a randomized or quasi-experimental design were included. Trials could randomize at individual patient or cluster level, and be phase 2 or 3.

Types of Interventions. Trials could test any recruitment strategy targeted at any step of the recruitment pathway (e.g., the different steps that could influence the participant being included in a study), and be directed at the individual patient, or recruiting site.

Types of Outcomes. Measures of recruitment could include number/percentage of participants recruited, number of institutions recruiting, recruitment per center, and mental capacity to provide one's own rather than proxy consent.

Data Collection and Analysis

Selection of Studies. Two reviewers (J.B., M.J.) reviewed all titles and abstracts. Full papers were retrieved for those eligible, or indeterminable from titles and abstracts. Two reviewers (J.B., M.J.) assessed the full text of all potentially relevant studies. Disagreement was resolved by consensus and with recourse to a third reviewer (A.W.).

Data Extraction. Data were extracted (J.B., C.P.) using a data extraction form based on areas influencing study recruitment (7) (Appendix). Unreported data were not requested.

Categorization of Studies. Studies were categorized according to the stage of the recruitment process at which the recruitment strategy they used was directed. A grade of evidence using the Jadad score was assigned for the randomized controlled trials (RCTs). This score is based on the following five questions: Was the study described as random, was the randomization scheme described and appropriate, was the study described as double-blind, was the method of double blinding appropriate (i.e., were both the patient and the assessor appropriately blinded), and was there a description of dropouts and withdrawals? The maximum score is 5 (18).

Analysis. The key features of the included studies (design, patient population, recruitment strategy evaluated, study outcome and effect on recruitment) are presented in tables

and analyzed with narrative description. Because of the clinical and methodological heterogeneity, a meta-analysis was considered inappropriate. Data are presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results

The search identified 549 studies of which 15 were eligible. The process of selection is shown in Fig. 1 and the studies are summarized in Table 4 (more detail in Table 4A, available at jpsmjournal.com). Table 5 lists the full-text articles that were retrieved but not included, with reasons for exclusion.

Description of Studies

Thirteen articles reported RCTs testing a recruitment strategy, with another two papers describing three quasi-experimental studies. Of the 13 RCTs, one was a three-arm parallel study, seven were two-arm parallel studies, five were cluster RCTs of potential recruiting sites/institutions, and one was a randomized cluster crossover feasibility study. In the individual patient randomized trials, the primary outcome was trial accrual, with one (19) focusing on whether the patient had the mental capacity to provide their own consent. The cluster trials all reported recruitment rate per site.

Quality of Included Studies. Only one study scored more than 3 of 5 on the Jadad scale.. Many of the studies lost two points because of lack of blinding, although this would have been difficult or impossible.

Description of Participants/Institution Clusters

Seven of the 15 studies recruited patients with cancer (20-26). The others included a range of participants who highlighted recruitment challenges associated with: reduced capacity to consent (two studies in dementia (19, 27), one in acutely unwell medical inpatients (28)); need

for urgent medical intervention (one in acute stroke (29)); and bereavement (one study of bereaved carers (30)). Two studies recruited people with cardiovascular disease (angina (31) and diabetic vascular disease (32)). The two quasi-experimental studies reported in one paper were of elderly community dwellers at risk of falling (33). Although not clearly in a study inclusion disease category, it was felt the studies were likely to include participants relevant to our question. Only one study included patients admitted to a palliative care unit (25).

Description of Interventions

The included studies targeted three specific challenges in recruitment:

1) Potential Participants with Reduced Cognitive Ability. These studies investigated the use of a memory and organizational aid; a research advance directive; or an augmented assessment of mental capacity to consent.

2) Potential Participants Requiring Emergency Treatment. One study used a method of advance information provision to specific potential participants. A cluster randomized trial of palliative care patients admitted for terminal care tested two methods of consent – either at a cluster level, or at the individual patient level.

3) Effective Dissemination of Trial Information and Raising Recruitment Willingness Among Potential Participants and Recruiting Site Staff. A variety of interventions were tested.

Effect on Rcruitment Rate.

1) Potential Participants with Reduced Cognitive Ability. A memory and organizational aid increased the number of participants with Alzheimer's dementia (Mini-Mental State Examination 18-27) able to provide their own consent compared with standard consent procedures (46% vs. 33%; $P = 0.004$) (19) but the use of advance consent versus usual consenting practice, for research in people with dementia, and their family proxies, did not

improve trial recruitment (27). In the latter trial, 149 patients and family proxies provided a research advanced directive (Planning Ahead Together [PAT] document). Over the following two years, 41 patients were invited to participate in a study of whom 27 consented. There was no difference in consent rate between those with or without a PAT (23 PAT, 18 no PAT).

