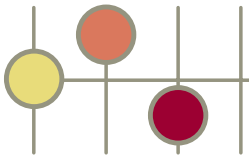

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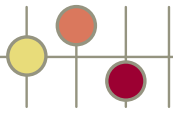
Systematic Review of Interventions to Increase Participation of Cancer Patients in Randomised Controlled Trials



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REPORT 32

Systematic review of interventions to increase participation of cancer patients in randomised controlled trials

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GLOSSARY

Attrition bias: Systematic differences between comparison groups in the withdrawal or exclusion of participants from the study sample. Inclusion of all participants in the analysis (intention to treat analysis) protects against this bias. [1]

Contamination: The control group receives an aspect of the experimental intervention; for example, through the same clinician delivering the experimental intervention and comparison or through contact between participants in the two groups.

Clinical equipoise: Lack of consensus within the expert clinical community about the comparative merits of the alternative treatments.[2] A related term that is used is the uncertainty principle. They are both based on the principle that when one of the alternative treatments being considered can be determined with reasonable confidence to be better, it is unethical to conduct a trial.[3]

Performance bias: Systematic differences in the care provided apart from the intervention being evaluated. Standardisation of the intervention protocol and blinding of clinicians and participants protects against this bias. [1]

Selection bias: Systematic differences between comparison groups that may lead to different responses to the intervention. Randomisation of participants, with concealment of their group allocation protects against this bias.

EXECUTIVE SUMMARY

Background

There are many barriers to patient participation in randomised controlled trials (RCTs) of cancer treatments. To increase participation in trials, strategies need to be identified to overcome these barriers. The National Cancer Research Network (NCRN) commissioned a systematic review of the evidence-base for interventions to increase cancer patient participation in trials.

Aim

To evaluate the effectiveness of interventions to overcome barriers to participation in RCTs of cancer treatments.

Methods

Fifteen electronic databases including MEDLINE, EMBASE, PsycINFO, and System for Information and Grey Literature in Europe, and Science and Social Science Citation Index were searched from inception to January 2005 for published and unpublished studies in any language. Bibliographies of potentially relevant articles were searched. Two reviewers independently assessed titles and abstracts and also full papers where these were obtained.

Studies of any interventions to improve cancer patient participation in RCTs, which reported participation rates, were eligible for inclusion. RCTs and non-RCTs as well as before and after studies reporting baseline rates specific to the population being investigated were included.

Data were extracted by one reviewer into structured summary tables and checked for accuracy by a second reviewer. Each included study was assessed against a checklist for methodological quality by one reviewer and checked by a second reviewer.

A narrative synthesis was conducted. Studies were grouped according to relevance to the UK setting and within this by study design.

Results

Eight studies were identified that met the inclusion criteria: three RCTs, two non-RCTs and three observational studies. Six of the studies had an intervention that had some relevance to the UK. The majority of studies were concerned with some aspect of the consent process. There was no evidence that any of the interventions investigated led to an increase in cancer patient participation in RCTs, though one good quality RCT found that urologists and nurses were equally effective at recruiting participants to a treatment trial for prostate cancer. Although there was no evidence of an effect in any of the studies, the evidence was not of sufficient quality to be able to conclude that these interventions therefore do not work. Overall, the studies had a range of methodological weaknesses. In particular, in most of the studies there was a risk of contamination between the experimental and comparison intervention leading to a possible dilution of the effect of the experimental intervention.

Conclusions

There is not a strong evidence-base for interventions that increase cancer patient participation in randomised trials. Further research is required to evaluate the effectiveness of strategies to increase participation in cancer treatment trials.

1. INTRODUCTION

1.1 Aim of the project

This systematic review is the second part of a three-part project which considers how participation rates in cancer clinical trials might be improved. The first part of the project was a systematic review of the literature relating to the barriers to participation in cancer clinical trials as perceived by patients and clinicians.[4]

The purpose of the second part of this project is to investigate the evidence-base for interventions to overcome barriers to participation in cancer clinical trials. Specifically, the aim is to undertake a systematic review to assess the effectiveness of interventions to improve patient participation in cancer trials.

If effective interventions are identified in this second part of the project, the intention for the third part is to assess whether such interventions could be implemented on a large scale with the wider public.

1.2 Background

Extent of participation in cancer clinical trials

Over the past five years the issue of patient involvement in cancer clinical trials has been an important focus within the field of cancer research. Although not a new concern, an important impetus has been the target set in 2000 in the NHS Plan of doubling the total proportion of cancer patients entering trials within three years.[5, 6] The National Cancer Research Network (NCRN) was established in 2001 by the Department of Health to assist meeting this target through the provision of an infrastructure to support cancer trials in England. The initial target of the NHS Plan was met by 2004, with an estimated 10.9% of all incident cancer cases being involved in cancer trials.[7] However, this remains a small proportion of all cancer patients. Similarly there has been evidence of recent increased participation in the United States, but overall participation rates are low.[8]

A recent analysis of 333 RCTs conducted in the UK between 1971 and 2000 found that recruitment levels varied between trials.[9] Just over one half did not reach the planned sample size, with one fifth recruiting at least 75% of the planned sample and one fifth recruiting less than 25% of the planned number of patients. This is despite the evidence that was found of an increasing trend in the number of patients participating in cancer trials over the thirty years.[9] There was also a trend towards larger, multicentre trials, larger recruitment targets and completion of trials within a shorter timescale. No data were reported on whether recruitment success varied by type of cancer. The authors caution that the trials are representative only of UK trials funded from public and charity funds. There is also the possibility that recruitment levels were over-estimated by missing smaller, more poorly resourced single-centre trials. There is some evidence that recruitment of children with cancer into trials is less problematic.[10]

Barriers to participation

The identification of barriers to participation in clinical trials, regardless of type of disease, has been the subject of a high level of research interest as evidenced by the volume of studies identified by systematic reviews. The most recent systematic review on barriers to patient and health professional participation in RCTs reviewed studies related to cancer, published between 1996 and 2004 and identified 56 relevant studies for this period alone.[4] This updated an earlier review of studies published between 1986 and 1996.[11] Clinicians' and patients' attitudes towards clinical research and the influence of these attitudes on accrual to clinical trials has also been investigated in a systematic review, covering the period 1982 to 1997.[12] These reviews are predated by earlier reviews of the literature on recruitment to

clinical trials, though systematic review methods were not used.[13, 14] Unlike previous reviews, which included all patient groups, the most recent systematic review conducted in the first part of the current project, focused specifically on cancer patients and barriers to their participation in trials.[4] Additionally, the quality of the literature was assessed, unlike most of the previous reviews.

The aim of the current review was to assess interventions aimed at overcoming any barriers to participation of cancer patients in RCTs. The original intention had been to use the most recent systematic review of barriers to participation to prioritise the interventions of interest in this second review. However, as outlined below, on the basis of the evidence available it was not possible to do so.

The key finding of the review of barriers to cancer trial participation was that many of the studies investigating barriers to participation in cancer trials were of poor quality with poor reporting as an additional problem.[4] A major concern was that the predictors of trial participation could be partially an artefact of what has been studied, and how the data have been collected or analysed. As a result it was not possible to make strong conclusions about the relative importance of various potential barriers on trial participation or the situations in which they might arise or how these might interact. Issues identified from the patient perspective included having a preference for a specific treatment arm; uncertainty and concern about the physician not knowing which treatment was best; level of knowledge about trials, although it was unclear what constituted sufficient information; being approached to participate in a trial when feeling vulnerable, perhaps shortly after diagnosis; practical issues such as the time commitment of being involved in a trial, distance from the clinic and transportation costs. Sociodemographic factors such as age and gender were found to be modifiers of trial participation in some studies, though not in a consistent direction.

Several issues were also identified from the physician perspective. These included practical barriers, such as the time commitment required for involvement in trials; poor organisational infrastructure; trials competing for the same patients; identifying eligible patients; lack of awareness of ongoing trials; preference for a particular treatment arm; and their own personal interests. The main conclusion of the review was that different barriers appear to act together in a unique way in individual trials. Therefore, potential barriers need to be considered in the context of individual trials, with those responsible for the conduct of trials prospectively identifying potential barriers to participation (in a particular trial) at the planning stage.

Moving beyond the attitudes and experiences of patients and health professionals, there are barriers at the macro level. In an analysis of patient recruitment to cancer trials within a single cancer research network, the main reasons for cancer patients not entering a trial were lack of an available trial and failure to meet the entry criteria of relevant trials.[15] An analysis of the characteristics of participants in National Cancer Institute sponsored trials in the US from 1996 to 2002 found that racial and ethnic minorities were underrepresented, as were women and elderly people.[8] There is some evidence across trials for different diseases conducted in the US that those with an invasive treatment arm enrolled fewer minority participants than those with a non-invasive arm.[16] However, this may be culturally specific. Similar population-level data is not available for the UK though underrepresentation of ethnic groups in trials in general has been highlighted as an important issue.[17] A recent investigation of barriers to involving South Asian patients in the UK in clinical trials made a number of recommendations for strategies to increase involvement.[18] These included use of multiple recruitment strategies for individual trials, training of staff and use of focus groups to identify potential barriers.

Interventions to improve participation

To improve participation in cancer trials, strategies need to be identified that are effective at overcoming the barriers to participation that have been identified. Some relevant systematic reviews have been conducted to address this question. Mapstone et al. investigated strategies to improve recruitment to randomised or quasi-randomised studies.[19] The review was not specifically concerned with participation in cancer trials. Both mock and real scenarios as well as healthy and patient groups were included. Fifteen eligible studies were identified, though the authors highlighted the possibility of missed studies. Additionally, the

only aspect of study quality assessed was allocation concealment. The interventions investigated to improve participation were varied. The effect of pre-warning, providing additional information, changing study design, changing the consent method and use of monetary incentives were evaluated. Most of the interventions did not lead to an increase in participation. Based on the evidence available it was concluded that it was not possible to predict the effect on recruitment of most of the interventions considered. Strategies that demonstrated some benefit were monetary incentives, an additional questionnaire at invitation and treatment information on the consent form; however, the specific studies are not easily generalisable.

Another review, which again included studies of hypothetical or simulated scenarios, investigated interventions to improve research participants' understanding during the informed consent process.[20] A range of different patient groups was included. The primary outcome of interest was improved understanding. Twelve of the 42 included studies also measured actual accrual or willingness to join a trial. There was an improvement in willingness to join an RCT in only three of these twelve studies. However, these all used simulated scenarios. Their applicability to a real situation is unclear. The authors recommended that future studies avoid using hypothetical scenarios.

Focus of the current review

The specific focus of the current review is cancer treatment trials. Improving participation of individuals without cancer to cancer prevention trials and cancer screening trials is also an important issue.[21] There is likely to be some overlap with treatment trials in terms of barriers to participation. However, many of the issues that an apparently healthy individual needs to weigh up before deciding to participate in a prevention or screening trial would seem to be inherently different from those that need to be considered by an individual with cancer, faced with the option of entering a treatment trial. Additionally, the context in which the decision is made is different, for example differences in individuals' current health state and potentially their level of distress. Related to this, from the perspective of the health professional carrying out the recruitment, the issues are likely to be different.

The current review was also focused specifically on randomised trials rather than non-RCTs or cancer studies with only one treatment arm and therefore no randomisation to treatment. These are phase I and generally phase II studies.[22] There is likely to be some overlap in barriers to participation between different study designs, but, the decision faced by the patient and the context in which it is made are quite different for phase III randomised trials. Potential participants in phase I and II trials are generally at an advanced disease stage with limited, if any, treatment options. In phase I trials there is the potential of high risk of toxicity and low benefit from the treatment, though the situation in relation to toxicity may be improving.[23] Additionally, there is evidence that being faced with the possibility of being randomised to a treatment arm as opposed to treatment choice on the basis of patient or clinician preference raises particular concerns for patients, and indeed sometimes clinicians.[4]

Interventions where participation was in relation to a hypothetical trial were not of interest. It has been argued that views expressed in relation to hypothetical trials and scenarios are unlikely to alter greatly when the individual is in a real situation.[24] While studies using a hypothetical scenario may be useful in generating ideas as to what might be effective in a real scenario, any interventions found to be effective in increasing willingness to participate in a hypothetical trial would require subsequent testing in a real scenario. Therefore, the decision was made in the current review to focus exclusively on interventions directed at real trials. Based on a similar rationale, the primary outcome of interest was patient participation. Patient knowledge and understanding[20] or the quality of clinician communication with patients about RCTs[25] are important outcomes in their own right. However, improvement in these outcomes does not necessarily translate into increased patient participation in cancer trials.[26]

We therefore conducted a systematic review of the available evidence on the effectiveness of any interventions to increase cancer patient participation in RCTs.

2. METHODS

2.1 Search strategy

Literature searches were run to identify interventions to increase participation in cancer clinical trials.

Many of the search terms used were similar to those used in Part 1 of this review, which aimed to review the barriers to and benefits of participation in clinical trials; however new terms were added to focus on ways of increasing trial participation and enrolment. The results were limited to only those references referring to cancer clinical trials.

The search strategies were run on a range of databases in order to identify references from the fields of medicine, nursing, psychology and the social sciences. The database SIGLE was also searched in order to identify grey literature, and the ASCO Proceedings website was searched for relevant conference proceedings. No limits by study design, language of publication or date of publication were applied.

The reference lists of all full papers obtained were also searched.

The following databases and resources were searched:
American Society of Clinical Oncology (ASCO) website
Cochrane Database of Systematic Reviews (CDSR)
Cochrane Database of Methodology Reviews (CDMR)
Database of Abstracts of Reviews of Effects (DARE)
Health Technology Assessment (HTA) Database
MEDLINE
EMBASE
CINAHL
Health Management Information Consortium (HMIC)
System for Information and Grey Literature in Europe (SIGLE)
PsycINFO
ISI Science Citation Index
ISI Social Science Citation Index
Sociological Abstracts
Applied Social Sciences Index and Abstracts (ASSIA)

The MEDLINE search strategy is described below. This strategy was translated as necessary for the other databases searched. Full search strategies are provided in Appendix A. All searches were conducted from the database date of inception to the most recent date available, which was January 2005 for most of the databases (see Appendix A for dates for specific databases).

