Chapter 1 - Introduction

1.1 Background

In the practice of evidence based medicine, randomised controlled trials (RCTs) provide the best evidence for evaluating treatment effects. One of the major challenges to the conduct of randomised controlled trials is the recruitment of adequate numbers of participants. In trials involving children, the problem of recruitment is more pronounced, with many paediatric trials having only small numbers of participants. Although recruiting children is often difficult, little is known about this important subject to help researchers working with children.

1.2 Aims

The aims of this thesis are to explore and analyse factors that impact on the recruitment of children to randomised controlled trials and to identify elements that can be modified to improve children's participation in trials in the future. This will be achieved by:

- summarising the literature on the effectiveness of different methods of recruiting study participants to RCTs;
- exploring and analysing attitudes of paediatricians to RCTs involving children;
- analysing and comparing paediatricians' and adult physicians' treatment philosophies and attitudes to RCTs participation;
- exploring and analysing attitudes of parents to RCTs involving children.

1.3 Overview of chapters

This thesis contains both qualitative and quantitative research, and explores issues surrounding the recruitment of children to RCTs. Research into research methodology is a relatively new area of enquiry, with previous work mostly confined to research methodology used in adult research. Although much has been learned about the recruitment of adults to trials, little is known about factors influencing decisions for trial participation for children. **Chapter 2** contains a review of the literature on research regarding children's participation in randomised controlled trials in the context of research on adult recruitment to trials and barriers to trial participation.

How do researchers recruit participants to RCTs? Although many different recruitment strategies have been used to facilitate the recruitment of study participants for RCTs, the relative effectiveness of each has not been assessed. The systematic review described in **Chapter 3** systematically reviews and summarises the literature on the effectiveness of different methods of recruiting study participants to RCTs and identifies effective and ineffective strategies. Because of the small number of RCTs available on this subject, the systematic review was expanded to also include observational studies.

As doctor-related factors have been identified in the adult literature as one of the main causes of poor trial recruitment, it is important to explore paediatricians' attitudes to RCTs involving children, and identify possible barriers to trial participation. It is hypothesised that paediatricians are more hesitant about children's participation in RCTs (compared with adult physicians), and that doctors' previous research

experience may have a positive influence on attitudes to trial participation. This thesis examines paediatricians' attitudes to children's participation in trials by qualitative analysis of focus group discussions (**Chapter 4**). It also quantitatively compares questionnaire responses between paediatricians and adult physicians on their treatment philosophies and attitudes to RCT participation (**Chapter 5**).

It is equally important to explore and analyse parents' attitudes to children's trial participation, and attempt to understand how parents make this decision. It is hypothesised that parents' decision making processes are influenced by their perception of risks and benefits for trial participation, their doctors' advice, their child's illness severity and their attitudes toward research and their child's involvement. This thesis explores parents' attitudes to children's participation in randomised controlled trial by qualitative analysis of focus group discussions and identifies important factors in parents' decision making process for trial participation (**Chapter 6**).

1.4 Conclusion

Evaluating therapies by RCTs involving children is essential for their health and well-being. The success of RCTs involving children depends on effective recruitment. This thesis is the only extensive work which addresses this issue, and plays a key role in understanding paediatricians' and parents' attitudes to children's participation in trials. The systematic review of literature on the effectiveness of recruitment strategies for RCTs is much needed for both adult and paediatric trials. Future research in the development of ethical and appropriate recruitment strategies for paediatric trials is needed to ensure that trials for children can be completed in a cost effective and

timely manner thus improving evaluation of therapies and minimising unanticipated adverse effects for children.

Chapter 2 - Literature Review

2.1 Randomised controlled trials

2.1.1 The role of randomised controlled trials

The last decade has seen the growth of the "Evidence Based Medicine" movement which is founded upon the ideal that decisions for patient care should involve the "conscientious, explicit and judicious use of current best evidence" (3). Randomised controlled trials (RCTs) and systematic reviews of RCTs provide the highest level of evidence for intervention questions and have become the "gold standard" by which the treatment recommendations are judged (1;2;4). Traditionally, decisions for patient care were based on personal experience, anecdotal case histories or non-random comparisons of groups of patients, which were subject to many biases. The randomised trial, allegedly first introduced in 1947 (5), provided a study design that resulted in a much more reliable estimate of the relative effects of different interventions. It has the potential to prevent the propagation of worthless treatments and confirm the value of effective treatments. It also allows identification of moderate benefits that would otherwise be obscured by bias and random effect (6). For example, the benefits of RCTs are clearly demonstrated by the improved five-year survival for childhood acute lymphoblastic leukaemia from 25% to over 70% as a result of evaluating therapies by multicentre trials (7).

2.1.2 Ethics of randomised controlled trials

The Nuremberg Code formulated in 1947 as a response to the inhumane experimentation conducted in Nazi camps (8) and the Declaration of Helsinki in 1964 (9) form the basis of ethical guidelines for involving human subjects in research.

There is a general ethical principle that the potential benefit of research (to the participant and to society as a whole) should outweigh the potential risks involved. The fundamental ethical issue surrounding clinical trials reflects a conflict between the need to safeguard individual patients versus the obligation to society to facilitate research which will result in improved outcomes for all in the future.

The ethical grounds for conducting RCTs arise from clinical equipoise, a state of collective uncertainty within the expert medical community about the relative merits of alternative treatments (10). For example, when there is a promising but unproven new treatment that may offer advantages over the standard treatment, or when there is a split in opinion within the clinical community about best treatment, a RCT is justified. It is argued that RCTs are justified if the following criteria are met (11):

- true clinical equipoise is present;
- the trial is designed as a crucial experiment between therapeutic alternatives;
- an institutional review board has reviewed and approved the protocol;
- it is certified that no physician has a conflict of interest or incentive that would threaten the physician-patient relationship;
- comprehensive informed consent has been obtained;
- placebos are not used if an effective treatment exists;
- a data monitoring committee will either end the trial when clinical equipoise is displaced by statistically significant data or will supply doctors and patients with significant safety and therapeutic information relevant to a reasonable person's decision to remain in or withdraw from the trial;

- the physicians have the right to recommend withdrawal and the patients have the right to withdraw at any time.

The public perception of clinical trials as experimentation involving patients being used as guinea pigs has led to a pronounced distinction being made between clinical practice and clinical research. It is often seen as more acceptable to use an untested medication on patients than to enrol them in a RCT where the effects of interventions can be monitored and pooled to provide information. A double standard exists whereby a treatment given outside a clinical trial is less stringently reviewed than a protocol treatment. Some have argued that where clinical equipoise exists, it is unethical not to recommend trial entry to eligible patients, because the doctor is implying he or she knows the best treatment despite the agreed lack of scientific proof (12).

2.1.3 Randomised controlled trials involving children

There is general agreement that involvement of children in trials is not merely desirable but necessary for the promotion of their health and well being (13). Clinicians are often faced with a lack of evidence when making treatment decisions because of a paucity of RCTs involving children. Too often, clinical decisions about the care of children are based on research conducted in adults or even no research at all (14). Indeed, many medications given to children are off label (prescribed for children despite being approved only for adults), unlicensed (not licensed for use in children), and often without adequate pharmacokinetic or safety data for children (15-19). For example, only 5 of the 80 drugs most frequently prescribed for children in the US have Food and Drug Administration (FDA) approval for children. It is argued that

extrapolation from adult studies is inappropriate because children are different from adults and their disease processes, drug metabolism and effects of intervention often differ (18). Treatments that are effective and safe in adults are not necessarily so in children. For example, many drugs including aspirin, tetracycline, thalidomide and chloramphenicol, which are safe for adults have specific adverse effects in children. Extrapolation from adult studies and treating children with untested drugs is therefore fraught with danger.

Voluntary informed consent by research participants is a fundamental prerequisite to the conduct of all health research, and the cornerstone of the Nuremberg Code (8). In research involving children the issues of consent by proxy by the child's parents or guardians and the age when children can competently give legally effective consent are controversial and hotly debated (13). Many guidelines stipulate that the child's assent should also be sought if they are old enough to comprehend their participation in research (20). The National Commission for Protection of Human Subjects of Biomedical and Behavioral Research established age 7 as a reasonable minimum age for involving children in the assent process (20).

More recent guidelines have also added a number of other conditions specifically designed to protect children. These include that children may participate only if the research cannot equally well be done on adults and the purpose of the research is to obtain knowledge relevant to the health needs of children. Some guidelines also recommend that older children be used before younger children, that the research be designed and carried out by people experienced in doing research with children and limiting the number of participants to what is scientifically and clinically essential (13).

2.1.4 Legislation for inclusion of children in trials

There has recently been a shift in the scientific community's attitudes, as the importance of clinical trials in children is increasingly recognised (21). Some view the trialling of drugs on adults before offering trials to children as depriving children of potentially useful therapy (22). Many government and research bodies are developing guidelines for the inclusion of children in research (23-30). The United States of America (US) has led the world in instituting legislative changes to address this issue. The FDA's Pediatric Rule of 1998 requires that new therapies or new indications for existing therapies that will be used by children have to be studied in children. Unfortunately, this regulation was suspended by court action in the US District Court for Columbia on October 17, 2002 (31) after being contested by several groups including the Competitive Enterprise Institute and the Association of American Physicians and Surgeons (32). However, the US Secretary of Health and Human Services and the FDA Commissioner are currently urging the US congress to codify the regulation and make it law, which would make the court action moot. The FDA Modernization Act (FDAMA)'s Pediatric Exclusivity Provision (1997- Dec 2001) (23) also provided incentives for industries to conduct paediatric studies by offering an additional six-month market exclusivity to existing patents or exclusivity period for all products that have been trialled in children. This exclusivity was reauthorised in the Best Pharmaceuticals for Children Act (Jan 2002). However, there is no legislation regarding paediatric licensing in Australia and Europe.

2.2 Participation in randomised controlled trials

2.2.1 Benefits

Participants of RCTs often derive many benefits from trial participation, including having an opportunity to access new treatments which may not be routinely available. The treatment offered to the control group represents the current best standard treatment while those allocated to the experimental group receive a treatment hypothesised to be as good or better than standard treatments. It can therefore be argued that well designed RCTs offer patients the optimum treatment approach (12;33). There may also be benefits for patients who receive treatment at a hospital or institution involved in RCTs, as doctors who participate in clinical trials are more likely to incorporate trial findings and published data into clinical practice (34).

There is an emerging body of literature demonstrating inclusion benefits for all trial participants (35). The improved outcomes of trial participants have also been noted in RCTs involving children (36). Participants of RCTs, including those assigned to a placebo arm, are found to have similar or improved outcomes compared with eligible non-participants. Participants have lower mortality, fewer clinical events and lower complication rates when compared with similar patients treated outside trials. This “survival advantage” is not explained by differences in pre-treatment disease status or factors of known prognostic significance (37). The improved outcomes may reflect volunteer bias, but may also be partly due to closer monitoring and better care of trial participants.

2.2.2 Risks

What constitutes acceptable risks for children participating in research is currently under debate. Most guidelines on research involving children draw a distinction between therapeutic research (which is intended to be of direct benefit to the participant), and non-therapeutic research (which is intended to produce knowledge of general importance with no direct benefit the participant). Higher degrees of ethically permissible risk are allowed in therapeutic research than non-therapeutic research involving children (13). Other potential risks of trial participation for children such as psychological trauma are increasingly being recognised and assessed (38;39).

2.2.3 Recruitment to trials

Recruitment is fundamental to RCTs, as the power of the study to detect a statistically significant treatment effect is directly related to the size of the trial. However, despite the rigorous scrutiny by ethics committees to ensure that RCTs are safe and ethical, and despite the benefits to participants and society, the majority of eligible people do not participate in RCTs (40-42). Participation rates are low in many trials (3%-20%), recruitment generally takes longer than investigators initially anticipate, and costs of recruitment can range from 4% to 16% of the total study budget (40;43). Problematic recruitment is the most common cause of delays, increased costs and failure to complete trials (44).

Most paediatric RCTs have only small numbers of participants (e.g. a review of trials published in “Archives of Disease in Childhood” from 1982 to 1996 showed that half of the trials had 40 or less participants in total) (14), and are therefore usually

inadequately powered to detect small or moderate treatment effects which may be of clinical significance (14;45). Although problems with recruitment are not new, the study of issues surrounding recruitment to trials has only emerged in the last few years.

Although much is known about reasons for poor recruitment to adult trials, little is known about paediatric recruitment. The reasons for low accrual rates for adults participants are multifactorial. There are factors relating to the doctor, the patient and the trial itself that influence willingness to participate in trials. One large review article identified 84 papers which reported findings relating to recruitment of clinicians or patients to clinical trials (41). The following describes what is known about trial participation for adults.

2.3 Research on barriers to trial participation in adults

2.3.1 Doctor factors

With the advent of RCTs, doctors often have to perform both the roles of scientists and clinicians, roles that were previously quite separate. Taylor believes that doctors' reluctance to participate in RCTs is a foreseeable consequence of the attempt to integrate these conflicting roles (46).

Doctors' reluctance to enrol patients is one of the most significant obstacles to trial success (47-49) as patients will rarely participate in a RCT unless actively recommended to do so by their physician (50;51). The major reason for nonparticipation in RCTs by eligible patients is physician preference. Extensive

literature has been written about doctors' barriers to trial participation (41;46;49;52-57). Common physicians' barriers include forgetfulness or lack of awareness of trials that are open for accrual (57;58), time (54;55;58-60) and financial constraints (61), the extra work involved for physicians (51), lack of resources including data management for trials (56), lack of rewards and recognition (46;53), difficulty with ethics requirements and the informed consent procedures (51;55;62), problems with complying with the protocol (55;56;60), concerns about the effect on the doctor-patient relationship (55;60;62;63), discomfort with randomisation (40;64), preference for a particular treatment (40;54;55;60), dislike of loss of autonomy (62) and open discussion involving uncertainty (55), mistrust of researchers (57), fear of losing patients (40;57), perceived conflict between the roles of caregiver and scientist (46;55) and concerns about the patient (40) such as feeling personally responsible for treatment failures (55).

2.3.2 Patient factors

The ultimate success of a RCT depends on patient participation. Many theories have been postulated to explain the variations observed in clinical decision making behaviour, including decisions for trial participation. The core issues include the probability of an expected outcome, the patient's (or parent's) perception of the severity of that outcome, the patient's (or parent's) or physician's idea of the probable usefulness of participating in a trial in affecting that outcome and the perceived risks or cost of trial participation (47).

Common reasons why patients participate in trials include recommendations by their doctor (65), altruistic reasons (such as benefiting others and advancing medical

knowledge) and to get the best care (66;67). There are many studies on patient barriers to trial participation. Barriers identified include additional demands on patients (such as extra procedures, time pressures, travel and extra costs) (66;68;69), patient preference for a particular treatment (41;69;70), fears of uncertainty and being an "experimental subject" (41;44;68), fear of being randomised to the less effective treatment (71), issues of consent and information (65), and the influence of significant others (41;71).

A number of demographic characteristics such as severity of illness, level of education, age and sex are suggested to be associated with willingness to participate in trials. However, the evidence is equivocal and conflicting in some instances (40;41;72) .

2.3.3 Trial factors

Physicians or patients may be concerned about certain aspects of the trial itself, which may impede participation. The trial question may be considered unimportant or irrelevant. There may also be concerns about the trial design (that the protocol is too complex or incompatible with normal clinical practice, the treatment being offered is too toxic or the control arm is not considered standard therapy).

The rationale for random allocation of treatment and the use of placebo is generally poorly understood (49;73). Many are discouraged from trial participation because of the presence of a placebo arm (74). It is also more difficult to recruit for trials where there is a large difference between treatment arms (e.g. between surgery and radiotherapy).

2.4 Research on barriers to trial participation in children

Recruitment issues in paediatric and adult RCTs are thought to be quite different (75). Although there has been no published data, it is postulated that the recruitment of children to RCTs is more difficult than the recruitment of adults (76) with the exception of paediatric oncology trials (75;77). The contrast between recruitment for paediatric and adult oncology trials is striking (75).

Childhood cancer is comparatively rare and referral patterns to tertiary (usually academic) centres are well-established. Paediatric cancer centres have long been organised into national and multi-national paediatric cancer cooperative groups which enrol high proportions of incident paediatric cancer cases in the population into clinical trials. Approximately 94% of children in the US younger than 15 years of age who have been diagnosed with cancer are seen at a multi-national paediatric cancer cooperative group (78). Through such paediatric cancer trial groups, the power of systematic clinical trials to improve outcomes has been amply demonstrated (79). This, together with widespread participation in trials, has combined to create a culture in which there is almost a fusion between clinical research and clinical practice in the field of paediatric oncology. The high participation rate in clinical trials of children with cancer (75) stands in marked contrast to the mere 2-3% of adults with cancer who are participating in trials (80). There are a variety of practical as well as philosophical reasons for the low rates of accrual to adult oncology trials, such as more widely dispersed and variable patterns of cancer care providers, as well as economic pressures (81).

2.4.1 Doctors' barriers

Very little is known about the recruitment of children to RCTs as previous research on recruitment of participants focuses on adult trials (55;64;72;82;82). Although much is known about doctors' barriers to trial participation for adults, little is known about paediatricians' attitudes to trials. There is one article about informed consent for trials in children, which suggests that paediatricians find obtaining informed consent for trials burdensome (83), and may preferentially approach certain parents (e.g. of patients who are less severe in illness) for trial participation, hence affecting the generalisability of the trial.

2.4.2 Children's barriers

There has been only one study on children's response to trial participation (84). This study assessed why adolescent diabetic patients refused to participate in a RCT of intensive therapy for diabetes. Cited reasons for nonparticipation include inconvenience (increased visits and transport difficulties) and dislike of extra blood tests and insulin injections.

2.4.3 Parents' barriers

There are several studies on parental response to their child's participation in trials, comparing consenting parents with those who refused trial participation. Motivators for trial participation that were identified include altruistic reasons and doctors' advice, and barriers to participation include inconvenience and safety concerns (65;85-88). Zupancic found that parents are influenced by risk and benefit assessments, attitudes

towards research and the integrity of the consent process when making consent decisions on behalf of their infants (88). It is debatable whether parental sociodemographic characteristics influence recruitment. Two studies identified parental attributes influencing willingness to participate in trials (68;89;90). Harth and Thong found that parents who volunteer their children for clinical trials were less educated and were from lower socio-economic groups, had less social support, consumed more habit-forming substances and displayed greater health-seeking behaviour than parents who declined participation (68;90). In contrast, the study by Zupancic found that sociodemographic characteristics did not significantly influence recruitment (88).

Several studies found that parents have a poor understanding of trials and the informed consent process (65;73;91). There is one study on the readability of paediatric biomedical research informed consent forms which suggests that the readability factor may compromise the informed consent procedure (92).

2.5 Recruitment strategies for trials

The study of recruitment strategies is a relatively new area of inquiry, with much of the work focusing on recruitment to non-randomised studies (such as to questionnaires (93-95), cohort studies (96) and epidemiological studies (97)), to screening programs (such as pap smear (98;99), mammography (100;101) and osteoporosis screening (102)), and to health promotional activities (such as smoking cessation(103-105), vaccination (106), blood donation (107;108) and alcohol (109), nutritional (110) and exercise programs (111)).

In the past, recruitment for RCTs has been by trial and error (112). More recently, with the recognition of the importance of the use of appropriate recruitment strategies, a number of different suggestions have been proposed to ensure adequate recruitment (41). These include better planning and monitoring of recruitment, and employment of recruitment methods such as the use of registries, occupational screening, neighbourhood recruiting, digital telephoning, media promotion, community campaigns, the offer of incentives, mass mailing and target mailing (40;41;43). Others have assessed different methods of communication such as written information using various writing styles (113;114), instructional audiotapes and videotapes, computer programs, personal communication and by presenting or framing the information in a certain way (115). Interestingly, full disclosure of information preserves patient autonomy and improves recall and understanding of information, but may reduce recruitment to clinical trials (116;117). Some have looked at different methods of obtaining informed consent (118). Zelen proposed a controversial randomised consent design whereby patients are randomised and consent is sought only from the patients randomised to the experimental arm (119;120). However, the relative effectiveness of each method remains unclear, and researchers continue to recruit by trial and error, wasting precious time and resources on inefficient methods (41).

There have been very few studies on recruitment strategies used for paediatric trials. Parental consent for trials is higher during a child's acute illness (e.g. children recruited from the emergency room and hospital admissions versus those identified through outpatient records (70); the proportion of parents who enrolled their baby into a clinical trial which required early entry was higher than those who enrolled in a

study which asked for later consent (71% vs. 43%) (121)) These differences in consent rates may reflect parental response to a “sense of urgency” during their child’s acute illness.Collet found the provision of group meetings for parents by highly qualified physicians to discuss trial participation helpful (76). The ethics of payment for children’s participation in research to encourage recruitment is a contentious issue (122;123), as almost 25% of paediatric trials offer payment to participants. This can be in the form of reimbursement, compensation, appreciation or incentive payments. There is concern that payment may distort parents’ and children’s decision-making. However, non-payment is unfair and may add unnecessary financial obstacles to trial participation. Very little is known about effective recruitment strategies for children.

The issue surrounding the recruitment of study participants for RCTs is a relatively new area of enquiry with little known about the recruitment of children. It is imperative to research this very important area as the demand for the inclusion of children in RCTs increases.

Chapter 3 - Recruitment strategies used to encourage participation in randomised controlled trials (systematic review)

3.1 Introduction

There is increasing reliance on RCTs for clinical and regulatory decision making. Recruitment of participants is often difficult (43), with poor recruitment reducing the power of studies to detect significant intervention effects (124) causing delays, increasing costs and ultimately leading to failure to complete trials in some cases (44).

In the past, recruitment has been by trial and error (112). More recently, novel strategies have been developed to facilitate adequate and timely recruitment (124;125). The aim of this systematic review is to assess the effectiveness of different methods of recruiting study participants into RCTs, which will help researchers in planning trials, as the success of future RCTs depends on cost-effective means of recruiting participants (126).

3.2 Methods

3.2.1 Inclusion and exclusion criteria

A systematic review of the literature was undertaken to include all experimental and observational studies comparing methods of recruiting study participants to RCTs (including 2 mock RCTs). Inclusion criteria were studies which compared methods of recruiting study participants to the same RCT or trials, where consent rates and proportion recruited by each method could be calculated. Exclusion criteria were studies comparing recruitment at different locations using the same recruitment

methods, studies where consent rates or proportion recruited by each method could not be calculated, and recruitment to non-randomised studies (e.g. recruitment to observational studies, questionnaires, health promotional activities and other healthcare interventions). Where more than one publication of the same study exists, the publication with the most complete data was included. It was necessary to expand the inclusion criteria to observational studies for assessing strategies for enhancing study participants for RCTs as there are very few RCTs of recruitment strategies for trials (with only 6 identified at the time the search was first commenced in 2000).

The search was limited to recruitment for RCTs because the effectiveness of recruitment strategies is hypothesised to vary depending on the type of research studies for which participation is sought (e.g. for questionnaire response compared with RCTs participation). Also, there is currently a Cochrane protocol for a systematic review of strategies to improve recruitment to research studies (127) which was submitted after 2000, when the search for this project was first commenced.

3.2.2 Searching

A comprehensive search of electronic databases included Medline (1966 to October Week 5 2002), Embase (1980 to 2002 Week 45), and the Cochrane Library (Cochrane Library 2002 Issue 4). Due to the time required to design appropriate methods for data analysis, the initial search was updated (November 2002) closer to the time of writing. The search strategy incorporated the “PICO” concept which identified “population” (potential participants for RCTs participation), “intervention” (recruitment strategies), “comparison“ (other recruitment strategies) and “outcome” (consent or enrolment to RCTs). In Medline and Embase, the “population” was

represented by “clinical trials” (exploded), the “intervention” and “comparison” were represented by “recruit$” and the “outcome” was represented by “recruit$ or enrol$ or accru$”. In the Cochrane Library, the “population” was represented by “random and trial”, the “intervention” and “comparison” by “recruitment” and the outcome by “consent or accrual” (see search strategy below).

For MEDLINE <1966 to October Week 5 2002>

and EMBASE <1980 to 2002 Week 46>

(recruit$ or enrol$ or accru$).tw.

exp Clinical Trials/

1 and 2

For the Cochrane Library (2002 Issue 4)

recruit* and (random* and trial*) and (consent or accru*)

Reference lists of relevant studies, reviews and proceedings of scientific meetings were also searched, and investigators known to be active in the field were contacted to ask about unpublished trials (ie the “grey literature”). Although it is important to attempt to identify unreported trials by searching the “grey literature”, as this reduces publication bias, this method has limitations as it is difficult to know how much unreported research exists. To further reduce bias, non-English language papers were translated.

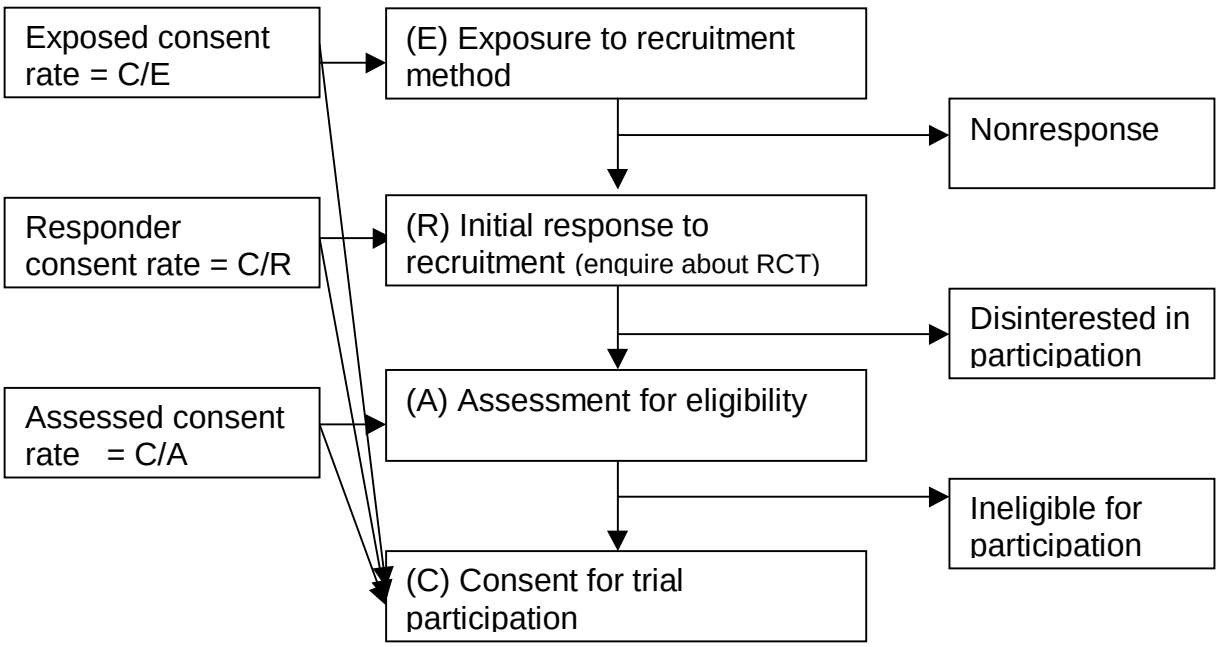
3.2.3 Data extraction

Two reviewers independently screened all titles or abstracts identified by the search strategy to identify potentially eligible studies which were then retrieved. Two reviewers independently assessed each paper retrieved and extracted data using a standard form (Appendix A), without blinding to authorship (Figure 3.1, the flow diagram for RCTs recruitment). The quality of the study and primary and secondary outcome measures were sought. Disagreements were resolved by discussion with a third reviewer.

For RCTs, the quality items allocation concealment, blinding of outcome assessors, loss to follow up and intention to treat analysis were assessed separately using the method developed by the Cochrane Renal Group (128). These quality items are known to influence the true treatment effect (129). A study was classified as quasi RCT if allocation of recruitment method was clearly not random (e.g. sequential or alternate allocation).

For observational studies, the quality items assessed were study type, blinding of outcome assessors, loss to follow up (for prospective cohort studies only), contamination between interventions, and adjustment for known confounders. These quality items were chosen because that have been postulated to influence true treatment effects (130-132)

Figure 3.1: Flow diagram of RCTs recruitment



Exposure consent rate = trial participants/those exposed to recruitment method
Response consent rate = trial participants/those who initially responded to recruitment method
Assessment consent rate = trial participants/those exposed to the recruitment method who underwent assessment for eligibility

The consent rate was the primary outcome of interest. Three consent rates were calculated capturing distinct stages of the recruitment process (Figure 3.1):

- from the time potential participant's were initially exposed to trial information (exposed consent rate: the number of participants who enrolled in the trial following exposure to that method divided by the total number of potential participants exposed to that method):
- to when interested responders enquire about the trial (responder consent rate: the number of participants who enrolled in the trial following exposure to that method divided by the total number of responders who enquired about the trial after exposure to that method):

- to when they are assessed for trial eligibility (assessed consent rate: the number of participants who enrolled in the trial following exposure to that method divided by the total number attending eligibility assessment after exposure to that method).

The secondary outcome measures were proportion enrolled by each method and recruitment cost per participant (ie the total recruitment cost for each method divided by the number of participants who enrolled by that method) for individual studies.

3.2.4 Data analysis

For comparison of consent rates and proportions enrolled by each method, studies were grouped into those that evaluated different categories of recruitment methods and those that evaluated variations of strategies within the same category. The studies were grouped in this way in order to compare consent rates and proportions between different categories of recruitment strategies where possible. For this group, the relative risk (RR) for consent rates for individual studies and summary effect measures were calculated in RevMan (133) using the random effects model, with RR greater than 1.0 indicating a more effective strategy. Heterogeneity was analysed using the Q statistic with an alpha of 0.1 used for statistical significance (134).