In a study of acutely unwell medical in-patients (N = 130), participants were randomized to have a formal assessment of mental capacity prior to the usual informed consent procedure or to have a single step procedure. Those receiving a formal assessment of mental capacity were less likely to be judged competent to provide informed consent (60% vs. 86%; P = 0.001) and less likely to be randomized (44% vs. 74%) (28). Unsurprisingly, those randomized had less severe delirium than the comparator group, indicating that selection bias had occurred (28).

A feasibility cluster trial assessed the effect of two levels of consent (at the cluster level [N = 24] or at an individual patient level using a Zelen design [N = 29]) for a trial of anti-emetics in patients admitted to a palliative care unit or oncology ward for terminal care (25). Using a Zelen design, participants are randomly allocated to either the intervention or control group prior to giving informed consent; participants randomized to receive the intervention are then approached, offered the intervention, which they can then decline or accept. In the cluster group, 13 patients consented of whom six were randomized, but in the Zelen group, only two were consented and none were randomized. Nursing staff were less willing to approach an individual patient for consent in the Zelen arm as it required consent for a change in treatment, whereas with a cluster design, the consent was only for a patient's data to be used (25).

2) Potential Participants Requiring Emergency Treatment. The two studies discussed above (25, 28) were both conducted in patients who, in addition to fluctuating cognition, may also require emergency treatment.

A trial testing early patient/proxy contact to invite study participation by potential stroke patients (*N* = 100) while awaiting medical evacuation to a tertiary treatment center increased the consent rate to 68% compared with 50% in those approached only on arrival (29).

3) Effective Dissemination of Trial Information and Raising Recruitment Willingness Among Potential Participants and Recruiting Site Staff.

Potential Participants. A cluster RCT comparing easy to read (*N* = 89) or standard consent information (*N* = 137) for a cancer trial did not influence either the decision to participate (82% vs. 89%; *P* = 0.21) or actual accrual rate (75% vs. 68%; *P*= 0.32) (20). An educational video about clinical trials for lung cancer patients (*N* = 63) did not statistically significantly increase enrolment rates over a control group (*N* = 63) for either therapeutic (18% vs. 11%; *P* = 0.3) or non-therapeutic trials (25% vs. 16%; *P* = 0.19) (22). Similarly, an RCT (*N* = 196) of enrollment into therapeutic breast cancer trials was unaffected by the use of an educational video; 10% (video group) vs. 6%; *P* = 0.3) (23). The provision of audiovisual information in addition to standard trial specific information did not lead to an increased recruitment rate (72% [audiovisual group; *N* = 86] vs. 76% [*N* = 87]; odds ratio 1.19, 95% confidence interval 0.55, 2.58; *P* = 0.66) (21). Two quasi-experimental studies testing the effect of study specific newspaper articles in addition to standard participant information did not statistically significantly increase the recruitment rate to a falls prevention study in primary care in those over 70 years of age (study 1, *N* = 4488: 3% [newspaper article group] vs. 3%; study 2, *N* = 2745: 4% vs. 4%).

Two studies tested an “opt out” versus “opt in” consent process. Junghans and colleagues randomized primary care patients with angina (*n* = 510) to have an “opt in” or “opt out” approach to recruitment in an observational study (31). The “opt out” group (*n* = 258) had a

higher recruitment rate (50% vs. 38%; *P* = 0.014). However, the "opt in" group who consented had fewer risk factors (*P* = 0.53), were on less treatment for angina (*P* = 0.01) and had less functional impairment (*P* = 0.02) than those in the "opt out" group. In a quasi-experimental study, bereaved carers (*N* = 1422) were contacted to take part in a survey and were allocated to an "opt in" or "opt out" response (30). Again, there was a higher response rate in the "opt out" group (40% vs. 26%; *P*< 0.01).