1. exp NEOPLASMS/
2. (cancer$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$ or neoplas$).ti,ab.
3. 1 or 2
4. ((increas$ or improv$ or motivat$ or encourag$ or influenc$ or effect$ or affect$ or attract$ or endors$ or promot$ or facilitat$ or enhanc$ or challeng$ or refus$ or reluctan$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
5. ((difficult$ or problem$ or obstacle$ or barrier$ or deter or deters or deterrent or discourag$ or impediment$ or failure) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
6. ((perception$ or perceiv$ or attitude$ or decision$ or process$ or reason$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
7. ((willing$ or agree$ or consent$ or permission or assent or permit$ or decide$ or deciding) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered

or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
8. ((declin$ or unwilling$ or discourag$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
9. ((strateg$ or method$ or intervention$ or incentive$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
10. or/4-9
11. 3 and 10
12. exp *Clinical Trials/
13. clinical trial.pt.
14. 12 or 13
15. *Patient Participation/
16. *Patient Selection/
17. *Informed Consent/
18. *Research Subjects/
19. or/15-18
20. 3 and 14 and 19
21. 11 or 20

2.2 Inclusion criteria

Two reviewers independently assessed the titles and, where available, abstracts of all articles retrieved from the literature search. Full paper publications were obtained, where possible, for potentially relevant studies. Two reviewers independently assessed the eligibility of full paper publications according to the criteria outlined below. Disagreements were resolved by discussion or with reference to a third reviewer if necessary. We contacted authors for clarification when it was unclear whether the intervention was directed at randomised or non randomised clinical trials.

Interventions

Studies of strategies or methods to improve patient participation rates in cancer RCTs were eligible for inclusion. Interventions directed at increasing participation of patients without cancer in cancer screening trials were excluded. Studies using hypothetical scenarios rather than real trials were also excluded. Improvement of participation included increasing participation or making recruitment or involvement in any way easier or more efficient. Strategies of interest included those aimed at the patient directly, the health professional involved in patient recruitment or system/organisational barriers to participation in cancer clinical trials.

Participants

Any participants were eligible for inclusion provided the other inclusion criteria were met. It was anticipated that participants would be cancer patients, parents of children with cancer and/or health professionals involved in recruitment to cancer treatment trials. Studies of recruitment of the general population or ‘at risk’ populations to cancer prevention trials were not eligible for inclusion.

Outcomes

The primary outcome of interest was participation in cancer trials. The definition of trial participation used by individual papers was accepted. Only studies reporting participation rates of cancer patients to trials were eligible for inclusion. Secondary outcomes of interest were changes in knowledge and attitudes of patients or professionals.

Study design

Any evaluative study was eligible for inclusion. This included randomised and non randomised controlled trials in addition to before and after studies. Before and after studies were required to report baseline rates specific to the population being investigated (for example, studies investigating an intervention at a Trust-wide level were required to report the level of participation in that Trust before and after the intervention). Studies that assessed the effectiveness of an intervention by comparison with national average recruitment rates were excluded.

2.3 Data extraction strategy

Data on study details, intervention, participants and outcomes were extracted for each included study by one reviewer and checked for accuracy by a second. Disagreements were resolved by consensus, with reference to a third reviewer if necessary.

2.4 Quality assessment

Studies were quality assessed using criteria specific to the main study designs (Appendix B). Separate tools were developed to assess RCTs, other study designs with a control group and before and after studies with no control group, based on CRD Report 4.[1] Most of the criteria assessed were common to all the study designs. Reviewers assessed whether measures had been taken by the study authors to avoid or minimise selection bias, attrition bias, performance bias and whether the study design protected against contamination between the intervention and the comparison. Studies were also assessed as to whether the nature of the intervention was clear and whether the target of the intervention was clearly defined.

The quality of each individual study was assessed by one reviewer and checked by a second. Disagreements were resolved by consensus and with reference to a third reviewer if necessary.

2.5 Data synthesis

A mapping of the included studies identifying key characteristics of the included studies is presented, as well as an overview of the quality of evidence available. Individual studies are summarised in a structured table and as a narrative. Studies are grouped according to their relevance to the UK setting and then according to study design. Full data extraction tables and the quality assessment for each individual study are presented in Appendix D.

3. RESULTS

3.1 Study selection

4,936 references were identified by searching electronic databases. Following de-duplication and further retrieval of references via additional methods, 3,385 references were available for initial screening. Of these, 136 full papers were ordered for more detailed examination. Eight studies met the inclusion criteria for the review; these were described in nine publications. 127 papers were excluded from the review (see Appendix C for full list); the majority of studies were excluded because there was no relevant intervention. Three studies were excluded because participation in randomised and nonrandomised trials were considered together with no separate data available for patient participation in RCTs.[27-29] It was not possible to fully assess six of these publications for inclusion: one was not received[30] and for five papers it was unclear whether the intervention had been directed at an RCT.[31-35]

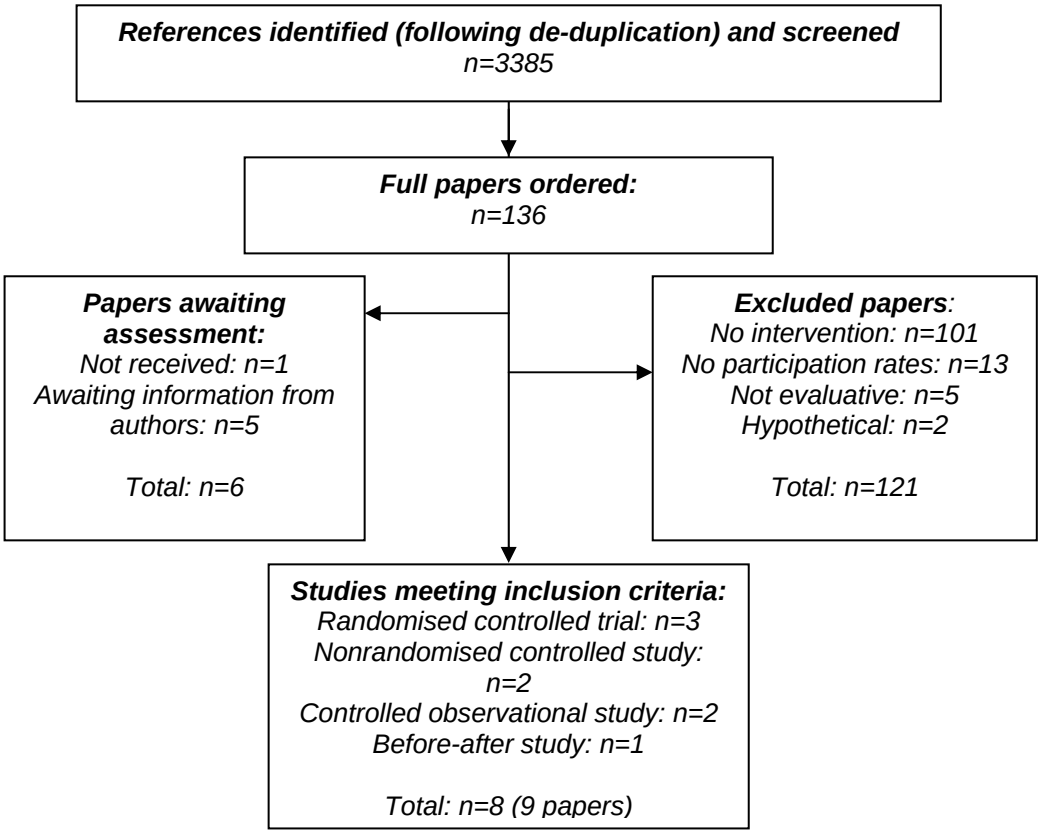

Figure 1: Process of study selection

3.2 Nature of the evidence

Included studies

Only eight studies were identified that met the inclusion criteria. This was a fairly diverse group of studies (see Table 1). There were three RCTs,[36-38] one of which was a cluster randomised trial.[38] There were two quasi-experimental studies in which the researchers had control over participant allocation, but allocation was not randomised[39, 40] and the remaining studies were of observational design,[41-43] two of which had a comparison group.[42, 43]

Of the three studies conducted in the United Kingdom,[37, 40, 41] only one was an RCT.[37] Two of the UK studies were concerned with participation in the same cancer treatment trial.[37, 41] The other studies were concerned with improving participation across more than one treatment

trial. In two of these studies, specific named trials were not targeted as the target was trials in general.[39, 42]

The interventions were directed at adult cancer patients, parents of children with cancer, health professionals and at system or organisational level. In five of the studies the intervention was focused on one of these groups only. [37, 38, 41-43] The majority of studies were concerned with some aspect of the consent process and the majority included patients with different forms of cancer. In most of the studies the interventions were treated as though they were a straightforward single component intervention. However, from the description of the delivery of the intervention, there were a number of possible components in the individual interventions (see data extraction tables, Appendix D). For example, as well as the specific intervention of interest, the influence of individual health professionals delivering the intervention is likely to be a very important factor in influencing patients' decision about trial participation.

The number of participants ranged from 57 to 2,440. In four of the studies of adults, the majority of participants were women.[36, 38-40] None of the studies investigated the effectiveness of the interventions with different ethnic groups. Half the studies did not report patient ethnicity[37, 40, 41, 43] and the remaining studies reported including predominantly white patients.[36, 38, 39, 42]

Table 1: Mapping of included studies

Study design	
Randomised controlled trial	n=3[36-38]
Nonrandomised controlled study	n=2[39, 40]
Controlled observational study	n=2[42, 43]
Before-after study	n=1[41]
Country	
United Kingdom	n=3[37, 40, 41]
United States	n=4[38, 39, 42, 43]
Australia	n=1[36]
Participants:	
Adult cancer patients	n=2[37, 38]
Parents of children with cancer	n=1[43]
Health professionals	n=1[41]
System level	n=1[42]
Adult cancer patients and health professionals	n=2[36, 40]
Adult cancer patients, health professionals and system level	n=1[39]
Intervention targeted at:	
Single trial	n=2[37, 41] (same trial)
Multiple trials	n=4[36, 38, 40, 43]
Global target	n=2[39, 42]
Barrier to participation addressed:	
Consent process	n=5[36-38, 40, 43]
Information	n=2[39, 41]
Financial	n=1[42]
Cancer types	
Prostate	n=2[37, 41] (same trial)
Childhood leukaemia	n=1[43]
Mixed	n=5[36, 38-40, 42]

Quality

The quality assessments of individual studies are detailed in the data extraction tables (Appendix D) with key aspects discussed in relation to individual studies in Section 3.3.

Across the group of studies in general, there was a risk of selection bias in all the studies that were not RCTs. Without random allocation, there was a risk that patients allocated to the experimental intervention had systematic differences to the comparison group that may have influenced their likelihood of agreeing to participate in a trial. For example, it is possible that patients perceived by the researcher as being less inclined to participate in the treatment trial of interest may, even inadvertently, have been more likely to have been allocated to the intervention aimed at increasing improvement as they might benefit most. This would lead to an underestimation of the effectiveness of the intervention. An alternative possibility is that patients perceived as more likely to participate may have been allocated to the intervention aimed at increasing participation. This would lead to an overestimate of the effectiveness of the intervention. The characteristics that might influence inclination to participate in a trial are unclear, as well as how they might best be measured. Therefore, it was not possible to assess what impact any selection bias may have had on the results. Only one of the three RCTs reported enough information to establish that the method used to assign patients was truly random and that allocation was concealed. [37] Therefore it was unclear whether the other two RCTs were susceptible to selection bias.[36, 38]

Given the nature of the interventions, blinding of those delivering the intervention or blinding of patients was not possible. Therefore, there was a risk of performance bias in all the studies. Performance bias occurs when there are systematic differences in how patients are treated or interacted with, apart from the intervention of interest. In studies of this nature, this may have been as simple as health professionals being friendlier, providing fuller explanations or spending more time with patients in one or other group. The fact that blinding was not possible does not negate the possibility of bias in these studies. The risk of performance bias was exacerbated by non-standardised implementation of the experimental intervention and comparator in some studies.

The three studies that attempted to record the implementation of the intervention in a systematic way found that the intervention was not implemented in a standardised way to individual patients.[36, 40, 43] Other aspects of how the interventions were defined and delivered were problematic. What was perceived as the active component of the intervention was adequately described in most of the studies. However, there appeared to be little recognition that there were aspects of the delivery of the intervention that may have influenced the outcome. For example, in one study the researcher interviewed parents in the time period between the intervention being delivered by the doctor and the parent making a decision about their child's participation in a treatment trial. [43] This may have had an interactive effect with the intervention or an independent effect on the outcome. Yet it was effectively treated as unrelated to the intervention. Specific instances of such occurrences in individual studies are identified below.

The risk of contamination between the experimental and comparison group was another important quality issue. There was a risk of contamination in all the studies apart from one cluster RCT[38] and a study of two geographical areas,[42] where the possibility of contamination was minimised. Contamination can take different forms. Where the same people are responsible for administering both the experimental and comparison intervention there is a risk that knowledge of the experimental intervention may influence how the comparison intervention is delivered. As a result there may be unplanned similarities between the experimental and comparison intervention. There may be a similar consequence where there are different people delivering the interventions but who also work together in the same setting. There is also the possibility that recruiting experimental intervention and comparison patients from the same setting may lead to sharing of information between the two groups. Contamination between the experimental and comparison intervention can dilute or attenuate any effect. In this group of studies it seems most likely that the effect would be a diluting one.

In six of the studies the experimental and comparison intervention were delivered by more than one health professional.[36-38, 40, 41, 43] As individual health professionals may vary in how

they deliver an intervention, or in how they interact with patients, the consequence for the study is that patients seen by the same health professional will be clustered. Such clustering reduces the effective sample size and therefore the power of the study to detect an effect.[44] The majority of studies had small samples and therefore may have been underpowered to detect an effect.

Trial participation

There was some variation in how trial participation as an outcome was defined. One study used two different definitions of trial participation: consent to randomisation and acceptance of allocation, with rates of 70% and 49% respectively.[41] The related RCT reported the proportion consenting to randomisation.[37] Four studies defined trial participation as the number of patients accrued or enrolled.[38, 39, 42, 43] However, it was unclear whether this referred to the proportion of patients who agreed to randomisation or the proportion who actually accepted their allocation. As illustrated by the study by Donovan and colleagues, there can be a difference between these figures.[41] One study defined trial participation as the number consenting to treatment[36] and one defined it as the number consenting to participation based on questionnaires completed by the patients following their meeting with their doctor to discuss trial participation.[40] This may have overestimated the number of patients who actually started the trial. One study found that using a self-reported decision to participate in a trial as an outcome measure, led to an overestimate compared with 'actual accrual'.[38] Although the variation is unlikely to have led to any systematic bias within studies, care needs to be taken when comparing trial participation between studies.