For studies evaluating recruitment strategy variations within the same category, proportion recruited by each method and “exposed consent rate” were considered together within each study. The “exposed consent rate” was considered significant if it was outside the 95% confidence interval of other methods. For example, in Leader’s study the exposed consent rates for the 2 methods were 0.9 (95%CI 0.0,1.8) and 9.7

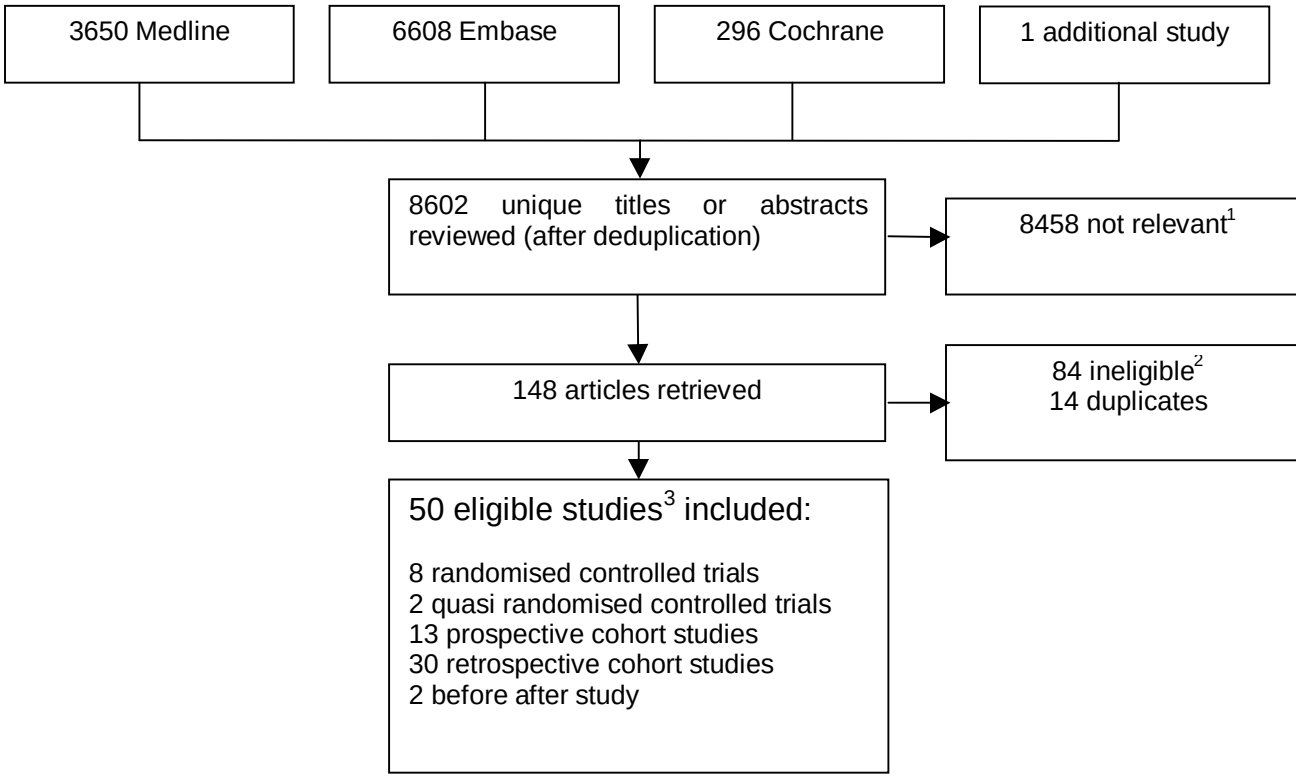
(95% CI 7.3,12.1). These exposed consent rates are significantly different from each other (see Table 3.5). The proportion enrolled by each method was considered significant if it was beyond expectation for the number of methods used in the study (i.e. 1/total number of methods used in the study). For example, in Leader's study, the proportion enrolled by the 2 methods were 7% and 93% when the expected proportion if there was no difference in the methods would be 50% for each method. The proportion enrolled by the 2 methods are significantly different from each other (see Table 3.6). This method of combining "exposed consent rate" and proportion recruited by each method was used for studies comparing variations of strategies within the same category of recruitment method because summary effect measures and meta regression of consent rates were difficult to measure in this group due to the small numbers of studies comparing the same variations within a category. This method was not used for studies comparing different categories of recruitment strategies because there were insufficient studies that provide data for calculating exposed consent rates in that group.

3.3 Results

3.3.1 Literature search

From 8602 unique titles, 50 eligible publications were identified assessing how over 4 million people were approached for RCTs participation, with 103,406 consenting to participate (Figure 3.2).

Figure 3.2: Search method for studies of recruitment strategies for systematic review



[1]Not relevant = study did not appear relevant to recruitment for RCTs from reading of title and abstract.
[2]Not eligible = 53 did not compare recruitment methods, 15 consent rates or proportions recruited by each method could not be calculated, 11 not about recruitment for RCTs, 3 comparing the same recruitment methods at different locations, 2 comparing recruitment between different trials.
[3]50 eligible studies (55 substudies) included.

3.3.2 Characteristics of included studies

The 50 eligible publications included data from 55 studies (Table 3.1, Appendix B). Three publications evaluated more than one method for assessing recruitment (135) and two reported 2 trials within the same publication (136;137).

Three publications evaluated more than one method for assessing recruitment (135) and two reported 2 trials within the same publication (136;137).

Eighty-seven different recruitment strategies were described which were grouped into 5 categories:

- personal methods (e.g. health care provider referral, recruitment by research staff, “word of mouth” referrals);
- community approach (community presentations, fliers, posters and screening at community sites, worksite recruitment);
- mailing (by mass mailing or direct mailing to people identified as potentially eligible);
- media (e.g. radio, television, newspapers);
- and other (e.g. different styles of giving informed consent, framing information about the trial, methods of information presentation and comparison of recruiter dependent variables).

Thirty-five studies assessed different categories of recruitment methods (Table 3.2) and twenty evaluated variations of strategies within one category (Table 3.3).

Table 3.1: Characteristics of included studies in the systematic review

STUDY TYPE	AUTHOR	HEALTH PROBLEM STUDIED	TRIAL TYPE	TRIAL DESCRIIPTION	Enrolled (n)	Approached for RCT (N)
RCT	Fleissig 2001	Cancer	multiple	Multiple RCTs of cancer therapies - chemotherapy, radiotherapy, endocrine, immune therapy and screening in adult cancer patients	205	265
	Martinson 2000	Smoking	prevention	Agreement to participate in a smoke cessation and prevention trial for adolescents	1560	4200
	Myles 1999	Mock trial for elective surgical patients	mock trial	Mock trial of an anaesthetic drug in adults scheduled for elective surgery	429	791
	Valanis2 1998	Lung cancer	prevention	Beta carotene and retinyl palmitate for the prevention of lung cancer in high risk individuals	(563)	(22546)
	Aaronson 1996	Cancer	treatment	Phase II or III clinical trials for cancer patients	146	346
	Gallo 1995	Mock trial for healthy subjects	mock trial	Mock trial of unnamed disease for healthy subjects attending a scientific exhibition	1623	2035
	Llewellyn-Thomas 1995	Mock trial for oncology patients	mock trial	Mock trial for outpatients cancer patients	52	100
	Wadland2 1990	Smoking	treatment	Nicotine gum for smoking cessation	(52)	(274)
QRCT	Wragg 2000	Mock trial for healthy subjects	mock trial	Mock trial of hormone replacement therapy for women	22	50
	Miller 1999	Depression	treatment	Psychotherapy and antidepressants for chronically depressed patients	50	347
PCS	Folmar 2001	Coronary heart disease	prevention	Effect of oestrogen vs oestrogen & progesterone vs placebo on coronary atherosclerosis in postmenopausal women.	305	73327+
	Gill 2001	Functional decline and disability in the elderly	prevention	A home-based physical therapy intervention trial to prevent functional decline in frail elderly	188	4637
	Bell-Syer 2000	Lower back pain	treatment	Trial of exercise class for improving subacute lower back pain in primary care patients	187	1588
	Margitic 1999	Physical inactivity	prevention	Interventions for increasing physical activity in sedentary adults	874	3908
	Fitzgibbon 1998	Cardiovascular disease in African-Americans	prevention	A community intervention to reduce fat intake in working class black people	420	5180
	Goodman 1998	Lung cancer	prevention	Beta carotene and retinyl palmitate for the prevention of lung cancer in high risk individuals	13186	1216549+
	Valanis1 1998	Lung cancer	prevention	Beta carotene and retinyl palmitate for the prevention of lung cancer in high risk individuals	(1502)	(42559)
	Adams 1997	Management of frail elderly	prevention	Trial of diagnosis and treatment of the elderly through outpatient geriatric assessment units vs routine physician care	442	1265
	Garcia-Losa 1995	Asthma	treatment	Drug treatment for mild to moderate asthma	24	465
	King 1994	Cardiovascular disease	prevention	Strategies for increasing activity in sedentary people age 50-65	357	2325
	Silagy 1991	Cardiovascular disease	prevention	Low dose aspirin for preventing cardiovascular disease in the elderly	400	697
	Wadland1 1990	Smoking	treatment	Nicotine gum for smoking cessation	94	2268
	Leader 1978	Cerebroarteriosclerosis	treatment	Vasodilator effects on the psychophysiological function of elderly people with moderate cerebroarteriosclerosis	60	1030
RCS	Kusek 2002	Cancer	prevention	Doxazosin/finasteride combinations vs placebo in preventing benign prostatic hyperplasia progression	2931	16723
	Tworoger 2002	Obesity	treatment	Moderate intensity exercise vs stretching in affecting body changes obese postmenopausal women	173	103577+
	Cambron 2001	Dysmenorrhoea	treatment	Lower back spinal manipulation therapy vs low force mimic in subjective reduction of dysmenorrhhoea	138	2312
	Wright 2001	Hypertension	treatment	Antihypertensive and lipid lowering therapy for high risk hypertensives	42419	unknown
	Chung 2000	Prostatic cancer	prevention	Finasteride for preventing prostatic cancer in high risk males	82	184
	Theoret 2000	Low birth weight	prevention	Program to reduce the incidence of low birth weight infants for pregnant women with very low socioeconomic status	439	1272
	Appel 1999	Hypertension	prevention	Diet modification on BP of healthy subjects with high normal BP	459	710000+
	Camerini 1999	Breast cancer	prevention	Fenretinide for the prevention of contralateral breast cancer in breast cancer patients.	1815	4030
	Cooler 1999	Depression	treatment	Trial of antidepressant medications for depressed elderly	24	257
	Cosgrove 1999	Cardiovascular disease	prevention	Trial of antihypertensive drugs for hypertensive elderly	4736	343554
	Arnold 1989	Cancer	prevention	Synthetic retinoid etretinate vs placebo in reducing level of bronchial atypia in heavy smokers	80	905
	Lewis 1998	Obesity	prevention	Reduction of dietary fat in postmenopausal women	2208	12434
	Coleman 1997	Falls and disability in elderly African-Americans	prevention	A community based intervention for reducing disability and falls in African-American elderly	120	262
	Whelton 1997	Hypertension	treatment	Weight loss and sodium reduction following withdrawal of antihypertensives for well controlled hypertensive elderly	975	8787
	Isaacman2 1996	Bacteraemia	diagnostic	Blood culture collection strategies for detecting bacteriaemia in febrile children	(157)	(532)
	Anderson 1995	Diabetes care	prevention	Trial of an intensive diabetes program for elderly diabetics	103	429
	Hollis 1995	Hypertension	prevention	Weight loss and sodium reduction in reducing hypertention in high risk population	2382	3089726
	Maurer 1995	Knee osteoarthritis	treatment	Quadriceps strength training for older adults with knee osteoarthritis	108	263
	Moon1 1995	Skin cancer	prevention	Retinol for the prevention of skin cancer among high risk individuals	2800	11000+
	Moon2 1995	Skin cancer	prevention	Retinol for the prevention of skin cancer among high risk individuals	525	1482
	Piotrowski 1994	Crack cocaine dependence	treatment	Crack-cocaine dependence treatments (drugs and psychotherapy combinations) for crack-cocaine dependent males	94	379
	Bjornson-Benson 1993	Chronic obstructive lung disease	prevention	Intervention program (smoking cessation and bronchodilators) to reduce the rate of lung function decline in patients with early chronic obstructive pulmonary disease (duplicate).	(189)	(1626)
	Carew1 1993	Congestive heart failure	treatment	ACE inhibitor vs placebo in treatment of patients with congestive heart failure	1647	55069
	Carew2 1993	Congestive heart failure	prevention	ACE inhibitor vs placebo in preventing congestive heart failure in patients with left ventricular dysfunction	2502	(see Carew1)
	Connett 1993	Chronic obstructive lung disease	prevention	Intervention program (smoking cessation and bronchodilators) to reduce the rate of lung function decline in patients with early chronic obstructive pulmonary disease.	5887	(73684)
	Kusek 1993	Renal failure	prevention	2 studies of different levels of protein/phosphorus intake and BP in reducing rate of decline in renal function in patients with chronic renal disease.	840	4300
	Rudick 1993	Chronic obstructive lung disease	prevention	Intervention program (smoking cessation and bronchodilators) to reduce the rate of lung function decline in patients with early chronic obstructive pulmonary disease (duplicate).	(577)	171602
	Burns 1990	Urinary incontinence	treatment	Behaviour treatment for stress urinary incontinence in elderly females	135	1042
	Schoenberger 1987	Coronary heart disease	prevention	Aspirin for the prevention of coronary heart disease in acute myocardial infarct patients	4524	5396+
	*Anon 1983	Coronary heart disease	prevention	Lowering of plasma cholesterol to reduce coronary heart disease in males	3810	436679
BAS	Isaacman1 1996	Bacteraemia	diagnostic	Blood culture collection strategies for detecting bacteriaemia in febrile children	166	534
	Brewster 2002	Cancer	prevention	Single visit cervical cancer prevention program vs usual care for low income Latino women with abnormal pap smears.	940	6041+
				Total	103,481	4,183,257

RCT = randomised controlled trials, QRCT = quasi randomised controlled trials, PCS = prospective cohort study, RCS = retrospective cohort study, BAS = before after study. ( ) indicates numbers not included in total

Table 3.2: Descriptions of strategies used in studies evaluating different categories of recruitment methods

STUDY TYPE	AUTHOR	RECRUITMENT METHODS			
		MEDIA	COMMUNITY BASED	MAILING	PERSONAL APPROACH
PCS	Folmar		Community presentations, fliers at community sites, hospital screening	Mass mailing & target mailing	
	Bell-Syer			Computerized medical record review with mailing to eligible patients	Referral by primary care physicians during routine office visit
	Margitic		Questionnaires in physicians' waiting room	Mass mailing	Referral by primary care physicians during routine office visit, telephone by research staff
	Fitzgibbon		House to house canvassing		Telephone by research staff
	Goodman	Magazines, local newspapers, radio & TV	Posters at community sites	Mass mailing, mailed advertising	
	Adams	Magazines, local newspapers, radio & TV	Community presentations, fliers at community sites	Mailing to people who may know of potential participants	Referral by healthcare provider, social service agencies and word of mouth, approach by research staff
	Garcia-Losa			Target mailing	By healthcare provider during office visit, phoned by nurse to attend standard visit, phoned by trial co-ordinator to participate in trial
	King	Newspapers, radio & TV + posters			Random digit dial telephone survey
	Silagy		Community presentations and brochures and posters at community sites + newspapers, radio	Target mailing & mass mailing using electoral roll lists	
RCS	Kusek 2002	Newspaper, newsletter, radio & TV	Community events, posters/display	Mass mailing	Referrals, word of mouth
	Tworoger	Newspapers, newsletters, TV and radio	Includes community presentations and fliers at community sites	Mass mailing	
	Cambron	Newspapers, radio & TV	Community college newspapers, posters, electronic sign		Word of mouth
	Chung	Newspapers, newsletters & TV	Community presentations, posters, community surveys, other methods including flies with paychecks		Referral by doctor, word of mouth
	Theoret		Posters and pamphlets at community sites	Mass mailing	Referral by healthcare provider and others including word of mouth
	Appel	Newspapers, newsletters, radio & TV	Coupon distribution, screening events and presentations	Mass mailing	Word of mouth and approaching prior study participants
	Camerini			Direct mailing or personal invitations to eligible patients identified by medical record review	Referral by healthcare provider during hospitalization or at routine follow up visit
	Cooler	Newspapers, newsletters, TV & radio	Flyers at community sites, community and hospital presentations		Referral by healthcare provider, social service agency, religious organization and word of mouth
	Cosgrove		Screening in the general community, at senior citizen centers, shopping malls, nutrition sites, drug stores, social security office and libraries	Mailing using electoral roll & commercially purchased lists	
	Lewis	Magazines, newspapers, radio and TV	Community presentations and brochures at community sites	Mass mailing	Referral by healthcare provider + word of mouth
	Coleman	Magazines and community newspapers + flyers and brochures at community sites	Other methods including community presentations, TV media campaign and observing the trial in progress		Phonathon using a bank of phones and personal phone calls and by word of mouth
	Whelton	Newspapers radio and TV + coupons and placemats distribution	Screening at community sites, recruiting previous research participants, worksite presentations, bill board and bus advertisements	Mass mailing	Referral by trial participants and encouraging referral by healthcare providers (medical presentations, flyers and brochures, recruitment material in clinical areas)
	Anderson	Newspapers	Posters and brochures at community sites, community presentations	Target mailing	Referral by previous research participants and letter campaign for encouraging referral by healthcare providers
	Hollis	Newspapers, radio & TV	Screening at community sites	Mass mailing	Others including referral by healthcare providers and word of mouth + posters & brochures
	Moon1	Newspapers, radio & TV + posters and fliers at community sites			Referral by dermatologists during routine office visit
	Moon2	Newspapers, radio & TV + posters and fliers at community sites		Review of skin cancer registry with invitation to potentially eligible patients	Referral by dermatologists during routine office visit
	Maurer	Newspapers, specialty publications, radio + TV	Posters at hospital clinics	Target mailing	Letter campaign to encourage referrals by healthcare providers and by word of mouth
	Piotrowski	Newspapers & radio	Mailed fliers + posters on buses		Recruitment of inpatients by research assistant and referral by other treatment programs, the courts and by word of mouth
	Bjornson-Benson	Newspaper, radio & TV	Brochures at community sites + worksite screening and promotion	Mass mailing	word of mouth (with prizes incentives)
	Connett	Newspaper, radio & TV	Screening at community sites + worksite screening	Mass mailing	Others including referral from clinical laboratories and physician referral
	Kusek 1993	Newspaper & TV			Referral by health care provider and word of mouth
	Rudick	Newspapers, radio & TV	Shopping mall recruitment, community screening and trial promotion, worksite screening and other methods including referrals (health care provider and trial participants), mailed advertisements, promotional material at community sites and campaign for encouraging referrals	Mass mailing	Phone follow up of people who received mailing
	Burns	Regional and suburban newspapers + TV	Brochures and posters at community sites		Referral by healthcare provider
	Schoenberger	Newspapers, radio, TV			Medical record review with personal invitation by trial staff or their own physician to eligible patients, referral by private physicians or by physicians directly involved in the study during routine office visits
	Anon	Mass media	Community screening + worksite screening	Mass mailing	Referral by doctors, other clinical studies, blood bank + clinical laboratories
BAS	Brewster	Newspapers and fliers		Target mailing	

PCS = prospective cohort study, RCS = retrospective cohort study, BAS = Before after study, Mass mailing =nondirect mailing to people on lists etc, Direct mailing = mailing to people identified as potentially eligibl

Table 3.3: Descriptions of strategies used in studies evaluating variations in one category of recruitment method

STUDY TYPE	AUTHOR	RECRUITMENT METHODS					
TYPE OF CONSENT							
RCTs	Myles	One sided informed consent - random assignment for participants, standard care for nonparticipants	Prerandomised to experimental drug - experimental drug for participants, standard care for nonparticipants	Prerandomised to standard drug - standard drug for participants, experiemental drug for nonparticipants	One sided physician modified informed consent - patients are told that the physician believes that the experimental drug may be superior to the standard drug, and if they give consent, they have a greater chance of receiving the experimental drug	One sided patient modified informed consent - patients are told that they are allowed to increase or decrease their chance of receiving the new experimental drug after consenting	
	Gallo	One sided informed consent - random assignment for participants, standard care for nonparticipants	Prerandomised to experimental drug - experimental drug for participants, standard care for nonparticipants	Prerandomised to standard drug - standard drug for participants, experiemental drug for nonparticipants	Two sided informed consent - random assignment for participants, choice of treatments for nonparticipants		
FRAMING OF RECRUITMENT INFORMATION							
QRCT	Wragg	Explicit information framed in a way which provide the current best estimates of effect of the experimental treatment			Ambiguous information framed in a way which emphasised the current state of uncertainty about the relative costs and benefits of the experimental treatment		
PCS	Leader	Normative approach emphasising data gathering			Symptomatic approach focusing on early diagnosis and treatment		
INFORMATION PRESENTATION							
RCTs	Aaronson	Standard informed consent			Additional phone based contact with oncology nurse		
	Llewellyn-Thomas	Tape recording of reading of the trial information			Interactive computer program with participant actively involved in the information search process		
	Wadland2	Patients reading the trial information themselves			Study coordinator reading and explaining the study to patients		
RCS	Arnold	Daily newspaper	Weekly newspaper	TV news	Community TV	Radio	
MAILING							
RCTs	Martinson	Standard mailing with no incentives	Mailing with prepaid $2 cash	Mailing with $15 cash contingent on response	Mailing with $200 prize draw		
	Valanis2	Mailing of the full recruitment packet	Advanced postcard one week prior to mailing of recruitment packet				
PCS	Valanis1	First class postage with a letter signed by the principal investigator of the trial	First class postage with a letter signed by the medical director of the insurance company	First class non profit postage with a letter signed by the principal investigator of the trial	First class non profit postage with a letter signed by the medical director of the insurance company	First class postage of single page questionnaire mailer	Bulk rate postage of a single page questionnaire mailer
RECRUITER DEPENDENT VARIABLES							
RCTs	Fleissig	Standard - doctors recruiting patients without being shown patient's responses to questionnaire regarding personal preferences and trial participation			Doctors shown patients' responses to questionnaire regarding personal preferences and trial participation before recruiting patients for trial		
QRCT	Miller	Recruitment by senior investigator			Recruitment by research assistance		
PCS	Gill	Referral by primary care physicians during routine office visit			Identified by medical records, phoned then assessed in the home by research staff		
	Wadland1	By a private family practice located in a semi-rural town			By an academic general internal medicine practice with previous research experience located in the University Health Center		
RCS	Wright	Referral by private solo practices	Referral by private group practices	Referral by health maintenance organisations	Referral by community health centres	Referral by university academic medical centres	Referrals from department of veteran affairs medical centres
	Isaacman2	Recruitment by investigator physician			Recruitment by research nurse		
	Carew1	Radionuclide lab	Cardiac catheter lab	Echocardiogram lab	Other referral		
	Carew2	Radionuclide lab	Cardiac catheter lab	Echocardiogram lab	Other referral		
BAS	Isaacman1	Recruitment by physician investigator			Addition of a research nurse		

RCT=randomised controlled trial, QRCT=quasi-randomised controlled trial, PCS=prospective cohort study RCS=retrospective cohort study, BAS=before after study

3.3.3 Study quality

Of the 8 RCTs and 2 quasi RCTs included, only 1 had adequate allocation concealment, 2 mentioned loss to follow up and none mentioned blinding. It was unclear whether intention to treat analysis was used in any studies.

Of the 45 observational studies, exposure to the different recruitment methods was impossible to measure in the retrospective cohort studies, and may be difficult to measure for some methods such as media or community approach in any study. Although outcome measurements were similar between interventions in each study (enrolment or intention to participate in a RCT), none mentioned blinding of outcome assessors. In 8 studies, only the proportion recruited by each method was provided (with no data provided for consent rate calculations). Although known confounders (e.g. gender, level of education, socio-economic status) were acknowledged in some studies, they were not adjusted for in any of the studies. Contamination between interventions was likely in at least 28 studies where subjects could potentially be exposed to multiple recruitment methods (e.g. media and community approach). Of the prospective cohort studies, only 3 provided data for calculating exposure to the recruitment methods and only 1 mentioned loss to follow up.

3.3.4 Consent rates and proportions enrolled by each method in studies comparing different categories of recruitment methods

3.3.4.1 Consent rates (Table 3.4.1 to 3.4.4 and Figure 3.4: Forest plots for consent rates comparing different categories of recruitment methods):

Although the exposed consent rate most closely reflects the true effectiveness of exposure to the recruitment method, only 6 studies compared exposed consent rates. Health care provider referral had a higher consent rate than target mailing: RR 1.84 (1.08, 3.13). In the 2 studies that assessed media, media had lower consent rates than all other methods (research staff recruitment versus media RR: 604.90 (354.63, 1031.78); community approach versus media RR: 106.22 (6.02, 1872.87) and mailing versus media RR: 21.33 (14.08, 32.32)). The denominator used for media is based on expected audience numbers for radio and television and circulation for printed media. As radio and television audience and readers of newspapers may not necessarily have seen or heard the recruitment material, the denominator used may not be true, and may partly explain the high RR.

Seventeen studies compared responder consent rates. Health care provider referrals again had higher consent rates than other methods (health care provider referral versus community presentation: RR 1.37 (1.06; 1.78); health care provider referral versus worksite approach: RR 25.20 (20.19, 31.45); health care provider referral versus general community approach: RR 2.53 (0.46, 14.05) not statistically significant; health care provider referral versus mailing: RR 3.29 (1.26, 8.60); health care provider referral versus media: RR 2.66 (1.31, 5.41)).

Of the 16 studies comparing assessed consent rates, no significant difference in consent rates by method of recruitment was found. This consent rate was the least useful for evaluating the effectiveness of recruitment strategies as it measures eligibility of potential participants and not their willingness to participate in the trial. (See Figure 3.4 which compares exposed, responder and assessed consent rates between the different categories of recruitment methods).

Table 3.4.1: Consent rates and proportions by personal methods for studies evaluating different categories of recruitment methods (Part 1)

STUDY TYPE	AUTHOR	Method	# Enrolled	Exposed Consent Rate	Respond Consent Rate	Assessed Consent Rate	% Recruited by Method
PCS	Folmar						
	Bell-Syer	HCP referral	104	19 (16 , 23)			56
	Margitic*	HCP referral	12				1
		Research staff	189				22
	Fitzgibbon	Research staff	117	7 (6 , 9)			28
	Goodman						
	Adams	HCP referral	85		45 (38 , 52)		19
		Research staff	26	7 (4 , 10)	65 (50 , 80)		6
	Garcia-Losa	HCP referral	5			13 (2 , 24)	21
		Research staff	7	3 (1 , 5)	16 (5 , 26)	27 (10 , 44)	29
		Other	3	6 (-1 , 13)	25 (1 , 50)	25 (1 , 50)	13
	King	Research staff	214	1 (1 , 1)	2 (1 , 2)	11 (10 , 13)	60
	Silagy						
RCS	Kusek 2002	HCP referral	280		41 (37 , 44)	78 (73 , 82)	10
		WOM	122		35 (30 , 40)	81 (75 , 88)	4
	Tworoger						
	Cambron	WOM	27		7 (4 , 9)	41 (29 , 53)	20
	Chung	HCP referral	4		40 (10 , 70)		5
		WOM	5		22 (5 , 39)		6
	Theoret*	HCP referral	154				35
		WOM	184				42
	Appel*	WOM	90				20
	Camerini	HCP referral	990	54 (52 , 56)			55
	Cooler	HCP referral	2		20 (-5 , 45)		8
		WOM	0		0 (0 , 0)		0
		Other	1		11 (-9 , 32)		4
	Cosgrove						
	Lewis	HCP referral	183		10 (9 , 12)		8
	Coleman	Research staff	40	6 (4 , 8)	11 (8 , 15)	40 (30 , 50)	33
		WOM	31		( )	74 (61 , 87)	26
	Whelton	WOM	23		12 (8 , 17)	30 (20 , 40)	2
		Other	9		21 (9 , 34)	47 (25 , 70)	1
	Anderson	WOM	3			21 (0 , 43)	3
		Other	4			19 (2 , 36)	4
	Hollis	Other	105				4
	Maurer*	HCP referral	32				31
		WOM	0				0
		Other	0				0
	Moon1	HCP referral	279		100 (100 , 100)		13
	Moon2	HCP referral	187		100 (100 , 100)		44
	Piotrowski	Research staff	21		10 (6 , 15)		22
		WOM	19		54 (38 , 71)		20
		Other	30		44 (32 , 56)		32
	Bjornson-Benson	WOM	25			13 (8 , 17)	13
	Connett	Other	791			9 (8 , 9)	13
	Kusek 1993*	HCP referral	378				56
		WOM	47				7
	Rudick	Research staff	114			6 (5 , 7)	22
	Burns	HCP referral	0		0 (0 , 0)	0 (0 , 0)	0
	Schoenberger*	HCP referral	732				18
		Research staff	1828				44
	Anon	HCP referral	161		14 (12 , 16)	29 (25 , 33)	5
		Other	1229		1 (1 , 1)	23 (22 , 25)	35
BAS	Brewster						

* Consent rates cannot be calculated, PCS = prospective cohort study, RCS = retrospective cohort study, BAS = before after study, HCP = health care provider, WOM = word of mouth

Table 3.4.2: Consent rates and proportions by community methods for studies evaluating different categories of recruitment methods (Part 2)

STUDY TYPE	AUTHOR	Method	# Enrolled	Exposed Consent Rate	Respond Consent Rate	Assessed Consent Rate	% Recruited by Method
PCS	Folmar	General	198		6 (5 , 7)	2 (2 , 2)	65
	Bell-Syer						
	Margitic*	General	284				33
	Fitzgibbon	Presentations	303	8 (8 , 9)			72
	Goodman	General	57	( )	42 (34 , 50)	42 (34 , 50)	0
	Adams	General	5	0 (0 , 1)	42 (14 , 70)		1
		Presentations	223	5 (5 , 6)	32 (29 , 36)		50
	Garcia-Losa						
	King						
	Silagy	General	100			83 (77 , 90)	25
RCS	Kusek 2002	General	364		27 (25 , 30)	75 (71 , 79)	13
	Tworoger	General	12		3 (1 , 5)	18 (99 , 27)	7
	Cambron	General	20		6 (4 , 9)	35 (22 , 47)	15
	Chung	General	0		0 (0 , 0)		0
		Presentations	7		54 (27 , 89)		9
	Theoret*	General	24				5
	Appel*	General	109				24
	Camerini						
	Cooler	General	1		5 (-5 , 15)		4
		Presentations	1		17 (-13 , 47)		4
	Cosgrove	General	678		0 (0 , 0)		14
	Lewis	General	51		12 (9 , 15)		2
	Coleman	General	10			71 (48 , 95) ( )	8
	Whelton	General	57		7 (5 , 9)	28 (22 , 34)	6
	Anderson	General	3			13 (-1 , 27)	3
		Presentations	0			0 (0 , 0)	0
	Hollis	General	275	0 (0 , 1)			12
	Maurer*	General	19				18
	Moon1						
	Moon2						
	Piotrowski	General	22		33 (22 , 44.)		23
	Bjornson-Benson	General	36			10 (7 , 13)	19
		Worksite	23			8 (5 , 11)	12
	Connett	General	406			4 (4 , 4)	7
		Worksite	458			5 (4 , 5)	8
	Kusek 1993*						
	Rudick	General	69				13
		Worksite	103				20
	Burns	General	26		8 (5 , 10)	8 (5 , 10)	20
	Schoenberger*						
	Anon	General	535		1 (1 , 1)	21 (19 , 22)	15
		Worksite	904		1 (1 , 1)	18 (17 , 19)	26
BAS	Brewster						

* Consent rates cannot be calculated, PCS = prospective cohort study, RCS = retrospective cohort study, BAS = before after study

Table 3.4.3: Consent rates and proportions by mailing strategies for studies evaluating different categories of recruitment methods (Part 3)