Potential Recruiting Sites. One cluster RCT allocated 53 institutions recruiting to cancer and leukemia trials to have extensive and time-consuming augmented information and support about ongoing trials targeted to increase recruitment of patients over 65 years of age (seminars, protocol lists, monthly reminders, case discussions) and 72 to have a standard approach only (website access and periodic notification of trials). The additional intervention did not improve the proportion of people over 65 recruited (proportion recruited at one year: 32% vs. 36%; *P* = 0.35; at two years: 31% vs. 31%; *P* = 0.83) (26). Another trial compared face-to-face site visits (*N* =68) with none (*N*=67). Although there were more sites that were classified as "excellent recruiters" in the visited group, overall, there was no statistically significant advantage (302 randomized patients in the visited group vs. 271 in the comparator group) (24). A third compared extensively augmented communication strategies from the co-ordinating trial center (85 sites) compared with usual strategies (82 sites). The augmented effort did not increase the median number of patients randomized by center during follow up (38 patients [augmented group] vs. 37 patients [comparator group]; *P* = 0.68) (32).

Discussion

This review identified highly relevant lessons for palliative care researchers from trials conducted by other disciplines providing care for patients with advanced disease. These lessons

address specific clinical considerations relating to potential patient involvement as well as the approaches being tested to improve participation and retention. The following discussion relates the findings to particular issues faced in palliative care studies.

Potential Participants with Reduced Cognitive Ability

Although, ethical procedures are agreed in most countries for proxy consent or consultee assent, strategies, such as a memory aid, which improve the opportunity for patients to provide their own consent are to be welcomed (19). However, formal assessment of mental capacity prior to consent reduced the patient-provided consent rate, and introduced selection bias (28).

Delirium is common in palliative care patients. Prevalence estimates range from 13-42% on admission to a palliative care unit, increasing to 88% in the days before death (34). The consenting process can be burdensome, and required when mental capacity is reduced, or fluctuating, in a context of distress for the patient and family and increased gatekeeping among clinical staff and ethics committees (14, 35-38). Symptom management interventions for dying patients commonly have low level evidence partly because of challenges of consenting dying patients to clinical trials (5, 39). The ethical challenges of recruiting palliative care patients to clinical trials of delirium have been summarized well in a recent discussion paper (25), which highlighted the importance of memory and other aids to facilitate capacity (such as that used by Rubright et al.) (19, 40). Research into delirium in palliative care is an example of progress made despite the enormous challenges, and where study design and conduct has benefited from collaboration between palliative care and other disciplines (34, 41).

The use of advance consent has been discussed, particularly in the field of dementia (42). However, in this review, the use of an advance research directive did not improve recruitment (27). This approach is possible in palliative care, as seen in an observational feasibility cohort

study of patients admitted for terminal care. Although half of those approached (*N*=107) provided advance consent (*n*=58), only 15 were randomized during eight months of follow up (43).

Potential Participants Who Require Emergency Treatment

Contact prior to arrival at the trial site increased consent rate to a stroke trial (29). Deferred consent is an accepted way of entering patients who cannot provide consent into emergency treatment trials (14, 44). Palliative care patients have fluctuating mental capacity and the challenge of requiring emergency management. However, the palliative care participant may *not* be expected to recover, and the issue then of whether their data can be used is unclear. Even where the patient has capacity, or a proxy is present, the urgent nature of the situation can make the recruiting process difficult. Therefore, contact prior to arrival at the trial site may be useful in palliative care trials. For example, as the use of telehealth increases in long-term conditions, this may help identify eligible trial participants who present as an emergency, and has been successfully used in another stroke study (45).

Cluster consent designs, more commonly used in complex intervention trials, also may be useful in situations where clinical staff gatekeeping is a significant barrier even with simple interventions (25). Recruitment is also challenging where, despite genuine uncertainty and thus ethical equipoise, there is a wish (patient or clinician) to receive the study intervention. Study designs such as crossover trials are useful in this situation (46), but are not always possible. Other designs, e.g., "wait-list" design RCTs, have been used in the palliative care setting (47), to allow all participants to receive the study intervention, but have not been tested as a recruiting strategy.

Strategies to Improve Trial Information and Research Willingness

Potential Particiants. The studies in this review that aimed to increase potential recruits' willingness did not show accrual rate benefit despite the "face validity" of the interventions. Given the effort and logistics required to use these interventions in practice, it is important to know they were ineffective when subjected to formal testing.

Efficient study-specific "advertising" strategies, therefore, should be developed and take into account knowledge of "patient flow" through the service at any recruiting site. For example, a study recruiting women with ischemic heart disease to a rehabilitation trial found that, despite a wide variety of invitation strategies, the majority (73%) were recruited via routine referral for cardiac rehabilitation (48). In another study of exercise in breast cancer survivors, potential participants were identified through a cancer registry and local media advertisements (49). Many responded through the cancer registry, but were less likely to consent compared with those who responded to advertisements.