Grouping of studies

Table 2 provides a summary of the characteristics of the included studies with further details available in the data extraction tables (Appendix D). Based on the nature of the intervention, the studies had varying relevance to increasing participation of cancer patients in treatment trials in the UK. Therefore, studies considered to have some direct relevance to the UK setting will be discussed separately from those with limited or no relevance. The key criterion for relevance was whether the intervention could be implemented in the UK.

Table 2: Description of included studies

(studies ordered alphabetically)

Study details	Study design	Target of intervention (who received the intervention; and the number of trials across which it was assessed)	Participant details*	Description of experimental intervention and comparator
Angiolillo et al. (2004)[43] United States	Controlled observational study	Parents of children with cancer Four Children Cancer Group Trials	E: n=36; C: n=104 Parents of children with acute leukaemia Age of children E: Mean 4.9yrs (SD 2.5); C: 7.8yrs (SD 5.1) Ethnicity not stated	**Intervention:** A two-stage process was used for one trial. 1. Written parental consent was sought for the induction phase of the trial during which all patients received the same induction chemotherapy. " Written consent ('4 weeks later) was then obtained for randomisation to one of four therapeutic regimens. **Comparator:** Parents of children in the other three trials did not receive the staged approach. No further details provided.
Coyne et al. (2003)[38] United States	Cluster randomised controlled trial	Adult cancer patients Three trials	E: n=78; C: n=129 Breast (85%) and lung cancer patients E: 92.3% female; C 90.7% female E: Mean 53yrs; C: mean 53 yrs E: 94% white; C: 92% white	**Intervention:** Easy to read version of the original written consent document (different for each of the three trials).Changes included text style, page layout, font size and vocabulary. Content was not altered. Readability was seventh to eighth grade level and length was 16 pages. **Comparator:** Original consent document (different for each of the three trials). E1594: 4 pages long and fourteenth grade reading level. C9741 and E2197: 7-8 pages long and twelfth to thirteenth grade reading level.
Donovan et al. (2003)[37] United Kingdom	Randomised controlled trial	Adult cancer patients Single trial	E: n=75; C: n=75 Prostate cancer patients 100% male Age not stated Ethnicity not stated	**Intervention:** Nurse conducted information appointment with the patient to recruit to the trial. **Comparator:** Urologist conducted information appointment with the patient to recruit to the trial.
Donovan et al. (2002)[41] United Kingdom	Before-after study	Health professionals Single trial	Baseline: n=30; E1: n=45; E2 n=67; E3: n=83; E4: n=155 Prostate cancer patients 100% male Age not stated Ethnicity not stated	**Intervention:** Three successive documents in relation to how best recruit patients to the trial were circulated to recruiters followed by a training programme. Consent to randomisation was measured at baseline (October 1999 to May 2000); August 2000 (following intervention E1); November 2000 (following intervention E2); January 2001 (following intervention E3); and May 2001 (following intervention E4)

*Experimental intervention (E) and comparator (C)

Fleissig et al. (2001)[40] United Kingdom	Nonrandomised controlled study	Health professionals and adult cancer patients Forty trials	E: n=135; C: n=130 10 different cancers E: 72% female; C: 72% female Age range 19-65 yrs E: 58% 45-64 yrs; C: 50% 45-64yrs Ethnicity not stated	**Intervention:** Patients completed the Patient Preferences for Information Questionnaire, Patient Attitudes to Trials Questionnaire and Spielberger State Trait Anxiety Inventory prior to consultation with their doctor. Doctors were then provided with each patient's completed questionnaires (only the first 2 questionnaires) prior to their consultation during which consent was sought for a specific trial. **Comparator:** Patients completed the same questionnaires prior to consultation with their doctor. Doctors were not provided with this information prior to their consultation with individual patients during which consent was sought for a specific trial.
Gross et al. (2004)[42] United States	Controlled observational study	System level Global target (National Cancer Institute phase II and III Clinical Trials Cooperative Group trials)	E: n=4569; C: n=20,443 (2,440 were in phase II trials) Breast, colon, lung and prostate cancer patients Sex not stated Age not stated 89% white	**Intervention:** Four states (Illinois, Louisiana, Virginia, New Jersey) that enacted legislation or developed a co-operative agreement with health insurers in 1999 to cover clinical trial patient care costs (coverage states). **Comparator:** 35 states that had not enacted any policies to cover clinical trial patient care costs by the end of 2001 (non-coverage states)
Paskett et al. (2002)[39] United States	Nonrandomised controlled study	Adult cancer patients, health professionals and system level Global target	Total number of participants not stated Breast and colorectal cancer patients Majority female Age not stated for E and C (mean age, which was reported by time period of recruitment and cancer type ranged from 62 to 75 yrs) 75% white	**Intervention:** There were four elements: 1) a rapid tumour reporting system, 2) a nurse facilitator responsible for alerting physicians about appropriate clinical trials for their patients, 3) a quarterly newsletter about cancer treatment and clinical trials targeted at physicians and 4) a health educator who provided community-based education about screening and treatment and trained lay health educators. Implemented in five rural counties in North Carolina. **Comparator:** No intervention in five rural counties in South Carolina.
Simes et al. (1986)[36] Australia	Randomised controlled trial	Adult cancer patients and healthcare professionals Thirteen trials at a single oncology unit	E: n=28; C: n=29 8 different cancers E: 82% female; C: 62% female E: mean 56yrs (31-63yrs); C mean 55yrs (40-74yrs) E: 96% white; C: 100% white	**Intervention:** Uniform policy of total disclosure of all information relevant to the trial to the patient. There was an opportunity to ask further questions. Information was provided verbally and in a written consent form. **Comparator:** Information about the aims, anticipated results and potential toxicities of treatment were provided with details of treatment provided at the discretion of the consultant. There was an opportunity for the patient to ask questions. Verbal consent was obtained.

3.3 Studies relevant to the UK

Six of the studies had an intervention that had some relevance to the UK.[37-41, 43] These are outlined below, grouped by study design.

Randomised controlled trials

Two of the studies were RCTs, one of which was conducted in the US[38] and one in the UK.[37] The UK RCT compared the effectiveness and cost-effectiveness of nurses and surgeons, across three centres, recruiting men with prostate cancer to a treatment trial with a two and three-arm comparison.[37] Nurses and urologists were equally effective in recruiting patients to the trial. 67% of patients approached by a nurse accepted randomisation compared with 71% approached by an urologist (difference in proportions 4%; 95% CI: -10.8%, 18.8%). Recruitment levels varied between the three centres (94%, 61% and 45%). Based on a cost minimisation analysis, recruitment by nurses was more cost-effective than recruitment by urologists. This finding was unchanged in six out of seven sensitivity analyses exploring different resource scenarios, though the size of the cost difference did change.

This was a good quality RCT, with appropriate randomisation, concealed allocation and at least 80% of patients considered at follow-up, with no between group differences in dropouts. An intention to treat analysis was used. There is a possibility that contamination between the two groups and performance bias may have influenced the findings. There appears to have been a centre effect and contamination is one possible explanation for this. As a result of contact between urologists and nurses within centres, the style of communication may have been more similar between urologists and nurses within each centre than it was within each professional group across the centres. As would be expected in a study of this nature, blinding was not possible. During the study there was another ongoing intervention which is discussed below.[41] During the project recruiters were given feedback and training about recruitment and it is likely that the same recruiters were involved in both studies. This may also have influenced the findings though it is unclear whether it would have had an unequal influence on nurses and urologists. The quality of the economic evaluation appears acceptable. The authors identified resource quantities (time) separately from costs, the most relevant direct costs appear to have been included, means and standard deviations were reported and sensitivity analysis were performed. There were some limitations: the price year was not identified and some additional costs (contacting patients and training) were not included, though these are likely to be the same across both groups.

The US cluster randomised trial compared patient trial participation rates following use of an 'easy to read' written consent document used in one trial (seventh to eighth grade reading level) compared with a standard version used in three other trials (twelfth to fourteenth grade reading level).[38] This reduced the reading difficulty from approximately college level in the UK to 12-13 years old. Most of the patients were white women with breast cancer and a high literacy level. Initially the treatment trial was explained to patients by a physician, nurse or clinical research associate, though no details were provided in the paper of what this entailed. Patients were then invited to participate in the informed consent study and those who agreed to take part were provided with the appropriate written consent document. There was no statistically significant difference in patient accrual to trials between the intervention and comparison groups. 75% of patients were accrued in the trial using the 'easy to read' document and 68% in the other trials (difference in proportions 3.1, p=0.32). Comprehension levels were similar between the two groups. There was a statistically significant difference in the mean satisfaction with the consent document; however, the size of the difference may not be clinically meaningful.

It was not possible to fully assess the quality of this trial as some of the processes were not clearly reported. The unit of randomisation was at the institutional level though details of the randomisation are not provided. It was unclear whether there was concealment of allocation. It was also unclear how individual patients within each of the institutions were selected for inclusion in the trial and what proportion agreed to participate. Therefore, there is a possibility of selection bias. At least 80% of participants were considered at follow-up and dropout was similar across groups. The unit of randomisation was maintained for the statistical analysis,

though the possible influence of the three different trials used for the control group was not considered. The design appeared to protect against contamination as only one consent statement was used at an individual centre. However it is unclear whether the design protected against performance bias. Undefined aspects of health professional behaviour during the verbal explanation of the treatment trial may have been important. Although the specific intervention was clearly described in relation to the written consent document, any verbal information provided to patients was not described or assessed. Given the high literacy levels of the participants, there may have been a ceiling effect.

Other study designs

There was one nonrandomised controlled study which was conducted in the UK[40] and one in the US.[39] The UK study investigated the effect, on subsequent patient participation, of providing a self-selected group of 15 doctors with information on individual patient information preferences and attitudes to trials prior to discussing trial participation. All 265 patients completed questionnaires on information preferences, attitudes to trials and anxiety prior to a consultation with their doctor when they were invited to participate in a trial. Doctors of patients in the experimental intervention group only were provided with copies of the patient questionnaires. There was no statistically significant difference in eventual trial participation between the intervention and control group with participation levels at 81% and 74% respectively (χ^2 = 2.566, df 3; p=0.46). Most patients were highly satisfied with their consultation with the doctor and there were no significant differences between the two groups. Similarly, doctors were generally satisfied with the consultations with no difference between the intervention and control group.

There is a high possibility of selection bias in this study.[40] Only the order of the intervention and control group consultations was randomised: doctors were randomised into two groups, which varied, in blocks of five patients, the order of intervention and control group consultations. It was not stated how patients were allocated to intervention or control group. It is likely that patients saw the doctor to which they had been referred for treatment. However, the process by which patients were selected for inclusion was not reported. There was also a high possibility of contamination between the intervention and control group: the same doctors were involved in both groups and there was also evidence that the intervention was not implemented in a standardised way. Patient questionnaires were not referred to in any of an independently assessed subset of 16 intervention consultations. Forty-one percent of patients were given additional information about the trial relevant to them by another health professional; however it was not reported whether the provision of this information varied between the intervention and comparison group. Again, as would be expected there was no blinding. Given the non-standardised intervention, undefined aspects of consultant behaviour are likely to have been important. Only 15 of 43 doctors invited to participate in the study took part. Although there was no difference between participants and non-participant doctors on demographic characteristics it is probable that there were differences in important unmeasured characteristics such as communication abilities and motivation regarding involvement in clinical trials. This has implications for the generalisability of the study.

The US non-RCT evaluated a multi-faceted intervention targeted at various aspects of information as a barrier to participation in clinical trials over a period of three years. [39] The intervention was targeted at health professionals, patients and also at the organisational/system level. The intervention was implemented in five rural counties in North Carolina and compared with five rural counties in South Carolina where the intervention was not implemented. Patients were predominantly white and female. Data were reported separately for colorectal and breast cancer patients at baseline in 1991 and at follow-up in 1996 for the intervention and control group. The authors did not conduct a statistical analysis of change in trial participation. There was no evidence that the intervention was effective. There was a drop in trial participation from 15% to 6% for breast cancer patients receiving the intervention though this was based on a fairly small actual number of patients: there were 24 participants with breast cancer in 1991 and 14 in 1996. In the control group trial participation increased in breast cancer patients from 6% to 50% though again this is based on a small total number of participants (6 and 16 patients respectively). The participation of patients with

colorectal cancer in the intervention group remained static (4% in 1991 and 5% in 1996). In the control group it changed from 5% to 0%. It was unclear how many participants were in the control group, but given the overall number of patients with colorectal cancer (228 patients in 1991 and 128 patients in 1996) this is unlikely to be a meaningful change.

Geographical area of residence determined whether or not health professionals and patients received the intervention. Data on patient trial participation were obtained from medical records; however it was unclear how specific cancer patients within regions were selected or whether all cases were detected. The risk of selection bias is unclear. This study was also susceptible to contamination between the intervention and control group. Improving participation of patients in all rural areas was a major focus of the Community Clinical Oncology Program (CCOP) and both geographical areas had active CCOP physicians.

The two remaining studies were of observational design; one was conducted in the US[43] and one in the UK.[41] The US study compared a standard procedure to a two-stage process for obtaining informed consent from parents of children with leukaemia. The first stage involved obtaining consent for participation in the induction phase of the trial during which all patients in the trial received the same treatment. Following this stage of treatment, consent was sought for randomisation to one of four therapeutic regimens. Very little information was provided (in the consent study) on the comparison intervention though, by implication, it was a one stage approach. There was no statistically significant difference between the two groups in eventual trial participation. Participation rates were 77% and 88% in the experimental and control groups respectively. There was no statistically significant difference in the level of understanding of the concept of randomisation. 61% of the experimental group and 45% of the control group (p=0.10) understood the concept following the informed consent process. More participants in the experimental group appeared to understand the distinction between the trial treatment and standard treatment and this was statistically significant. Parental trust was also significantly higher in the experimental group though the meaningfulness of the difference in scores is unclear.

This study had a high possibility of selection bias. Allocation to the groups was not described. By implication, children who met the selection criteria for the treatment trial used for the informed consent intervention also met the criteria for that intervention. Children meeting the criteria for the other three trials of interest received the standard informed consent procedure. However, no process was reported for selecting individual participants. The authors do not state whether or not the same doctors were involved in obtaining consent for all the trials; therefore it is unclear whether there was a risk of contamination. The intervention was not implemented in a standardised way. Almost half the parents in the two-stage consent group did not have a second interview with the doctor and some patients in the comparison group did have a second interview. Researcher interviews with parents between the intervention and their final decision about trial participation may have had an influence. Although this study is classified as having potential relevance to the UK setting based on the intervention, the extent to which it is generalisable is unclear due to poor description of aspects of the intervention, the setting, the specific trials being targeted and the doctors involved.