STUDY TYPE	AUTHOR	Method	# Enrolled	Exposed Consent Rate	Respond Consent Rate	Assessed Consent Rate	% Recruited by Method
PCS	Folmar	Mass mailing	40	0 (0 , 0)	0 (0 , 0)	36 (27 , 45)	13
		Direct mailing	67	1 (0 , 1)	1 (1 , 1)	28 (22 , 33)	22
	Bell-Syer	Direct mailing	83	8 (6 , 10)			44
	Margitic*	Mass mailing	379				44
	Fitzgibbon Goodman Adams	Mass mailing	12240	1 (1 , 1)	10 (9 , 10)	10 (9 , 10)	95
		Direct mailing	52	0 (0 , 0)	37 (29 , 46)		12
	Garcia-Losa	Direct mailing	9	5 (2 , 9)	13 (5 , 21)	45 (23 , 67)	38
	King Silagy	Mass mailing	100	6 (5 , 7)		65 (57 , 73)	25
		Direct mailing	200	18 (16 , 21)		47 (43 , 52)	50
RCS	Kusek 2002	Mass mailing	783		11 (10 , 12)	77 (74 , 79)	27
	Tworoger Cambron Chung	Mass mailing	144	0 (0 , 0)	2 (2 , 2)	13 (11 , 15)	83
	Theoret*	Mass mailing	77				18
	Appel*	Mass mailing	194				42
	Camerini Cooler	Direct mailing	825	38 (36 , 40)			45
	Cosgrove	Mass mailing	4058	0 (0 , 0)	3 (3 , 3)		86
	Lewis Coleman	Mass mailing	1097		11 (10 , 12)		50
	Whelton	Mass mailing	737	0 (0 , 0)	11 (11 , 12)	32 (30 , 34)	76
	Anderson	Direct mailing	3	0 (0 , 0)	2 (0 , 4)	9 (-1 , 18)	3
	Hollis	Mass mailing	1745	0 (0 , 0)	2 (2 , 2)		73
	Maurer*	Direct mailing	7				7
	Moon1 Moon2 Piotrowski	Direct mailing	75		68 (59 , 76)		18
	Bjornson-Benson	Mass mailing	30			20 (14 , 26)	16
	Connett	Mass mailing	2180			9 (9 , 10)	37
	Kusek 1993*						
	Rudick	Mass mailing	193			6 (6 , 7)	37
	Burns Schoenberger*						
	Anon	Mass mailing	212		1 (1 , 1)	17 (15 , 19)	6
BAS	Brewster	Direct mailing	405			26 (24 , 29)	43

* Consent rates cannot be calculated, PCS = prospective cohort study, RCS = retrospective cohort study, BAS = before after study

Table 3.4.4: Consent rates and proportions by media for studies evaluating different categories of recruitment methods (Part 4)

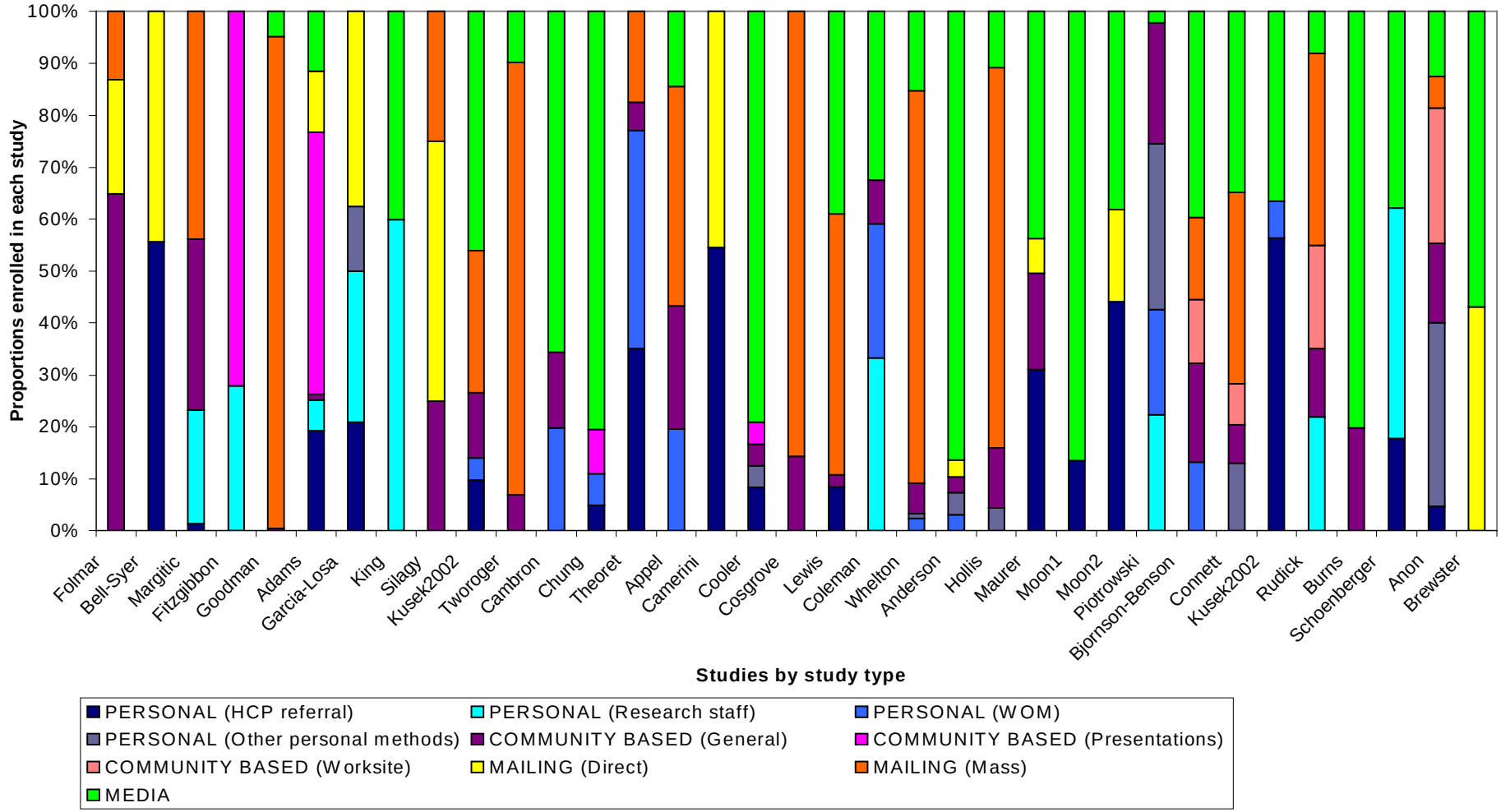
STUDY TYPE	AUTHOR	Method	# Enrolled	Exposed Consent Rate	Respond Consent Rate	Assessed Consent Rate	% Recruited by Method	Total recruited in the study
PCS	Folmar							305
								305
	Bell-Syer							187
	Margitic*							864
								864
	Fitzgibbon							420
	Goodman	Media	622	0 (0 , 0)	31 (29 , 33)	31 (29 , 33)	5	12919
	Adams	Media	51	0 (0 , 0)	30 (23 , 36)		12	442
								442
	Garcia-Losa							24
								24
								24
	King	Media	143			32 (28 , 36)	40	357
	Silagy							400
								400
RCS	Kusek 2002	Media	1325		21 (20 , 22)	78 (77 , 80)	46	2902
								2902
	Tworoger	Media	17		3 (2 , 5)	21 (12 , 29)	10	173
	Cambron	Media	90		6 (5 , 7)	38 (32 , 44)	66	137
	Chung	Media	66		50 (42 , 59)		80	82
								82
	Theoret*							439
								439
	Appel*	Media	66				14	459
	Camerini							1815
	Cooler	Media	19		10 (6 , 14)		79	24
								24
								24
	Cosgrove							4736
	Lewis	Media	851		13 (12 , 14)		39	2182
	Coleman	Media	39			38 (28 , 47)	33	120
								120
	Whelton	Media	149		(10 , 14)	31 (27 , 35)	15	975
								975
	Anderson	Media	83			27 (22 , 32)	86	96
								96
	Hollis	Media	257				11	2382
	Maurer*	Media	45				44	103
								103
								103
	Moon1	Media	1790		16 (15 , 17)		87	2069
	Moon2	Media	162		13 (11 , 14)		38	424
	Piotrowski	Media	2		33 (-4 , 71)		2	94
								94
								94
	Bjornson-Benson	Media	75			12 (9 , 14)	40	189
								189
	Connett	Media	2052			10 (10 , 10)	35	5887
								5887
	Kusek 1993*	Media	245				37	670
								670
	Rudick	Media	42			8 (6 , 11)	8	521
								521
	Burns	Media	105		16 (13 , 18)	16 (13 , 18)	80	131
	Schoenberger*	Media	1561				38	4121
								4121
	Anon	Media	437		2 (2 , 3)	23 (21 , 25)	13	3478
								3478
BAS	Brewster	Media	535		51 (48 , 54)		57	940

* Consent rates cannot be calculated, PCS = prospective cohort study, RCS = retrospective cohort study, BAS = before after study

3.3.4.2 Proportions enrolled by each method (Figure 3.3):

The proportion enrolled by the different categories varies between studies. Generally studies have higher absolute numbers of participants enrolled by methods that expose large numbers of potential participants to trial information irrespective of the consent rate for that method. For example, in one study 27% of participants were recruited by mass mailing and 46% by media compared with 10% by health care provider referral because many more potential participants were exposed to trial information by mailing and media, despite the higher consent rate for health care provider referral (11.1%, 20.9% and 40.6% responder consent rates respectively).

Figure 3.3: Proportions enrolled by each method for studies comparing different categories of recruitment methods



3.3.5 Consent rates and proportions enrolled by each method in studies comparing variations of methods within one category (Tables 3.5, 3.6)

Effective strategies identified were framing of recruitment information (e.g. information emphasising uncertainty was more effective than providing estimates of effect, and focusing on early diagnosis and treatment was more effective than emphasising data collection) (115;138), the addition of monetary incentives with mailing (irrespective of size of the incentive) (139), the use of an interactive computer program to learn about the trial compared with listening to an audio-tape of trial information (140), mailing of recruitment material accompanied by a letter from the trial investigator (141), and informing doctors of patients' preferences (142) (with both high consent rates and proportions enrolled). Although the addition of a research nurse for supplementing recruitment (by being more available, and to act as a reminder about the existence of the trials) is beneficial (135), the addition of a nurse for the purpose of information provision is uncertain (59;105). Methods that did not influence proportions and consent rates include advance postcard prior to mailing of recruitment material (141) and different methods of informed consent (118;143). In studies where exposed consent rates could not be calculated, proportions enrolled by each method may be associated with exposure of potential participant by the method.

Table 3.5: Consent rates and proportions by strategy for studies evaluating variations within one category of recruitment method

STUDY TYPE	AUTHOR	Method	# Enrolled	Exposed Consent Rate	Responder Consent Rate	Assessed Consent Rate	% by Method	Method	# Enrolled	Exposed Consent Rate	Respond Consent Rate	Assessed Consent Rate	% by Method	Total Recruited in Study
						FRAMING								
QRCT	Wragg	Providing estimates of effect	8	30.8 (13.0, 48.5)	30.8 (13.0,48.5)		36	Emphasising uncertainty	14	58.3 (38.6, 78.1)	58.3 (38.6, 78.1)		64	22
PCS	Leader	Emphasising data gathering	4	0.9 (0.0,1.8)	0.9 (0.0, 1.8)	2.7 (0.1, 5.2)	7	Focusing on early diagnosis and treatment	56	9.7 (7.3, 12.1)	9.7 (7.3, 12.1)	26.7 (21.5, 33.9)	93	60
						INFORMATION PRESENTATION								
RCT	Aaronson	Control	78	86.7 (79.6, 93.7)	86.7 (79.6, 93.7)	86.7 (79.6, 93.7)	53	Additional contact with oncology nurse	68	75.6 (66.7, 84.4)	75.6 (66.7, 84.4)	75.6 (66.7, 84.4)	47	146
	Wadland2	Control	25	47.2 (33.7, 60.0)			48	Additional study coordinator reading and explanation	27	52.9 (39.2, 66.6)			52	52
	Llewellyn-Thomas	Tape recording of trial information	21	42.0 (28.3, 55.7)			40.4	Interactive computer program	31	62.0 (48.5, 75.5)			59.6	52
RCS	Arnold	Daily newspaper	39		11.8 (8.3, 15.3)		51	Weekly newspaper	13		9.5 (4.6, 14.4)		17	76
		Community TV	1		3.3 (-3.1, 9.8)		1	TV news	12		9.4 (4.3, 14.4)		16	
		Radio	11		9.6 (4.2, 14.9)		14							
						MAILING								
RCT	Martinson	Mailing with no incentive	288	27.4 (24.7, 30.1)		59.6 (55.3, 64.0)	18	Prepaid $2 cash	423	40.3 (37.3, 43.3)		65.1(61.4, 68.7)	27	1560
		$15 cash contingent on response	452	43.0 (40.1, 46.0)		62.7 (59.2, 66.2)	29	$200 prize draw	397	37.8 (34.9, 40.7)		67.4 (64.6, 71.2)	25	
	Valanis2	Full recruitment packet	259	2.3 (2.0, 2.6)	5.3 (4.7, 6.0)		46	Advanced postcard prior to recruitment packet	304	2.7 (2.4, 3.0)	5.6 (5.0, 6.2)		54	563
PCS	Valanis1	First class postage & letter from trial investigator	369	2.0 (1.8, 2.2)	3.6 (3.2, 3.9)		25	First class postage & letter from medical director	138	1.2 (1.0, 1.4)	3.3 (2.8, 3.9)		9	1502
		First class non profit postage & letter from trial investigator	302	2.5 (2.2, 2.8)	4.1 (3.7, 4.6)		20	First class non profit postage & letter from medical director	281	1.1 (1.0, 1.2)	3.9 (3.4, 4.3)		19	
		First class postage of questionnaire	280	1.0 (0.9, 1.1)	3.3 (2.9, 3.7)		19	Bulk rate postage of questionnaire	132	0.9 (0.7, 1.0)	2.6 (2.2, 3.1)		9	
						RECRUITER								
RCT	Fleissig	Standard	96	73.8 (66.3, 81.4)			47	Doctor aware of patient's responses	109	80.7 (74.1, 87.4)			53	205
QRCT	Miller	Senior investigator	28		17.3 (11.5, 23.1)	17.3 (11.5, 23.1)	56	Research assistance	22		11.9 (7.2, 16.6)	11.9 (7.2, 16.6)	44	50
PCS	Gill	Primary care physicians referral	101		6.6 (5.4, 7.9)	36.6 (30.9, 42,3)	54	Research staff recruitment	87		8.5 (6.8, 10.2)	35.2 (29.3, 41.2)	46	188
RCS	Isaacman2	Investigator physician	73		84.9 (77.3, 92.5)	84.9 (77.3, 92.5)	46	Research nurse	84		79.2 (71.5, 87.0)	79.2 (71.5, 87.0)	54	157
BAS	Isaacman1	Physician investigator	40	14.2 (10.1, 18.3)	80.0 (68.9, 91.1)	80.0 (68.9, 91.1)	24	Physician investigator + research nurse	126	49.8 (43.6, 56.0)	83.4 (77.5, 89.4)	83.4 (77.5, 89.4)	76	166
PCS	Wadland1	Semi-rural private family practice	58			10.1 (7.6, 12.5)	62	Academic university practice	36			2.1 (1.4, 2.8)	38	94
RCS	Wright*	Private solo practices	13791				36	Private group practices	8568				22	38523
		Health maintenance organisations	1591				4	Community health centers	3641				9	
		University academic medical centers	3865				10	Department of veteran affairs medical centers	7067				18	
	Carew1*	Radionuclide lab	955				59	Cardiac catheter lab	296				18	1629
		Echocardiogram lab	230				14	Other referral	148				9	
	Carew2*	Radionuclide lab	1151				46	Cardiac catheter lab	676				27	2477
		Echocardiogram lab	350				14	Other referral	300				12	
						CONSENT								
RCT	Myles	One sided informed consent	84	55.6 (47.7, 63.6)			20							429
		Prerandomised to experimental drug	90	53.3 (45.7, 60.8)			21	Prerandomised to standard drug	79	53.0 (45.0, 61.0)			18	
		One sided physician modified informed consent	91	60.7 (52.8, 68.5)			21	One sided patient modified informed consent	85	56.7 (48.7, 64.6)			20	429
	Gallo	One sided informed consent	521	83.8 (80.9,. 86.7)			32	Two sided informed consent	304	80.9 (76.9, 84.8)			19	1623
		Prerandomised to standard drug	156	50.8 (45.2, 56.4)			10	Prerandomised to experimental drug	642	87.9 (85.6, 90.3)			40	

* Consent rates cannot be calculated. RCT=randomised controlled trial, QRCT=quasi-randomised controlled trial, PCS=prospective cohort study, RCS=retrospective cohort study, BAS=before after study

Table 3.6: Comparing consent rates and proportions for studies evaluating variations of one category of recruitment method

AUTHOR	METHOD	Exposed Consent Rate %		% Recruited		METHOD	Exposed Consent Rate %		% Recruited		METHOD	Exposed Consent Rate		Proportion Recruited		Total Enrolled
						FRAMING										
Wragg	Providing estimates of effect	30.8	low	36	low	Emphasising uncertainty	58.3	high	64	high						22
Leader	Emphasising data gathering	0.9	low	7	low	Focusing on early diagnosis	9.7	high	93	high						60
						INFORMATION PRESENTATION										
Aaronson	Control	86.7	high	53	high	Additional nurse	75.6	low	47	low						146
Wadland2	Control	47.2	NS	48	low	Additional study coordinator	52.9	NS	52	high						52
Llewellyn-Thomas	Tape recording	42.0	low	40.4	low	Interactive computer program	62	high	59.6	high						83
Arnold	Daily newspaper			51	high	Weekly newspaper			17	low	TV news			16	low	76
	Community TV			1	low	Radio			14	low						
						MAILING										
Martinson	Mailing with no incentive	27.4	low	18	low	Prepaid $2 cash	40.3	high	27	high	$15 cash contingent on response	43.0	high	29	high	1560
	$200 prize draw	37.8	high	25	high											
Valanis2	Full recruitment packet	2.3	NS	46	low	Advanced postcard	2.7	NS	54	high						563
Valanis1	First class postage & letter from trial investigator	2.0	intermediate	25	high	First class postage & letter from medical director	1.2	low	9	low	First class non profit postage & letter from trial investigator	2.5	high	20	high	1502
	First class non profit postage & letter from medical director	1.1	low	19	high	First class postage of questionnaire	1.0	low	19	high	Bulk rate postage of questionnaire	0.9	low	9	low	1502
						RECRUITER DEPENDENT FACTORS										
Fleissig	Standard	73.8	NS	47	low	Doctor aware of patient's responses	80.7	NS	53	high						205
Miller	Senior investigator			56	high	Research assistance			44	low						50
Gill	Primary care physicians referral			54	high	Research staff recruitment			46	low						188
Isaacman2	Investigator physician			46	low	Research nurse			54	high						157
Wadland1	Semi-rural private family practice			62	high	Academic university practice			38	low						94
Wright	Private solo practices			36	high	Private group practices			22	high	Health maintenance organisations			4	low	38523
	Community health centers			9	low	University academic medical centres			10	low	Department of veteran affairs medical centres			18	high	
Carew1	Radionuclide lab			59	high	Cardiac catheter lab			18	low	Echocardiogram lab			14	low	1629
	Other referral			9	low											
Carew2	Radionuclide lab			46	high	Cardiac catheter lab			27	high	Echocardiogram lab			14	low	2477
	Other referral			12	low											
Isaacman1	Physician investigator	14.2	low	24	low	Physician investigator & research nurse	49.8	high	76	high						166
						METHOD OF INFORMED CONSENT										
Myles	One sided informed consent	55.6	NS	20	same	Prerandomised to experimental drug	53.3	NS	21	same	Prerandomised to standard drug	53.0	NS	18	low	429
	One sided physician modified informed consent	60.7	NS	21	same	One sided patient modified informed consent	56.7	NS	20	same						
Gallo	One sided informed consent	83.8	high	32	high	Prerandomised to experimental drug	87.9	high	40	high	Prerandomised to standard drug	50.8	low	10	low	1623
	Two sided informed consent	80.9	high	19	low											

Exposed consent rate relative to each other (if 95% CI does not cross, consent rates considered significantly different). NS = not significant

Proportion of study recruited by each method: Observed proportion compared with expected proportion. "High" if proportion > 1/number of strategies used in the study, "low" if proportion < 1/number of strategies used in the study

3.3.6 Recruitment cost per participant

Recruitment costs for some or all methods of recruitment used were described in 20 studies (Table 3.7). The stated cost per participant enrolled ranged from US $0 for some personal referrals to $1108.00 for bus advertisements. When subcategories were combined, the average costs were US $113.26 for mailing, $164.69 for media, $242.98 for personal methods and $452.99 for community approach.

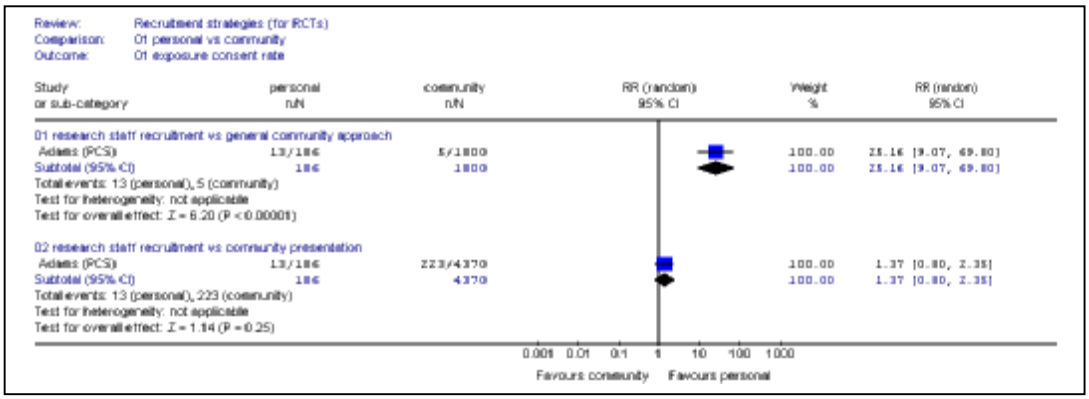
Table 3.7: Recruitment costs per participant enrolled by method of recruitment

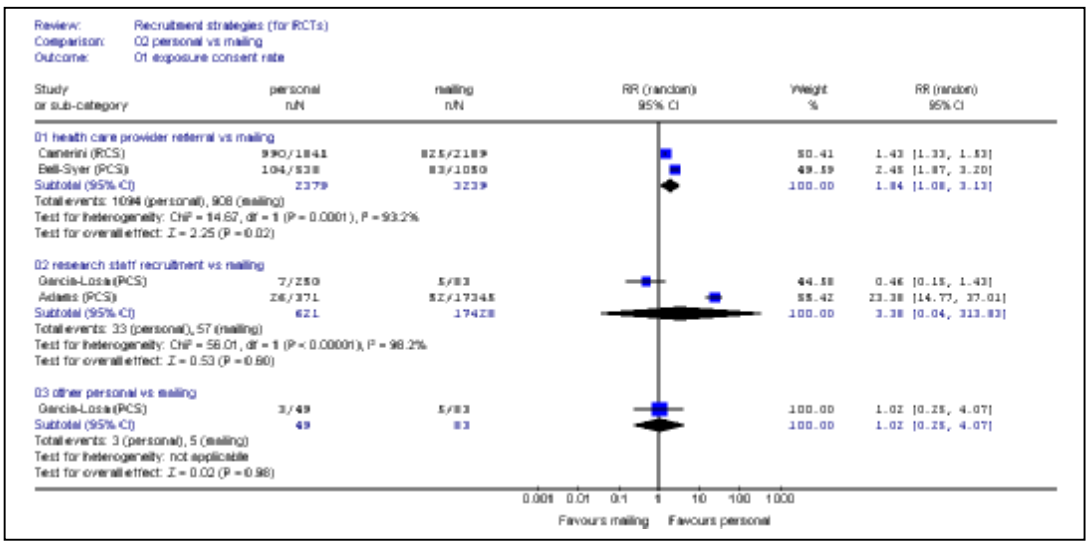
AUTHOR	PERSONAL		COMMUNITY		MAILING		MEDIA	
Martinson					No incentives	18.45		
					$2 cash (prepaid)	17.52		
					$15 cash (on response)	35.68		
					$200 prize draw	18.42		
Miller	Senior investigator	$78.48						
	Research assistant	$50.28						
Folmar	Research staff	$1,715.00	General community	$1,152.00				
Gill	HCP referral	$868.00						
	Research staff	$764.00						
Margitic (D)	Research staff	$80.00	Questionnaires	$14.00				
Margitic (S)			Questionnaires	$253.00	Mass mailing	$58.00		
Goodman					Mass mailing	442.00		
Valanis1					First class postage (letter from investigator)	83.00		
					Non profit postage (letter from investigator)	58.00		
					First class postage (letter from insurance medical director)	138.00		
					Non profit postage (letter from insurance medical director)	128.00		
					First class postage with mailer	169.00		
					Bulk rate postage with mailer	151.00		
Adams	HCP referral	$58.00	Presentation	$108.00	Target mailing	$114.00	combined media	$84.00
	Research staff	$142.00	Fliers	$203.00				
King	Research staff	$168.45					combined media	$61.51
Silagy			General community	$42.54	Mass mailing	$59.37		
					Target mailing	$48.36		
Tworoger	First class postage	$188.12						
	Bulk rate postage	$131.98						
Lewis (A)					Mass mailing	$103.00	combined media	$33.00
Lewis (B)					Mass mailing	$144.00	combined media	$207.00
Coleman	Research staff	$42.00					combined media	$45.00
Whelton					Mass mailing	$127.00	Printed media	$51.00
Anderson	HCP referral	$62.50	Presentation	$906.25	Target mailing	$294.33	combined media	$37.00
	Promoting to HCP	$40.75	Posters and brochures	$904.00				
Moon1	HCP referral	$75.00					combined media	$57.48
Moon2	HCP referral	$75.00			Target mailing	$36.35	combined media	$431.02
Piotrowski	HCP referral	$0.00	Fliers	$365.00			combined media	$999.00
			Posters and brochures	$196.00				
			Bus ads	$1,108.00				
Bjornson-Benson	HCP referral	$77.00	Worksite	$82.00	Mass mailing	$135.00	combined media	$54.00
			General community	$670.00				
Burns	HCP referral	$0.00	Posters and brochures	$338.00			TV, radio	$28.00
							Printed media	$52.90
Average costs	Personal	$242.98	Community	$452.99	Mailing	$113.26	Media	$164.69

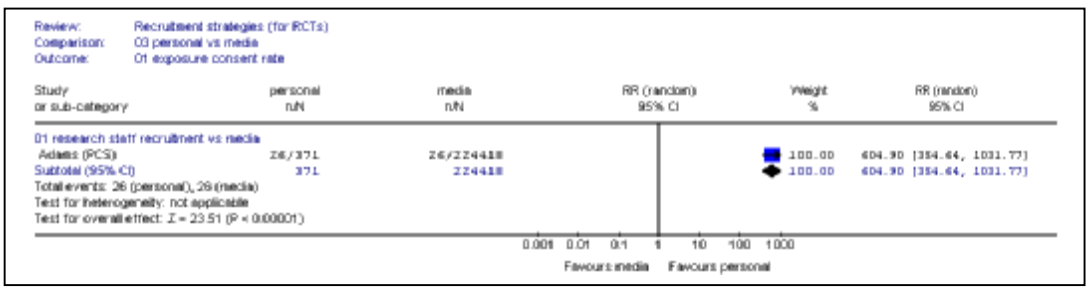
HCP = health care provider, WOM = word of mouth, Cost calculated in US dollars

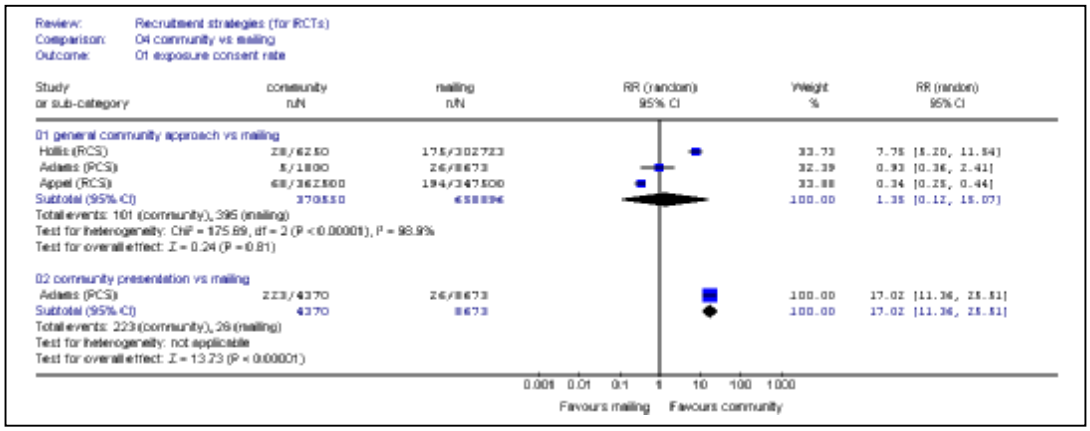
Figure 3.4: Forest plots of consent rates comparing different categories of recruitment methods