"Opt out" consent options increased recruitment in this review (30, 31). Although this method also has been noted to be effective in a Cochrane review of recruitment strategies tested in a broad range of studies, specific limitations need to be taken into account (50).

Potential Recruiting Sites. Educational and other initiatives, again with face validity, to support recruiting site clinical staff were not effective in increasing site recruitment when formally tested.

Gatekeeping may be by individuals, committees, or by institutions. Services may be organized leaving no space or time for patients to be approached, resulting in a culture whereby research is thought of as a burden, or not at all (7). In a palliative care prognostication study, gatekeeping by clinical staff accounted for 24% of inaccessibility (51). Thus, raising a trial's profile and changing an institution's culture are necessary. Contacts with the clinicians most

likely to refer eligible patients are often achieved through personal relationships (52). The importance of study-specific researchers is highlighted in a U.K. primary care study, where accrual was improved by study researchers being in direct contact with general practices, rather than depending on generic research network staff intervening between researchers and general practitioners (53).

Limitations

There are no unique search terms to identify palliative care studies, or those involving people with advanced disease. Therefore, it is likely that useful papers will have been overlooked. We have not entered into the debate about the definition of the "palliative care patient," which we feel is beyond the scope of this paper.

However, the aim of the review was to seek studies of recruitment strategies in populations that, although not explicitly stated to be "palliative," would be informative to researchers in this field, rather than to gain exhaustive inclusion in order to complete an accurate meta-analysis of efficacy. Many of the studies varied in their standard of reporting (18). Although some study interventions would have been difficult or impossible to blind, two of the cluster RCTs only had a Jadad score of 1/5 as the method of randomization, withdrawals and dropouts was not described (20, 26).

Implications for Future Research Practice

These studies highlight options that could be considered and tested. Of particular note, many of these studies used well-defined strategies with good face validity but did not achieve the desired outcomes. Further research on recruitment would ensure that the work of researchers and the contributions of patients, their carers, and families are used to best effect.

Conclusions

Palliative care trials do not have the monopoly on "difficult to recruit" participants and neither is clinician gatekeeping exclusively a problem in palliative care settings. Accrual to clinical trials is always challenging but clinical trials are crucially important to develop evidence-based management for our patient group, so we can stop "experimenting on our patients" and "settling for low level evidence" (5, 6). There are good examples where well-designed palliative care trials that include explicit and flexible recruitment strategies are completing **AU: COMPLETING?** to answer important clinical questions to inform daily practice (8, 12, 13). Palliative care researchers can learn from colleagues in different disciplines about how to overcome challenges of gatekeeping and consent in populations with reduced capacity requiring emergency treatment. Tailored and efficient evidence-based strategies to optimize recruitment must be developed for each study, learning the lesson that techniques that appeared to be appropriate and useful were not necessarily the most effective.

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Table 1. Strategies Used in Successful Palliative Care Clinical Trials

- realistic recruitment timescales
- close monitoring of recruitment with regular adjustment of strategy as necessary
- adequate dedicated research staff
- multi-center
- adequate trial unit infrastructure support
- careful attention to the consenting process, study design, study duration and study assessment burden

Table 2. Search Strategy

Limits:

Date: 2002-2012 (#1 to #17);
Language: English – all searches
Study design: randomized or controlled clinical trials; therapy – all databases except Cochrane
Methodological studies - Cochrane database search only
Humans; adults – all searches

Terms were mapped to MeSH headings and text word searches used the terms:
‘‘Recruit*,’’ OR ‘‘Recruitment strategy,’’ OR ‘‘ethics research,’’ OR ‘‘Experimental ethics,’’ OR ‘‘informed consent,’’ OR ‘‘methodology,’’ OR ‘‘experimental subjects’’ “end stage”, OR ”advanced disease”, AND “lung”, OR “pulmonary”, OR “renal”, OR “heart”, OR “cardiac” OR “oncology” OR “cancer”

Searches:
#1 exp Patient, selection/
#2 exp Ethics, Research/
#3 exp Research subjects/
#4 exp Patient recruitment/
#5 #1 or #2 or #3 or #4
#6 remove duplicates from#5
#7 exp Lung/
#8 exp Kidney/
#9 exp Heart/
#10 exp Liver/
#11 exp Neoplasm/
#12 exp Dementia/
#13 exp Delirium
#14 exp Stroke/
#15 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#16 remove duplicates from#15
#17 #6 and #16