The UK based study[41] was directed at the same treatment trial for prostate cancer as the RCT described above.[37] Patient participation in the treatment trial was measured at baseline and following each of three successive documents circulated to recruiters providing guidance on how to best recruit patients. There was also a training programme. The content of the documents was based on observations made of recruitment practices and the views of patients using qualitative research methods. Recruiter difficulty in explaining equipoise and presenting treatments equally was identified as a barrier to effective recruitment from the qualitative research. As a result, changes were made to the terminology used to describe the three treatments, the order in which they were presented and how randomisation and equipoise were explained. Further details of the three successive documents are available in Appendix D.

There was a trend of increasing participation rates (consent to randomisation) following each intervention, though statistical analyses were not conducted: baseline 30-40% participation; following intervention 1, 51%; following intervention 2, 58%; following intervention 3, 61%;

following intervention 4, 70%. However, this is an uncontrolled study; therefore it is not possible to rule out the influence of other factors influencing patient participation. It is also likely that there was contamination between the different interventions over the time period. Therefore it is inappropriate to attribute the increases in participation to the preceding intervention. The authors of this study describe the particular prostate trial as controversial. This, together with the considerable differences between the treatment arms, may limit the generalisability of the findings.

3.4 Studies of low relevance to the UK

There were two studies which were unlikely to have any relevance to the UK. One was a RCT conducted almost 20 years ago in Australia.[36] This study investigated a uniform policy of full disclosure of all relevant information when seeking patient consent to trial participation compared with disclosure of information at the discretion of the consultant. A written consent document was completed for the full disclosure intervention whereas only verbal consent was obtained for the comparison intervention. In this comparison intervention, information about the study aims, anticipated results and potential toxicities of the treatment were provided with the details of treatment at the discretion of the consultant. In the UK setting, the option of anything but full disclosure of information with written consent is not an option, particularly in the context of clinical trials regulations.[45]

There was no statistically significant difference in participation levels between the groups. However, it was not possible to assess whether the study was vulnerable to selection bias due to poor reporting and there was a high risk of contamination between the two interventions.

The second study investigated the effect of legislation requiring health insurers to cover clinical trial patient care costs on trial participation rates in the US.[42] The funding of trials in the UK is an important issue; however, due to differences in the funding of patient healthcare in the UK this particular study has no relevance to the UK.

3.5 Summary of the evidence

Only a small number of studies met the inclusion criteria. Very few were RCTs. The interventions to improve participation in cancer treatment trials were diverse. This is not surprising given the complexity of barriers that need to be addressed to increase participation. Although six of the experimental interventions investigated were classified as having potential relevance to the UK setting, only three of these were actually conducted in the UK, the other three in the US. Therefore, although the nature of the interventions may have relevance to the UK, the actual generalisability of the findings to the UK is unclear. Trial participation rates were high in the majority of studies in both the experimental and comparison groups which may also have implications for generalisability.

There was no evidence that any of the interventions investigated led to an increase in cancer patient participation in clinical trials. Equally, the evidence was not of sufficient quality to be able to conclude that these interventions therefore are not effective. Overall the studies had a range of methodological weaknesses. In particular, in most of the studies there was a risk of contamination between the experimental and control intervention leading to a dilution of the effect of the experimental intervention. If this aspect had been taken into consideration in the study design then there is a possibility that some of the experimental interventions may have been effective.

4. DISCUSSION

4.1 The evidence-base

Overall there is not a strong evidence-base for interventions that increase cancer patient participation in trials. Despite the large volume of research that is available on barriers to participation in cancer trials, only a small body of research was identified on interventions to overcome these barriers. One good quality RCT was identified and two RCTs where the quality was unclear. The five remaining studies were nonrandomised controlled studies or observational studies.

Only three studies were identified that were concerned with interventions implemented in a UK context. One was a good quality RCT that found that nurses and urologists were equally effective at recruiting participants to a treatment trial for prostate cancer, with nurses being the most cost-effective.[37] In an uncontrolled study, directed at the same trial, there was evidence of increasing participation rates following amendments to the nature and emphasis of the information that patients were given.[41] These changes were based on the findings from a qualitative research project involving patients and recruitment staff. The third study carried out in a UK setting was a nonrandomised controlled study with a high risk of selection bias.[40] It investigated the effect of providing doctors with information on patient information preferences and attitudes towards trials prior to discussing trial participation. There was no difference in eventual trial participation between the experimental and comparison group.

Across all the studies there was no strong evidence that any of the experimental interventions investigated led to an increase in cancer patient participation in RCTs compared with the comparison intervention. However, this cannot be interpreted as evidence of the ineffectiveness of these interventions: the body of evidence is not of sufficient quality to establish whether or not the interventions work. The findings of this systematic review are similar to previous systematic reviews with an overlapping scope. In one review of interventions to increase participation in mock and real trials, in healthy individuals and all patient groups, over 75% of the included studies found no evidence of an effect on participation.[19] A similar proportion of studies found no evidence of an effect on accrual to real or mock trials, in a review of interventions to improve research participants' understanding during the informed consent process.[20] The quality assessment in both reviews was fairly limited and possible reasons for the lack of effect in so many of the studies were not explored.

4.2 Why was there no evidence of an effect?

There are a number of possible explanations for the lack of effect in the current group of studies. Most striking is that in five of the seven studies with a control group, participation levels were high in both the experimental and the control group. Participation levels in the latter group ranged from 68% to 93%. This raises the question of whether there was a Hawthorne effect i.e. that the experience of participation in a study per se led to an increase in participation in the cancer trial. This could have been sufficient to mask an effect of the experimental intervention, especially given the fairly small sample sizes in these studies.

An alternative explanation for a lack of effect is that the interventions investigated are simply ineffective. However, the evidence is not sufficient to make this conclusion. There is the possibility that the specific interventions investigated do not work in the particular contexts in which they were used. They may prove effective with a different patient group or in relation to a different trial/s. For example, if the effect on participation levels of an 'easy to read' informed consent form, as used in the study conducted by Coyne et al.,[38] had been investigated with patients with a lower level of literacy than the women in the study, it may have been found to be effective.

The barriers to participation in cancer trials are numerous, complex and probably interact in a unique way in relation to individual trials.[4] In contrast, six of the eight studies investigated single component interventions targeted at very specific aspects of recruitment to trials. This

is not surprising as it is probably the most straightforward way to evaluate an intervention. However, if the intervention did not target the key barrier to participation in a particular trial, it may not show any evidence of effectiveness in that particular situation. Indeed, some cancer trials experience rapid and successful recruitment, which may relate for example, to the particular treatment being investigated.[46] An alternative explanation to the Hawthorne effect suggested above may be that the particular cancer trials in these studies may have had high recruitment levels regardless of any intervention to increase participation. This may have lead to a ceiling effect in individual trials.

There is also the possibility that the effect of the experimental intervention was underestimated. The most likely source of an underestimate of an effect of the experimental intervention was the risk of contamination between groups. Apart from two studies that minimised the risk through study design, there was a fairly high risk of contamination across the studies. Contamination would most likely have led to a dilution of the effect of the experimental intervention compared to the control intervention.

Therefore, despite the lack of strong evidence for the effectiveness of the interventions investigated, they are certainly worthy of further investigation. The evidence that nurses and urologists are equally effective at recruiting patients to a trial is important from both a cost-effectiveness and resources point of view.[37] Given that time and workload are reported barriers to doctors recruiting patients to trials, interventions investigating whether other health professionals can be effectively involved in patient recruitment are important. This is an area that would benefit from further investigation.

There were other interventions investigated in the included studies that would merit further investigation; in particular, the use of qualitative methods to tailor information provided to potential trial participants. The included study which investigated this approach has limitations in its ability to assess the effectiveness of the specific interventions.[41] Recruitment rates increased, but it was not clear what, in particular, led to the increase. However, the study does show that it is possible to use qualitative research methods within a treatment trial to identify aspects of the recruitment process that are weak and require changing. The resulting interventions were closely tailored to the specific recruitment issues in the treatment trial. In this respect, the approach used came closer than any other included study in addressing the recommendation made, in the systematic review on barriers to participation, that trialists should consider barriers in the context of specific trials.[4]

In a similar way the intervention investigated by Angiolillo et al. seemed to be tailored to a specific barrier.[43] This study attempted to address the tension between obtaining truly informed parental consent and the limited time available due to the requirement for fairly immediate consent to allow chemotherapy to commence in children with newly diagnosed leukaemia. Given that both the experimental and control group received standard induction chemotherapy for the first 28 days parents were able, in the first instance, to consent to the standard therapy. This gave them additional time to consider their decision about randomisation to the next stage of therapy. Further investigation of how this technique could be used in other cancer trials would be worthwhile.

4.3 Ethical issues

There is no strong evidence that participation in RCTs leads to a harmful or beneficial effect compared with treatment received outside trials.[47] However, the decision to participate in a particular trial may not always be the 'right' decision for an individual patient. In particular it is important that their decision is an informed one and that it is made without any pressure or even subtle coercion. The majority of included studies examined interventions targeted at the informed consent process. Where this process is the target of an intervention, trial participation cannot be considered in isolation from the quality of the informed consent process. The dangers of coercion when tailoring the information to maximise patient trial participation rates requires careful consideration.[41, 48, 49] Some of the included studies assessed understanding or knowledge as well as trial participation as an outcome. However the extent to which understanding or knowledge are an indicator for the quality of the consent

process is unclear. Work has been carried out to develop a questionnaire to assess the quality of the informed consent process.[50] This is a complex area and there may be conflicting views about what constitutes coercion.[51]

4.4 Limitations of the current review

Extensive searches were conducted to identify references for potential inclusion in this review. However, given the nature of the topic, no relevant indexing terms were available for any of the databases searched, and the search strategy was heavily reliant on textword searching. This meant that the searches were limited to the terms used by authors in the title and abstract fields of each reference. Because of this, there is always the possibility that studies have been missed.

This review focused on interventions to improve participation in trials that were specifically evaluated with cancer patients. Studies of interventions with other patient groups may provide useful information that is transferable to cancer treatment trials. Therefore the review might have excluded studies of patients with other conditions that may have highlighted interventions worthy of further investigation with cancer patients.

4.5 Recommendations

- There is a clear need for further research assessing interventions aimed at increasing cancer patient participation in cancer trials. Conducting research on increasing patient participation in real cancer treatment trials is challenging both methodologically and logistically. Some of the limitations of the included studies, such as lack of blinding, are unavoidable. However, there are a number of important methodological issues to consider in future research:

    - Wherever feasible, RCTs should be the method of choice to minimise the risk of selection bias.

    - The interventions in this field are effectively complex interventions and would benefit from being treated as such.[52, 53] This could include use of qualitative as well as quantitative methods and piloting to define the intervention. Similar methods could be used to assess whether the intervention is being used in the appropriate context in terms of the barriers to patient participation in the trial/s being considered. Examples of such approaches are available in other areas of research.[54, 55]

    - The risk of contamination between the experimental and comparison intervention needs to be assessed and taken into consideration. Cluster randomised trials are one approach to minimising the risk of contamination.[56] They do have disadvantages, in particular they usually require a larger sample size and can be susceptible to bias in the recruitment of individuals.[56,57] Therefore, increasing the sample size of an individual randomised trial should also be given consideration.[57] There may be other practical steps that could be considered in individual studies. For example, where feasible, studies should avoid having the same health professional delivering both the experimental and control intervention.

    - There is evidence that clinicians in the UK employ unique styles when discussing participation in cancer trials with patients.[58] The sample size therefore needs to take into consideration the possibility of clustering where more than one health professional delivers the intervention.[44]

    - The problem raised by a lack of blinding of health professionals cannot be avoided as blinding is not possible in these studies. However measures could perhaps be taken to systematically document the implementation of the intervention and comparison.

- Given the paucity of studies investigating interventions targeted specifically at cancer patients, future updates of this systematic review should consider inclusion of interventions with different patient groups. It may also be beneficial to examine whether interventions to improve recruitment to nonrandomised trials exist which may be applicable to randomised trials.

- When interventions to increase cancer patient participation in cancer trials are directed at the informed consent process, an assessment of the quality of the informed consent process should also be carried out. This could be through use of an appropriate questionnaire, interviews with patients or recording of informed consent discussions.

- When designing studies to assess interventions to increase participation in cancer trials, consideration needs to be given to generalisability to different ethnic and social groups. This would appear to be an under researched area. A recent systematic review of recruitment strategies to increase participation of underrepresented group in cancer treatment and prevention trials identified only five studies, despite no study design restrictions.[59]

4.6 Conclusion

There is not a strong evidence-base for interventions that increase cancer patient participation in randomised trials. Good quality RCTs are required to evaluate the effectiveness of strategies to increase participation in cancer treatment trials.