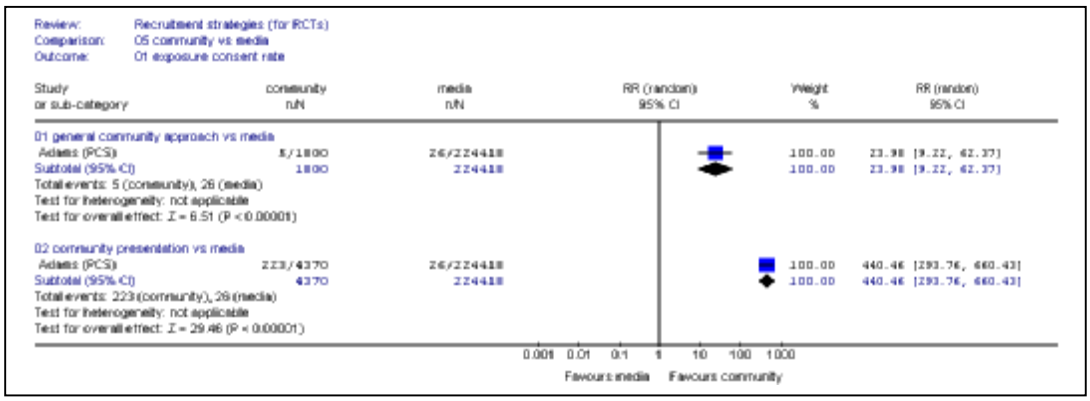
Exposure consent rates

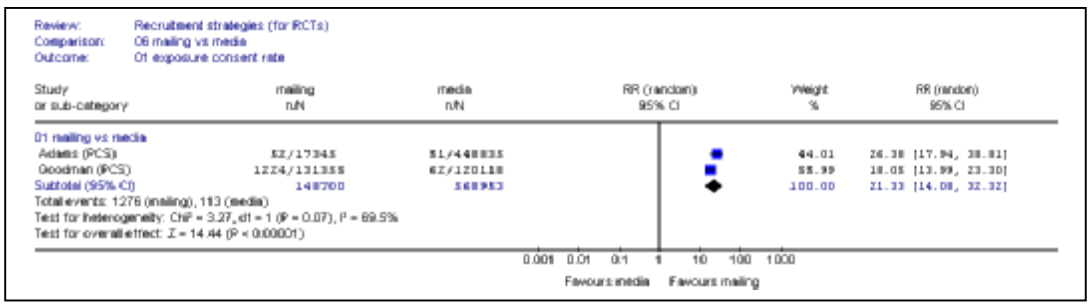




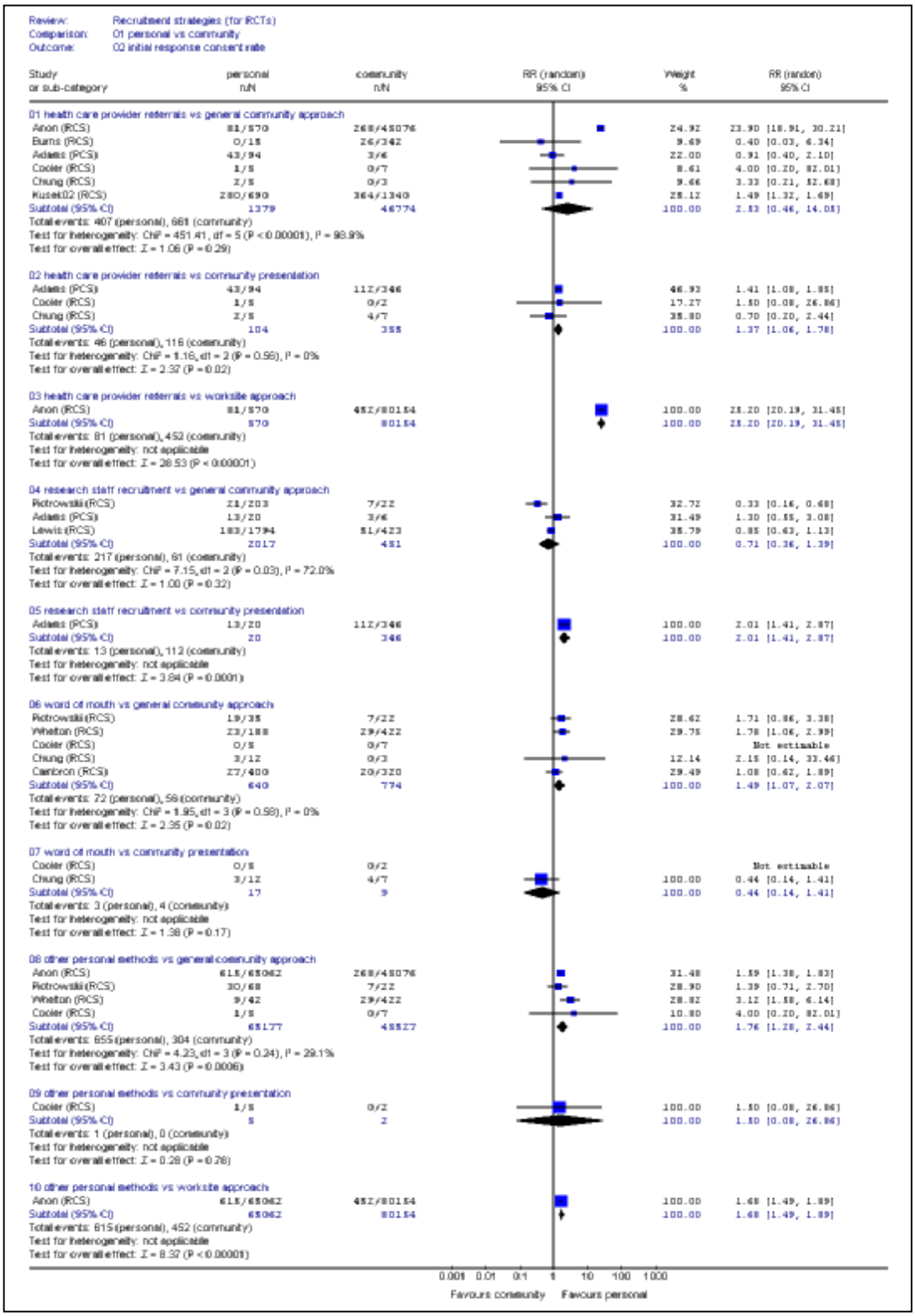


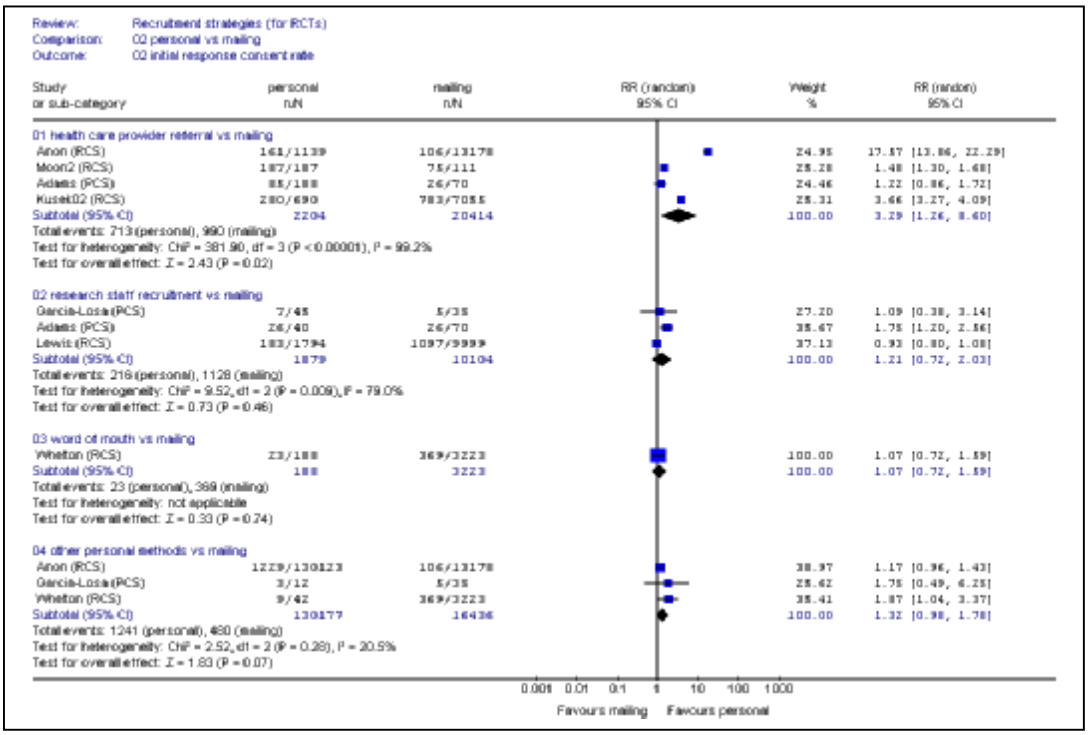

Review: Recruitment strategies (for RCTs)
Comparison: 04 community vs mailing
Outcome: 01 exposure consent rate
Study or sub-category
community n/N
mailing n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
01 general community approach vs mailing
Hollis (RCS) 28/6250 175/302723 33.73 7.75 [5.20, 11.54]
Adams (PCS) 5/1800 26/8673 32.39 0.93 [0.36, 2.41]
Appel (RCS) 68/362500 194/347500 33.88 0.34 [0.25, 0.44]
Subtotal (95% CI) 370550 658896 100.00 1.35 [0.12, 15.07]
Total events: 101 (community), 395 (mailing)
Test for heterogeneity: Chi² = 175.89, df = 2 (P < 0.00001), I² = 98.9%
Test for overall effect: Z = 0.24 (P = 0.81)
02 community presentation vs mailing
Adams (PCS) 223/4370 26/8673 100.00 17.02 [11.36, 25.51]
Subtotal (95% CI) 4370 8673 100.00 17.02 [11.36, 25.51]
Total events: 223 (community), 26 (mailing)
Test for heterogeneity: not applicable
Test for overall effect: Z = 13.23 (P < 0.00001)
0.001 0.01 0.1 1 10 100 1000
Favours mailing
Favours community

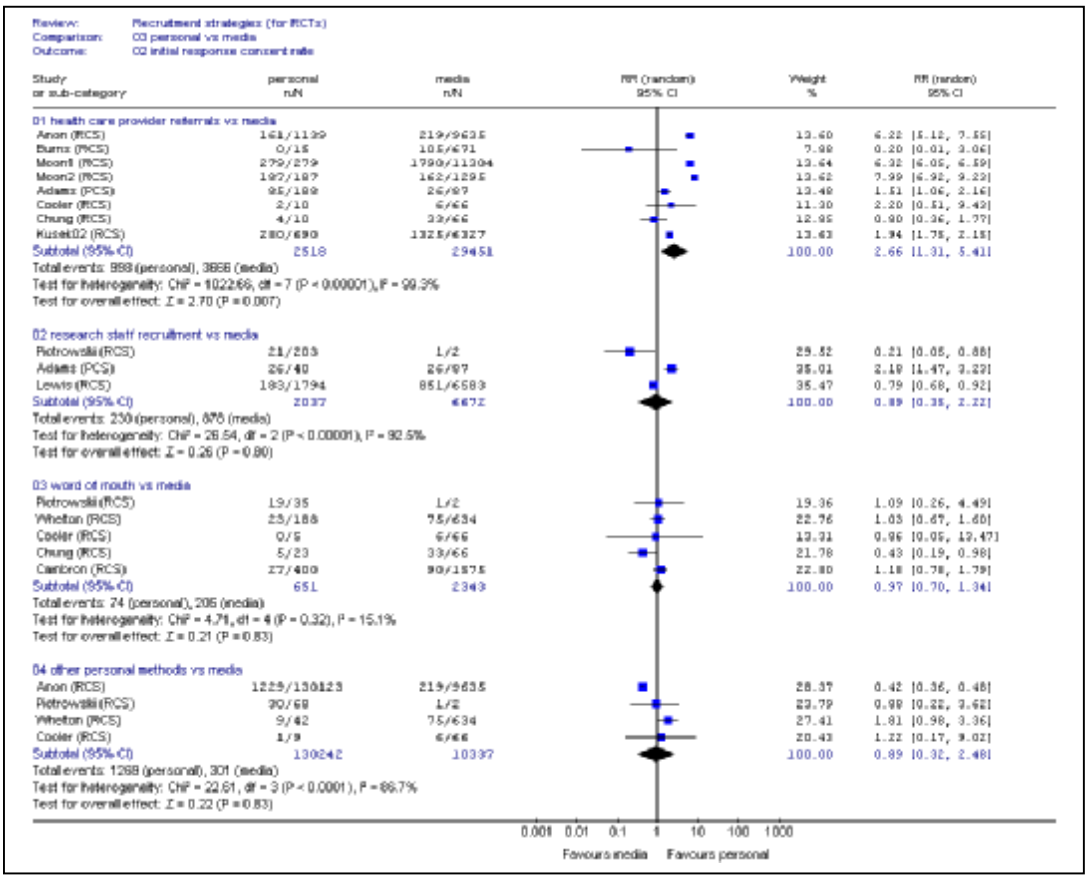

Review: Recruitment strategies (for RCTs)
Comparison: 05 community vs media
Outcome: 01 exposure consent rate
Study or sub-category
community n/N
media n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
01 general community approach vs media
Adams (PCS) 5/1800 26/224418 100.00 23.98 [9.22, 62.37]
Subtotal (95% CI) 1800 224418 100.00 23.98 [9.22, 62.37]
Total events: 5 (community), 26 (media)
Test for heterogeneity: not applicable
Test for overall effect: Z = 6.51 (P < 0.00001)
02 community presentation vs media
Adams (PCS) 223/4370 26/224418 100.00 440.46 [293.76, 660.43]
Subtotal (95% CI) 4370 224418 100.00 440.46 [293.76, 660.43]
Total events: 223 (community), 26 (media)
Test for heterogeneity: not applicable
Test for overall effect: Z = 29.46 (P < 0.00001)
0.001 0.01 0.1 1 10 100 1000
Favours media
Favours community

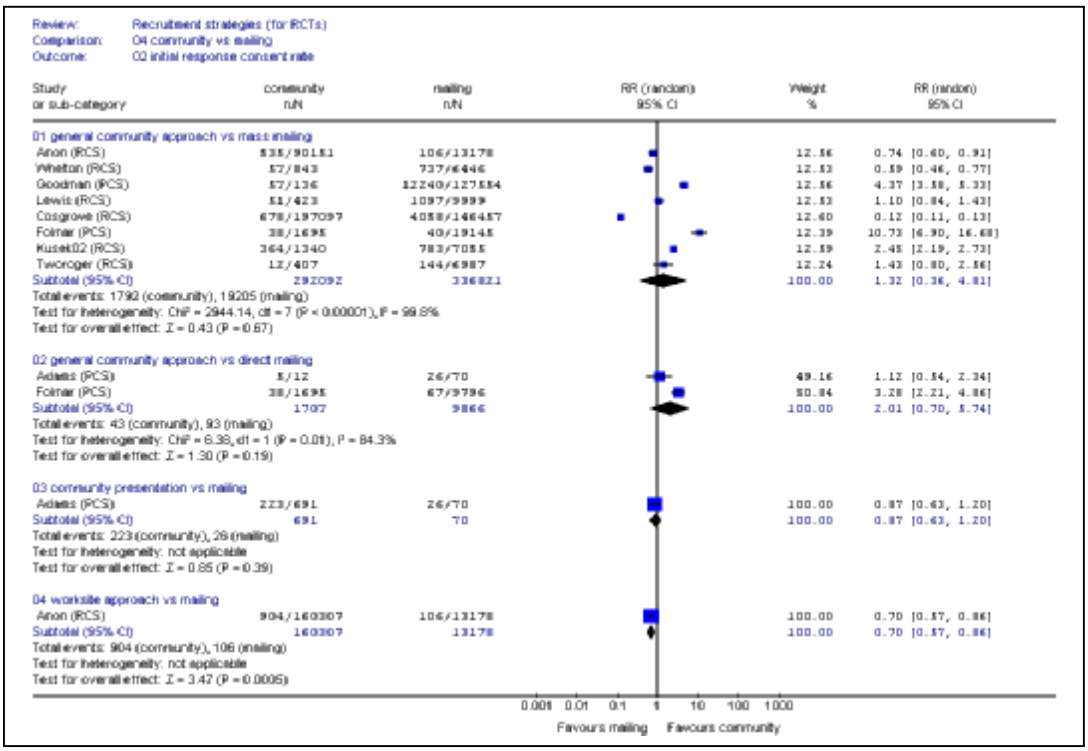

Review: Recruitment strategies (for RCTs)
Comparison: 06 mailing vs media
Outcome: 01 exposure consent rate
Study or sub-category
mailing n/N
media n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
01 mailing vs media
Adams (PCS) 52/17345 51/448835 44.01 26.38 [17.94, 38.81]
Goodman (PCS) 1224/131355 62/120118 55.99 18.05 [13.99, 23.30]
Subtotal (95% CI) 148700 568953 100.00 21.33 [14.08, 32.32]
Total events: 1276 (mailing), 113 (media)
Test for heterogeneity: Chi² = 3.27, df = 1 (P = 0.07), I² = 69.5%
Test for overall effect: Z = 14.44 (P < 0.00001)
0.001 0.01 0.1 1 10 100 1000
Favours media
Favours mailing

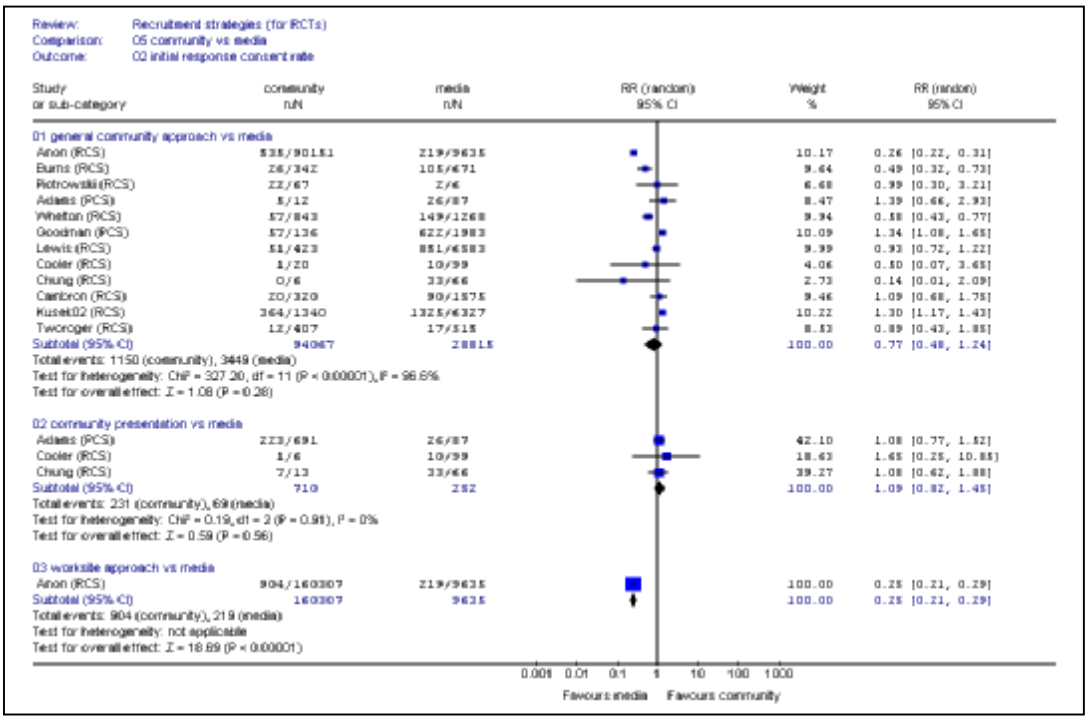
Responder consent rates

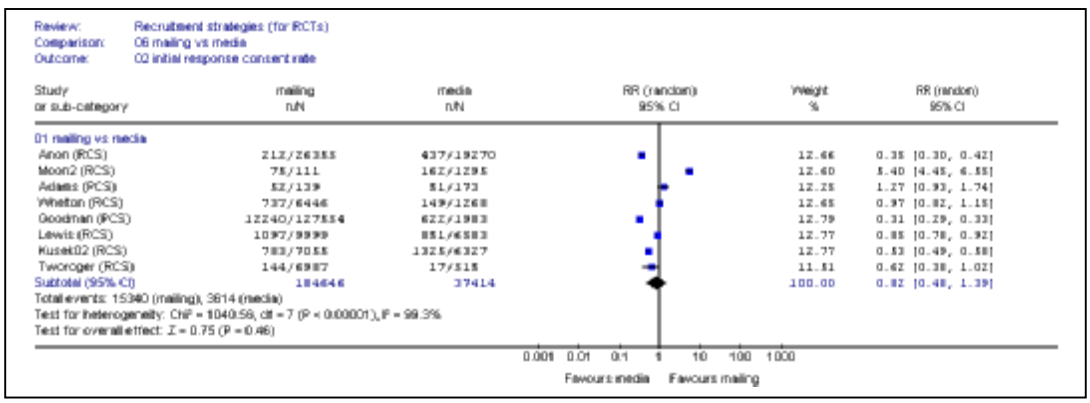



Review: Recruitment strategies (for RCTs)
Comparison: 02 personal vs mailing
Outcome: 02 initial response consent rate
Study or sub-category
personal n/N
mailing n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
01 health care provider referral vs mailing
Anon (RCS) 161/1139 106/13178 24.95 17.57 [13.86, 22.29]
Moon2 (RCS) 187/187 75/111 25.28 1.48 [1.30, 1.68]
Adams (PCS) 85/188 26/70 24.46 1.22 [0.86, 1.72]
Kusek02 (RCS) 280/690 783/7055 25.31 3.66 [3.27, 4.09]
Subtotal (95% CI) 2204 20414 100.00 3.29 [1.26, 8.60]
Total events: 713 (personal), 990 (mailing)
Test for heterogeneity: Chi² = 381.90, df = 3 (P < 0.00001), I² = 99.2%
Test for overall effect: Z = 2.43 (P = 0.02)
02 research staff recruitment vs mailing
Garcia-Losa (PCS) 7/45 5/35 27.20 1.09 [0.38, 3.14]
Adams (PCS) 26/40 26/70 35.67 1.75 [1.20, 2.56]
Lewis (RCS) 183/1794 1097/9999 37.13 0.93 [0.80, 1.08]
Subtotal (95% CI) 1879 10104 100.00 1.21 [0.72, 2.03]
Total events: 216 (personal), 1128 (mailing)
Test for heterogeneity: Chi² = 9.52, df = 2 (P = 0.009), I² = 79.0%
Test for overall effect: Z = 0.73 (P = 0.46)
03 word of mouth vs mailing
Wheton (RCS) 23/188 369/3223 100.00 1.07 [0.72, 1.59]
Subtotal (95% CI) 188 3223 100.00 1.07 [0.72, 1.59]
Total events: 23 (personal), 369 (mailing)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.33 (P = 0.74)
04 other personal methods vs mailing
Anon (RCS) 1229/130123 106/13178 38.97 1.17 [0.96, 1.43]
Garcia-Losa (PCS) 3/12 5/35 25.62 1.75 [0.49, 6.25]
Wheton (RCS) 9/42 369/3223 35.41 1.87 [1.04, 3.37]
Subtotal (95% CI) 130177 16436 100.00 1.32 [0.98, 1.78]
Total events: 1241 (personal), 480 (mailing)
Test for heterogeneity: Chi² = 2.52, df = 2 (P = 0.28), I² = 20.5%
Test for overall effect: Z = 1.83 (P = 0.07)
0.001 0.01 0.1 1 10 100 1000
Favours mailing
Favours personal

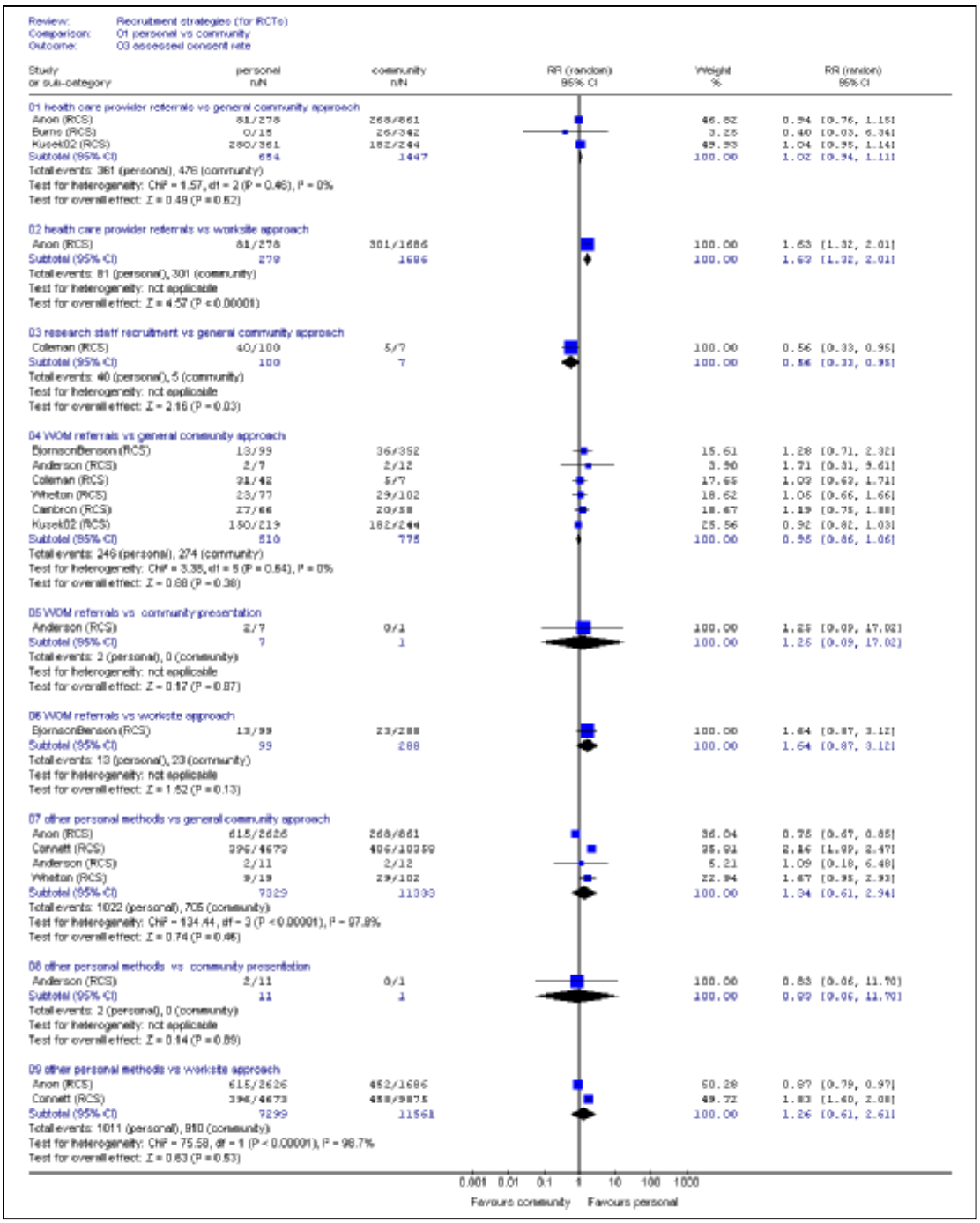

Review: Recruitment strategies (for RCTs)
Comparison: 03 personal vs media
Outcome: 02 initial response consent rate
Study or sub-category
personal n/N
media n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
01 health care provider referrals vs media
Anon (RCS) 161/1139 219/9635 13.60 6.22 [5.12, 7.55]
Burns (RCS) 0/15 105/671 7.98 0.20 [0.01, 3.06]
Moon1 (RCS) 279/279 1790/11304 13.64 6.32 [6.05, 6.59]
Moon2 (RCS) 187/187 162/1295 13.62 7.99 [6.92, 9.22]
Adams (PCS) 85/188 26/97 13.48 1.51 [1.06, 2.16]
Cooler (RCS) 2/10 6/66 11.30 2.20 [0.51, 9.42]
Chung (RCS) 4/10 33/66 12.95 0.80 [0.36, 1.77]
Kusek02 (RCS) 280/690 1325/6327 13.63 1.94 [1.75, 2.15]
Subtotal (95% CI) 2518 29451 100.00 2.66 [1.31, 5.41]
Total events: 998 (personal), 3868 (media)
Test for heterogeneity: Chi² = 1022.66, df = 7 (P < 0.00001), I² = 99.3%
Test for overall effect: Z = 2.70 (P = 0.007)
02 research staff recruitment vs media
Piotrowski (RCS) 21/203 1/2 25.52 0.21 [0.05, 0.88]
Adams (PCS) 26/40 26/97 35.01 2.10 [1.47, 3.22]
Lewis (RCS) 183/1794 851/6583 39.47 0.79 [0.68, 0.92]
Subtotal (95% CI) 2037 6682 100.00 0.89 [0.38, 2.22]
Total events: 230 (personal), 878 (media)
Test for heterogeneity: Chi² = 26.54, df = 2 (P < 0.00001), I² = 92.5%
Test for overall effect: Z = 0.26 (P = 0.80)
03 word of mouth vs media
Piotrowski (RCS) 19/35 1/2 19.36 1.09 [0.26, 4.49]
Wheton (RCS) 23/188 75/634 22.76 1.03 [0.67, 1.60]
Cooler (RCS) 0/5 6/66 13.21 0.96 [0.05, 17.47]
Chung (RCS) 5/23 33/66 21.78 0.43 [0.19, 0.98]
Cambron (RCS) 27/400 90/1875 22.80 1.18 [0.78, 1.79]
Subtotal (95% CI) 651 2343 100.00 0.97 [0.70, 1.34]
Total events: 74 (personal), 205 (media)
Test for heterogeneity: Chi² = 4.71, df = 4 (P = 0.32), I² = 15.1%
Test for overall effect: Z = 0.21 (P = 0.83)
04 other personal methods vs media
Anon (RCS) 1229/130123 219/9635 28.37 0.42 [0.36, 0.48]
Piotrowski (RCS) 20/69 1/2 23.79 0.99 [0.22, 3.62]
Wheton (RCS) 9/42 75/634 27.41 1.81 [0.98, 3.36]
Cooler (RCS) 1/9 6/66 20.43 1.22 [0.17, 9.02]
Subtotal (95% CI) 130242 10337 100.00 0.89 [0.32, 2.48]
Total events: 1268 (personal), 301 (media)
Test for heterogeneity: Chi² = 22.61, df = 3 (P < 0.0001), I² = 86.7%
Test for overall effect: Z = 0.22 (P = 0.83)
0.001 0.01 0.1 1 10 100 1000
Favours media
Favours personal