Table 3. Study Inclusion/Exclusion Criteria

Inclusion:

- Population: adults with chronic organ failure (including cognitive), cancer
- Design: Clinical studies – RCTs, quasi-experimental
- Intervention: any recruitment strategy,
- Language limits: English

Exclusion:

- Population: studies that only included people requiring proxy consent; children; general population (e.g., public health initiatives)
- Design: systematic literature review, observational studies, qualitative pieces, opinion pieces, case histories

Table 4. Randomized Controlled Trials Evaluating Recruitment Strategies in Populations with Organ Failure or Cancer

Thematic Grouping		**Study** (Jadad score, RCTs)	**Target Population**	**Intervention and Comparator**	**Significantly Increased Recruitment**
PARTICIPANT – RELATED STUDIES	***Participants with decreased cognition***	**Rubright 2010** (3)	Alzheimer's dementia	I: Memory / organizational aid C: Usual consent process	Yes
		Stocking 2007 (2)		I: Research advance directive C: Usual consent process	No
		Adamis 2005 (3)	Unwell inpatients >70yrs	I: Formal assessment of mental capacity C: Usual consent process	No[a]
		Fowell 2006 (2)	Dying people eligible for anti-emetic studies	# I: Cluster consent B C: Zelen consent+ C	Yes (cluster consent)
	Improving trial information for individual participants	**Coyne 2003** (1)	Cancer treatment trial population	I: Easy-to-read consent C: Usual consent process	No
		Hutchison 2007 (3)		I: Audio-visual information about clinical trials C: Usual consent process	No** C

		Junghans 2005 (5)	People with angina	# I: Opt-in C: Opt-out	Yes^^ D
		Du 2008 (3)	People with lung cancer	I: Clinical trial video C: Usual consent process	No
		Du 2009 (2)	People with breast cancer		No
		Hunt 2013	Bereaved relatives ##	# I: Opt-in C: Opt-out	Yes^^ D
		Pighills 2009	People at risk of falls >70yo ##	I: Newspaper article C: Usual consent process	No
	Potential participants requiring emergency treatment	**Leira 2009** (3)	People having had a stroke awaiting medi-evac to a major center	# I: Study information and contact with researcher while awaiting transfer C: Contact on arrival at tertiary treatment center	Yes
SITE-RELATED STUDIES	***Improving trial information for trial sites***	**Kimmick 2005** (1)	CALGB^ sites	I: Addition of educational seminar C: Usual web access and periodic reminders	No

		Lienard 2006 (2)	Sites recruiting to a chemotherapy study	I: Face-to-face visits for site initiation C: No visits	No
		Monaghan 2007 (2)	Sites recruiting to diabetes and vascular disease interventions	I: Tailored feedback to sites about recruitment performance C: Usual process	No

[a] Significantly *reduced* entry to appropriate clinical trials as a result.

** When adjusted for cancer stage and ethnicity, there was significantly increased recruitment

B# Evaluated a control group unless noted

Quasi-experimental design

^ Cancer and Leukaemia Group B

^^ Opt-out favoured over opt-in

C+ Zelen consent – participant consent after randomisation

Table 5. Full-Text Articles Excluded, with Reasons

Article	Reason for Exclusion
Abbott 2005 (54)	Not assessing a recruitment methodology
Abboud 2006 (55)	Hypothetical trial
Avenell 2004 (56)	Wrong patient group
Beckie 2009 (48)	Wrong trial design
Bentley 2004 (57)	Hypothetical trial
Brandt 2006 (58)	Not assessing a recruitment methodology
Chang 2004 (59)	Not assessing a recruitment methodology
Chen 2005 (60)	Not assessing a recruitment methodology
Couper 2008 (61)	Not assessing a recruitment methodology
68De Boer 2011 (62)	Wrong trial design
Diguiseppi 2006 (63)	Hypothetical trial
Edland 2010 (64)	Not assessing a recruitment methodology
Ellis 2002 (65)	Hypothetical trial