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APPENDIX A: SEARCH STRATEGIES

ASCO web site
http://www.asco.org/
1995-2005 (49 records)
Searched: 12/05/05

accru* or recruit* or enrol* or particip* or enlist* or join* or enter* or entry

The Cochrane Library Database 2004 Issue 4
http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME
Cochrane Database of Systematic Reviews (26 records)
Cochrane Database of Methodology Reviews (2 records)
Database of Abstracts of Reviews of Effects (3 records)
HTA Database (0 records)
Searched: 07/01/05

#1 MeSH descriptor Neoplasms explode all trees
#2 (cancer* or tumor* or tumour* or malignan* or oncolog* or carcinoma* or neoplas*) in All Fields
#3 (#1 OR #2)
#4 MeSH descriptor Clinical Trials explode all trees
#5 MeSH descriptor Patient Participation explode all trees
#6 MeSH descriptor Patient Selection explode all trees
#7 MeSH descriptor Informed Consent explode all trees
#8 MeSH descriptor Research Subjects explode all trees
#9 (#5 OR #6 OR #7 OR #8)
#10 (#4 AND #9)
#11 (#3 AND #10)
#12 (increas* or improv* or motivat* or encourag* or influence* or effect* or affect* or attract* or endors* or promot* or facilitat* or enhanc* or challeng* or refus* or reluctan*) near (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) near (trial* or study or studies or research or rct* or randomised or randomized)
#13 (difficult* or problem* or obstacle* or barrier* or deter or deters or deterrent or discourag* or impediment* or failure) near (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) near (trial* or study or studies or research or rct* or randomised or randomized)
#14 (perception* or perceiv* or attitude* or decision* or process* or reason*) near (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) near (trial* or study or studies or research or rct* or randomised or randomized)
#15 (willing* or agree* or consent* or permission or assent or permit* or decide* or deciding) near (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) near (trial* or study or studies or research or rct* or randomised or randomized)
#16 (declin* or unwilling* or discourag*) near (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) near (trial* or study or studies or research or rct* or randomised or randomized)
#17 (strateg* or method* or intervention* or incentive*) near (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) near (trial* or study or studies or research or rct* or randomised or randomized)
#18 (#12 OR #13 OR #14 OR #15 OR #16 OR #17)
#19 (#18) in Record Title
#20 (#18) in Abstract
#21 (#19 OR #20)
#22 (#3 AND #21)
#23 (#11 OR #22)

MEDLINE - Ovid host
1966 - Wk 3 Nov 2004 (1206 records)
Searched: 07/01/05

MEDLINE In-Process - Ovid host
Jan 2005 (40 records)
Searched: 07/01/05

1. exp NEOPLASMS/
2. (cancer$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$ or neoplas$).ti,ab.
3. 1 or 2
4. ((increas$ or improv$ or motivat$ or encourag$ or influenc$ or effect$ or affect$ or attract$ or endors$ or promot$ or facilitat$ or enhanc$ or challeng$ or refus$ or reluctan$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
5. ((difficult$ or problem$ or obstacle$ or barrier$ or deter or deters or deterrent or discourag$ or impediment$ or failure) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
6. ((perception$ or perceiv$ or attitude$ or decision$ or process$ or reason$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
7. ((willing$ or agree$ or consent$ or permission or assent or permit$ or decide$ or deciding) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
8. ((declin$ or unwilling$ or discourag$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
9. ((strateg$ or method$ or intervention$ or incentive$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
10. or/4-9
11. 3 and 10
12. exp *Clinical Trials/
13. clinical trial.pt.
14. 12 or 13
15. *Patient Participation/
16. *Patient Selection/
17. *Informed Consent/
18. *Research Subjects/
19. or/15-18
20. 3 and 14 and 19
21. 11 or 20

EMBASE - Ovid host
1980 - Wk 1 2005 (816 records)
Searched: 07/01/05

1. exp Neoplasm/
2. (cancer$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$ or neoplas$).ti,ab.
3. 1 or 2
4. ((increas$ or improv$ or motivat$ or encourag$ or influenc$ or effect$ or affect$ or attract$ or endors$ or promot$ or facilitat$ or enhanc$ or challeng$ or refus$ or reluctan$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
5. ((difficult$ or problem$ or obstacle$ or barrier$ or deter or deters or deterrent or discourag$ or impediment$ or failure) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or

randomi?ed)).ti,ab.
6. ((perception$ or perceiv$ or attitude$ or decision$ or process$ or reason$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
7. ((willing$ or agree$ or consent$ or permission or assent or permit$ or decide$ or deciding) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
8. ((declin$ or unwilling$ or discourag$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
9. ((strateg$ or method$ or intervention$ or incentive$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
10. or/4-9
11. 3 and 10
12. exp *Clinical Study/
13. *Patient Selection/
14. *Informed Consent/
15. *Research Subject/
16. or/13-15
17. 3 and 12 and 16
18. 11 or 17

CINAHL - Ovid host
1982 - Wk 2 Dec 2004 (204 records)
Searched: 07/01/05

1. exp neoplasms/
2. (cancer$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$ or neoplas$).ti,ab.
3. 1 or 2
4. ((increas$ or improv$ or motivat$ or encourag$ or influenc$ or effect$ or affect$ or attract$ or endors$ or promot$ or facilitat$ or enhanc$ or challeng$ or refus$ or reluctan$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
5. ((difficult$ or problem$ or obstacle$ or barrier$ or deter or deters or deterrent or discourag$ or impediment$ or failure) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
6. ((perception$ or perceiv$ or attitude$ or decision$ or process$ or reason$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
7. ((willing$ or agree$ or consent$ or permission or assent or permit$ or decide$ or deciding) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
8. ((declin$ or unwilling$ or discourag$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
9. ((strateg$ or method$ or intervention$ or incentive$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
10. or/4-9
11. 3 and 10
12. exp *Clinical Trials/
13. clinical trial.pt.
14. 12 or 13
15. *Consumer Participation/
16. *Patient Selection/
17. *Consent/
18. *Research Subjects/

19. or/15-18
20. 3 and 14 and 19
21. 11 or 20

HMIC - Ovid host
November 2004 (25 records)
Searched: 07/01/05

1. exp NEOPLASMS/
2. (cancer$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$ or neoplas$).ti,ab.
3. 1 or 2
4. ((increas$ or improv$ or motivat$ or encourag$ or influenc$ or effect$ or affect$ or attract$ or endors$ or promot$ or facilitat$ or enhanc$ or challeng$ or refus$ or reluctan$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
5. ((difficult$ or problem$ or obstacle$ or barrier$ or deter or deters or deterrent or discourag$ or impediment$ or failure) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
6. ((perception$ or perceiv$ or attitude$ or decision$ or process$ or reason$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
7. ((willing$ or agree$ or consent$ or permission or assent or permit$ or decide$ or deciding) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
8. ((declin$ or unwilling$ or discourag$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
9. ((strateg$ or method$ or intervention$ or incentive$) adj2 (accru$ or recruit$ or enrol$ or particip$ or enlist$ or join$ or enter or enters or entered or entry) adj2 (trial$ or study or studies or research or rct$ or randomi?ed)).ti,ab.
10. or/4-9
11. 3 and 10
12. exp CLINICAL TRIALS/
13. exp PATIENT PARTICIPATION/
14. exp CLIENT PARTICIPATION/
15. exp HUMAN RESEARCH SUBJECTS/
16. exp CONSENT/
17. exp PATIENT SELECTION/
18. exp PATIENT ALLOCATION/
19. or/13-18
20. 3 and 12 and 19
21. 11 or 20

SIGLE - ARC Ovid host
1980 - 06/2004 (2 records)
Searched: 07/01/05

#1 (cancer* or tumor* or tumour* or malignan* or oncolog* or carcinoma* or neoplas*) in ti,ab
#2 ((increas* or improv* or motivat* or encourag* or influenc* or effect* or affect* or attract* or endors* or promot* or facilitat* or enhanc* or challeng* or refus* or reluctan*) near2 (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry)) in ti,ab
#3 ((difficult* or problem* or obstacle* or barrier* or deter or deters or deterrent or discourag* or impediment* or failure) near2 (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry)) in ti,ab
#4 ((perception* or perceiv* or attitude* or decision* or process* or reason*) near2 (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry)) in ti,ab

#5 ((willing* or agree* or consent* or permission or assent or permit* or decide* or deciding) near2 (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry)) in ti,ab
#6 ((declin* or unwilling* or discourag*) near2 (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry)) in ti,ab
#7 ((strateg* or method* or intervention* or incentive*) near2 (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry)) in ti,ab
#8 #2 or #3 or #4 or #5 or #6 or #7
#9 (trial* or study or studies or research or rct* or randomi?ed) in ti,ab
#10 #1 and #8 and #9

PsycInfo - ARC Ovid host
1872 - 12/2004 (16 records)
Searched: 07/01/05

#1 explode "Neoplasms-" in MJ,MN
#2 (cancer* or tumor* or tumour* or malignan* or oncolog* or carcinoma* or neoplas*) in ti,ab
#3 #1 or #2
#4 ((increas* or improv* or motivat* or encourag* or influenc* or effect* or affect* or attract* or endors* or promot* or facilitat* or enhanc* or challeng* or refus* or reluctan*) near2 (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) near2 (trial* or study or studies or research or rct* or randomi?ed)) in ti,ab
#5 ((difficult* or problem* or obstacle* or barrier* or deter or deters or deterrent or discourag* or impediment* or failure) near2 (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) near2 (trial* or study or studies or research or rct* or randomi?ed)) in ti,ab
#6 ((perception* or perceiv* or attitude* or decision* or process* or reason*) near2 (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) near2 (trial* or study or studies or research or rct* or randomi?ed)) in ti,ab
#7 ((willing* or agree* or consent* or permission or assent or permit* or decide* or deciding) near2 (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) near2 (trial* or study or studies or research or rct* or randomi?ed)) in ti,ab
#8 ((declin* or unwilling* or discourag*) near2 (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) near2 (trial* or study or studies or research or rct* or randomi?ed)) in ti,ab
#9 ((strateg* or method* or intervention* or incentive*) near2 (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) near2 (trial* or study or studies or research or rct* or randomi?ed)) in ti,ab
#10 #4 or #5 or #6 or #7 or #8 or #9
#11 #3 and #10
#12 explode "Experimental-Design" in MJ,MN
#13 explode "Experimental-Methods" in MJ,MN
#14 #12 or #13
#15 explode "Experimental-Subjects" in MJ,MN
#16 explode "Informed-Consent" in MJ,MN
#17 explode "Client-Participation" in MJ,MN
#18 explode "Patient-Selection" in MJ,MN
#19 #15 or #16 or #17 or #18
#20 #3 and #14 and #19
#21 #11 or #20

Science Citation Index - Web of Science host
1945 - 01/2005 (2,067 records)
Searched: 11/01/05

Social Science Citation Index - Web of Science host
1945 - 01/2005 (280 records)
Searched: 11/01/05

#1 (cancer* or tumor* or tumour* or malignan* or oncolog* or carcinoma* or neoplas*)
#2 ((increas* or improv* or motivat* or encourag* or influenc* or effect* or affect* or attract* or endors* or promot* or facilitat* or enhanc* or challeng* or refus* or reluctan*) same (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) same (trial* or study or studies or research or rct* or randomised or randomized))
#3 ((difficult* or problem* or obstacle* or barrier* or deter or deters or deterrent or discourag* or impediment* or failure) same (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) same (trial* or study or studies or research or rct* or randomised or randomized))
#4 ((perception* or perceiv* or attitude* or decision* or process* or reason*) same (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) same (trial* or study or studies or research or rct* or randomised or randomized))
#5 (willing* or agree* or consent* or permission or assent or permit* or decide* or deciding) same (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) same (trial* or study or studies or research or rct* or randomised or randomized))
#6 ((declin* or unwilling* or discourag*) same (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) same (trial* or study or studies or research or rct* or randomised or randomized))
#7 ((strateg* or method* or intervention* or incentive*) same (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry) same (trial* or study or studies or research or rct* or randomised or randomized))
#8 #2 or #3 or #4 or #5 or #6 or #7
#9 #1 and #8

Sociological Abstracts - CSA host
1963 - 01/2005 (48 records)
Searched: 11/01/05

ASSIA - CSA host
1987 - 01/2005 (153 records)
Searched: 11/01/05

(cancer* or tumor* or tumour* or malignan* or oncolog* or carcinoma* or neoplas*) and ((increas* or improv* or motivat* or encourag* or influenc* or effect* or affect* or attract* or endors* or promot* or facilitat* or enhanc* or challeng* or refus* or reluctan* or difficult* or problem* or obstacle* or barrier* or deter or deters or deterrent or discourag* or impediment* or failure or perception* or perceiv* or attitude* or decision* or process* or reason* or willing* or agree* or consent* or permission or assent or permit* or decide* or deciding or declin* or unwilling* or discourag* or strateg* or method* or intervention* or incentive*) near (accru* or recruit* or enrol* or particip* or enlist* or join* or enter or enters or entered or entry)) and (trial* or study or studies or research or rct* or randomi?ed)

APPENDIX B: ASSESSMENT OF STUDY QUALITY

Selection bias (RCTs only)		
Was the method used to assign patients really random?*	Yes/no/unclear	**Comments:**
Was the allocation to intervention concealed?*	Yes/no/unclear	**Comments:**
Selection bias (Studies with a control group only)		
Retrospective or prospective study?		
Was the assignment of patients to intervention group described?	Yes/no	**How were they assigned/allocated?**
Were the groups comparable at baseline?	Yes/no/unclear	**Comments:**
Were they matched for any confounding factors or the effect of any difference evaluated in a valid statistical analysis?	Yes/no/unclear	**Comments:**
Selection bias (uncontrolled/before and after studies)		
Retrospective or prospective study?		
Was the patient selection process described?	Yes/no	**How were they selected?**
Were details provided of the population from which the sample was selected?	Yes/no	**Comments:**
Were there inclusion criteria?	Yes/no/unclear	**Comments:**
Were all eligible patients invited to participate?	Yes/no/unclear	**Comments:**
Is it possible that the investigators had discretion over who was selected?	Yes/no/unclear	**Comments:**
Attrition bias (all studies)		
Were at least 80% of participants considered at follow-up?	Yes/no/unclear	**Comments:**
Was it similar across groups?	Yes/no/unclear	**Comments:**
Was a valid ITT analysis carried out?[1]	Yes/no/unclear	**Comments:**
The intervention (all studies)		
Did the design protect against contamination?[2]	Yes/no/unclear	**Comments:**
Did the design protect against performance bias?	Yes/no/unclear	**Comments:**
Further comments:		
Relevance (all studies)		
Was the nature of the intervention clear?	Yes/no/partially	**Comments:**
Was the target of the intervention clearly defined?	Yes/no/partially	**Comments:**
General comments on relevance/applicability		

* According to CRD Report No. 4 criteria[1]
[1] Not relevant to uncontrolled studies
[2] Unlikely to be relevant to most uncontrolled studies

APPENDIX C: EXCLUDED STUDIES

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APPENDIX D: DATA EXTRACTION TABLES

(Data extraction table and quality assessment form for each study in alphabetical order)

Publication details

Author: Angiolillo et al.[43] **Year:** 2004 **Related publications:**

Stated aim: To compare a staged approach to the informed consent process with a non-staged process in RCTs for childhood leukaemia.

The intervention

Study design: controlled observational study

Country:	**Complexity:**	**Directed at:**
US	Single	Parents of children with cancer

Targeted at:	**Specify trial/s if stated:** 4 trials for childhood leukaemia
Multiple trials	Children Cancer Group (CCG) -1991; CCG-1952; CCG-1961; CCG-2961

Was the intervention targeted at a single barrier to participation? Yes	**Patient related barrier/s**	**Health professional barrier/s**	**Organisational barrier/s**
	Informed consent process		

Description of experimental intervention: Recruitment to the CCG-1991 trial involved a two-stage process. First written parental consent was sought for the induction phase of the trial (initially they were asked to consent to 14 days of induction treatment but this was later changed to 28 days) during which all patients received the same induction chemotherapy. Written consent ('typically' 4 weeks following start of induction) was then obtained for randomisation to one of four therapeutic regimens.