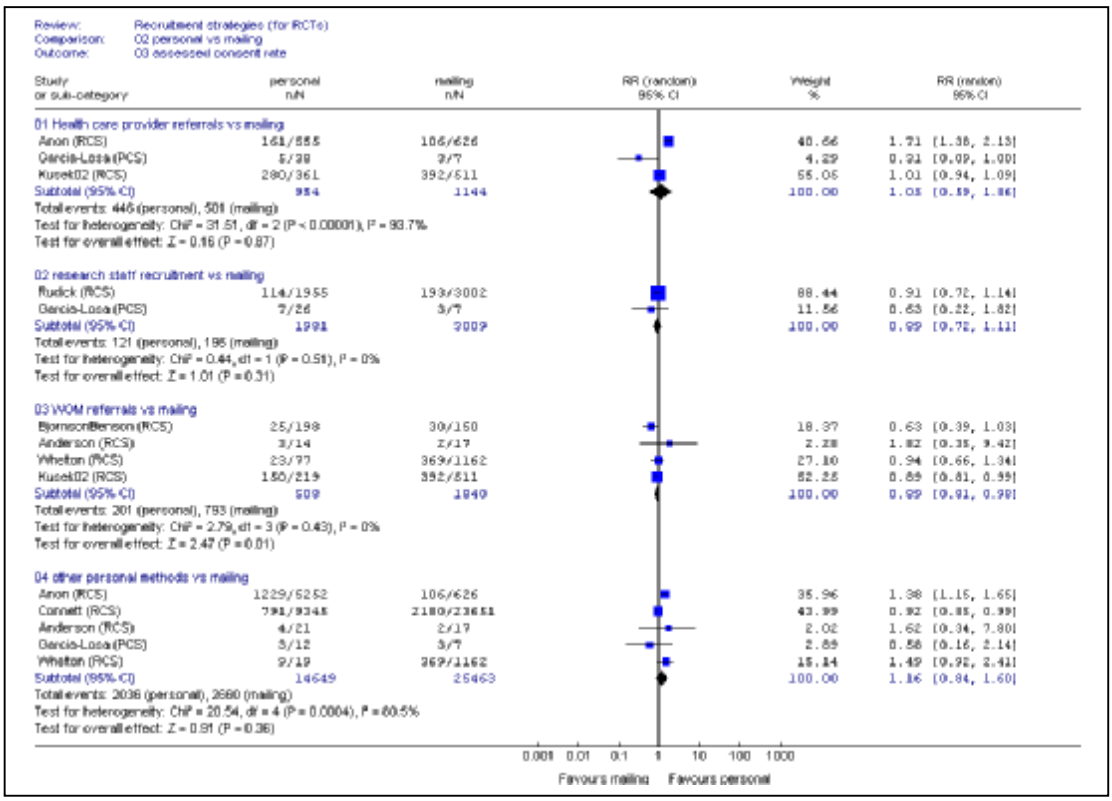

Review: Recruitment strategies (for RCTs)
Comparison: 04 community vs mailing
Outcome: 02 initial response consent rate
Study or sub-category
community n/N
mailing n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
01 general community approach vs mass mailing
Anon (RCS) 535/90151 106/13178 12.86 0.74 [0.60, 0.91]
Whelton (RCS) 57/843 737/6446 12.53 0.59 [0.46, 0.77]
Goodman (PCS) 57/136 12240/127554 12.56 4.37 [3.58, 5.33]
Lewis (RCS) 51/423 1097/9999 12.53 1.10 [0.84, 1.43]
Cosgrove (RCS) 678/197097 4088/146457 12.60 0.12 [0.11, 0.13]
Folmar (PCS) 38/1695 40/19145 12.39 10.73 [6.90, 16.68]
Kuset02 (RCS) 364/1340 783/7055 12.59 2.45 [2.19, 2.73]
Tworoger (RCS) 12/407 144/6987 12.24 1.43 [0.80, 2.56]
Subtotal (95% CI) 292092 336821 100.00 1.32 [0.36, 4.81]
Total events: 1792 (community), 19205 (mailing)
Test for heterogeneity: Chi² = 2944.14, df = 7 (P < 0.00001), I² = 99.8%
Test for overall effect: Z = 0.43 (P = 0.67)
02 general community approach vs direct mailing
Adams (PCS) 5/12 26/70 49.16 1.12 [0.54, 2.34]
Folmar (PCS) 38/1695 67/9796 50.84 3.28 [2.21, 4.86]
Subtotal (95% CI) 1707 9866 100.00 2.01 [0.70, 5.74]
Total events: 43 (community), 93 (mailing)
Test for heterogeneity: Chi² = 6.38, df = 1 (P = 0.01), I² = 84.3%
Test for overall effect: Z = 1.30 (P = 0.19)
03 community presentation vs mailing
Adams (PCS) 223/691 26/70 100.00 0.87 [0.63, 1.20]
Subtotal (95% CI) 691 70 100.00 0.87 [0.63, 1.20]
Total events: 223 (community), 26 (mailing)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.85 (P = 0.39)
04 worksite approach vs mailing
Anon (RCS) 904/160307 106/13178 100.00 0.70 [0.57, 0.86]
Subtotal (95% CI) 160307 13178 100.00 0.70 [0.57, 0.86]
Total events: 904 (community), 106 (mailing)
Test for heterogeneity: not applicable
Test for overall effect: Z = 3.47 (P = 0.0005)
0.001 0.01 0.1 1 10 100 1000
Favours mailing
Favours community

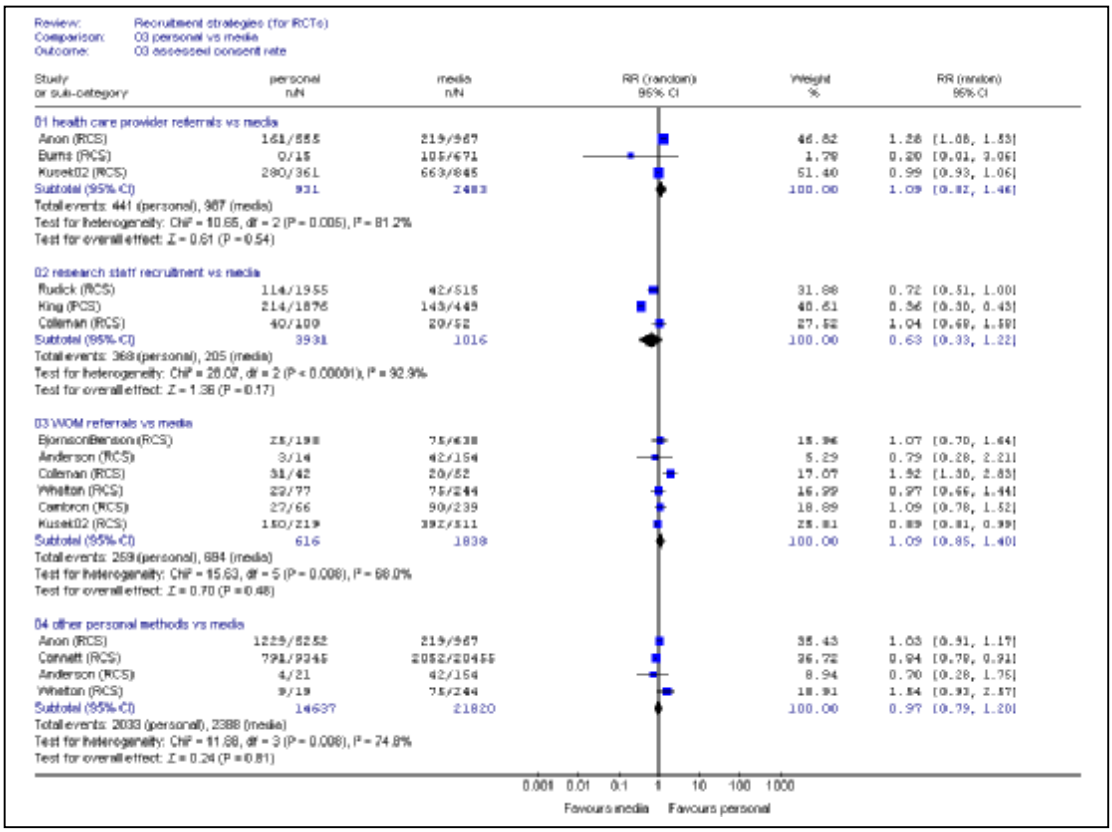

Review: Recruitment strategies (for RCTs)
Comparison: 05 community vs media
Outcome: 02 initial response consent rate
Study or sub-category
community n/N
media n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
01 general community approach vs media
Anon (RCS) 535/90151 219/9635 10.17 0.26 [0.22, 0.31]
Burns (RCS) 26/342 105/671 9.64 0.49 [0.32, 0.73]
Piotrowski (RCS) 22/67 2/6 6.68 0.99 [0.30, 3.21]
Adams (PCS) 5/12 26/87 8.47 1.39 [0.66, 2.93]
Whelton (RCS) 57/843 149/1268 9.94 0.58 [0.43, 0.77]
Goodman (PCS) 57/136 622/1983 10.09 1.34 [1.08, 1.65]
Lewis (RCS) 51/423 851/6583 9.99 0.93 [0.72, 1.22]
Cooler (RCS) 1/20 10/99 4.06 0.50 [0.07, 3.65]
Chung (RCS) 0/6 33/66 2.73 0.14 [0.01, 2.09]
Cambron (RCS) 20/320 90/1575 9.46 1.09 [0.68, 1.75]
Kuset02 (RCS) 364/1340 1325/6327 10.22 1.30 [1.17, 1.43]
Tworoger (RCS) 12/407 17/515 8.53 0.89 [0.43, 1.85]
Subtotal (95% CI) 94067 28815 100.00 0.77 [0.48, 1.24]
Total events: 1150 (community), 3449 (media)
Test for heterogeneity: Chi² = 327.20, df = 11 (P < 0.00001), I² = 96.6%
Test for overall effect: Z = 1.08 (P = 0.28)
02 community presentation vs media
Adams (PCS) 223/691 26/87 42.10 1.08 [0.77, 1.52]
Cooler (RCS) 1/6 10/99 18.63 1.65 [0.25, 10.85]
Chung (RCS) 7/13 33/66 39.27 1.08 [0.62, 1.88]
Subtotal (95% CI) 710 252 100.00 1.09 [0.82, 1.45]
Total events: 231 (community), 69 (media)
Test for heterogeneity: Chi² = 0.19, df = 2 (P = 0.91), I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)
03 worksite approach vs media
Anon (RCS) 904/160307 219/9635 100.00 0.25 [0.21, 0.29]
Subtotal (95% CI) 160307 9635 100.00 0.25 [0.21, 0.29]
Total events: 904 (community), 219 (media)
Test for heterogeneity: not applicable
Test for overall effect: Z = 18.89 (P < 0.00001)
0.001 0.01 0.1 1 10 100 1000
Favours media
Favours community

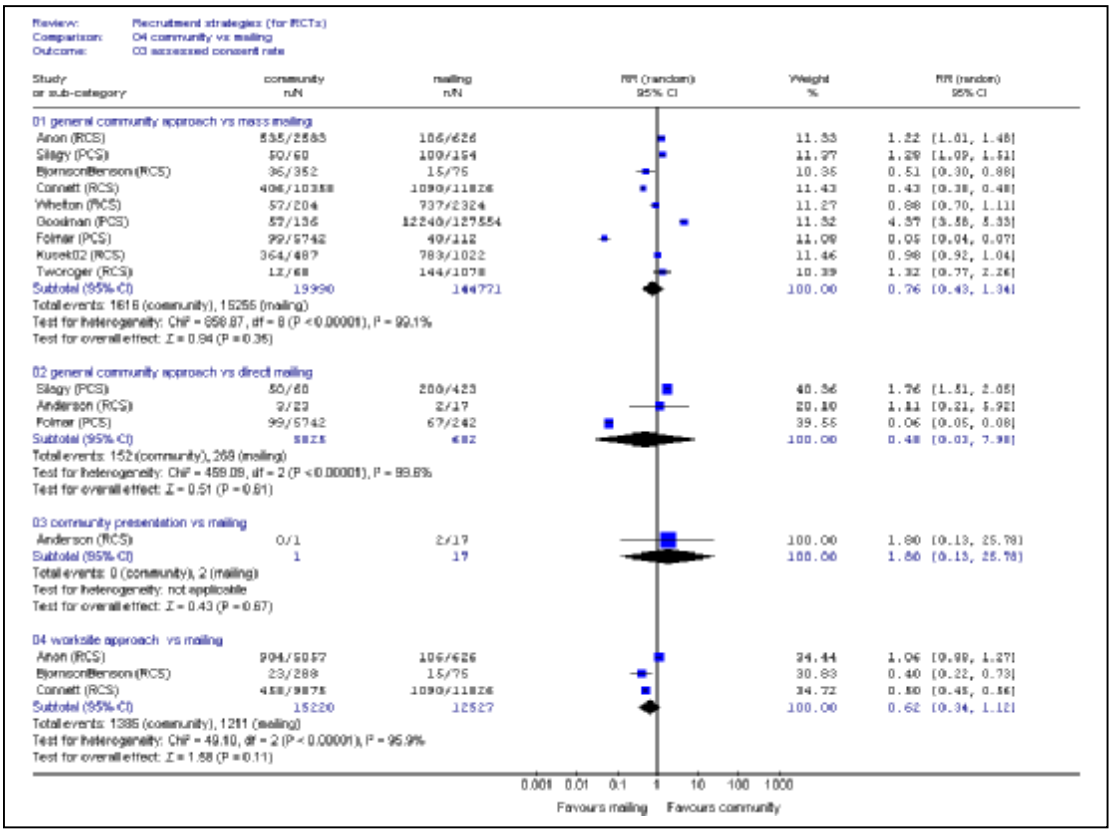

Review: Recruitment strategies (for RCTs)
Comparison: 06 mailing vs media
Outcome: 02 initial response consent rate
Study or sub-category
mailing n/N
media n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
01 mailing vs media
Anon (RCS) 212/26385 437/19270 12.66 0.35 [0.30, 0.42]
Moon2 (RCS) 75/111 162/1295 12.60 5.40 [4.45, 6.55]
Adams (PCS) 52/139 51/173 12.25 1.27 [0.93, 1.74]
Whelton (RCS) 737/6446 149/1268 12.65 0.97 [0.82, 1.15]
Goodman (PCS) 12240/127554 622/1983 12.79 0.31 [0.29, 0.33]
Lewis (RCS) 1097/9999 851/6583 12.77 0.85 [0.78, 0.92]
Kuset02 (RCS) 783/7055 1325/6327 12.77 0.53 [0.49, 0.58]
Tworoger (RCS) 144/6987 17/515 11.51 0.62 [0.38, 1.02]
Subtotal (95% CI) 184446 37414 100.00 0.82 [0.48, 1.39]
Total events: 15340 (mailing), 3614 (media)
Test for heterogeneity: Chi² = 1040.56, df = 7 (P < 0.00001), I² = 99.3%
Test for overall effect: Z = 0.75 (P = 0.46)
0.001 0.01 0.1 1 10 100 1000
Favours media
Favours mailing

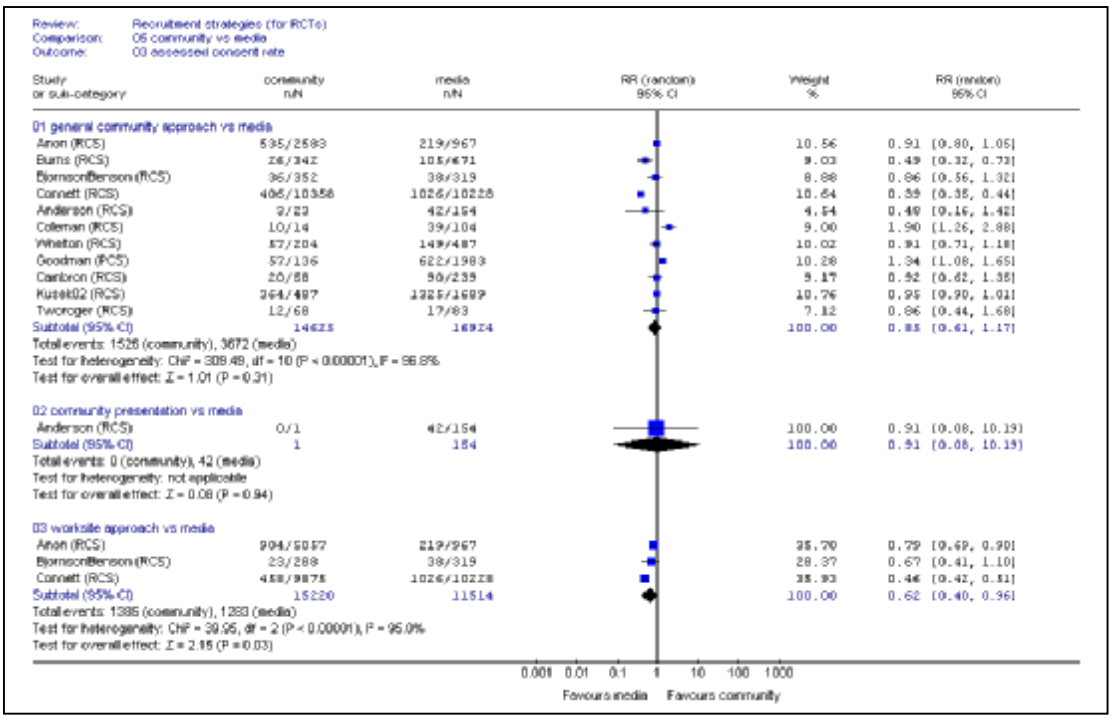
Assessed consent rates

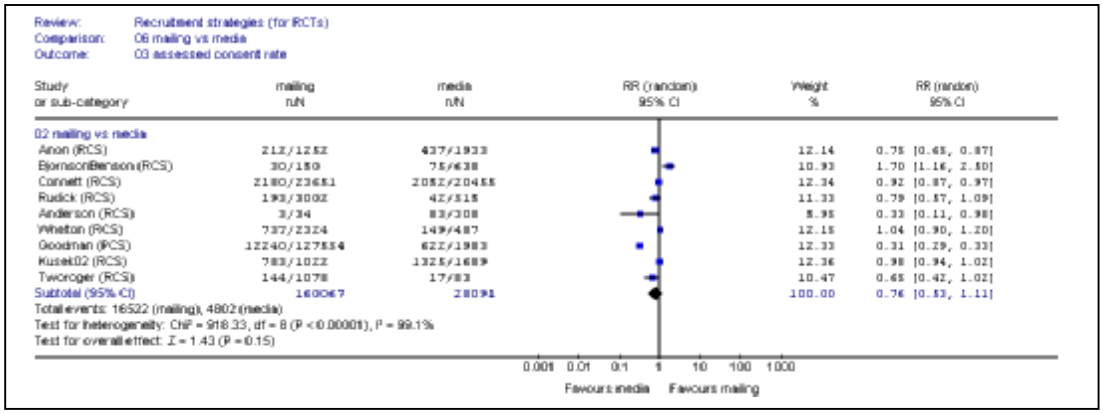



Review: Recruitment strategies (for RCTs)
Comparison: 02 personal vs mailing
Outcome: 03 assessed consent rate
Study or sub-category
personal n/N
mailing n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
01 Health care provider referrals vs mailing
Anon (RCS) 161/555 106/626 40.66 1.71 [1.38, 2.13]
Garcia-Losa (PCS) 5/39 3/7 4.29 0.91 [0.09, 1.00]
Kusek02 (RCS) 280/361 392/511 55.05 1.01 [0.94, 1.09]
Subtotal (95% CI) 954 1144 100.00 1.03 [0.59, 1.86]
Total events: 446 (personal), 501 (mailing)
Test for heterogeneity: Chi² = 31.51, df = 2 (P < 0.00001), I² = 93.7%
Test for overall effect: Z = 0.16 (P = 0.87)
02 research staff recruitment vs mailing
Rudick (RCS) 114/1955 193/3002 88.44 0.91 [0.72, 1.14]
Garcia-Losa (PCS) 7/26 3/7 11.56 0.63 [0.22, 1.82]
Subtotal (95% CI) 1981 3009 100.00 0.89 [0.72, 1.11]
Total events: 121 (personal), 196 (mailing)
Test for heterogeneity: Chi² = 0.44, df = 1 (P = 0.51), I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)
03 WOM referrals vs mailing
BjornsonBenson (RCS) 25/198 30/150 18.37 0.63 [0.39, 1.03]
Anderson (RCS) 3/14 2/17 2.28 1.82 [0.35, 9.42]
Whelton (RCS) 23/77 369/1162 27.10 0.94 [0.66, 1.34]
Kusek02 (RCS) 150/219 392/511 52.25 0.89 [0.81, 0.99]
Subtotal (95% CI) 509 1840 100.00 0.99 [0.91, 0.99]
Total events: 201 (personal), 793 (mailing)
Test for heterogeneity: Chi² = 2.79, df = 3 (P = 0.43), I² = 0%
Test for overall effect: Z = 2.47 (P = 0.01)
04 other personal methods vs mailing
Anon (RCS) 1229/5252 106/626 35.96 1.38 [1.15, 1.65]
Connett (RCS) 791/9345 2180/23651 43.99 0.92 [0.85, 0.99]
Anderson (RCS) 4/21 2/17 2.02 1.62 [0.34, 7.80]
Garcia-Losa (PCS) 5/12 3/7 2.59 0.58 [0.16, 2.14]
Whelton (RCS) 9/19 369/1162 15.44 1.49 [0.92, 2.41]
Subtotal (95% CI) 14649 25463 100.00 1.16 [0.84, 1.60]
Total events: 2038 (personal), 2660 (mailing)
Test for heterogeneity: Chi² = 20.54, df = 4 (P = 0.0004), I² = 80.5%
Test for overall effect: Z = 0.91 (P = 0.36)
0.001 0.01 0.1 1 10 100 1000
Favours mailing
Favours personal


Review: Recruitment strategies (for RCTs)
Comparison: 03 personal vs media
Outcome: 03 assessed consent rate
Study or sub-category
personal n/N
media n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
01 health care provider referrals vs media
Anon (RCS) 161/555 219/967 46.82 1.28 [1.08, 1.53]
Burns (RCS) 0/15 105/671 1.79 0.20 [0.01, 3.06]
Kusek02 (RCS) 280/361 663/845 51.40 0.99 [0.93, 1.06]
Subtotal (95% CI) 931 2483 100.00 1.09 [0.82, 1.46]
Total events: 441 (personal), 987 (media)
Test for heterogeneity: Chi² = 10.65, df = 2 (P = 0.005), I² = 81.2%
Test for overall effect: Z = 0.61 (P = 0.54)
02 research staff recruitment vs media
Rudick (RCS) 114/1955 42/515 31.88 0.72 [0.51, 1.00]
King (PCS) 214/1876 143/449 40.61 0.36 [0.30, 0.43]
Coleman (RCS) 40/109 29/52 27.52 1.04 [0.69, 1.58]
Subtotal (95% CI) 3931 1016 100.00 0.63 [0.33, 1.22]
Total events: 368 (personal), 205 (media)
Test for heterogeneity: Chi² = 26.07, df = 2 (P < 0.00001), I² = 92.9%
Test for overall effect: Z = 1.36 (P = 0.17)
03 WOM referrals vs media
BjornsonBenson (RCS) 25/198 75/638 15.96 1.07 [0.70, 1.64]
Anderson (RCS) 3/14 42/154 5.29 0.79 [0.28, 2.21]
Coleman (RCS) 31/42 20/52 17.07 1.92 [1.30, 2.83]
Whelton (RCS) 23/77 75/244 16.99 0.97 [0.66, 1.44]
Cambron (RCS) 27/66 90/239 18.69 1.09 [0.78, 1.52]
Kusek02 (RCS) 150/219 392/511 25.81 0.89 [0.81, 0.99]
Subtotal (95% CI) 616 1838 100.00 1.09 [0.85, 1.40]
Total events: 259 (personal), 694 (media)
Test for heterogeneity: Chi² = 15.63, df = 5 (P = 0.008), I² = 68.0%
Test for overall effect: Z = 0.70 (P = 0.48)
04 other personal methods vs media
Anon (RCS) 1229/5252 219/967 35.43 1.03 [0.91, 1.17]
Connett (RCS) 791/9345 2052/20455 36.72 0.94 [0.79, 0.91]
Anderson (RCS) 4/21 42/154 8.94 0.70 [0.28, 1.76]
Whelton (RCS) 9/19 75/244 18.91 1.84 [0.93, 3.57]
Subtotal (95% CI) 14637 21820 100.00 0.97 [0.79, 1.20]
Total events: 2033 (personal), 2388 (media)
Test for heterogeneity: Chi² = 11.88, df = 3 (P = 0.008), I² = 74.8%
Test for overall effect: Z = 0.24 (P = 0.81)
0.001 0.01 0.1 1 10 100 1000
Favours media
Favours personal


Review: Recruitment strategies (for RCTs)
Comparison: 04 community vs mailing
Outcome: 03 assessed consent rate
Study or sub-category
community n/N
mailing n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
01 general community approach vs mass mailing
Anon (RCS) 535/2585 106/626 11.53 1.22 [1.01, 1.48]
Silagy (PCS) 50/60 109/154 11.27 1.29 [1.09, 1.51]
BjornsonBenson (RCS) 36/352 15/75 10.36 0.51 [0.30, 0.88]
Connett (RCS) 406/10388 1090/11826 11.43 0.43 [0.38, 0.48]
Whelton (RCS) 57/204 737/2324 11.27 0.88 [0.70, 1.11]
Goodman (PCS) 57/136 12240/127554 11.52 4.57 [3.56, 5.85]
Folmer (PCS) 99/5742 40/112 11.09 0.05 [0.04, 0.07]
Kusek02 (RCS) 364/487 783/1022 11.46 0.98 [0.92, 1.04]
Tworoger (RCS) 12/68 144/1078 10.39 1.32 [0.77, 2.26]
Subtotal (95% CI) 19990 144771 100.00 0.76 [0.43, 1.34]
Total events: 1616 (community), 15255 (mailing)
Test for heterogeneity: Chi² = 658.87, df = 8 (P < 0.00001), I² = 99.1%
Test for overall effect: Z = 0.94 (P = 0.35)
02 general community approach vs direct mailing
Silagy (PCS) 50/60 280/423 40.56 1.76 [1.51, 2.05]
Anderson (RCS) 2/23 2/17 20.10 1.11 [0.21, 5.92]
Folmer (PCS) 99/5742 67/242 39.55 0.06 [0.05, 0.08]
Subtotal (95% CI) 5825 682 100.00 0.48 [0.03, 7.98]
Total events: 152 (community), 268 (mailing)
Test for heterogeneity: Chi² = 459.09, df = 2 (P < 0.00001), I² = 99.6%
Test for overall effect: Z = 0.51 (P = 0.61)
03 community presentation vs mailing
Anderson (RCS) 0/1 2/17 100.00 1.80 [0.13, 25.78]
Subtotal (95% CI) 1 17 100.00 1.80 [0.13, 25.78]
Total events: 0 (community), 2 (mailing)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.43 (P = 0.67)
04 worksite approach vs mailing
Anon (RCS) 904/5057 106/626 34.44 1.06 [0.88, 1.27]
BjornsonBenson (RCS) 23/288 15/75 30.83 0.40 [0.22, 0.73]
Connett (RCS) 458/9875 1090/11826 34.72 0.50 [0.45, 0.56]
Subtotal (95% CI) 15220 12527 100.00 0.62 [0.34, 1.12]
Total events: 1385 (community), 1211 (mailing)
Test for heterogeneity: Chi² = 49.10, df = 2 (P < 0.00001), I² = 95.9%
Test for overall effect: Z = 1.58 (P = 0.11)
0.001 0.01 0.1 1 10 100 1000
Favours mailing
Favours community


Review: Recruitment strategies (for RCTs)
Comparison: 05 community vs media
Outcome: 03 assessed consent rate
Study or sub-category
community n/N
media n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
01 general community approach vs media
Anon (RCS) 535/2583 219/967 10.56 0.91 [0.80, 1.05]
Burns (RCS) 26/342 105/671 9.03 0.49 [0.32, 0.73]
BjornsonBenson (RCS) 36/352 38/319 8.88 0.86 [0.56, 1.32]
Connett (RCS) 406/10388 1026/10228 10.64 0.39 [0.35, 0.44]
Anderson (RCS) 2/23 42/154 4.54 0.49 [0.16, 1.42]
Coleman (RCS) 10/14 39/104 9.00 1.90 [1.26, 2.88]
Whelton (RCS) 57/204 149/487 10.02 0.91 [0.71, 1.18]
Goodman (PCS) 57/136 622/1983 10.28 1.34 [1.08, 1.65]
Cambron (RCS) 20/88 50/235 5.17 0.92 [0.62, 1.35]
Kusek02 (RCS) 364/487 1325/1689 10.76 0.95 [0.90, 1.01]
Tworoger (RCS) 12/68 17/83 7.12 0.86 [0.44, 1.68]
Subtotal (95% CI) 14625 16924 100.00 0.85 [0.61, 1.17]
Total events: 1526 (community), 3672 (media)
Test for heterogeneity: Chi² = 309.48, df = 10 (P < 0.00001), I² = 96.8%
Test for overall effect: Z = 1.01 (P = 0.31)
02 community presentation vs media
Anderson (RCS) 0/1 42/154 100.00 0.91 [0.08, 10.19]
Subtotal (95% CI) 1 154 100.00 0.91 [0.08, 10.19]
Total events: 0 (community), 42 (media)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.08 (P = 0.94)
03 worksite approach vs media
Anon (RCS) 904/5057 219/967 35.70 0.79 [0.69, 0.90]
BjornsonBenson (RCS) 23/288 38/319 28.37 0.67 [0.41, 1.10]
Connett (RCS) 458/9875 1026/10228 35.93 0.46 [0.42, 0.51]
Subtotal (95% CI) 15220 11514 100.00 0.62 [0.40, 0.96]
Total events: 1385 (community), 1283 (media)
Test for heterogeneity: Chi² = 39.95, df = 2 (P < 0.00001), I² = 95.0%
Test for overall effect: Z = 2.15 (P = 0.03)
0.001 0.01 0.1 1 10 100 1000
Favours media
Favours community


Review: Recruitment strategies (for RCTs)
Comparison: 06 mailing vs media
Outcome: 03 assessed consent rate
Study or sub-category
mailing n/N
media n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
02 mailing vs media
Anon (RCS) 212/1252 437/1933 12.14 0.75 [0.65, 0.87]
BjornsonBenson (RCS) 30/150 75/638 10.93 1.70 [1.16, 2.50]
Connett (RCS) 2180/23681 2052/20455 12.34 0.92 [0.87, 0.97]
Rudick (RCS) 193/3002 42/515 11.33 0.79 [0.57, 1.09]
Anderson (RCS) 3/34 83/308 5.95 0.33 [0.11, 0.98]
Whelton (RCS) 737/2324 149/487 12.15 1.04 [0.90, 1.20]
Goodman (PCS) 12240/127554 622/1983 12.33 0.31 [0.29, 0.33]
Kusek02 (RCS) 783/1022 1325/1689 12.36 0.98 [0.94, 1.02]
Tworoger (RCS) 144/1078 17/83 10.47 0.65 [0.42, 1.02]
Subtotal (95% CI) 160067 28091 100.00 0.76 [0.53, 1.11]
Total events: 16522 (mailing), 4802 (media)
Test for heterogeneity: Chi² = 918.33, df = 8 (P < 0.00001), I² = 99.1%
Test for overall effect: Z = 1.43 (P = 0.15)
0.001 0.01 0.1 1 10 100 1000
Favours media
Favours mailing

3.4 Discussion

This systematic review of strategies for increasing recruitment to RCTs has identified 50 publications examining how more than 4 million potential participants were approached to RCTs participation.

There were 87 different recruitment strategies evaluated which were grouped into 5 major categories including personal methods, community approach, mailing, media and other (such as styles of informed consent, framing of recruitment information, methods of information presentation and comparison of recruiter dependent variables).

The primary outcome of interest was the consent rate. Although the exposed consent rate most closely reflects the effectiveness of a recruitment strategy, exposure is often difficult to measure (e.g. media), and can be misreported. The small number of studies describing exposure consent rates limits the application of our findings. The responder consent rate was easier to measure, and was more often reported. The assessed consent rate measured eligibility rather than potential participants' willingness to enrol in a trial, and therefore is the least useful consent rate for assessing the effectiveness of recruitment strategies.

The study types of included publications ranged from RCTs to before after studies, with poor methodological quality identified in most studies. This limited

generalisability of the results, with uncertainty remaining about the relative effectiveness of the different methods.

When evaluating consent rates in studies comparing different categories of recruitment, a trend for personal methods being more effective than impersonal methods such as mailing and media was demonstrated, with health care provider referrals having the highest consent rate. This is not surprising, as the influence of doctors' recommendations for trial participation has been reported in other studies (50;51). However, not all strategies within a category of recruitment method are the same. For example, health care provider referrals generally have higher consent rates than other personal methods of recruitment such as research staff recruitment, and community presentations are more effective than general community methods such as fliers and brochures. Even within a category of recruitment method, the trend again favours a more personal approach.