Ferris 2006, (66)	Not assessing a recruitment methodology
Flaherty 2008 (67)	Wrong trial design
Ford 2004 (68)	Wrong patient group
Freer 2009 (69)	Wrong patient group
Gallagher-Thompson 2004 (70)	Wrong trial design
Graham 2007 (71)	Wrong patient group
Halpern 2004 (72)	Hypothetical trial
Hanratty 2012 (53)	Wrong patient group
Harris 2008 (73)	Wrong patient group
Hemminki E 2004 (74)	Wrong patient group
Howard 2006 (75)	Wrong trial design
Irwin 2008 (49)	Not assessing a recruitment methodology
Jeste 2009 (76)	Hypothetical trial
Kaas 2005 (77)	Wrong trial design
karlawish 2008 (78)	Not assessing a recruitment methodology
karunaratne 2010 (79)	Hypothetical trial

Kennedy 2011 (80)	Wrong patient group
Kerr 2004 (81)	Hypothetical trial
Kye 2009 (82)	Wrong trial design
Larkey 2002 (83)	Wrong patient group
Leathem 2009 (84)	Not assessing a recruitment methodology
Mangset 2008 (85)	Not assessing a recruitment methodology
Melchart 2002 (86)	Not assessing a recruitment methodology
Mount 2012 (87)	Not assessing a recruitment methodology
Nystuen 2004 (88)	Wrong patient group
Pearl 2003 (89)	Not assessing a recruitment methodology
Rees 2003 (43)	Wrong trial design
Sano 2010 (90)	Not assessing a recruitment methodology
Serfaty 2012 (91)	Not assessing a recruitment methodology
Sisk 2008 (92)	Not assessing a recruitment methodology
Stone 2013 (51)	Wrong trial design
Switzer 2010 (45)	Wrong trial design

Treschan 2003 (93)	Wrong patient group
Trevena 2006 (94)	Wrong patient group
Tworoger 2002 (95)	Wrong patient group
Warner 2008 (96)	Wrong trial design
Webb 2009 (97)	Wrong patient group
Weinfurt 2008 (98)	Hypothetical study
Whitehouse 2006 (99)	Wrong patient group
Williams 2005 (100)	Not assessing a recruitment methodology

Appendix

Study Design/Conduct Aspects Addressed by Recruitment Strategies

Data Extraction Form

Article details:

What was the research question?

hypothesis

P) Description of patient population in study

Study population:

Number of subjects:

Age range:

Gender:

PS description:

Method of recruitment:

Other _____

I) What is the intervention? _____

C) Comparator: _____

O) Outcome

Primary

Secondary

Was it effective? Yes/no

Measure of effectiveness (e.g., in results or said what they measured – total recruitment, finished study on time):

Study design

RCT

Quasi experimental study

Observation Cohort (stat what retro/prospective/Before and after study)

Substudy of an RCT

Post hoc opinion (we did this and thought this helped)

Other ……

Table 4A. Included trials (ONLINE ONLY)

Strategies to Address the Challenge of Potential Participants with Reduced Cognitive Ability				
Study, Design and Quality of Evidence (Jadad score for RCTs)	**Patient Population**	**Intervention and Comparator**	**Outcome**	**Effect on recruitment**
Rubright 2010 (19) RCT **Jadad 3**	Group 1: people with AD N=40; MMSE 18–27 Age: mean (range): 74 (45 to 92) Gender: 43% Female Group 2: people with AD N=40; MMSE 18–27 Age: 77 (59–89)	Intervention (group 1): Standard consent plus a memory and organizational aid Comparator 1 (group 2): standard consent Comparator 2 (group 3): standard consent	Primary outcome: AD participants assessed as competent to provide their own consent Secondary outcome : effect on decision making abilities	Increased number of consented participants assessed as competent and able to provide their own consent Group 1: n=19 Group 2: n=7 P= 0.004

	Gender: 58% Female Group 3: Cognitively normal older adults N= 30; MMSE 28–30 Age, mean (SD): 78 (60–89) Gender: 57% Female			
Adamis 2005 (28) RCT **Jadad 3**	Unwell hospital medical inpatients over 70 years within 3 days of an acute admission N=130 Age, mean (SD): 84 (SD 6.5) Gender: 56% female	Intervention: Two step procedure. Formal assessment of mental capacity *prior* to informed consent procedure Comparator: Single step procedure. Usual practice (informal assessment of mental	Primary outcome: Consented patients Secondary outcome: representativeness of sample	Primary outcome Recruitment: Intervention: 44% Comparator: 74% Secondary outcome: Assessed as having capacity Intervention: 60%