Description of comparator: Parents of children in the other three trials (CCG-1952; CCG-1961; CCG-2961) did not receive the staged approach. No further details provided.

Delivery

Patients were recruited into the trial (CCG-1991) from 6 CCG institutions that routinely treat children with acute leukaemia.

Initial doctor patient interviews to discuss treatment options and trial participation were observed and audiotaped by researchers. These were independently coded by 3 researchers based on a checklist for behaviours relating to discussion of the disease, treatment and trial participation.

Within 48 hours of their interview with the doctor, researchers interviewed parents from both groups prior to their decision regarding their child's participation in the trial. A subsequent interview was conducted by researchers following the parental decision.

A second consent interview with the doctor was carried out with 52.8% of parents in the experimental intervention group and 12.5% in the comparison group.

The duration of the doctor-parent interview was 95.8 minutes (SD 35.9) for the intervention group, 72.9 minutes (SD 29.3) for the comparison group (p=0.0002). There were no statistically significant differences between the experimental intervention and comparison groups regarding the proportion of interviews in which the concept of randomisation was explained and the number of times RCT and standard treatment were distinguished.

No information was reported about the doctors who carried out the consent interviews or the time period of the study.

The cancer patients

Total number of participants:	**Total number lost to follow-up:**
Intervention: n=36 Control: n=104	Intervention: not stated Control: not stated

Cancer site: single	**Details:** acute childhood leukaemia

Age (Mean, SD)	**Sex:** Mixed	**Ethnicity:**	**Previous participation in a trial?** Yes/No
Patients Intervention: 4.9yrs (2.5) Control: 7.8 yrs (5.1) p<0.001 Parents Intervention: 33.6yrs (8.3) Control: 36yrs (7.3)	Patients Intervention: 44.4% (n=16) female Control: 42.3% (n=44) female Parents Intervention: 66.7% female Control 58.7% female	Intervention: unclear Control: unclear Interviews conducted in English: intervention 86.1%; control 78.8%	Intervention: n= not stated Control: n=not stated

Parent characteristics are for 140 parents though in 13 cases both parents were interviewed.

Outcomes	
Trial participation: Described as number enrolled	**Secondary outcome measures?** Yes i) parental trust score (based on a Trust Scale administered at the two follow-up interviews by the researcher; ii) parental understanding (based on data from researcher conducted interviews)
Were stratified data reported for trial participation? No	**Specify:**
Results	
Trial participation Intervention group: 76.5%	Control group: 86.7% p=0.16
Secondary outcome: Parental trust (the higher the score, the greater the trust) Intervention group: mean (SD)=95.1 (3.9)	Control group mean (SD) 92 (9.8) p=0.009
Secondary outcome: Understood concept of randomisation Intervention group: 61.1%	Control group: 45.2% p=0.10
Secondary outcome: Information received improved understanding Intervention group: 82.4%	Control group: 66% p=0.13
Secondary outcome: Understood distinction between RCT and standard treatment Intervention group: 80.6%	Control group: 62.5% p=0.05
Author's conclusion: The results suggest that a consent process with a staged approach can help investigators obtain a more truly informed consent.	
Comments:	

Quality assessment		
Retrospective or prospective study?		Prospective
Was the assignment of patients to intervention group described?	No	**How were they assigned/allocated?** By implication, children who met the selection criteria for CCG-1991 received the two stage informed consent and children meeting the criteria for the other three trials received the comparison.
Were the groups comparable at baseline?	No	**Comments:** Children in the intervention group were younger than the comparison.
Were they matched for any confounding factors or the effect of any difference evaluated in a valid statistical analysis?	No	**Comments:**
Were at least 80% of participants considered at follow-up?	Unclear	**Comments:** Most of the results were reported as percentages only, therefore not possible to assess.
Was it similar across groups?	Unclear	**Comments:**
Was a valid ITT analysis carried out?	Unclear	**Comments:**
Did the design protect against contamination?	Unclear	**Comments:** Do not state whether the same doctors were involved in obtaining consent for all the trials. The intervention was not implemented in a standardised way. Almost half the parents in the intervention group did not have a second interview and some in the control group did have a second interview.
Did the design protect against performance bias?	No	**Comments:** No blinding. Researcher interviews with parents between the intervention and their final decision may have had an influence.
Further comments: Some discussions may not have been observed or taped.		
Was the nature of the intervention clear?	No	**Comments:** Poorly described. No information provided on the comparison.
Was the target of the intervention clearly defined?	No	**Comments:** Although demographic information was provided on the children and parents, the setting, the trials, and the doctors delivering the intervention were poorly described.
General comments on relevance/applicability Trial participation rates were high in both groups. This study was carried out in the United States in major academic children's hospitals in an urban setting.		

Publication details

Author: Coyne et al.[38] **Year:** 2003 **Related publications:**

Stated aim: To investigate the effect of using an easy-to-read consent document compared with a standard consent document on patient comprehension of the trial protocol, anxiety, satisfaction and accrual.

The intervention

Study design: cluster randomised controlled trial

Country: US	**Complexity:** Single	**Directed at:** Adult cancer patients

Targeted at: Multiple trials	**Specify trial/s if stated:** Trial in metastatic non-small-cell lung cancer (E1594); trial of adjuvant treatment in women with node-positive stage II/III breast cancer (C9741); trial of adjuvant treatment for node positive or high risk node-negative breast cancer (E2197)

Was the intervention targeted at a single barrier to participation? Yes	**Patient related barrier/s**	**Health professional barrier/s**	**Organisational barrier/s**
	Informed consent (readability of consent form)		

Description of experimental intervention: Easy to read version of the original written consent document (different for each of the three trials). Changes included text style, page layout, font size and vocabulary. Content was not altered. Readability was seventh to eighth grade level and length was 16 pages.

Description of comparator: Original consent document (different for each of the three trials). E1594: 4 pages long and fourteenth grade reading level. C9741 and E2197: 7-8 pages long and twelfth to thirteenth grade reading level.

Delivery of intervention/comparator
Patients eligible for inclusion in one of three specified trials from 1998 to 2000 were recruited.

A physician, clinical research associate or research nurse explained the treatment trial to patients (no further information provided). Patients were then invited to participate in the informed consent study. Those who consented were then provided with the appropriate written consent statement.

Other relevant information
44 institutions (members and affiliates of three cooperative oncology groups) were randomly assigned to intervention or control group. For two of the oncology groups the unit of randomisation was the Institutional Review Board (shared by many affiliate institutions) and in one cooperative the unit of randomisation was the institution.

The cancer patients*

Total number of participants:	**Total number lost to follow-up:**
Intervention: n=78 Control group: n=129	Intervention group: n=11 Control group: n=8 (for secondary outcomes only)

Cancer site: Mixed	**Details:** Breast (85%), lung

Age (Mean)	**Sex:** Mixed	**Ethnicity:**	**Previous participation in a trial?**
Intervention: 53 yrs Control: 53 yrs	Intervention: 92.3% (n=72) female Control group: 90.7% (n=117) female	Intervention: 93.6% (n=73) white Control: 92.3% (n=119) white	Not stated

The mean reading level of both groups was similar and was equivalent to ninth grade or above (the maximum level possible on the Rapid Estimate of Adult Literacy in Medicine)
A similar proportion of patients in each group were involved in each of the three trials.

Outcomes

Trial participation: Described as actual accrual	**Secondary outcome measures?** Yes i) comprehension (23 multiple choice questions); ii) patient satisfaction (4 item 4-point scale); iii) decision to participate (self-reported) (all assessed at telephone interview 1 to 2 weeks after reading written consent statement)

Were stratified data reported for trial participation? No	**Specify:**

Results		
Trial participation Intervention group: 75% (based on 89 patients)		Control group: 68% based on 137 patients) difference in proportions 3.1**, p=0.32
Secondary outcome: comprehension (% correct) Intervention group: 72%		Control group: 69% difference in proportions 2.31, p=0.21
Secondary outcome: Satisfaction (mean score) Intervention group: 3.56		Control group: 3.28 difference in proportions 0.35, p=0.004
Secondary outcome: decision to participate Intervention group: 82.4%		Control group: 89.3% difference in proportions –4.1, p=0.26
Author's conclusion: Easy to read informed consent statements are associated with reduced patient consent anxiety, increased satisfaction with the written consent document but not with patient comprehension.		
Comments: The analyses used random effects models with the randomisation unit as the random effect.		
Quality assessment		
Was the method used to assign patients really random?*	Unclear	**Comments:** Unit of randomisation was at institutional level. Details of randomisation not provided. There is a possibility of selection bias**:** it is unclear how individual patients were selected for inclusion in the study and what proportion agreed to participate.
Was the allocation to intervention concealed?	Unclear?	**Comments:**
Were at least 80% of participants considered at follow-up?	Yes	**Comments:**
Was it similar across groups?	Yes	**Comments:**
Was a valid ITT analysis carried out?	Unclear	**Comments:**
Did the design protect against contamination?	Yes	**Comments:** Institutions were randomised
Did the design protect against performance bias?	Unclear	**Comments:** No blinding. Undefined aspect of health professional behaviour during the verbal explanation of the study may have been important.
Further comments: Statistical analysis preserved unit of randomisation		
Was the nature of the intervention clear?	Yes	**Comments:** The intervention was clearly described. Any verbal information provided to patients was not described or assessed and this may have been influential. No information provided on the health professionals delivering the intervention
Was the target of the intervention clearly defined?	Yes	**Comments:** Information provided on patient characteristics and the treatment trials.
General comments on relevance/applicability Most of the patients were white women with breast cancer with a high literacy level		

* Demographic details are not reported for 19 patients who were lost to follow-up for all outcomes except actual accrual

**Intervention minus control after adjusting for correlation within the same randomisation units

Publication details

Author: Donovan et al.[37] **Year:** 2003 **Related publications:** Donovan et al. (2003)[61]; Donovan et al. (2002)[41]

Stated aim: To assess the effectiveness and cost-effectiveness of nurses and surgeons in recruiting patients.

The intervention

Study design: randomised controlled trial

Country: UK	**Complexity:** Single	**Directed at:** Adult cancer patients
Targeted at: Single trial	Specify trial/s if stated: Consisted of a three-arm comparison: radical surgery, radical radiotherapy or monitoring; and a two-arm comparison: radical surgery and radical radiotherapy (which were part of the Prostate Testing for Cancer and Treatment study – ProtecT)	

Was the intervention targeted at a single barrier to participation? Yes	**Patient related barrier/s**	**Health professional barrier/s**	**Organisational barrier/s**
		Informed consent (Who is the most effective recruiter)	

Description of experimental intervention: Nurse conducted information appointment with the patient to recruit to the trial.

Description of comparator: Urologist conducted information appointment with the patient to recruit to the trial.

Delivery of intervention/comparator
The advantages and disadvantages of each treatment and the need for a treatment trial were explained in detail.
As part of the initial screening programme to identify men with localised prostate cancer (which took place 1999-2001) they were provided with information regarding the uncertainties about and need for a randomised trial of treatments.
There appeared to be three recruitment centres. The number of nurses and urologists involved in recruitment was not reported.
Other relevant information: At an initial appointment with a urologist, consent was sought for randomisation to an information appointment with a nurse or urologist.

The cancer patients

Total number of participants:	**Total number lost to follow-up:**
Intervention group: n=75 Control group: n=75	Intervention group: none reported Control group: none reported

Cancer site: single **Details:** localised prostate cancer

Age (Mean, range)	**Sex:** 100% male	**Ethnicity:** Not stated	**Previous participation in a trial?** Not stated
Intervention: not stated Control: not stated Target group for initial screening was 50-69 yrs			

Outcomes

Trial participation: proportion consenting randomisation	Secondary outcome measures? No
Were stratified data reported for trial participation? No	Specify:

Results

Trial participation
Intervention group: 67% (n=50)
Control group: 71% (n=53)
difference in recruitment rates 4% (95% CI: -10.8%, 18.8%), p=0.60
Recruitment levels at the three centres: 94% (of 63); 61% (of 31); 45% (of 56), p<0.001
The authors state that the differences between nurses and urologists within centres were considerably smaller than centre differences (data not presented)

Economic evaluation (a cost minimisation analysis)

Nurse: mean (standard deviation)	Urologist: mean (standard deviation)	
Nurse time use 56.6 mins (23.0); cost £35.93 (£14.66) Urologist* time use 0.5 mins (SD 3.4); cost: £0.48 (3.47)	Nurse time use 2.4 mins (10.2); cost: £1.56 (£6.72) Urologist* time use 41.3 mins (19.8); cost: £41.73 (£19.95)	
Total mean time use: 57.1 mins (22.1) Total mean cost: £36.40 (£13.86)	Total mean time use: 43.7 mins (17.1) Total mean cost: £43.29 (£17.58)	Time difference (95% CI) -13.4 (-21.9, -4.9), p=0.0024 Cost difference (95% CI) £6.89 (0.3, 13.4), p=0.039)

Some patients had more than one meeting with staff to discuss trial participation or had telephone discussions. There was uncertainty about the amount of time this involved. Sensitivity analyses were performed based on 4 different assumptions about the proportion of second and third appointments. Four sensitivity analyses were also carried out based on different assumptions about the number of appointments that had a second member of staff present. Nurses were more expensive in only one of these scenarios (assumption that 50% of nurse led appointments had another nurse present) which the authors said was a rare occurrence.		
Author's conclusion: Nurses were as effective and more cost-effective recruiters than urologic surgeons. This suggests an increased role for nurses in recruiting patients to randomised trials.		
Comments: The authors' conclusions regarding cost-effectiveness were based on data that have not been extracted given that the examination of cost-effectiveness is outside the scope of this review.		
Quality assessment		
Was the method used to assign patients really random?*	Yes	**Comments:** Allocation was stratified by centre and age
Was the allocation to intervention concealed?*	Yes	**Comments:**
Were at least 80% of participants considered at follow-up?	Yes	**Comments:**
Was it similar across groups?	Yes	**Comments:**
Was a valid ITT analysis carried out?	Yes	**Comments:** Authors state that analysis was conducted according to ITT
Did the design protect against contamination?	Unclear	**Comments:** There appears to have been a centre effect. Contamination is one possible explanation for this
Did the design protect against performance bias?	No	**Comments:** No blinding. During the consent trial there was an ongoing action research project[41]during which recruiters were given feedback and training about recruitment. This may have had an important influence on the findings.
Further comments:		
Was the nature of the intervention clear?	No	**Comments:** Ongoing action research project may have been an important influence.
Was the target of the intervention clearly defined?	Partially	**Comments:** Limited information on the setting, the recruiters and the participants
General comments on relevance/applicability		

Publication details

Author: Donovan et al.[41] | **Year:** 2002 | **Related publications:** Donovan et al. (2003)[37]; Donovan et al. (2003)[61]

Stated aim: To improve the design and conduct of RCTs by embedding them in qualitative research

The intervention

Study design: Other (action research)

Country: UK	**Complexity:** Multi-component	**Directed at:** Health professionals

Targeted at: Single trial	**Specify trial/s if stated:** A treatment trial comparing radical surgery, radical radiotherapy or monitoring (which was part of the Prostate Testing for Cancer and Treatment study – ProtecT)

Was the intervention targeted at a single barrier to participation? No	**Patient related barrier/s**	**Health professional barrier/s**	**Organisational barrier/s**
	Consent process (Information)	Consent process (Information)	

Description of experimental intervention: Three successive documents were circulated to recruiters followed by a training programme.
Document 1: Recruiters were asked to present treatments in the following order: monitoring, surgery and radiotherapy and to describe their advantages and disadvantages in equivalent detail. In addition, recruiters were advised to avoid the terms 'trial' and 'watchful waiting' replacing the latter with monitoring. Emphasis was also placed on patients being eligible for all treatments and randomisation as a reasonable way to reach a treatment decision.