When evaluating consent rates for the studies comparing different variations of recruitment within one category, several strategies were identified as effective. The use of monetary incentives is effective, but whether this is ethical (particularly for children) has been questioned by many (122;123). The suggestion that framing recruitment information (e.g. by emphasising uncertainty) may improve recruitment is very exciting and warrants further research. This strategy has implications for researchers, as it attracts little additional cost and can be incorporated into other methods of recruitment.

However, the use of framing by emphasising uncertainty when inviting potential participants for trial participation without exploring the values of the individual or informing them of prior probabilities, was thought by some to be inadequate and misleading (144). Other effective methods such as the use of an interactive computer program for potential participants to find out more about the trial and informing recruiting doctors of patients' preferences regarding treatment and trial participation increase involvement of potential participants in the decision making process. These may be considered ideal methods.

The difference between consent rates and absolute number enrolled by each method suggests that both need to be considered in cost calculations. There is a trade-off between increasing exposure of potential participants to trial information and using methods with higher consent rates. Although health care provider referrals have the highest consent rates, the small number of potential participants who are exposed to trial information by this method compared with other methods such as mailing and media limits its application. It may therefore be faster and more cost effective to recruit by mailing of trial information to potential participants than by health care provider referral.

The cost of recruitment by recruitment method was not measured in the same way between studies because infrastructure and other costs were not consistently included (e.g. the reported cost per participant recruited by health care provide referrals ranged from $0 to $868), making comparisons difficult.

However, identification of ineffective methods of recruitment (such as bus advertisements, community presentations, community fliers etc) should steer researchers to abandon (or at least question) these methods.

3.5 Conclusions

How do researchers decide which methods to employ when recruiting participants for RCTs? Consideration must be given to exposure of potential participants to trial information, the consent rates of the recruitment methods used and costs of recruitment. Personalised referral by healthcare providers had the highest consent rate but mailing of trial information to potential participants was the most cost effective method overall.

Success of future trials depends on using ethical and cost effective means of recruiting study participants. Future research on framing of recruitment information, informing doctors of patients' preferences regarding treatment and trial participation and interactive methods which allow potential participants opportunity to find out about trials is needed.

Chapter 4 – Paediatricians' attitudes to children's participation in randomised controlled trials (focus group research)

4.1 Introduction

Doctors' reluctance to enrol patients is one of the most significant obstacles to trial success (47-49) as patients will rarely participate unless actively recommended to do so by their physician (51;145). This reluctance is considered a foreseeable consequence of the attempt to integrate the conflicting roles of clinician and researcher in RCTs (46). Taylor suggests the participation of doctors in trials can be predicted by their primary affiliation as either "clinicians" (with primary allegiance to the individual patient), or "researchers" (with primary allegiance to the community to generate scientific data) (46;48).

The RCT recruitment process is a relatively new area of inquiry, with previous research mostly confined to studies of adult recruitment (41;52;72;82;146;147). Recruitment issues in paediatric and adult RCTs are thought to be quite different (75). With the exception of paediatric oncology, children's recruitment to trials was thought to be more difficult (148). Although there are some studies that address paediatric trial recruitment (44;86;89;149;150), most address parental attitudes to trials (65;73;87;88;91;120;151). Little is known about paediatricians' attitudes to trials (83). With the increasing recognition of the need to include children as participants in RCTs (14;22;24;29), it has become even more important to explore barriers to children's participation in trials. The aim of this

study was to examine paediatricians' attitudes and identify possible physician-related barriers to children's participation in RCTs.

4.2 Methods

4.2.1 Participants

In Australia, primary care paediatricians and trainees refer children to RCTs, who are then enrolled by the trial investigators. These paediatricians do not generally receive any reward for recruiting patients, apart from departmental approval and a sense of personal achievement. Clinical pharmacologists, while playing an important role in trial conduct, do not recruit patients to trials.

Paediatricians and trainees from The Children's Hospital at Westmead (CHW), a 350-bed paediatric tertiary teaching hospital in Sydney, were invited to participate in the study. Purposive sampling was employed to ensure that all groups with unique views were represented (152;153). Participating doctors varied in occupation, experience, research activity, age, gender, ethnicity and parenthood experience (see Table 4.1). Unavailability at the scheduled time was the main reason for non-participation in the study.

Table 4.1: Characteristics of participating paediatricians

Characteristics	No. (%)
Sex	
Male	13 (62)
Female	8 (38)
Age	
25 – 34 years	4 (19)
35 – 44 years	7 (33)
45 – 54 years	5 (24)
55 – 65 years	5 (24)
Position	
Admitting medical officers with private practice	4 (19)
Staff specialists – general paediatrics	2 (10)
Staff specialists - subspecialties	9 (43)
Trainee paediatricians	5 (24)
Career medical officer	1 (5)
Length of medical practice	
Less than 10 years	4 (19)
11 – 20 years	7 (33)
21 – 30 years	5 (24)
31 – 40 years	5 (24)
Research experience	
Previously conducted research ("Research-clinician")	10 (48)
Limited research experience ("Nonresearch-clinician")	6 (29)
Trainees with research experience	3 (14)
Trainees with no research experience	2 (10)
Ethnic origin	
Australian	14 (67)
Asian	3 (14)
Eastern European	2 (10)
Other Caucasian	2 (10)
Parenting experience	
No children	8 (38)
Have children	13 (62)
Age of children	
Toddler (<5 years)	1 (5)
School age (5-18 years)	7 (33)
Adult (>18 years)	8 (38)
(Note: children may be in more than age group)	

4.2.2 Focus groups

Verbal consent was obtained from each participant. Semi-structured group discussions were conducted using an open-ended questioning approach. A "prompts sheet" for the focus group discussion was designed to cover the topic in adequate depth and in a consistent manner between groups (Appendix C). To ensure free discussion and interaction, consultant paediatricians and trainees attended separate groups. All participants completed a sociodemograpic questionnaire (Appendix D). Because the researcher was known to most of the participants, a professional facilitator unknown to them who is skilled at using probing techniques and pacing the group and who was thought to possibly be less threatening, conducted the discussions, with the researcher observing and taking field notes. Each session lasted 60 minutes and was audiotaped. Recruitment ceased when informational redundancy was reached (when no further information was gained), after 4 focus groups involving 21 participants.

4.2.3 Analysis

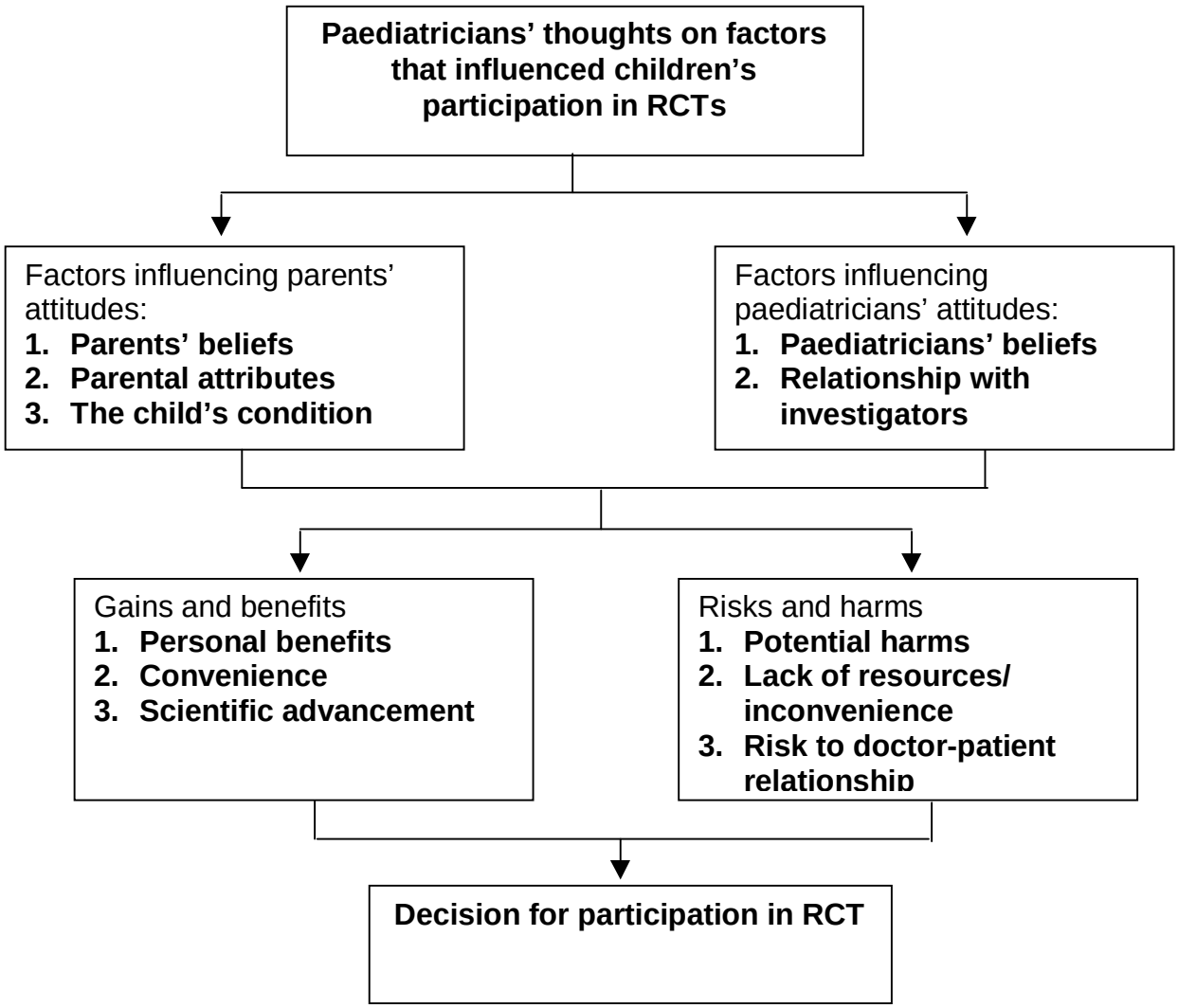
The audiotapes were transcribed and checked against field notes for accuracy and inclusion of non-verbal details. The transcribed audiotape data were organised and coded into discrete categories using the constant comparative method where each item is compared with the rest of the data to establish analytical categories that are mutually exclusive (153;154) and then further examined to identify emergent over-arching themes (152). Analyses of differences in responses between participants from the various occupations,

experience, research activity, age, gender, ethnicity and parenthood experience subgroups groups were undertaken. All participants had an opportunity to read and comment on the results.

4.3 Results

Participant views were organised into two broad themes encompassing factors thought to influence parents' and paediatricians' attitudes to children's trial participation (Figure 4.1). As research experience differentiated participant responses, these differences are highlighted in the results presented below.

Figure 4.1: Paediatricians' thoughts on factors that influenced children's participation in randomised controlled trials



4.3.1 Paediatricians' beliefs about parental attitudes

4.3.1.1 Parents' beliefs and knowledge

Most paediatricians believed that there is poor community awareness of RCTs, with confusion about equipoise (a state of collective uncertainty about the relative merits of alternative treatments), placebo usage (to demonstrate the real effects

of treatment) and random allocation (so that any differences at the end of a study will be attributable to the treatment alone).

"I also think, yeah, people just don't know much about trials. I don't think its something that's generally out there, in the community."

"But when you got to the bit about "I can't tell you which one it will be, it's determined by chance," they really, found that a really big sticking point … that they couldn't choose which treatment their baby was going to get."

"Even if they actually have heard of the word "placebo", I think they haven't thought it through to think what it really means. That it really means, theoretically, no treatment."

".. they find it (randomisation) uncomfortable"

They speculated that most parents did not understand equipoise, believing newer treatments were better than old, more treatment was better than less, and any treatment was better than none. Paediatricians observed greater difficulty recruiting for placebo-controlled trials compared with trials of active treatments.

"..they want the drug or the substance or the treatment. They don't want to have any risk of being put into a non-treatment group and I think that that really is a general rule."

"(regarding trials of active treatments) I think that is often easier than treatment or no treatment, depending on the study."

Participants also observed that consumer groups promoted these attitudes, demanding new treatments without evaluation

"..they didn't have good evidence for it. But as soon as some new thing is suggested, they want it and then they don't want trials".

"..the media influences the patient or the public knowledge about the trials."

However, some "research-clinicians" sensed increasing community awareness and acceptance of RCTs.

"I think people are becoming increasingly aware of it and I guess, certainly when you talk to them about these sorts of studies, they can understand the rationale.."

Paediatricians believed their opinions influenced parents' decisions for trial participation. They also thought parents were more willing to participate in trials they considered important because of media promotion or doctors' recommendations.

"..if their doctor recommends it and someone that they respect talks to them about it, that they will consider it… might, under those circumstances participate"

"If it's something like immunisation, a lot of people see the worthwhileness of that, I think community awareness is good enough for immunisation, people do see the advantage".

Participants sensed fear and mistrust of research by many parents. This anxiety was thought to be exaggerated in paediatric trials because of parental protectiveness and apprehension regarding experimentation on children (treating them as *"guinea pigs"*). Some felt parents may respond differently about participation in trials themselves.

"I think people who don't do research, find research a bit scary, a bit frightening.."

"..a parent's job … is to get the best possible care for their child.."

"..you've got to convince parents and nobody particularly wants to make their child a guinea pig."

"It's different when you're consenting for yourself."

4.3.1.2 Parents' attributes

The paediatricians identified a spectrum of parents ranging from those willing to participate in any trials to those always against participation. Likely participants were thought to be middle class, educated, Internet information seekers who were "..'PLOs' (people like ourselves)". However, some "research-clinicians" refuted this. Paediatricians admitted preferentially approaching "PLOs" because of easier communication and likelihood of trial participation.

> *"..inherently you get a biased sample, because there are psychologically two types of parents, one who'll say I'll be in a trial and one who'll say I wouldn't be in a trial for quids."*

> *"..I use PLO's (people like ourselves) to mean educated…this is the volunteer effect, educated, rather middle classed, in general… those people are much easier to interact with, because we have ways of communicating, that happen naturally, without us even trying and we relate to them in all sorts of ways, of which we are unaware."*

> *" I think you do sniff out middle class families because you think they're likely to say, yes… they're more likely to understand, you have to put less effort into convincing them."*

> *"I guess you always feel better about well-educated parents as well…you feel that they will understand what's involved."*

Those from low socio-economic, non-English speaking or Aboriginal backgrounds were thought less likely to participate, although this was also refuted by some "research-clinicians". Other culturally related factors such as non-attendance at follow-up and particular treatment preferences were also thought to impede participation.

> (people less likely to participate are) *"..low socioeconomic status, Aboriginal background"*

> *"A language barrier is always another thing. If you've got parents who don't speak particularly good English, and you haven't got an interpreter around, it's nigh on impossible to do recruiting."*

> *"I have also had lots of good experiences with people who are obviously not well educated but who are very willing to participate in the trial and who seem to understand the basics of it."*

Many paediatricians believed the child's doctor should decide which patients to approach about trials because they judged some parents incapable of coping with the demands of participation or unable to give informed consent because of language barriers or level of distress.

> *"I think that's up to the individual physician to who is referring or being asked to refer patients to trial."*

"I wouldn't ask anyone who was obviously upset or was obviously very anxious about their child. It depends.."

"..you meet families who would believe that they lack sufficient resources to get a bus ticket. They might be extremely pleasant people, but you think, I'm going to ask them to this, this, this and this ….. and it just won't work.."

"I don't think they would cope with this study."

4.3.1.3 The child's condition

Patients with a poor prognosis were thought to be less likely to participate in trials. In particular, parents desperate for hope might refuse participation in placebo-controlled trials.

"..this desperate group…see the proposed therapy as potentially lifesaving, and the proposed alternative, as doing nothing".

"I think it brings up the point that the more desperate the group, the harder it is.."

However, parents exposed to disciplines with a "research culture" were thought to be more willing to participate in trials. Some "research-clinicians" thought

parents with chronically ill children might view trial participation as another treatment option, but some were considered poor trial candidates because they were unable to alter their entrenched response to illness.

> *"..in oncology, the whole philosophy of the place is that the treatment of children with cancers is an ongoing clinical trial… and parents are very happy to go into trials on that basis because the philosophy is completely different."*

> *"..and usually these people are quite keen to participate in things … the condition is such that they are sort of looking for anything, and I actually like the idea of there being another facet to their management"*

> *"..some patients who have particularly chronic disease, who have got into a certain psychosocial situation where there is no point in trying to modify, or getting those people to do something different.."*

4.3.2 Paediatricians' attitudes

4.3.2.1 Paediatricians' beliefs

Most paediatricians acknowledged the importance of paediatric RCTs because of children's particular health issues.

> *"..a lot of the conditions we treat in childhood are different to adults and as well as obviously children having different responses, to also dealing with*

different sorts of diseases that really need their own sort of randomised clinical trials in some situations."

"..they have health issues that are peculiar to them and you can't just do it as a flog off from adult research."

"Nonresearch-clinicians" preferred safety-testing treatments on adults first *"..so I quite like a little bit of early trialing in adults before you actually then transfer to children"*, whereas "research-clinicians" perceived this as *"..just depriving children of potentially useful therapy".*

"Well that whole process before you hear about these new drugs, and we know from past experience we may not get them for 5 or 7 years, something like that. Whereas, if the drug's got promise, we may want to use it now, not in 5 years time."

Many paediatricians expressed discomfort about placebo usage and randomisation, particularly for terminally ill patients:

"..but certainly up in departments where I work, there is a bit of a move against randomised controlled trials. Why do we need to do them anyway. Is it ethical to randomised someone?"

"..I am always very sad for them when they get randomised to the control group… you want them to be in one of the other arms."

"..a treatment that is potentially life-saving… a treatment of last resort… You can't ethically randomise that, can you? Because, by the time you have got to the entry point, you've said there is no useful treatment."

"Research-clinicians", aware of published data on superior outcomes of all trial participants, perceived "inclusion benefits" for all participants whereas "Nonresearch-clinicians" saw no benefits for those on placebo.

"It's been well documented… there have been nice studies which show that up to 40% placebo effect with treatment and that probably is related to the fact that they come in more regularly and are seen more regularly. They are more aware of their disease."

"..if the child's going to be randomised into one or two streams, in that situation, one would have a hunch that in certain circumstances it's going to be of no benefit whatsoever."

All paediatricians favoured trials that they considered are clinically relevant. Many, despite community equipoise, had personal preferences about treatment options, which, although not outwardly acknowledged, were thought to subtly influence parents' decisions about participation. Some were reluctant to test current therapies by RCTs, preferring to rely on anecdotal evidence. However, most claimed they trusted ethics committees' approval of trials.

"..looking at a question that has a clinical implication: …questions that are purely scientific are necessary but,: being a clinician, I am much more interested in trials that look at the clinical application of what we do or how we do it. Or assessing what we are doing to see if actually it makes a difference."

"I think that it depends on if you agree with what they are doing, to start with. If you're not comfortable with the original treatment, it is very hard to put your patient through that and then send them onto a trial that somebody else is dictated."

"If you're uncomfortable about not treating someone, it means you believe there is a difference."

"If they read from the person running the trial, that the person running the trial believes that the treatment works, and now there's a chance that you won't get the treatment, they won't go on that …she thinks this thing ought to work. Well, I'll just go and get it, thank you."

"..they might not have that evidence based view, they might feel that what I do now is adequate, I've done it before with kids, it works.."

"..if the thing's been passed by the Ethic's Committee and that's….some fairly prestigious scientists, well it's good enough for me."

4.3.2.2 The paediatrician's relationship with investigators

Paediatricians acknowledged their relationship with investigators affected recruitment.

"..but it does contaminate the culture of involvement in studies, the next time you see a request to be involved in a study, you get contaminated by your last experience.."

Some acknowledged rivalry between research groups, admitting referring patients was often *"..not a matter of suitability (but)…a matter of competition".*

Investigators' communication with paediatricians was generally considered poor, with lack of consultation and inadequate feedback about recruitment closure, trial progress and patient follow-up. Trial unfamiliarity was identified as a particular problem in departments with high staff turnover because of poor communication. All paediatricians agreed on the importance of a trial contact who was available, enthusiastic and *"..recognised by everybody as being competent and skilful, but also isn't a competitor"*. Lack of consultation and support by investigators and lack of ownership were experienced by many, especially "trainees" who resented the expectation of their involvement. Enlisting the support of key gatekeepers

(community paediatricians, senior consultants, nursing staff) as well as staff involved in recruitment who derive little benefit from participation was considered essential.

"..we don't believe we're engaged enough in the functioning of this hospital as visitors … maybe there's some merit in formulating a study to engage one of us on the study group to give some ideas as to how best they may be recruited in private practice."

"no-one has actually bothered to explain to me what the randomised control trial is about, so I don't feel like I have any ownership of it.."

"..Particularly when you've got such a flux in staff, and you've got so many people coming and going, it is hard to get communication… you've got people coming and they might be here for a few weeks… don't really hear unless somebody really specifically goes round and educates them."

"..quite effective if you have someone who is dedicated to it, in terms of, not as much a single person whose job it is to do it, but in terms of someone who wants to actually do it. So, if it's an enthusiastic person, that gets the message across much more effectively."

"So, you really have to have the local paediatricians on side, or they just refuse. They by-pass it completely."

4.3.3 Gains and benefits

4.3.3.1 Personal benefits

Paediatricians speculated that parents who perceived personal benefits for their child were more likely to participate in trials. These benefits include thorough follow up, special attention, access to information about the underlying condition and to extra resources including new treatments not routinely unavailable. "Research-clinicians" also thought "emotional bribes" were used, such as giving participants priority in accessing restricted treatments at the completion of trials.

> *"I think for the parents and children participating… it's that feeling of being special and being looked after, as well as obviously the hope that they will derive some benefit from participating which they wouldn't, otherwise, have access to."*

> *"..basically, they felt they were special, that they got a lot of attention and that … things were being looked after very well"*

> *"..it's not available …But it will be costly, when it is available, and they're kind of, they're in on the first run.."*

> *"..they would get priority as far as clinical appointments were concerned afterwards… It's not really a bribe, it's kind of a bribe, it's an emotional bribe I suppose."*

"Research-clinicians" perceived most professional gains from trial participation, and "Nonresearch-clinicians" the least. "Research-clinicians" recognised the discipline of adhering to a research protocol improved their clinical practice, and thought participation *was "..a way of propagating (appropriate management) and actually adjusts clinical practice"*. They acknowledged that *"..those skills may actually go on and live longer than the outcome."* They also sought professional recognition and enjoyed increased interaction with specialists from different fields as a result of participation. "Trainees" enjoyed learning about conducting research. "Nonresearch-clinicians" perceived few professional gains.

> *"..I think that's very important if you're going to put some time and effort into something and you want that time and effort to be recognised. I don't mean you must win a medal but I mean, you got to…it's got to appear to you that you're being appropriately acknowledged - if you have made a major contribution, that you are an author, if you have simply provided some material, that you're acknowledged at the end of the article."*

> *"..I have sometimes learnt a lot by the process of participating. Either running one or actually being a participant."*

> *"Sometimes conducting a clinical trial is an extremely useful way of getting a whole bunch of people who don't ordinarily work in the same direction,*

so it can be a very powerful tool, … of harnessing different groups of people to a common purpose."

(Trainee) *"…I found that it's interesting to see how they do things, even though I've not really been involved other than trying to collect kids as they come through. It just gives you a little bit of an idea about how people go about conducting research and the kind of hassles that they get."*

"*And then the next question is 'what's in it for me?"*

4.3.3.2 Convenience

"Research-clinicians" noted that recruitment is enhanced by making participation more convenient for families by offering home visits, travel cost reimbursements and provision of free medication. However, all participants objected ethically to offering monetary incentives for children.

"..was really very successful in achieving a truly randomised sample, because a) we went to them, and b) we only went once."

"One thing which was far more successful than we ever thought was going to be, was we just offered to pay for travel costs to and from the hospital which for some of our families, in fact made the difference between I'm sure …coming and not coming."

"..I used to say " well otherwise it would cost a lot of money, you will get it for free.."

"..I know they pay a lot of the adults to actually take part in it. I don't actually think that's a great idea for the childhood studies…I know their parents are supposed to be their best advocates and so on, but I think if you say "we're going to pay you to have your child take part in this study", I just don't – I don't find that right."

Paediatricians preferred trials with easy referral, where they only had to identify eligible patients, or trials that decreased their workload, where routine investigations were organised by the research team.

"I think one of the important things from my point of view, if I'm very honest, is a combination of how common is the condition and how much is involved in my referring to that trial. So, if it's very easy to refer to the Trial…because it's so easy -it's easy. If it gets to be harder…. and requires more of my time, if it's a fairly common condition, I'll let myself off every second time, because I just frankly haven't got the time to go to the trouble that's involved"

"..trial was actually doing the follow-up investigations you were going to have organise anyway. So it actually took some work away from us, which was really good, because it's fiddly trying to make all those

appointments. ..And that's what was quite attractive about it, there was actually incentive there to do it."

Referring patients for trials at the time of the consultation was considered more convenient for consultant paediatricians. However, "trainees" responsible for overseeing treatments disliked trials where decisions for enrolment were made at presentation, because it increased their workload.

"The closer the recruiting is to the diagnosis (the better)…Lag factor is bad."

4.3.3.3 Scientific advancement and future patient benefit

All paediatricians acknowledged scientific advancement and future patient benefits as important altruistic motives for parents and doctors. Many derived satisfaction from contributing to scientific evidence, which some believed should be a community responsibility, even if there were no immediate benefits. Others were more concerned with personal benefits for their patients.

"There is a satisfaction to knowing that you're not just doing it, you're doing it because you've shown or you help show, that it is some sort of positive benefit to the patient. That is what I would find most satisfying.

4.3.4 Risks or harms

4.3.4.1 Potential harms

Paediatricians were concerned about the potential side effects of the treatments being tested. Although acknowledged as unlikely, many had difficulty explaining these to parents. “Research-clinicians” were less willing to expose patients to potential side effects in trials requiring large sample sizes designed to detect a small treatment effect.

> *“..side effects of drugs is another one, if we’re involved in certain drug trials, you know there is usually long lists of potential side effects that you have to go through and that can be a bit difficult. I mean, one knows that these are almost certainly not going to apply but because this is a trial situation you’ve actually got to be very careful about explaining, you’ve got to get consent on each occasion, you know, it can be difficult..”*

> *“Although the potential harm may not be that great. That you would have to treat so many of them to get any benefit. That’s a bit of concern.”*

4.3.4.2 Inconvenience/ lack of resources

Identified patient inconveniences included additional investigations, follow-up visits, travelling and additional costs. Most paediatricians disliked trials requiring unpleasant non-routine procedures such as blood tests *“..where it wouldn’t normally have been done, it’s something that you feel a bit hesitant about ..”.*

Time constraint was a major obstacle to trial involvement for all participants. Most "Nonresearch-clinicians" resented the extra demands of explaining about trials and data collecting. "Research-clinicians" blamed lack of time for suboptimal recruitment efforts.

> *"..but all studies involve a lot of time and a lot of paperwork, huge amounts of paperwork, normally."*

> *"I think that as a clinician doing trials, you find that it (ie recruiting for trials) is an additional work load that you don't have time for… time is a huge factor, and if you had more time you could spend it actively recruiting and being on the floor, or being in the focus and around and accessible and finding people and writing letters to everybody whose involved, saying what you're doing and spending a lot more time communicating and making sure everyone knows what is happening and where they're up to and, you know, the people in the trials as well as those people who are involved in their care."*

Inadequate funding and resources were also considered hindrances to trial participation. Although pharmaceutical trials are believed to be better funded, many "research-clinicians" resented the extra administrative demands of pharmaceutical companies, acknowledging a conflict of interest between requirements for product registration and information for clinicians using those products.

"..the money is always horrendously underdone. It's the difference between being able to do a study, being that it be under-funded, versus not being able to do it because of the funding issue.."

"..I think there's a difference between trials, studies that you've initiated yourself, or have come out of good institutions versus ones that a particular industry group has asked you to conduct because they need that information for registration for a drug. …there are differences there in terms of how much the agenda is driven by an outside group versus driven by you."

4.3.4.3 Risk to the doctor-patient relationship/ quality of care

Some participants were concerned about their patients' quality of care under the research team, fearing that research would take priority over patients' needs. Others thought trial participation may threaten the doctor-patient relationship if patients formed a bond with the research team. The potential loss of patients and the resulting economic effects for paediatricians in private practice when referring to trials was a serious concern.

"..for some of the patients, the people doing the study are really interested in doing the study rather than managing the patient, and whereas the patient sometimes falls between the cracks… we have moved away a bit from the usual person because they're doing these other things with these other people …won't take on all of their care.."

"If you feel that it impinges on your ability to continue your relationship with your patient, then you would think twice about subjecting them, your patient, to that risk."

"..where we can have difficulty finding patients we can hang on to… is that the study group, snavell up our patients and take over.."

Many resented the imposition of trial protocols on their style of practice. Most disliked directly approaching parents for trial participation and felt "rejected" by parents who declined participation. Some were uncomfortable expressing uncertainty, fearing mistrust by parents who expected doctors to know all the answers. Many regarded their role as being the families' advocates, feeling obligated to protect families from excessive invasion by investigators.

"..If you were doing an RCT, for example, that will actually impose a format on you that may not be part of your normal style… That can actually impinge a bit, if you look at a protocol, and you think 'Oh, gee, I'm going to feel very uncomfortable in the way… this doesn't suit my style' "

"No-one likes rejection.."

"It's not part of their culture…, that we are still carrying on research. There's very much still an expectation that we do have all the answers.

And, to say that we don't actually know the answer and this is why we're doing this, I think freshly shatters that expectation, so then they don't particularly trust you because you've just said you don't know the answer.."

"My concern, always with these trials, …is it going to be of benefit to the individual child in the process, not looking at the group but the individual child."

"I guess we also need to protect them against going into multiple trials, because they are often being asked to either act as a control with a different chronic disease or.."

4.3.5 Suggested improvements for the future

The participants made a number of suggestions for improving children's participation in RCTs. "Trainees", acknowledging poor understanding of RCTs, recommended education of doctors and medical students. Paediatricians suggested increasing community awareness of trials through media promotion and advertising in waiting rooms *because ".. it makes it acceptable and worthwhile"*, preferring to respond to parents' inquiries rather than *"solicit"* participation.

"New graduate course, medical course, they are doing research, so they're learning about it much earlier on, and I think that probably doing it,

is the only way… doing research is the only way you really get a feel for why you're doing it and you de-mystify it, you realize it's got its own problems and its own merits and its own barriers."

"..generally raising community …, it would be nice if people were aware that, yes, we do do these things, that we don't have all the answers and that we may ask you to think about participating, or ask you to think about your child participating in this. So, it's not such a complete shock when you suddenly mentioned the word research or study."

Enlisting the support of paediatricians was recommended *"..because the parents will often ask (their paediatrician) … what do you think about this study… it's really up to the physician to say, well, I think it is appropriate or I don't.."* Also, improving investigators' communication with paediatricians about trial progress and findings, and involving paediatricians in the follow up of trial participants were suggested.

"I wonder how many people who actually involve, or involve their children in trials, actually get feedback at the end of the trial about the outcome. I wonder if that is actually a helpful thing as a process in terms of improving people's overall willingness to participate."