		capacity during informed consent procedure)		Comparator: 86% P=0.001 Participants discharged to a nursing home: Intervention: 5% Comparator: 28.6% P=0.03 Lower severity of delirium in intervention group
Stocking 2007 (27) RCT **Jadad 2**	Patients with AD and their family proxies N=149 MMSE 2-29. Age, median (range): 78.6 (52 to 94) Gender: 62% Female	Intervention: Planning Ahead Together (PAT) document (research advance directive) Comparator: usual practice	Recruitment into research projects over 2 years Ease of decision of enrolment	41 patients invited to participate in a study (23 PAT, 18 no PAT) 27 consented No difference between groups for either outcome (patients or proxies; PAT or no PAT)

Fowell 2006 (25) Feasibility Cluster vs patient consent crossover RCT **Jadad 2**	Eligible cancer patients admitted to 1 oncology ward and 1 palliative care unit in the context of a trial of anti-emetics in dying patients Group 1: patients dying during the cluster design phases N = 24 Gender: 58% male Group 2: patients dying during the Zelen consent phase N = 29	Group 1: cluster consent * Group 2: Zelen** consent * - cluster guardian and cluster gatekeeper obtained consent from eligible patient ** patient consent after randomisation to trial intervention	i) Patients consenting ii) Patients randomised	i) Patients consenting group 1: 13 group 2: 2 ii) Patients randomised group 1; 6 group 2: 0

	Gender: 59% male			
Strategies to Address the Challenge of Potential Participants Requiring Emergency Treatment				
Study/ Design	**Patient Population**	**Intervention and Comparator**	**Outcome**	**Effect on recruitment**
Leira 2009 (29) RCT **Jadad 3**	Consecutive patients/or surrogates presenting with stroke to a community hospital ED awaiting helicopter transfer to tertiary centre. N= 100 Age, mean (SD): 63.9 (13.3) Gender: 56% male	Intervention: 1) faxed study information to patient/surrogate whilst awaiting helicopter arrival 2) telephone call from the co-investigator to the patient/surrogate from the helicopter whilst en-route. Comparator: patient/surrogate approached with study	Consent rate in group receiving pre-arrival fax and telephone call	Intention to treat; Consent rate: Intervention group: 54% control group: 50% p=0.69 Per-protocol analysis (When faxed information *and* telephone call were both successfully achieved)

		information on arrival at the tertiary hospital		Consent rate 69% P=0.04
Strategies to Improve Trial Information and Research Willingness to 1) Potential Participant				
Study/ Design	**Patient Population**	**Intervention and Comparator**	**Outcome**	**Effect on recruitment**
Coyne 2003 (20) Cluster RCT of 44 institutions across 3 oncology collaboratives **Jadad 1**	Cancer patients eligible to participate in cancer treatment trials Group 1) standard consent N =137 Age (mean): 53 Gender: male 9.3% Group 2) easy to read consent N =89	Group 1: standard consent information Group 2: easy to read consent information	Accrual rates Participant anxiety and satisfaction re consent information	Decision to participate (actual accrual) Group 1: 89%; (68%) Group 2: 82%; (75%) P = 0.21; (P = 0.32) Consent anxiety Group 1: 2.1 Group 2: 1.8 P = 0.016 Consent satisfaction Group 1: 3.3

	Age (mean): 53 Gender: male 7.3%			Group 2: 3.6 P = 0.004
Junghans 2005 (31) RCT **Jadad 5**	Patients in primary care with angina N= 510 Group 1: N = 252 Group 2: N = 258	Group 1: opt in approach to recruitment into an observational trial Group 2: opt out approach to recruitment into an observational trial	Recruitment rate Patient characteristics	Group 1: 38% (96/252) Group 2: 50% (128/258) P = 0.014 Participants in group 1 had fewer risk factors (P = 0.053), less treatment for angina (P = 0.01) and less functional impairment (P = 0.023) than group 2
Du 2008 (22) RCT	Lung cancer patients Group1) N = 63	Group 1: view 18 minute video about clinical trials before first oncology clinic visit	Enrolment rates for i) therapeutic trials; ii) therapeutic and non-	Enrolment i) therapeutic trials group 1:17.5%