Document 2: This re-emphasised monitoring as regular testing and review with the possibility of radical treatment if disease localised; emphasised eliciting and challenging patients' views if at odds with evidence; and re-emphasised no compulsion to accept treatment allocation.

Document 3: Provided 'good' and 'not so good' examples of presentation of information to facilitate equal presentation of treatments
The intensive training programme covered the following issues: equal presentation of treatments, challenging patients' views, the need for a RCT, randomisation as a reasonable method of treatment choice and description of non-radical arm as 'active monitoring'. Role-play was used in two centres.

Description of comparator:
Consent to randomisation was measured at baseline (October 1999 to May 2000); August 2000 (following intervention 1); November 2000 (following intervention 2); January 2001 (following intervention 3); and May 2001 (following intervention 4)

Delivery of intervention/comparator
Qualitative research methods were used to develop the appropriate interventions at each stage. These were in-depth interviews with patients to elicit their interpretation of study information and experiences of the study including treatment preferences; audiotaping of recruitment interviews to examine delivery of information by recruiters and patient interpretation; audiotaping of recruitment interviews to investigate reasons for different levels of recruitment between centres and over time.

There appeared to be three recruitment centres. The number of nurses and urologists involved in recruitment was not reported.

Other relevant information

The cancer patients

Total number of participants:	**Total number lost to follow-up:**
Intervention: Base line (October 1999 to May 2000) n=30 Intervention 1 (August 2000) n=45 Intervention 2 (November 2000) n=67 Intervention 3 (January 2001) n=83 Intervention 4 (May 2001): n=155	Intervention group: Unclear (some baseline data on number consenting to randomisation may be missing as these data are presented as a range)

Cancer site: Single | **Details:** Prostate

Age (Mean, range)	**Sex:** 100% male	**Ethnicity:** Not stated	**Previous participation in a trial?** Not stated
Intervention: not stated Target group for initial screening was 50-69 yrs			

Outcomes	
Trial participation: 1) number who consented to randomisation and 2) number who accepted their treatment allocation (expressed as a proportion of those consenting to randomisation) From the data presented it was not possible to calculate acceptance of allocation as a proportion of those eligible at baseline though sufficient data were available to allow calculation of trial participation rate according to this definition for follow-up.	Secondary outcome measures? No
Were stratified data reported for trial participation? No	**Specify:**
Results	
Trial participation (consent to randomisation) Baseline 30-40% Intervention 1: 51% (n=23) Intervention 2: 58% (n=39) Intervention 3: 61% (n=51) Intervention 4: 70% (n=108) **Trial participation** (acceptance of allocation as a proportion of patients consenting to randomisation) Baseline 60-70% Intervention 1: 78% (n=18) Intervention 2: 77% (n=30) Intervention 3: 75% (n=38) Intervention 4: 70% (n=76) **Trial participation** (acceptance of allocation as a proportion of eligible patients) Intervention 1: 40% (n=18) Intervention 2: 45% (n=30) Intervention 3: 46% (n=38) Intervention 4: 49% (n=76)	
Author's conclusion: Changes to information and presentation resulted in efficient recruitment acceptable to patients and clinicians.	
Comments:	

Quality assessment		
Retrospective or prospective study?		Prospective
Was the patient selection process described?	Yes	**How were they selected?** Patients who were eligible for an RCT of treatments for prostate cancer were eligible for the study
Were details provided of the population from which the sample was selected?	Yes	**Comments:** All eligible patients were included
Were there inclusion criteria?	Yes	**Comments:** Men aged 50-69yrs diagnosed with localised prostate cancer.
Were all eligible patients invited to participate?	Yes	**Comments:**
Is it possible that the investigators had discretion over who was selected?	No	**Comments:**
Were at least 80% of participants considered at follow-up?	Unclear	**Comments:** Results were only presented for those patients for whom final treatment data were available.
Did the design protect against contamination?	No	**Comments:** There may have been contamination between the different interventions.
Did the design protect against performance bias?	No	**Comments:** Other changes over time may have had a confounding influence.
Further comments: This is an uncontrolled study therefore it is not possible to rule out the influence of other factors in influencing patient participation.		
Was the nature of the intervention clear?	Yes	**Comments:** Further information also available from authors.
Was the target of the intervention clearly defined?	Partially	**Comments:** Limited information on the setting, the recruiters and the participants.
General comments on relevance/applicability The authors describe the prostate treatment trial as controversial. This and the considerable differences between the treatment arms may limit the generalisability of the findings.		

Publication details

Author: Fleissig et al[40] **Year:** 2001 Related publications:

Stated aim: To investigate whether providing doctors with information on individual patient information preferences and attitudes to trials prior to a discussion about trial participation improved participation, doctor and patient satisfaction and reduced consultation time.

The intervention

Study design: controlled study

Country: UK	**Complexity:** Single	**Directed at:** Health professional and adult cancer patients

Targeted at: Multiple trials	**Specify trial/s if stated:** 13 breast cancer trials including 4 with placebo arm (5 chemotherapy, 4 endocrine, 4 other); 8 ovarian cancer trials including 1 with placebo arm (all chemotherapy); 3 testicular cancer trials (2 chemotherapy, 1 CT scan surveillance schedules); 1 prostate cancer trial with placebo arm (endocrine); 5 colorectal cancer trials including 1 with placebo arm (4 chemotherapy, 1 immunotherapy); 4 lung cancer trials including 2 with placebo arm (all chemotherapy); 1 bladder cancer trial (radiotherapy); 1 pancreatic cancer trial (chemotherapy); 2 lymphoma cancer trials (all chemotherapy); 2 melanoma cancer trials both with placebo arms (1 immunotherapy, 1 chemotherapy)

Was the intervention targeted at a single barrier to participation? Yes	**Patient related barrier/s** consent process (poor communication)	**Health professional barrier/s** consent process (poor communication)	**Organisational barrier/s**

Description of experimental intervention: Patients completed the Patient Preferences for Information Questionnaire, Patient Attitudes to Trials Questionnaire and Spielberger State Trait Anxiety Inventory prior to consultation with their doctor. Doctors were then provided with each patient's completed questionnaires (only the first 2 questionnaires) prior to their consultation during which consent was sought for a specific trial.

Description of comparator: Patients completed the Patient Preferences for Information Questionnaire, Patient Attitudes to Trials Questionnaire and Spielberger State Trait Anxiety Inventory prior to consultation with their doctor. Doctors were not provided with this information prior to their consultation with individual patients during which consent was sought for a specific trial.

Delivery of intervention/comparator

15 of 43 invited doctors at District General and University Teaching Hospitals undertook the consultations with patients in the period 1997-2000 (8 clinical/radiation oncologists, 6 medical oncologists, 1 surgeon).

93.3% (n=126/135) of intervention group consultations and 91.5% (n=119/130) of control group consultations were audiotaped. The main items covered in the consultation were assessed using a grid matrix. Patient questionnaires were not referred to in 78% (n=98) of the intervention group consultations. Patient questionnaires were not referred to in any of an independently assessed subset of 16 intervention consultations,
Length of consultation: intervention group 13.9 minutes (range 1-35 minutes); control group 14.7 minutes (range 2-38 minutes).
Following the consultation with the doctor, 40.8% (n=108/264) of patients were given additional information about the relevant trial by another health professional (breakdown not provided for intervention and control group.
17 trials (involving 27 participants) were offered to the intervention group or control group only.

There were no statistically significant differences between the intervention and control group on the Patient Preferences for Information Questionnaire. 87.1% of patients (n=230/264) preferred to have all possible information about their diagnosis and treatment.

Other relevant information:
Doctors were randomised into two groups, which varied, in blocks of 5 patients, the order of the intervention and control group consultations.
An independent assessor blinded to intervention group checked 30 randomly selected audiotapes for content.

The cancer patients

Total number of participants:	**Total number lost to follow-up:**
Intervention group: n=135 Control group: n=130	Intervention group: not stated Control group: not stated Total: 30 of 295 patients who agreed to participate in the study were excluded from the analysis because they did not complete follow-up postal questionnaires.

Cancer site: mixed	**Details:** Breast, ovary, testicular, prostate, colorectal, lung, bladder, pancreas, lymphoma, melanoma

Age (Mean, range):	**Sex:** Mixed	**Ethnicity:**	**Previous participation in a trial?** Yes
Intervention group: 19-44 yrs 13.3% (n=18); 45-64 yrs 57.8% (n=78); 65 yrs and above 28.9% (n=39) Control Group: 19-44 yrs 20% (n=26); 45-64 yrs 50% (n=65); 65 yrs and above 30% (n=39)	Intervention group: 71.9% (n=97) female Control group: 72.3% (n=94) female	Intervention group: not stated Control group: not stated	Intervention group: n=13 Control group: n=15

Outcomes

Trial participation: number consenting to participation based on questionnaires completed after the consultation	**Secondary outcome measures?** Yes i) Patient satisfaction with doctor-patient interaction (based on 17 item questionnaire adapted from Medical Outcomes Study PSQIII) . This was given to patients following the consultation and they returned it by post. ii) Doctors satisfaction with doctor-patient interaction and patient distress rating using a visual analogue scale
Were stratified data reported for trial participation? Yes (though intervention and control group were collapsed)	**Specify:** Patient participation in chemotherapy trials with a 'no treatment' arm compared with all other trials

Results

Trial participation

Intervention group: n=109 (80.7%) Control group: n=96 (73.8%) x^2=2.566, df=3, p=0.463

In total n=205 agreed to participate, n=53 declined and n=7 did not know. It was unclear whether the third group was included in the chi-square analysis.

Patients were less likely to agree to participate in chemotherapy trials which involved a 'no treatment' arm (n=22/45) than all the other trials (n=178/208) x^2=21.0, df=1, p=0.001

Trial participation was not associated with age or gender. There were no differences between the intervention and control group in the reasons given for accepting or declining trial entry.

Nine of the 16 patients who said at baseline they would decline participation in a RCT, subsequently accepted; 18 of 35 patients who were unsure at baseline subsequently accepted randomisation; 177 of 213 patients who said they would participate in a trial subsequently accepted.

Secondary outcome: Patient satisfaction with the consultation

Most patients were highly satisfied with their consultation. There were no significant differences between the intervention and control groups.

Secondary outcome: Doctors' satisfaction with the consultations (maximum score was 10)

In general doctors were highly satisfied with their consultations.

Intervention group: average 8.1 (range 1.6 to 10) Control group: average=7.8 (range 2.5 to 10) t=-1.26, df=263, p=0.21, 95% CI: -0.684, 0.151)

Author's conclusion: Providing doctors with a copy of their patients' information requirements and attitudes towards participation in trials, prior to asking them to participate in a trial, made little differences to the outcomes assessed.

Comments:

Quality assessment		
Retrospective or prospective study?		Prospective
Was the assignment of patients to intervention group described?	No	**How were they assigned/allocated?** No information provided
Were the groups comparable at baseline?	Yes	**Comments:** Comparable for age, sex, marital status, cancer site, previous participation in a trial, trait anxiety
Were they matched for any confounding factors or the effect of any difference evaluated in a valid statistical analysis?	No	**Comments:** The authors state that trial participation was not associated with age or gender but was associated with type of trial. However this was not stratified by intervention group.
Were at least 80% of the participants considered at follow-up?	Yes	**Comments:**
Was it similar across groups?	Unclear	**Comments:** Not reported by group.
Was a valid ITT analysis carried out?	No	**Comments:** 30 patients who did not complete a follow-up questionnaire were excluded from all the analyses. Varying numbers of patients were excluded from analyses due to missing data.
Did the design protect against contamination?	No	**Comments:** The same doctors were involved in the intervention and comparison. The intervention was not implemented in a standardised way. It was unclear whether the provision of information by a second health professional varied between the intervention and comparison group

Did the design protect against performance bias? **Further comments:**	No	**Comments:** No blinding Undefined aspects of consultant behaviour may have been important.
Was the nature of the intervention clear?	Yes	**Comments:** The intervention and comparison were described. However, although the focus of the intervention appeared to be doctor provision of information, the process of completing the questionnaires may also have influenced patient decision-making.
Was the target of the intervention clearly defined?	Yes	**Comments:** Information on patient characteristics provided and patient inclusion criteria specified. Some information provided on doctors and detailed information provided on the individual trials.
General comments on relevance/applicability Trial participation rates were high in both groups.		

Publication details

Author: Gross et al.[42] **Year:** 2004 **Related publications:**

Stated aim: To investigate whether state policies that ensure coverage of routine medical care costs for cancer trial participants are associated with an increase in clinical trial enrolment.

The intervention

Study design: controlled observational study

Country: US	**Complexity:** Single	**Directed at:** System level	
Targeted at: Global target	**Specify trial/s if stated** National Cancer Institute (NCI) phase II and III Clinical Trial Cooperative Group (CTCG) trials		
Was the intervention targeted at a single barrier to participation? Yes	**Patient related barrier/s** Cover of routine medical care costs by private insurers	**Health professional barrier/s**	**Organisational barrier/s**

Description of experimental intervention: Four states (Illinois, Louisiana, Virginia, New Jersey) that enacted legislation or developed a co-operative agreement with health insurers in 1999 to cover clinical trial patient care costs (coverage states).