"You should build into it, that they (ie general paediatricians) are going to follow them up and you do it as part of your consultation. Otherwise, you are not going to recruit your patients."

Providing a trial contact would encourage paediatricians' involvement by minimising the extra work required for recruitment. "Research-clinicians" suggested more "protected time" for research as another solution, as many researchers in Australia do not have protected research time, with funded research time often pressured by clinical commitments.

"And you are far more likely to refer them… If you had somebody that was dedicated to going through all that extra work of convincing the parents and getting the consent and explaining the trial, you're more likely to do it because you don't have to spend that hour trying to convince them to do it."

"…we can all do with more time to allocate to clinical research."

4.4 Discussion

This study has highlighted some attitudes and beliefs held by paediatricians that have implications for researchers wanting to involve children and medical educators who teach trial theory and practice. Paediatricians' views about trials involving children are complex. They must balance their own attitudes, what they

believe to be the parents' views, and their perception of the benefits and risks of a specific trial, in the decision making process.

In general, the balance of perceived gains versus risks for paediatric RCTs participation means that non-participation will be the outcome in many instances. For many paediatricians the individual doctor-patient relationship is paramount and RCTs tend to be seen as a hindrance and not a help. Participation in trials is viewed as involving many negatives - more work, less money, sharing clinical responsibilities with someone else, lack of control over interventions used, and a threat to the trust of the patient in the doctor (who "does not know what is best"). Paediatricians have a very strong commitment to the care of their individual patients so that giving an intervention which the individual paediatrician thinks is best may often outweigh the long-term, community-orientated benefits of improving the health of children by appropriately evaluating interventions by RCTs.

Does this study suggest any solutions? Reducing disadvantages of trial participation and increasing advantages by making participation more convenient for paediatricians and families and building better relationships between investigators and clinicians based upon communication and trust may tip the balance towards increased participation. Further, increasing community awareness of trials in general and current, relevant trials in particular, coupled with a favourable disposition to trials may encourage paediatricians in their

support of RCTs involving children. This study also suggests that medical educators may need to use alternative strategies in communicating the limitations of using healthcare interventions that have not been appropriately studied (44).

Many of the findings were similar to those of studies involving adult physicians. It is not surprising that paediatricians and physicians have similar attitudes to trial participation. Similarities include the influence doctors believe they have on their patients' decisions about trial participation (51) and the perception that patients feared and mistrusted researchers (155). They also considered patients from non-English speaking backgrounds (156) or with poor prognosis (49) less willing to participate in RCTs. Interestingly, although paediatricians in this study preferred approaching middle class patients, this group was considered more difficult to approach in one adult study because they were likely to ask probing questions (49). Paediatricians thought that parents exposed to disciplines with a "research culture" such as oncology were more willing to participate in trials. (46;49;157).

Paediatricians' objection to offering monetary incentives for children, despite acknowledging adult subjects are sometimes compensated, reflect the complex issues of consent by proxy and the fear that parents may participate in trials for personal gain instead of for the best interest of their child (13). Ironically,

paediatricians had no objection to financial compensation for their own role in trial recruitment.

In general, paediatricians appeared to have more “clinician” than “researcher” attributes. The differences in response between participants with and without previous research experience in this study confirmed the “researcher-clinician” framework developed by Taylor et al (46;48). Do paediatricians develop a “researcher” attitude as a result of their involvement in trials, or do they become actively involved in trials because they have an interest in research?

Further research is needed to address the issues raised by this study and to assess attitudes of parents who make the final decision for trial participation.

Are the results of this study generalizable to other places in Australia? The participants of the focus group discussion were recruited from the Children’s Hospital at Westmead, a 350 bed children’s hospital which is a tertiary referral centre serving all children in the state of New South Wales in Australia. This teaching hospital has a strong research focus in many subspecialties. Paediatricians working here have a high exposure to research and their responses therefore cannot be generalised to paediatricians outside of that setting. It is postulated that paediatricians outside of that setting are likely to be less research focused, and the results of this study therefore highlight the plight of paediatric clinical research in Australia.

Can the results of this Australian study be applied to other countries? It is likely that the general issues raised here are very applicable to other settings, with some exceptions. In some settings the paediatrician may be both the primary physician and the investigator on a trial so the discussion on paediatrician-investigator relationships would not be relevant. This is an extreme case of the general principle which is that the weight given to each factor will vary across countries and within any given country, but the factors shaping paediatricians' attitudes to trials provided here are likely to be common to all. This requires confirmation with similar studies carried out in other countries and settings.

4.5 Conclusion

Paediatricians' attitudes to children's participation in RCTs are likely to impact on recruitment. Typically when recruitment targets are not met, changes are made to the trial design and recruitment strategies. This study suggests that other methods that address paediatricians' concerns may also encourage participation. This has implications for researchers working with children and for medical educators. Educating paediatricians about RCTs and involving them in trials will increasing their awareness of RCTs. Also closely scrutinizing each step of the RCTs process to reduce disadvantages and increase advantages whenever possible may tip the gains-hazard balance to favour participation.

Chapter 5 – Australian paediatricians' and adult physicians' attitudes to randomised controlled trials (survey)

5.1 Introduction

Doctor-related factors have been cited as one of the primary reasons for poor recruitment in clinical trials (47;51;145). Barriers to trial participation for doctors previously identified (41-43) include perceived conflicts between the roles of clinician and scientist (46), time and financial constraints (61), lack of rewards (46;53), dislike of loss of autonomy (62), problems with complying with protocols (55), discomfort with randomisation (64), preference for particular treatments (40;54-56;60), difficulty with ethics requirements and informed consent (51), and concerns about patients' wellbeing (40) and the doctor-patient relationship (40;55;60;62;63). Previous studies on doctor barriers focused on recruitment for oncology trials (54). However, little is known about paediatric trials (34;49;158).

The "Physician Oriented Profile" (POP) is a questionnaire designed to assess doctors' treatment philosophies. It has been used in several studies of cancer specialists (46;48;49;64) to assess 5 indices of physician attitudes and behaviour regarding RCTs: primary allegiance, professional activities, decision making under uncertainty, perceived rewards and peer group influence (46;48). The questionnaire provides individual scores, with mean scores ranging along a continuum from the extremes of pure therapist (clinician-oriented) to pure experimenter (research-oriented), which are predictive of doctors' participation in RCTs. Doctors with higher "POP" scores were considered to be more research-

oriented, reported higher past accrual to trials and showed greater intention to accrue in the future (64).

As little is known about Australian paediatricians' attitudes to trial participation, a modified "POP" was used in this study to compare responses between paediatricians and adult physicians in Australia. Results were also compared with UK/US data.

5.2 Methods

5.2.1 Participants

Five hundred doctors (250 adult physicians and 250 paediatricians) were randomly selected by computer from the 7378 doctors registered with the Royal Australasian College of Physicians and invited to participate (using RAND, a computerised random number generator: Microsoft Excel 97). Doctors were sent a questionnaire by mail and email together with a prepaid envelope, response slip and explanatory letter. Non-responders were contacted at least twice to minimise response bias.

5.2.2 The questionnaire

The questionnaire (Appendix E) is based on the "Physician Oriented Profile" (POP), a previously validated questionnaire which assesses doctors' treatment philosophies and attitude to RCTs. It assesses 5 indices of physician attitudes and behaviour regarding RCTs: primary allegiance, professional activities,

decision making under uncertainty, perceived rewards and peer group influence (46;48). The questionnaire provides individual scores along a continuum ranging from the extremes of pure therapist (clinician oriented) to pure experimenter (research oriented), which are predictive of doctors' participation in RCTs.

The theoretical framework for the "Physician Oriented Profile" was based on results from a preliminary study including in-depth observation and interviews of 42 breast cancer specialists (48). The "Physician Oriented Profile" has previously been used in 4 separate studies:

- it was first applied as a 30-item typology to 484 breast cancer specialists from 57 institutions in five countries between 1981 and 1985. The responses differentiated physicians with regard to their attitude to participation in scientific research.
- A tailored version of the "POP" was applied to 101 physician-investigators of the Collaborative Ocular Melanoma Study (COMS) in the US and Canada (46). This version consisted of 15 demographic questions, 45 binary option questions and 6 open ended questions.
- The third study was a survey of the 1737 physician members of the Eastern Cooperative Oncology Group (ECOG), where each physician's actual patient accrual was recorded. This confirmed that doctors with higher "POP" scores were more research oriented,

reported higher past accrual to trials and showed greater intention to accrue in the future (64).

- The fourth study was conducted with 553 cancer specialists in the UK using a 45-item questionnaire, and compared responses between the UK and US studies.

The questions in this study are based on the wording from the fourth study.

The “POP” questionnaire was chosen in this setting because it qualitatively measures doctors’ treatment philosophies and attitudes to RCTs and because “POP” scores had been previously demonstrated to correlate with trial participation. The application of this questionnaire on paediatricians and adult physicians was limited by the original design, which was intended for cancer specialists. Questions that were not relevant for the non-oncology context was therefore excluded. This 44-item questionnaire was piloted by 10 doctors for acceptability and content. After feedback from the pilot study, three questions were reworded for the Australian context, and 2 questions were added. The final questionnaire consisted of 11 items identifying demographic and practice details of participants (which served as predictors of doctors’ treatment philosophies) and 33 items assessing the doctor’s treatment philosophy and attitude to RCTs using binary-option questions where possible.

5.2.3 Analysis

When answers were divergent to given options, responses were matched to the closest option given or were excluded if they did not match given options. “POP” scores for doctors’ treatment philosophies were calculated using a similar method to previous studies (48);(46;49;64) where each item was assigned a score from 0 to 1, with pure “researcher or scientist” responses scoring 1 and pure “clinician or therapist” responses scoring 0. The mean “POP” score was derived by dividing the total “POP” score by the number of questions answered and expressed as a number between 0 and 1 (sum of “POP” score /number of questions answered).

Only 28 of 33 items assessing doctors’ treatment philosophies were compared with UK and US data, as there was altered wording in 3 questions (Questions 18, 25 and 44) and 2 other questions were unique to the Australian questionnaire (Questions 30 and 34), and comparison is therefore inappropriate.

Demographic and practice variables and response to individual questions were compared between adult physicians and paediatricians using χ^2 for differences in proportions. Overall mean “POP” scores were compared across demographic and practice variables using ANOVA for differences in means. Backwards stepwise regression of the variables found to be significant ($p<0.05$) on univariate analysis was performed to identify independent predictors of “POP” score.

Australian data was compared with UK and US data using χ^2 for differences in proportions. Level of significance was defined as < 0.05.

5.3 Results

5.3.1 Respondents' demographics

Three hundred doctors in total returned completed questionnaires (60% response rate). Significantly more paediatricians (164/250 vs 134/250) responded (p=0.004). Most respondents were males (72.8%) and practised in an urban setting (87.2%). The median age was 47 years (47.0 for adult physicians and 46.5 for paediatricians) with a range from 32 to 94 years. Respondents worked in private practice (33.1%), were salaried hospital staff specialists (44.8%) or academics (11.4%) (Table 5.1).

5.3.2 Respondents' research experience

Many respondents had limited research experience with 31.5% having never enrolled a patient in a RCT and 44.9% who had not enrolled a patient within the previous year. Many (26.9%) were not currently involved in research at all, and 78.9% spent less than 30% of time in research activities. Only 56% had published an article in the past 12 months (Table 5.1).

5.3.3 Comparison between paediatricians and adult physicians

Demographic data were similar between paediatricians and adult physicians. There were more hospital staff specialists (51.5% vs 36.2%, p<0.01) and females

(34.1% vs 17.9%, p<0.004) among the paediatricians. Although research time and publications were similar among both groups, fewer paediatricians had experience with enrolling patients in trials (62.2% vs 76.3%, p<0.009) (Tables 5.1 and 5.2).

Table 5.1: Comparison of demographics and research experience of adult physicians and paediatricians who responded to the questionnaire on attitudes to RCTs (questions 1 to 11)

Demographics and research experience		Adult Physicians		Paediatricians		Total		p value*
		N	%	N	%		%	
Specialty (298)		134	45.0	164	55.0	298		
Gender (298)	Male	110	82.1	107	65.2	217	72.8	0.004
Primary setting (298)	Private practice	42	31.3	44	26.8	86	28.9	0.3
	Teaching hospital	64	47.8	96	58.5	160	53.7	
	Both teaching hospital and private practice	10	7.5	9	5.5	19	6.4	
	Others**	18	13.4	15	9.1	33	11.1	
Appointment (290)	VMO/private practice (fee for service)	45	35.4	51	31.3	96	33.1	0.01
	Staff specialist (salaried)	46	36.2	84	51.5	130	44.8	
	Academic (salaried)	22	17.3	11	6.7	33	11.4	
	Other	14	11.0	17	10.4	31	10.7	
Location of practice (288)	Urban	113	88.3	138	86.3	251	87.2	0.7
	Rural	15	11.7	22	13.8	37	12.8	
Patients seen per week (293)	0	14	10.8	11	6.7	25	8.5	0.04
	1 to 20	25	19.2	53	32.5	78	26.6	
	21 to 50	47	36.2	59	36.2	106	36.2	
	>50	44	33.8	40	24.5	84	28.8	
Ever enrolled patients in an RCT (295)	Never	31	23.7	62	37.8	93	31.5	0.009
Patients enrolled in an RCT in the last year (285)	0	46	35.9	82	52.2	128	44.9	0.01
	1 to 10	42	32.8	46	29.3	88	30.9	
	>10	40	31.3	29	18.5	69	24.2	
Research time (294)	no research	36	27.5	43	26.4	79	26.9	0.5
	<30%	68	51.9	85	52.1	153	52.0	
	30-50%	12	9.2	22	13.5	34	11.6	
	>50%	15	11.5	13	8.0	28	9.5	
Articles published in the last year (293)	None	56	42.7	73	45.1	129	44.0	0.7
	1	14	10.7	60	13.0	35	11.9	
	2	24	18.3	23	14.2	47	16.0	
	3	14	10.7	12	7.4	26	8.9	
	>3	23	17.6	33	20.4	56	19.1	

*p value for differences in proportions between adult physicians and paediatricians
** 5 community, 4 government, 7 research, 12 retired and 5 others
( ) = number of responses to each question; RCT = randomised controlled trial

Table 5.2: Comparison of adult physicians' and paediatricians' treatment philosophies and attitudes to trials (questions 12 to 44)

Question	Response	Adult Physicians		Paediatricians		p value
		N/T	%	N/T	%	
		134		164		
Q12. As a doctor my primary commitment is to:	future generations of patients (society)	11/130	8.5	21/163	12.9	0.5
	present patients (individual)	115	88.5	137	84.0	
Q13. When there is controversy in the literature as to which treatment is best:	I enter the patient in a clinical trial if one exists	50/123	40.7	49/154	31.8	0.3
	I personally select a treatment for the patient	71	57.7	102	66.2	
Q14. If I had to choose, I would say my primary task is:	caring for individual patients	118/130	90.8	144/160	90.0	0.8
	contributing to scientific knowledge	12	9.2	16	10.0	
Q15. In my hospital, doctors are given more reward for:	clinical skills with patients	84/121	69.4	101/157	64.3	0.4
	contributing to scientific knowledge	34	28.1	54	34.4	
Q16. If written informed consent was not required, I would approach more patients to enter clinical trials	true	13/125	10.4	14/161	8.7	0.6
	makes no difference	112	89.6	147	91.3	
Q17. When making critical and controversial decisions, I usually:	seek major input from my patients	118/127	92.9	156/159	98.1	0.03
	• do not seek major input from my patients	9	7.1	3	1.9	
Q18. Ideally I would like to refer or enter the following proportion of my potentially eligible patients into RCTs:	none	3/126	2.4	6/156	3.8	0.07
	some	72	57.1	80	51.3	
	half	11	8.7	4	2.6	
	most	29	23.0	42	26.9	
	all	11	8.7	24	15.4	
Q19. The time I devote to publications, lectures and research commitments, compared to clinical work, is relatively:	totally clinical work	16/126	12.7	15/158	9.5	0.2
	mainly clinical work	77	61.1	97	61.4	
	equally and research	18	14.3	33	20.9	
	mainly research	10	7.9	12	7.6	
	totally research	5	4.0	1	0.6	
Q20. My income is:	dependent on my research activities	16/131	12.2	14/161	8.7	0.3
	not dependent on my research activities	115	87.8	147	91.3	
Q21. I would like to assess how successful I was as a physician by:	my research contribution	23/130	17.7	19/159	11.9	0.4
	how I helped individual patients	97	74.6	125	78.6	
	(both)	10	7.7	15	9.4	
Q22. I would rather be somewhat:	too involved with my patients	103/120	85.8	124/147	84.4	0.7
	too detached from my patients	17	14.2	23	15.6	
Q23. If a patient refuses to participate in an RCT, I would:	treat the patient off the study	124/124	100.0	155/157	98.7	0.2
	refer the patient to another doctor	0	0.0	2	1.3	
Q24. I would rather be known for:	my interpersonal skills with patients	100/128	78.1	124/161	77.0	0.3
	my research accomplishments	26	20.3	29	18.0	
Q25. Overall I feel the quality of patient care:	increases when a patient is in a clinical trial	59/128	46.1	70/158	44.3	0.4
	decreases when a patient is in a clinical trial	8	6.3	5	3.2	
	does not change when a patient is in a clinical trial	61	47.7	83	52.5	
Q26. When published data and my clinical judgement conflict, I am more likely to rely on:	my clinical experience	57/129	44.2	71/158	44.9	0.8
	published data	69	53.5	85	53.8	

Question	Response	Adult Physicians		Paediatricians		p value
		N/T	%	N/T	%	
Q27. RCTs restrict my ability to individualize patient care	true	34/127	26.8	45/160	28.1	0.8
	makes no difference	93	73.2	115	71.9	
Q28. In my hospital the pressure to participate in an RCT is relatively:	low	105/120	87.5	143/159	89.9	0.5
	high	15	12.5	16	10.1	
Q29. Detailed monitoring of my management of trial patients deters me from participating in RCTs:	yes	14/126	11.1	16/160	10.0	0.8
Q30. The increased paperwork involved in treating patients on trials deters me from participating in RCTs:	yes	50/127	39.4	58/160	36.3	0.6
Q31.When a potentially eligible patient chooses not to enrol on a trial that I have suggested, I:	often feel disappointed	36/125	28.8	42/154	27.3	0.8
	seldom feel disappointed	89	71.2	112	72.7	
Q32. Frequent publications are important to my career advancement:	yes	61/131	46.6	76/162	46.9	1.0
Q33. When a protocol includes a treatment that is more aggressive than I would usually give:	I am often reluctant to participate	63/123	51.2	78/151	51.7	0.9
	it makes no difference	60	48.8	73	48.3	
Q34. When a protocol includes a treatment that is less aggressive than I would usually give:	I am often reluctant to participate	54/122	44.3	55/151	36.4	0.2
	it makes no difference	68	55.7	96	63.6	
Q35. I am reluctant to participate in a trial that may randomise the patient to a 'no treatment' group:	yes	46/127	36.2	34/158	21.5	0.006
Q36. The opinions of the patient's usual doctor regarding RCTs affects my decision to approach an eligible patient:	true	47/124	37.9	56/156	35.9	0.7
Q37. The thought of having to spell out details of a trial discourages me from approaching eligible patients:	true	28/127	22.0	28/160	17.5	0.3
Q38. A major reason for my participation in RCTs is that it financially benefits my institution or department:	agree	20/126	15.9	9/157	5.7	0.005
Q39. Overall, involvement in randomised clinical trials:	enhances my reputation	62/128	48.4	64/155	41.3	0.2
	does not enhance my reputation	66	51.6	91	58.7	
Q40. When I am personally uncertain as to which treatment is best, I am likely to:	enter the patient in an RCT if I am aware one exists	71/124	57.3	83/155	53.5	0.5
	personally select a treatment	53	42.7	72	46.5	
Q41. If research activities were to enhance my income, I would enter more patients in RCTs:	agree	36/127	28.3	36/160	22.5	0.3
Q42. I am more likely to attend a conference that focuses on:	clinical issues	99/130	76.2	117/160	73.1	0.8
	research issues	26	20.0	37	23.1	
Q43. The patient's right to select treatments is more important than knowledge advancement:	true	91/128	71.1	109/158	69.0	0.7
Q44. When I participate in a randomised clinical trial, it is more likely that I:	increase my patient population	10/123	8.1	4/158	2.5	0.04
	lose patients I might otherwise keep	10	8.1	7	4.4	
	it makes no difference to my patient population	103	83.7	147	93.0	

N/T = number of responses/ total number of adult physicians or paediatricians who answered that question
RCT= randomised controlled trials

Responses to the questions assessing treatment philosophies were also similar between paediatricians and adult physicians. However, adult physicians were more reluctant to participate in RCTs involving placebo use (36.2% vs 21.5%, p<0.006), more frequently thought trial participation affected their patient population (16.2% vs 6.9%, p<0.04) and more often identified financial benefits for their institution or department as a reason for trial participation (15.9% vs 5.7%, p<0.005).

5.3.4 Comparison of doctor demographics with "POP" score

Univariate analysis showed that doctors who were younger (p<0.0001), in salaried positions (p<0.0001) or in urban settings (p<0.0001) had higher "POP" scores (ie were more research-oriented) than doctors who were older, in private practice or in rural settings respectively. There was an association between number of patients seen per week and mean "POP" score, with clinicians who saw fewer patients having a higher "POP" score (p<0.0001). Research involvement (i.e. experience with enrolling patients in trials, time assigned to research activities and number of publications in the last year) also correlated with higher "POP" scores (all p<0.0001). On multivariate analysis three independent variables were found to significantly predict "POP" scores: the presence of any allocated research time (8.6% higher "POP" score (95% CI 5.6%, 11.5%, p<0.0001)); history of enrolling a patient in a RCT in the past (4.2% higher "POP" score (95% CI 1.5%, 7.0%, p=0.003)); and the doctor's age (decrease by 0.1% for each year increase (95% CI 0.06%, 0.3%, p=0.042)). The

overall R^2 for the model was 0.162 (ie 16.2% of participants' mean "POP" score can be explained using these 3 variables) (Table 5.3).

Table 5.3: Comparison of mean "POP" score by doctors' demographics and research experience

Doctors' demographics		N	Mean "POP" score (95%CI)	p value
Age	median = 47 years	296	0.44 (0.43 , 0.46)	0.01
Gender	Male	216	0.44 (0.42 , 0.46)	0.5
	Female	80	0.45 (0.43 , 0.48)	
Adult physician vs paediatrician	Adult physician	132	0.44 (0.42 , 0.46)	0.6
	Paediatrician	164	0.45 (0.43 , 0.46)	
Oncologists vs nononcologists	Oncologists	12	0.52 (0.41 , 0.63)	0.03
	Non oncologists	285	0.44 (0.43 , 0.45)	
Appointment	Staff specialist/academics	163	0.47 (0.45 , 0.49)	0.0001
	VMO/private practice	97	0.40 (0.38 , 0.42)	
Primary setting	Salaried	180	0.47 (0.45 , 0.49)	0.0001
	Fee for service	86	0.38 (0.36 , 0.41)	
Location of practice	Urban	252	0.45 (0.44 , 0.47)	0.0001
	Rural	37	0.38 (0.35 , 0.40)	
Patients seen per week	1 to 20	78	0.49 (0.46 , 0.52)	0.0010
	21 to 50	106	0.44 (0.42 , 0.46)	
	51 to 100	79	0.41 (0.39 , 0.43)	
	>100	6	0.37 (0.23 , 0.51)	
Ever enrolled patients in RCT	Never	93	0.40 (0.37 , 0.43)	0.0001
	Have enrolled pts	203	0.46 (0.45 , 0.48)	
Patients enrolled in RCT in the last year	0	128	0.41 (0.39 , 0.43)	0.0001
	1 to 10	88	0.44 (0.42 , 0.46)	
	>10	70	0.50 (0.47 , 0.53)	
Research time	None	79	0.37 (0.36 , 0.39)	0.0001
	<30% research	154	0.44 (0.42 , 0.46)	
	30 to 50% research	34	0.53 (0.49 , 0.56)	
	50 to 70% research	11	0.56 (0.50 , 0.62)	
	>70% research	17	0.61 (0.56 , 0.66)	
Articles published in the last year	0	129	0.40 (0.38 , 0.41)	0.0001
	1	35	0.45 (0.41 , 0.49)	
	2	47	0.45 (0.41 , 0.48)	
	3	27	0.47 (0.42 , 0.52)	
	>3	56	0.55 (0.51 , 0.58)	

Mean "POP" score ranges from 0-1: 1= extreme researcher, 0= extreme clinician

N= number of responses to each question

5.3.5 Comparison with UK and US data

Comparison of Australian data with UK/US needs to be made with caution as the Australian study was conducted 5-15 years later, and attitudes are likely to have changed. The Australian responses to 9 of 28 questions significantly differed from UK and US responses (Questions 13, 16, 28, 31, 36, 38, 39 and 40, and US data only for 27–Table 5.4). There appears to be less motivation for Australian general physicians and paediatricians to participate in RCTs compared with cancer specialists from the UK and US (doctors reporting relatively low pressure from hospitals for participation, little financial incentive for participating institutions and trial involvement not being perceived to enhance their reputation) and were less concerned about participation (reporting that written consent requirements and the opinions of the referring doctors have less influence on their approaching patients for trial participation, seldom feeling disappointed when eligible patients chose not to participate, and less often feeling their individual patient care is restricted by RCTs). Australian doctors were also more likely to personally choose treatments for their patients rather than enter them in a trial if there is controversy in the literature ($p<0.0001$) or when they were personally uncertain of best treatment ($p<0.0001$).

Table 5.4: "POP" questions which elicit significant response differences between Australian and UK/ US doctors

Questions	Choices	Aus (300) %	UK (357) %	US (1485) %	Aus vs UK p Value	Aus vs US p Value
Q13: When there is controversy in the literature as to which treatment is best:	I enter the patient in a clinical trial if one exists	36	84	85	0.0001	0.0001
	I personally select a treatment for the patient	64	16	15		
Q14: If I had to choose, I would say my primary task is:	caring for individual patients	90	95	86	0.02	0.05
	contributing to scientific knowledge	10	5	14		
Q16: If written informed consent was not required, I would approach more patients to enter clinical trials	true	10	36	15	0.0001	0.02
	makes no difference	91	64	85		
Q17: When making critical and controversial decisions, I usually:	seek major input from my patients	96	93	92	0.1	0.03
	• do not seek major input from my patients	4	7	8		
Q19: The time I devote to publications, lectures and research commitments, compared to clinical work, is relatively:	low	73	75	63	0.5	0.002
	high	28	25	37		
Q20: My income is:	dependent on my research activities	10	5	10	0.01	0.8
	not dependent on my research activities	90	95	90		
Q24: I would rather be known for:	my interpersonal skills with patients	80		73		0.01
	my research accomplishments	20		27		
Q26: When published data and my clinical judgement conflict, I am more likely to rely on:	my clinical experience	45	50	55	0.2	0.003
	published data	55	50	45		
Q27: Randomised clinical trials restrict my ability to individualize patient care	true	28		77		0.0001
	makes no difference	72		23		
Q28: In my hospital the pressure to participate in a randomised clinical trial is relatively:	low	89	66	64	0.0001	0.0001
	high	11	34	36		
Q29: The need for detailed monitoring deters me from participating in randomised clinical trials:	yes	11	21	9	0.0004	0.4
	no	89	79	91		
Q31: When a potentially eligible patient chooses not to enroll on a trial that I have suggested, I:	often feel disappointed	28	53	58	0.0001	0.0001
	seldom feel disappointed	73	47	42		
Q33: When a protocol includes a treatment that is more aggressive than I would usually give:	I am often reluctant to participate	51	51	40	1.0	0.0008
	it makes no difference	49	49	60		
Q36:The opinions of the patient's usual doctor regarding randomised clinical trials affects my approaching eligible patients	true	36	74	70	0.0001	0.0001
	false	64	26	30		
Q37: Having to spell out all the details of a trial discourages me from approaching patients to participate:	true	20	41	23	0.0001	0.2
	false	80	59	77		
Q38: A major reason for my participation in trials is that it financially benefits my institution or department:	agree	10	40	54	0.0001	0.0001
	disagree	90	60	46		
Q39: Overall, involvement in randomised clinical trials:	enhances my reputation	44	91	97	0.0001	0.0001
	does not enhance my reputation	56	9	3		
Q40: When I am personally uncertain as to which treatment is best, I am likely to:	enter the patient in a randomised clinical trial if I am aware one exists	55	85	84	0.0001	0.0001
	personally select a treatment	45	15	16		
Q43:The patient's right to select treatment options is always more important than the advancement of science	true	69	74	75	0.2	0.04
	False	31	26	25		

(For the purposes of comparing with US and UK data, answers which were outside the given choices were excluded)
( ) = number of respondents in the study

5.4 Discussion

For most Australian physicians, primary allegiance is to the individual patient. Active participation in research plays a limited role in professional activities, with many having never participated in a RCT and only a minority assigning time for research or publishing articles within the last year. When making decisions under uncertainty, many preferred to personally select a treatment rather than enter a patient in a clinical trial. There are few perceived rewards for trial participation and peer group influence plays a minor role.

Australian paediatricians and adult physicians were similar in their attitudes to RCTs. This finding is interesting because recruitment to non-oncology RCTs is usually thought to be more difficult for children (75;76). This suggests that the added complexities of the parent-child interaction, rather than doctor factors, are the causes of this difference. Demographic and practice data were similar for both groups with a higher proportion of females and hospital staff specialists among the paediatricians, reflecting the practice trend in Australia (159). Limited experience with RCTs among paediatricians may reflect the small number of paediatric trials available (19;45).

Allocated research time, experience with enrolling patients in trials in the past and age have the strongest correlation with mean “POP” scores, with younger, salaried doctors with research experience and time assigned for research working in an urban setting having the most favourable attitude towards trial

participation. This is consistent with findings from the previous study (Chapter 4) that doctors with research experience perceived most benefits for trial participation and those in private practice the least (158).

Overall, Australian data were similar to that from the UK and US, with differences reflecting a smaller impact of RCTs in Australia. However, these differences may partly be due to changes over time (this study was conducted some 5 –15 years later). Another possibility is that there are different attitudes to RCTs among different specialties, as the UK and US studies were with cancer specialists (48), and respondents in our questionnaire were physicians from a broad range of subspecialties. Although Australian haematologists/oncologists responses were closer to US/UK oncologists compared with other Australian physicians, comparison with the subgroup of Australian haematologists/oncologists is difficult to interpret due to the small number (twelve) of Australian haematologists/oncologists who participated. There is reported reluctance for trial participation among cancer specialists in the literature. Our sample of predominantly non-oncologists were even less “researcher-oriented” in their treatment philosophies.

5.5 Conclusions

Australian doctors are clinician-oriented rather than research-oriented in their attitudes to RCTs participation, highlighted by their personal preference for selecting treatment to referring for trial participation in the face of treatment

uncertainty. Research plays a small role in their professional activities, and the importance of research participation is undervalued. However, the association between doctors' attitudes to RCTs and modifiable factors such as allocated research time and experience with enrolling patients in trials suggests that there is potential for attitude change.