Jadad 3	Age (mean) = 58.2 Gender = 49% male Group 2) N = 63 Age (mean) = 58.7 Gender = 52% male	Group 2: usual care	therapeutics trials	group 2: 11.1% P = 0.3 ii) non-therapeutic and therapeutic trials group 1: 24.5% group 2: 15.9% P = 0.19
Du 2009 (23) RCT **Jadad 2**	Breast cancer patients N = 196 Ethnicity: 55% white; 45% African American Gender: 0% male	Group 1: view 18 minute video about clinical trials before first oncology clinic visit Group 2: usual care Stratified by race: White or African American women	Enrolment rates for i) therapeutic trials; ii) effect of race Attitude (likelihood of entering trial if offered)	Enrolment i) therapeutic trials group 1:10.4% *vs* group 2: 6.1% P = 0.3 ii) effect of race white 11.2% *vs* black 4.5% P = 0.087 when adjusted for stage of disease P = 0.049 Attitude – "extremely likely

				to enrol” white 23% vs black 12% P = 0.05 no “improvement” in AA attitude in follow up in seen video vs those who had not
Pighills 2009 (33) Two quasi-controlled trials	Potential participants for a falls prevention study in primary care (age >70) Study 1. N = 4488 Study 2. N = 2745	Study 1. Group 1: newspaper article about the study + participant information Group 2: participant information only Study 2. Group 1: favourable newspaper article about the study + participant information	Recruitment rate	Percentage enrolled Study 1. Group 1: 3.25% Group 2: 3.16% NS Study 2. Group 1: 4.15% Group 2: 3.94% NS

		Group 2: participant information only		
Hutchison 2007 (21) RCT **Jadad 3**	Cancer patients eligible for entry into a cancer therapeutic trial Group 1: N = 86 Gender: 23.3% male Group 2: N = 87 Gender:23 % male	Group 1: audiovisual patient information + standard trial specific information Group 2: standard trial specific information	Recruitment rate	Recruitment rate Group 1:72.1% Group 2: 75.9% OR 1.19 (95% CIs 0.55 – 2.58) p = 0.661

Hunt 2013 (30) Quasi-experimental (alternate numbers allocated to different groups)	Bereaved relatives contacted to take part in a survey N = 1422	Group 1: opt in – had to send to get survey in response to invitation Group 2: opt out – survey included in invitation letter	Response rate to survey Distress caused by survey	Response Overall response; 473/1422 (33%) Group 1: 188/ 711 (26.4%) Group 2: 285/711 (40%) P < 0.01 No difference in distress
Strategies to Improve Trial Information and Research Willingness to 2) Potential Recruiting Sites				
Study/ Design	**Patient Population**	**Intervention and Comparator**	**Outcome**	**Effect on recruitment**
Kimmick 2005 (26) Cluster RCT **Jadad 1**	Member institutions of the Cancer and Leukaemia group B Group 1: institutions	Group 1: standard = website access and periodic notification of trials Group 2: standard +	Proportion of older (>65) cancer patient accrual to trials at baseline, 1 year and 2	Baseline proportion of >65 recruited: Group 1: 36% Group 2: 40% P = 0.4

	receive standard information about trials N = 72 institutions Group 2: institutions receive standard plus educational intervention N = 53 institutions	educational seminar and materials + list of protocols + monthly reminders + case discussion seminar	year	One year Group 1: 32% Group 2: 36% P = 0.35 Two year Group 1: 31% Group 2: 31% P = 0.83
Lienard 2006 (24) Cluster RCT **Jadad 2**	Sites recruiting to an RCT comparing two types of chemotherapy for cancer Group 1: 68 sites Group 2: 67 sites	Group 1: systematic face to face site visits for study initiation Group 2: not visited	Recruitment rate per site	Number of patients recruited Group 1: Total 302 patients - Poor recruiting sites 11 - Average recruiting sites 48 - Good recruiting sites 36 - Excellent recruiting sites 207

				Group 2: Total 271 patients - Poor 11 - Average 42 - Good 70 - Excellent 148
Monaghan 2007 (32) Cluster RCT **Jadad 2**	Clinical centres recruiting to an RCT for diabetes and vascular disease intervention Group 1: N = 85 Group 2: N = 82	Group 1: additional communication strategies from trial co-ordinating unit (individual tailored feedback about recruitment rate using email, updates, certificates) Group 2: usual communication strategies (occasional generic newsletters, emails and faxes)	Recruitment rate per centre	Median number of patients randomised by centre Group 1: 37.5 patients Group 2: 37 patients P = 0.68

Figure Legend

Fig. 1. PRISMA flow diagram.

Figure 1: PRISMA Flow Diagram