Description of comparator: 35 states that had not enacted any policies to cover clinical trial patient care costs by the end of 2001 (non-coverage states).
Delivery of intervention/comparator: Not stated
Other relevant information

The cancer patients

Total number of participants:	**Total number lost to follow-up:**
Intervention group: n= 4569 Control group: n=20443 For phase II and III trials combined. (n=22612 participants were in phase III trials)	Intervention group: n/a Control group: n/a (Only patients enrolled on trials were included)

Cancer site: Mixed **Details:** Breast, colon, lung, prostate

Age (Mean, range)	**Sex**	**Ethnicity:**	**Previous participation in a trial?**
Not stated Only patients aged 20 to 64 were included	Mixed Intervention: not stated Control: not stated	Overall: 88.8% white Intervention: not stated Control: not stated	Not stated

All participants were privately insured (patients with no private insurance or unclear insurance status were excluded)

Outcomes

Trial participation: Percent annual increase in enrollment. Enrollment data was from the NCI Clinical Data Update System. The denominator was the total number of cancer cases diagnosed annually in group of states (using American Cancer Society Data)	Secondary outcome measures? No
Were stratified data reported for trial participation? Yes	**Specify:** For phase II and phase III trials. Multivariate analysis was also conducted investigating the influence of secular enrolment trends, cancer type and ethnicity

Results

Trial participation (for phase III trials only)
Premandate period (1996-1999)
Intervention: 23.9% (95%CI: 19.2%, 28.8%) Control: 24.1% (95% CI: 21.8%, 26.5%), p=.95
Postmandate period (1999-2001)
Intervention: 16.2% (95%CI; 10.9%, 21.6%) Control: 25.7% (95% CI: 23.0%, 28.4%), p=.002
Adjustment for secular enrolment trends, cancer type and ethnicity in a multivariate analysis did not alter the findings.

Author's conclusion: Statewide policies ensuring reimbursement for routine medical care costs did not increase phase III cancer trial enrolment.

Comments:

Quality assessment		
Retrospective or prospective study?		Retrospective
Was the assignment of patients to intervention group described?	Yes	**How were they assigned/allocated?** Based on state of residence
Were the groups comparable at baseline?	No	**Comments:** Baseline enrolment rates (1996) were statistically significantly higher in coverage than noncoverage states

Were they matched for any confounding factors or the effect of any difference evaluated in a valid statistical analysis?	Yes	**Comments:** Multivariate analysis adjusting for secular enrolment trends, cancer type and ethnicity
Were at least 80% of participants considered at follow-up?	N/A	**Comments:** Only included patients who had enrolled on trials
Was it similar across groups?	N/A	**Comments:**
Was a valid ITT analysis carried out?	N/A	**Comments:**
Did the design protect against contamination?	Yes	**Comments:**
Did the design protect against performance bias?	Unclear	**Comments:** Lack of enforcement in coverage states and behaviour of physicians in noncoverage states to compensate for lack of coverage could have had an influence.
Further comments: Lack of enforcement of the mandates may have limited the impact on trial participation.		
Was the nature of the intervention clear?	Yes	**Comments:**
Was the target of the intervention clearly defined?	Yes	**Comments:**
General comments on relevance/applicability No relevance to UK situation. From a US perspective applicability is limited by the exclusion of NCI funded trials not conducted through CTCGs.		

Publication details			
Author: Paskett et al.[39]	**Year:** 2002	**Related publications:**	
Stated aim: To examine the effect of a rural community clinical oncology program-based cancer-care intervention programme aimed at increasing the number of rural patients with cancer enrolled in clinical trials.			
The intervention			
Study design: controlled study			
Country: US	**Complexity:** Multi-component	**Directed at:** Adult cancer patients, health professional and system level	
Targeted at: Global target	**Specify trial/s if stated**		
Was the intervention targeted at a single barrier to participation? No	**Patient related barrier/s** Information	**Health professional barrier/s** Information	**Organisational barrier/s** Information
Description of experimental intervention: There were four elements: 1) a rapid tumour reporting system, 2) a nurse facilitator responsible for alerting physicians about appropriate clinical trials for their patients, 3) a quarterly newsletter about cancer treatment and clinical trials targeted at physicians and 4) a health educator who provided community-based education about screening and treatment and trained lay health educators. Implemented in five rural counties in North Carolina. **Description of comparator:** No intervention in five rural counties in South Carolina. **Delivery of intervention/comparator** The various components of the intervention were implemented from 1993 to 1996. Both geographical areas had active Community Clinical Oncology Program (CCOP) physicians. Improving participation of patients in rural areas in cancer trials was a major focus of the CCOP programme. **Other relevant information**			
The cancer patients			
Total number of participants: Intervention Breast*: 1991 n= 160?; 1996 n= 233? Colorectal: 1991 n= not stated; 1996 n= not stated Control Breast*: 1991 n= 100?; 1996 n= 32? Colorectal: 1991 n= not stated; 1996 n= not stated (there were a total of 228 colorectal cases in 1991 and 128 cases in 1996) * These have been calculated from proportions reported in the paper. However, the total number of cases adds to n=525 whereas the papers states that there were a total of 486 breast cancer cases	**Total number lost to follow-up:** Intervention group: not applicable Control group: not applicable		
Cancer site: Mixed	**Details:** breast, colorectal		
Age (Mean, range) Intervention: not stated Control: not stated Overall: Breast 1991 68 years; 1996 62 years Colorectal 1991 75 years (30 to 102); 1996 71 years (31 to 97)	**Sex:** Mixed Intervention: not stated Control: not stated Overall Breast 100% female Colorectal 1991 45% female; 1996 42% female	**Ethnicity:** Intervention: not stated Control: not stated Overall: Breast 1991 75% white; 1996 74% white Colorectal 199175% white; 1996 75% white	**Previous participation in a trial?** Not stated
Outcomes			
Trial participation: Proportion of patients enrolled in a clinical trial (data were obtained from medical records; no further details provided)	Secondary outcome measures? Proportion of physicians referring or enrolling at least one cancer patient to a trial (based on physician self-reports)		
Were stratified data reported for trial participation? Yes	**Specify:** By cancer site		

Results

Trial participation

Intervention group:	Control group:
Breast 1991 15% (n=24); 1996 6% (n=14)	Breast 1991 6% (n=6); 1996 50% (n=16)
Colorectal 1991 4%; 1996 5%	Colorectal 1991 5%; 1996 0%

Secondary outcome: Physician referral of at least one patient to a trial

Intervention group: 1991: 8%; 1996: 25%	Control group: 1991: 4%; 1996: 11% ($p<0.05$)

Author's conclusion: According to physician self-reports there was a greater increase in the proportion of physicians in the intervention area who had referred or enrolled at least one patient with cancer into a clinical trial. However, there were no clear patterns of improvement in actual clinical trial participation.

Comments:

Quality assessment

Retrospective or prospective study? Prospective (but it is unclear whether the trial enrolment data obtained from medical records were gathered prospectively)

Was the assignment of patients to intervention group described?	Yes	**How were they assigned/allocated?** By geographical region. However it is unclear how specific cases within regions were selected.
Were the groups comparable at baseline?	Yes	**Comments:** For sex and ethnicity
Were they matched for any confounding factors or the effect of any difference evaluated in a valid statistical analysis?	No	**Comments:**
Was loss to follow-up greater than 80%?	N/A	**Comments:**
Was it similar across groups?	N/A	**Comments:**
Was a valid ITT analysis carried out?	Unclear	**Comments:**
Did the design protect against contamination?	No	**Comments:** The authors state that they were unable to prevent contamination in the comparison region.
Did the design protect against performance bias?	No	**Comments:** Other changes over time may have influenced the findings.

Further comments:

Was the nature of the intervention clear?	Partially	**Comments:** Limited information on the multi-component intervention
Was the target of the intervention clearly defined?	Partially	**Comments:** Limited information on the setting

General comments on relevance/applicability

This is a US study and the findings may have limited relevance to the UK.

Publication details

Author: Simes et al.[36] **Year:** 1986 **Related publications:** N/A

Stated aim: To compare two procedures for obtaining informed consent to randomised treatment.

The intervention

Study design: randomised controlled trial

Country:	**Complexity:**	**Directed at:**
Australia	Single component	Adult cancer patients and health professionals

Targeted at:	Specify trial/s if stated: Patients were candidates for any one of 13 trials at a single oncology unit.
Multiple trials	

Was the intervention targeted at a single barrier to participation? Yes	**Patient related barrier/s**	**Health professional barrier/s**	**Organisational barrier/s**
	Consent process		

Description of experimental intervention: Uniform policy of total disclosure of all information relevant to the trial to the patient. This included a) that they had cancer; b) the aims of treatment and likelihood of success; c) that treatment was part of a research study; d) that treatment was allocated randomly; e) appropriate alternative treatments; f) all possible side-effects; g) that they were free to withdraw from the study and still receive the treatment they wanted h) opportunity to ask further questions. Information was provided verbally and in a written consent form. The patient kept the form overnight and written consent was obtained the next day.

Description of comparator: Information about the aims, anticipated results and potential toxicities of treatment were provided with details of treatment provided at the discretion of the consultant. There was an opportunity for the patient to ask questions. Verbal consent was obtained.

Delivery of intervention/comparator
Four doctors undertook 93% of the consent interviews in the period 1981-1984.

The information covered by the consultant in the discussion with each patient was recorded at the time by an oncology registrar or by the consultant immediately following the discussion. The required information was not always covered in the full disclosure intervention, though all patients received the written information. Diagnosis, details of treatment and opportunity to ask questions were covered with a similar frequency in both groups. The following were covered less frequently in the individual approach: prognosis (n=22 vs n=28); that treatment was part of a research study (n=20 vs n=28); randomisation explained (n=19 vs n=27); alternatives to treatment (n=16 vs n=23); the right to withdraw from treatment (n=15 vs n=23); right to withdraw from the study (n=17 vs n=25); percentage of possible side effects mentioned (54%, SE 6 vs 86%, SE 4).

Other relevant information

The cancer patients

Total number of participants:	**Total number lost to follow-up:**
Intervention: n=28 Control: n=29	Intervention: n=2 (for secondary outcomes only: one failed to answer questionnaire, one was to ill) Control: n=0

Cancer site: mixed	**Details:** Ovarian, breast, head and neck, gastric, small cell lung, unknown primary, colorectal, bladder

Age Median (range)	**Sex :** Mixed	**Ethnicity:**	**Previous participation in a trial?** Not stated
Intervention: 56 yrs (31-68) Control: 55 yrs (40-74)	Intervention: n=23 female Control: n=18 female	Intervention: n=27 white Control: n=29 white	

Outcomes

Trial participation: number consenting to treatment	**Secondary outcome measures?** Yes i) Knowledge of treatment and side-effects; ii) knowledge of research aspects; iii) decided on an individual basis treatment; iv) confidence in doctors; v) perception of doctor-patient relationship and anxiety. The questionnaires were administered following randomisation to treatment and 3 to 4 weeks later.
Were stratified data reported for trial participation? No	**Specify:** Brief summary of multivariate analysis of variance provided. Factors of interest were patient characteristics, type of trial and main interviewer seeking consent. However data and details of analysis not reported.

Results

Trial participation
Intervention group: n=23 (82%) Control group: n=27 (93%) p=0.25

Secondary outcome: confidence in doctors (based mainly on questions scored on a 5-point scale)
Intervention group: mean (SE)=73% (3) Control group: mean (SE)=73% (3) p=0.90

Secondary outcome: perception of doctor-patient relationship (based mainly on questions scored on a 5-point scale)
Intervention group: mean (SE)=77% (3) Control group: mean (SE)=76% (2) p=0.87

Secondary outcome: treatment decided on an individual basis (based mainly on questions scored on a 5-point scale)
Intervention group: mean (SE)=66% (3) Control group: mean (SE)=71% (3) p=0.17

Secondary outcome (knowledge of treatment and side-effects)
Intervention group: mean (SE)=82% (4) Control group: mean (SE)=56% (3) p=0.0001

Secondary outcome (knowledge of research aspects)
Intervention group: mean (SE)=73% (5) Control group: mean (SE)=59% (4) p=0.03

Secondary outcome (anxiety assessed by Spielberger State-Trait Anxiety Inventory: possible range 20-80)
Intervention group: mean (SE)=49 (2) Control group: mean (SE)=42 (2) p=0.02

Author's conclusion: The main effects of total disclosure of all information compared to an individual approach to seeking consent were: a better understanding of treatment and side effects and of research aspects of the treatments, less willingness to agree to randomised treatment and increased anxiety.

Comments: The authors state that adjusting for patients' characteristics, type of trial and main interviewer seeking consent led to similar conclusions (results of multivariate analysis of variance not reported). 80% of participants completed the questionnaires 3 to 4 weeks later and there was no significant difference between the intervention and comparison group (data not reported).

Quality assessment		
Was the method used to assign patients really random?*	Unclear	**Comments:** Authors state that patients were stratified on the basis of age and type of randomised trial for which treatment was sought and balance randomisation was used. No further information provided.
Was the allocation to intervention concealed?	Unclear	**Comments:** Sealed envelopes were used. No further information provided.
Was loss to follow-up less than 80%?	Yes	**Comments:**
Was it similar across groups?	Yes	Comments:
Was a valid ITT analysis carried out?	No	**Comments:**
Did the design protect against contamination?	No	**Comments:** The same doctors were involved in the intervention and comparison. An attempt was made to establish whether the intervention and comparison were standardised across patients. However, it was not possible to establish whether the method used was sufficiently rigorous.
Did the design protect against performance bias?	No	**Comment:** No blinding. Undefined aspects of consultant behaviour may have been important.

Further comments:
The authors state that the study was underpowered to detect a difference in trial participation rates between groups.

Was the nature of the intervention clear?	Yes	**Comments:** The intervention and comparison were described. However the intervention is complex varying in content and in whether there was written or verbal consent.
Was the target of the intervention clearly defined?	Yes	**Comments:** Information on patient characteristics provided and inclusion criteria specified. Information was provided on patients who were eligible for one of the treatment RCTs but were not included in the study. However, no information was available on the nature of the RCTs.

General comments on relevance/applicability
Written informed consent is currently required in the U.K. therefore the comparison intervention is not an option. Trial participation rates were high in both groups.