The crisis in clinical research has been highlighted by the Clinical Research Roundtable in the US (160) and also by the National Health and Medical Research Council (NHMRC) in Australia (161). Taskforces have been formed to address this issue. This study identified major structural reasons for research having a low priority for clinicians and suggests that the problems in clinical research are unlikely to be resolved unless the role of research is restructured in a setting that is primarily clinically orientated.

Chapter 6 - Parents' attitudes to children's participation in randomised controlled trials (focus group research)

6.1 Introduction

Recruitment issues are thought to differ for adults and children (75), with children's recruitment being more difficult (148). With the recognition of the need for the inclusion of children in trials, paediatric RCTs are increasingly demanded by legislative bodies (24;162).

Because of children's vulnerability and inability to give full informed consent, parents play a key role in making decisions for trial participation on their behalf There are very few studies of parental attitudes to children's participation in trials (see section 2.4.1).

This study explored parents' attitudes to children's participation in trials, identifying factors that influence the decision for participation, and perceived risks and benefits for parents. It also compared responses across a range of parents of children with health problems of varying severity (from none to life threatening). Although this study is limited to reporting parental claims rather than observation of parental response, it offers suggestions for methods of increasing trial participation from a parent's perspective, which could be tested in future studies. The recognition of motivators and barriers to trial participation for parents may aid in the design of future trials and recruitment strategies to enhance

participation for children in trials that meet appropriate scientific and ethical standards.

6.2 Participants and methods

6.2.1 Participants

The ethics committee of the Children's Hospital at Westmead (CHW) approved the focus group research and written consent was obtained from participants. Purposive sampling of parents was employed to ensure that all groups with unique views were represented (163). Relevant paediatricians and researchers from the hospital were requested to identify parents who may provide a range of views to participate in the focus groups. Parents were recruited from The Children's Hospital at Westmead (a tertiary referral teaching hospital for sick children) and a local primary school. Parents recruited from CHW were from the Oncology Unit ("oncology parents" with children who have life threatening illness), the Renal Treatment Centre ("renal parents" with children who have chronic conditions), various research groups involved in RCTs ("trial parents") and hospital wards ("hospital parents" with hospitalised children). Interested parents were then invited by the researcher to participate in the focus group discussions. Due to poor focus group attendance of parents of hospitalised children, other suitable parents were approached to participate in individual interviews in the ward. Parents from a local primary school ("school parents" with healthy children) were invited to participate in the focus groups by advertisement in the school newsletter with endorsement by the school principal. Because of

poor response, additional parents were personally invited, with an improvement in response.

The poor response from parents for focus group participation is interesting. Parents of healthy children were generally indifferent about participating in children's health research, as demonstrated by the poor response to the school newsletter, but responded well to personal invitation. As expected, parents who had previously participated in research were most willing to be involved in the focus groups. Parents of children who were admitted to hospital responded particularly poorly to focus group participation, despite verbally agreeing to come. However, many parents were willing to be interviewed in the ward. This may be because it was more convenient for parents to be individually interviewed near their sick child at a time suitable to them than to attend a focus group meeting located in another part of the building held at a set time. The poor focus group attendance may also reflect parents' preoccupation with their child's acute illness during hospitalisation. This observation has implications for the optimal timing of when and how to approach parents for focus group participation.

6.2.2 Focus groups

Semi-structured group discussions were conducted using an open-ended questioning approach using a "prompts sheet" (Appendix F). To ensure free discussion and interaction, parents from different recruitment sources attended separate groups. All participants completed a socio-demograpic questionnaire

(Appendix G). A medical researcher unknown to the participants facilitated the discussions, with an observer taking field notes. Each session lasted 60 minutes and was audiotaped. Recruitment ceased when informational redundancy was reached (when no further information was gained), after 4 focus groups and 5 individual interviews involving 33 participants.

6.2.3 Analysis

The audiotapes were transcribed and checked against field notes for accuracy and inclusion of non-verbal details. The data were organised and coded into discrete categories using the constant comparative method where each item is compared with the rest of the data to establish analytical categories that are mutually exclusive (153;154) and then further examined to identify emergent over-arching themes (152). Analyses of differences in responses between participants from the various recruitment sources, levels of education, age, gender, ethnicity and research experience subgroups were explored.

6.3 Results

Thirty-three parents participated in the study. The parents varied in age, gender, ethnicity, level of education, geographic locality and research experience (Table 6.1).

Table 6.1: Characteristics of participating parents

Characteristics of participating parents	No. (%)
Source	
School (healthy children)	9 (27)
Inpatients (children with acute illness)	6 (18)
Renal Treatment Centre (children with chronic illness)	5 (15)
Oncology Unit (children with life threatening illness)	6 (18)
RCT participants (children with research experience)	7 (21)
Relationship to child	
Father	4 (12)
Mother	29 (88)
Age	
21 – 30 years	5 (15)
31 – 40 years	18 (55)
41 – 50 years	9 (27)
51 – 60 years	1 (3)
Level of education	
Up to School Certificate (junior high)	14 (42)
Higher School Certificate (senior high)	7 (21)
Tertiary education	12 (36)
Ethnic origin	
Australian/New Zealand	26 (79)
Asian	4 (12)
Eastern European	1 (3)
Pacific Islands	1 (3)
No of children	
1	9 (27)
2	13 (39)
3	8 (24)
4+	3 (9)
Residence (distance from CBD)	
0-20km	2
21-50km	23
51-100km	4
>100km	4
Previous participation in RCTs	
Yes	9 (27)
No	24 (73)

To achieve the numbers required, “hospital parents” were approached to participate in either focus groups or individual interviews in the ward and some “school” parents were personally invited to participate. The proportion of parents who attended the focus groups (number attended/ number agreed to attend) was clearly significantly different among the five groups of parents (Fishers exact test $2p < 0.0001$), with the lowest response from parents of hospitalised children (Table 6.2).

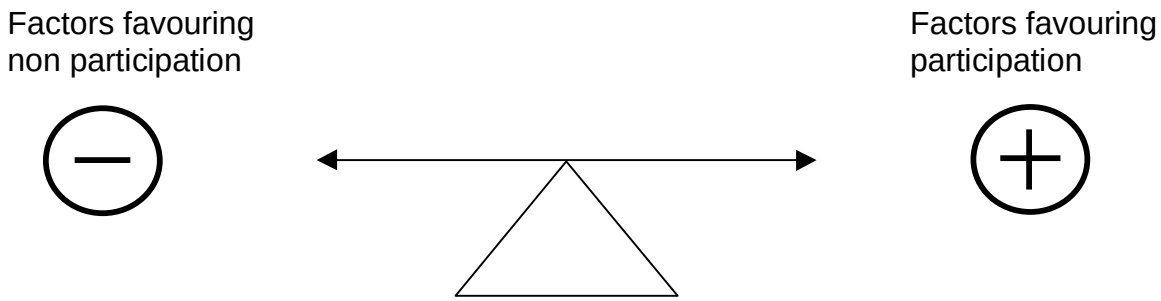
Table 6.2: Parents’ focus group participation

Source of recruitment	Approached[1]	Verbal agreement of attendance[2]	Attendance[3]	% Attendance[4]
RCT participants	15	9	7	78
Oncology Unit	15	12	6	50
Renal Treatment Centre	19	10	5	50
Hospital Inpatients				
(focus group)	46	17	0	0
(individual interview)	10	6	6	100
Total			6	26
School				
(newsletter)	760	1	1	100
(personal invitation)	17	8	8	100
Total			9	100

[1] Number of parents approached by investigator
[2] Number of parents who verbally agreed to attend the focus group
[3] Number of parents who attended the focus group
[4] Number attended/ number agreed to attend

Participant views were organised into factors influencing parents’ decisions for trial participation for their child (Figure 6.1). As participant responses were different for parents from different sources of recruitment (a surrogate for their child’s health status), these differences are highlighted in the results below, which are based on views reported by parents rather than observation of their actual response.

Figure 6.1: Factors influencing parents' decisions for trial participation



Gains-hazard considerations

Risks	Benefits
Side effects of new medication	Free medication
Randomised to the less effective treatment	New medication
Additional blood tests	An alternative treatment option
Extra hospital visits	Source of hope
Too time consuming	Doing their best for their child
Extra travel	Helping others
Other financial disincentives	Better care of their child
	Better monitoring
	Additional information about child's condition
	Increased access to healthcare professionals
	Meeting others in similar situation

Parental factors

Beliefs and knowledge	
General fear of research and researchers	Research is important for children
Specific fear of child treated as "guinea pig"	Gratitude for their child's care
Lack of knowledge about trials	Trials are beneficial for their child
Emotional response to trials	
Protective parental instinct	
Difficulty with consent by proxy	

Child factors

Child's condition	
Healthy child	Child has life threatening illness
Increased protectiveness	Increased awareness of need for trials
Quality of life trials if child sick but stable	
Child's choice	
Child's choice (if non life threatening)	Child's choice

Trial factors

Placebo controlled trials	Trials with active arms
Uncertainty and loss of control	

Doctor factors

Own doctor not supportive of trial	*Own doctor supportive of trial*
Informed by unknown researcher	Informed by own doctor
Poor communication of trial information	*Good communication of trial information*

**Italics* denote modifiable factors

6.3.1 Gains-hazard balance

Parents face a dilemma when making decisions about trial participation, weighing the risks against the benefits of participation.

> *"..two ends of the scale, the fear of the unknown and the possibility that it might resolve your child's problem".*

6.3.1.1 Perceived benefits

Perceived benefits of trial participation include provision of free medication, which may be otherwise very expensive and the chance to access new and effective treatments not routinely available.

> *"They might get the new drugs that work.."*

> *"..If there's a chance of a slight improvement of quality of life …you are able to take that risk."*

Some parents viewed trials as an alternative treatment option and a source of hope. Some view participation as the best treatment option. Many liked participating because it also contributes to helping other children.

> *"It's reassuring to know something can be done (ie participation in a trial when there are no other treatment options).."*

"..it would show that I was doing the most that I could possibly do for the child ….As a parent it is something I could do to help the child."

"..there's a part that we felt good about it, because we felt we had done the best we could.."

"..the main benefit is the feel good factor…you feel like you're not only trying to help your child, but you're trying to help other people's children."

"You feel like you're doing something for society, you're helping…contributing towards something."

"Oncology" and "trial" parents also believed there were benefits for all participants including better care and monitoring of their child, additional information about their child's health and underlying condition, access to healthcare professionals, and the social benefits of meeting other parents and children in similar circumstances. Overall, "trial" parents perceived most personal gains from trial participation.

"Improved health care, improved knowledge and I think you're better off.."

"..They're the ones missing out (those not participating): we're getting the benefit."

6.3.1.2 Perceived risks

Safety issues were parents' main concern regarding trials. Many preferred initial testing of new treatments on adults. Parents, fearful of unknown side effects in new experimental treatments, were more willing to participate in trials where treatments had been previously tested.

> *"..I'd be worried about possible side effects … but otherwise, I wouldn't hesitate."*

> *"..if it's … never, ever been used before. That would be pretty scary, the side effects.."*

> *"..I would be more likely to say yeah… because they're not using untried treatments."*

The risk of their child being randomised to the less effective treatment also worried many parents, who felt responsible if their child deteriorated.

> *"..it's a worry thinking you're doing the wrong thing…people don't want to …(be) the one being responsible once again."*

> *"..you don't want to put them into a treatment that may, at the end of the day, make them worse off than when they went in."*

> *"..If it didn't work, that was it"*

Parents identified many inconveniences for trial participation including additional blood tests, hospital visits, time demands, travel, parking and other financial disincentives. Long waiting times, inadequately equipped waiting rooms and their child's distress also added to the problem. Some thought the constant reminder of their child's illness may be stressful for parents.

> *"My son had the same thing, he had to go for injections and blood tests as well, and I'm hopeless with needles, and I thought immunisations well O.K. until they did the blood tests and he just screamed blue murder. The needle went with the patches, he was just completely beside himself. It wasn't the pain, it was the fact that we had to hold him down."*

> *"For me to come down for my visit, by the time we stop and have lunch and buy petrol, I'm looking at $50-60 each fortnight."*

> *"Keeping them still in the waiting room is a big job. And you have appointments that are not on time, like 10 o'clock appointment and you get home at 3 o'clock, stuff like that.."*

> *"..The stress and anxiety … that goes on by continually being…assessed and questioned and having to come back to hospital."*

6.3.2 Parental factors

6.3.2.1 Parents' beliefs and knowledge

All parents thought research with children is necessary for improving their health and well being and believed children and adults' responses to treatment often differ.

> *'Without research, there will never be a cure, or there will never be any answers to all the questions that we have. So, you have to do research on children, it relates to children, so it's very important.."*

However, with the exception of "oncology" and "trial" parents who had a good understanding about RCTs and the informed consent process, most of the other parents had little knowledge about RCTs. Some were unaware that trials are conducted with children. Many were confused between RCTs participation and trying untested treatments. Some thought RCTs always involved placebo use. Some parents thought children could not discontinue once they enrolled in a trial. Many, believing that doctors and scientists already know which treatments are superior, were not aware that RCTs are conducted only when there is equipoise or uncertainty about best treatment.

> *"..initially my thought was it might be good drug against bad drug. You would be very worried that your child is going to get the bad drug… whereas you're saying that it is when you don't know which drug is the best."*

"..to randomly, what's the word, 'Pot-luck' sort of thing, you playing with the odds that …is one better than the other, you don't know."

Many parents were fearful of their child being a *"guinea pig"*, and being subject to experimentation and exploitation. Some worried that researchers were more concerned about the research results than their child's welfare because *".. it's not their child.."*

"They (the researchers) are worried about money."

"I would be thinking 'I don't want my kid being a guinea pig here'… Are they going to possibly use your child in an experimental way?"

However, "oncology parents" expressed gratitude for their child's care and felt an obligation to participate in trials.

"..we're willing to give back what was given to us.."

"..I explained that it is for research and I said that in the past, lots of other children have done things for research and that's why your treatment is better today. I explained to her that it's not going to help her but it could benefit others in the future."

"Trial parents", despite negative responses from friends and family, believed trial participation was personally beneficial for their child.

"You feel for them (the children having blood tests), but you think you're doing good for them."

"Our family and friends looked at us sideways, you know. Like – you're going to let them do that?…Well, we looked into it … but we found ourselves justifying ourselves to our parents and friends."

6.3.2.2 Parents' emotional response to trials

Despite overall support for paediatric research, many parents were reluctant to involve their own child in research, preferring that they *"..do it on someone else..".* Many acknowledged their decisions are influenced by their protective parental instincts, which may defy reason.

"It's hard because, they (children) are such a precious thing to every parent, but if we don't research on somebody then others miss out on some results that might come from it… someone's got to be able to do it"

"..what happens to other people's children, that's fine, but when you're actually dealing with your own, the logic does get very much swayed by the emotional attachment."

"because of natural parental protectiveness, would want to protect their children from anything that the child might not necessarily need."

Many parents found the responsibility of consent by proxy difficult, claiming they would personally be willing to participate in a RCT, but were more hesitant about their child's participation.

> *"..It's a lot easier to make a decision for yourself rather than for somebody else. Taking responsibility for other people is very difficult, because you just don't know if you've done the right thing."*

> *"I wouldn't be as hesitant (about trial participation) because you're making your own decision about your body."*

> *"..I would feel differently, but I may not act differently."*

6.3.3 Child factors

6.3.3.1 Child's condition

Parents thought that those who had a child with a life threatening condition would be more prepared to participate trials, in the hope of finding the "miracle cure". "Oncology parents" confirmed feeling they had no choice about trial participation for their child's cancer treatment. However, they and the "renal parents" were reluctant to participate in trials addressing quality of life if their child's condition was stable, for fear of causing deterioration.

> *"..it's like a big decision, depends on how desperate you are and what the situation is."*

"I think if the child was desperately ill, you would be prepared to try it. I would be worried about having the placebo."

"..I would do anything to get the miracle cure."

"..I didn't feel like I had a choice at all." (oncology parent)

"..I can't do that (ie enrol in a quality of life trial), because at this stage I've seen that everything is going along nicely and he's happy and well, and I just couldn't warrant doing something like that, even though I know how important it is … He's doing fine, I would rather not touch him.."

Many parents admitted their child's illness influenced their support of research, but reasoned that other parents, traumatised by the ordeal, may be unwilling to participate in trials. They thought parents of healthy children do not have that insight, and often trivialise minor illnesses and regard trial participation as an unnecessary inconvenience.

"..you can be blasé, 'ah that's a common thing, you don't need to know about that…' So, you don't get involved.."

"..(if he was well) am I going to drag him all the way here ?… But if he was sick, and there was a chance that a new treatment might help him, I would take the chance.."

"..I am not prepared to take the risk if I have a normal child unless my child has a certain disease, I think it's alright."

6.3.3.2 Children's choices

Parents thought children's preferences about trial participation need to be considered, and judged teenagers capable of making this decision, particularly for quality of life trials. However, parents preferred to make the final decision in treatment trials for life threatening situations.

"..I don't think anybody should be put through it without their total understanding and total assent to it.."

"..If a child knows that he's sick and he knows something could go wrong, I think it boils down to the child - he must make that decision because it's his life, it's his future, it's not the parents, it's his body."

"..well research, yes. Treatment, unfortunately, is not optional (re children making choices)"

"..if they were going to die without it, then I would make the decision for them, but .. if it were only going to prolong their life …I would give them the right to choose that because they are choosing the quality of their life.."

6.3.4 Trial factors

6.3.4.1 Placebo controlled trials versus active trials

Most parents preferred newer or more aggressive treatments to standard treatments or placebo, believing they were more likely to be effective.

> *"He would be peeved off if he got the jelly beans … he would want the real thing.."*

> *"..if it were life threatening for your child, or the chances are it could become life threatening, you certainly wouldn't want to think that maybe your child had the placebo."*

> *"..am I going to drag him all the way here to get all those needles and to find out that he had nothing ?…so I would seriously think about participating in a placebo trial.."*

> *"..I would probably go for that (trials with active treatment arms), because you get treatments, so long as the sugar pill business isn't involved.."*

Few parents understood the rationale for placebo use, equating placebo with abandonment of treatment. Many parents preferred trials with all active arms to placebo controlled trials because they reasoned their child would still be receiving effective therapy. Parents were particularly opposed to placebo-controlled trials for treatment of life threatening conditions.

"..that's just like going to the doctor and them saying well we are just not going to treat this child."

6.3.4.2 Trial uncertainty

Many parents, misunderstanding the concept of randomisation, assumed treatment decisions were made by doctors or researchers. Some thought "randomisation" meant that children were randomly chosen to participate in trials. Many parents were hesitant about random allocation of treatment, preferring their doctor to choose "the best treatment." Some parents preferred trying untested treatment by trial and error to the uncertainty of randomisation.

".. we are all scared of the unknown, what's going to happen.."

"..I like to know where things are going. I think you can still trial them (i.e. the new treatment)… on an individual control basis …trial and error."

Parents of chronically ill children were concerned about blinding to treatment because it accentuates their sense of loss of control. Many "oncology parents" wanted to be able to double-check their child's medication because of previous experiences with drug errors. Many claimed they would be more willing to participate in trials that are not blinded.

"..I'd have a problem with the checking mechanism."

"..mistakes are still being made from nurses, nurses can't even go back and double check things because they can't have it written in the same manner in the medication chart."

"..I think you will find that most oncology parents become control freaks."

"..there is really a lack of control when you walk into this hospital … Everyone is deciding for you, telling you what to do …but you do need to (have) as much control as … you want to take… you need to know that this child is taking this …If you take that away, it's like, I can't control his health, he's sick, I can't help him.."

6.3.5 Doctor factors

Parents claimed they would seek their doctor's advice on trial participation because they trusted their opinion and medical knowledge. They appreciated being informed about trials relevant for their child, and thought this should be the doctor's duty. Many were indignant that doctors were sometimes selective about informing parents about relevant trials.

"..I would consult my doctor, and get the best advice I can."

".. I would go via the doctor, they have had enough experience to know … the doctors need to be involved and make that decision."

"..it was wonderful that the paediatrician told me (about the trial)…otherwise I would know nothing about it."

"..it's not for doctors to decide I don't think who deserves to have what. It's for parents to decide if they want to do something better for their children."

"I don't think you can ever underestimate the value of giving people information… they understand that they have got a choice, I don't think the doctors should make that choice … it's assuming something that they don't know."

6.3.6 Parents' suggestions

6.3.6.1 Improved communication

Because of perceived poor public knowledge about trial methods and RCTs currently being conducted, parents suggested advertising with posters and pamphlets in health clinics, positive media presentations and informing via hospital internet websites. They also acknowledged the importance of "word of mouth", and suggested research newsletters or telephone "hotlines" for interested parents.

"Letting the general public know that there are a lot of different trials going on at different trials. It may not be applicable to them at that time, to be aware that there is a lot of study going on …It's just there in the back of your mind, a little bit of knowledge."

"I think this word of mouth thing is quite important, because we all know people with children."

Parents' attitudes to trials were thought to be influenced by how the trial was presented to them and how they were treated. Some parents preferred being informed about trials by their own doctor whom they trust, rather than an unknown researcher. Parents' understanding about trials may also improve by simplifying information.

"..the most important thing I found was being treated like an intelligent person … if it is explained to people … you are more likely to get a positive sort of response."

"..I think also it's how it's explained to you as well, because if someone came up to me, and I didn't know anything at all about trials, I'd be thinking trials to me sound experimental, placebo to me sounds like it's not a real drug. So, I think it's all depends on how it's been worded and how it's been explained.."

"..A lot of it's bedside manner and the need for the doctor to communicate and to get on the right side of you rather than to set you off against him from the start."

"..the obstetrician should have informed me not someone I had no connection with.."

"..Simplifying the information. Making it like user friendly, so the average Joe off the street can simply read something like this.."

6.3.6.2 Increasing incentives and decreasing disincentives

The provision of a child-friendly play area, minimising waiting times and reimbursement for travel and parking costs were practical suggestions for reducing disincentives.

"I just think in the area of the behaviour thing, that there could be an area where the children can be put in, not like caged in or anything like that, like an area that's fenced in, with lots of toys."

Some "trial parents" found the offer of the proven effective treatment at the completion of the trial a powerful incentive, particularly for placebo controlled trials where they were desperate to access the new treatment.

"..I was at the end of my rope…if it was the placebo, well that means that we can try the real thing anyway."

6.3.6.3 Aids for decision making

As decisions for trial participation are often difficult for parents, aids for decision making such as a parent discussion group was suggested.

"I would be very happy to be a part of that (a parent discussion group) and to make an informed decision, so I've got it all in front of me, whether I understand it or not, but to be there, to be helped by someone, perhaps to be encouraged by someone to make an informed decision."

"..It's good to hear other people's opinions, it would help you to make your own mind up."

6.4 Discussion

6.4.1 Risk benefit considerations

(See Figure 6.1 for factors influencing parents' decisions for trial participation). In this study, risk-benefit considerations were important for parents in deciding about trial participation. Parents perceived risks such as side effects of the new treatment, being randomised to the less effective treatment and inconveniences that are often modifiable (such as additional blood tests, extra hospital visits, travel and costs and being too time consuming). These are balanced against perceived benefits such as free medication, the opportunity to access new treatments, better care of their child, greater access to healthcare professionals and health information, the support of meeting others in similar circumstances, the offer of hope and altruistic benefits. Although many factors are fixed, some factors are modifiable (see factors in italics on Figure 6.1). Modifying these may enhance trial participation. Parents also need to be informed that formal clinical

trials are better than informal trial and error in reducing risks, increasing benefits, and more accurately distinguishing therapeutic advances.

Parents from this study who were willing to participate in trials viewed the benefits of trial participation outweighed the risks, confirming Zupancic's findings of the importance of risk benefit assessments for parents (88). The child's health status, however, modifies the risk benefit balance. In this study, parents of chronically and terminally ill children were prepared to take greater risks in treatment trials but not necessarily in quality of life trials because they highly valued curing their child's illness. In Morrow's paper, factors influencing accrual to cancer "treatment" trials are thought to be different from "control" trials (47).

6.4.2 Differences between groups

The response from the "oncology" and "trial" parents differed from the other parents. They were more knowledgeable about trials, viewed participation as beneficial for their child and were more willing to consider participation, suggesting that increased knowledge about trials may enhance trial participation. However, there is conflicting evidence that increasing patients' knowledge about trials improves trial participation (59;164). Although "trial" parents in our study had the most positive views about trial participation, it is unclear whether they participated in trials because they had positive views beforehand, or whether their views changed as a result of the positive experiences with trial participation.

6.4.3 Parents' emotional response to trial participation

The finding that parents' emotional responses often hindered rational decision making for trial participation is not surprising. Parents' fear of experimentation and mistrust of researchers may reflect society's reaction to unethical experimentation on human subjects, which led to the development of the Nuremberg Code and Helsinki Declaration to protect the interest of research participants (165). Parents were also uncomfortable with "blinding" and random allocation of treatment, as has been previously noted (91;166;167). Medical research may require more effective education to overcome existing negative attitudes and unfounded fears. Parents need to be informed that a double standard exists where treatments given outside clinical trials may cause harm from unpredicted adverse events and are less stringently reviewed than protocol treatments within the trial context. They also need to know that treatment offered to the control group should be the current best standard treatment, while treatment allocated to the experimental group is hypothesised to be as good as or better than standard treatments. Parents need help to understand that the rationale for blinding is to ensure that the assessment of the child's response to treatment is accurate and not biased by physician expectations. In future research, it would be critical to explore the role of parental fears in the decision making process and develop strategies for addressing parental fears.

6.4.4 Parents' treatment preferences

Parents' negative attitudes about placebo use, although partly caused by lack of understanding, may reflect their optimism for new treatments. This view, however, may not be totally unfounded. Although there have been notable exceptions (168), in many trials conducted in the past few decades new experimental treatments have had better outcomes than standard treatments (116). Parents' preference for newer and more aggressive treatments, however, contradicts their stated concerns about the safety of newer treatments.

6.4.5 The doctor's role

The importance of the doctor's role was again highlighted in this study where parents acknowledged seeking their doctor's advice regarding participation. This is similar to adult studies where patients rarely participate in a trial unless actively recommended to do so by their physician (50).

Parents in this study thought that doctors should inform all eligible patients about relevant trials. However, in the previous study from Chapter 4 (158) and other studies (83), doctors acknowledged preferentially informing patients whom they considered likely participants, about trials and were more likely to invite those who were less severely ill to participate in trials because of concerns about informed consent (83). Surprisingly, parents in this study thought that their willingness to participate in trials correlated with their child's severity of illness.

Understanding parent's attitudes may encourage researchers in approaching parents, particularly those who are considered less likely candidates.

6.5 Conclusions

By understanding parents' attitudes to trial participation, recruitment to paediatric trials may be improved. Researchers should regard parental risk-benefit considerations when planning trials, and alter modifiable factors whenever possible to enhance participation (such as by minimising additional blood tests and hospital visits and by reimbursing travel and other costs). There needs to be better education of the public about trials, and improved communication between researchers and parents (such as by simplifying trial information for parents). The development of decision aids incorporating all the factors that influence parental decisions for trial participation, including addressing the impact of parents' emotional response to their child's involvement in trials, may help parents with the decision making process.

Chapter 7 - Conclusion

7.1 Overview

Problems with recruiting adequate numbers of children for randomised controlled trial participation are commonly faced by researchers working with children. This thesis is one of the first major attempts to address the issues surrounding the recruitment of children to RCTs.

The method by which potential participants are approached for trial participation, the influence of their health care provider and the attitude of potential participants (or their parents, in the case of children) are critical to the understanding of the decision making process for trial participation. These three important areas are explored in this thesis using both qualitative and quantitative techniques.

7.2 Key findings

7.2.1 Recruitment strategies used to encourage participation in randomised controlled trials (systematic review)

Referral by health care professionals had the highest consent rates when potential candidates were initially approached for trial participation or when they initially enquired about the trial. However, no differences in consent rates were distinguished by method of recruitment by the time potential candidates were assessed for trial eligibility. Despite lower consent rates, higher numbers of study participants were recruited by methods that approached large numbers of potential candidates. Other methods such as framing of recruitment material, the

offer of monetary incentives, the use of an interactive computer programme and mailing of recruitment material accompanied by a letter signed by the trial investigator were also effective. Stated recruitment costs ranged from US$0 to $1108 per participant, with mailing being the most cost-effective method and community approach the least effective overall.

7.2.2 Paediatricians' attitudes to children's participation in randomised controlled trials (focus group research)

Paediatricians believed parents balanced perceived gains and risks when deciding about trial participation. They thought the child's condition, parents' health beliefs and personal attributes, the doctors' beliefs and relationship with the investigators influenced parents' attitudes. Perceived gains included professional benefits for paediatricians, improved patient care, convenience for the families and themselves and scientific advancement. Perceived risks included inconvenience, inadequate resources and potential harms to the patient and doctor-patient relationship. Paediatricians with previous research experience were most knowledgeable about RCTs and perceived greatest gains from trial participation. Paediatricians' personal treatment preferences hindered trial support.

7.2.3 Australian paediatricians' and adult physicians' attitudes to randomised controlled trials (survey)

Australian paediatricians and adult physicians are very similar in their treatment philosophies, and are clinician-oriented rather than research-oriented in their attitudes, with primary allegiance to their patients and preference for selecting treatment rather than referring for trial participation in the face of treatment uncertainty. Professional activities are clinically focused, with limited time assigned for research. Australian doctors perceive little reward for trial participation. Predictors of favourable attitudes to trial participation are time allocation for research, past history of enrolling patients to trials and younger age.

7.2.4 Parents' attitudes to children's participation in randomised controlled trials (focus group research)

Findings from this study confirmed some of the paediatricians' insights regarding parents' decision making for trial participation. Parents balance risks and benefits when deciding about trial participation for their child. Perceived benefits for parents include the offer of hope, better care of their child, the opportunity to access new treatments, healthcare professionals and health information, meeting others in similar circumstances and helping others. Perceived risks include potential side effects, being randomised to ineffective treatments and the inconvenience of participation. The decision for trial participation is also influenced by parental factors (parents' knowledge, beliefs and emotional response), child factors (the child's health status and preference about participation), trial factors (the use of placebos and uncertainties of participation)

and doctor factors (doctor's recommendations and communication of trial information).

7.3 Limitations

7.3.1 Recruitment strategies used to encourage participation in randomised controlled trials (systematic review)

Many challenges were encountered when conducting the systematic review. Because of the small number of RCTs assessing strategies for recruiting participants into RCTs, the inclusion criteria was expanded to include observational studies, which were more difficult to assess. Difficulties encountered in systematically reviewing observational studies include a lack of consensus about how this should be conducted, including what items should be measured to assess study quality, as well as methodological issues of combining results of non-random studies.

Due to the broad nature of the terms used in the search strategy (such as recruitment, enrolment, accrual, and consent), a very large number (>8600) of titles and abstracts had to be reviewed which was very time consuming. The chance of missing an eligible study was minimised by including any studies found by either researcher reviewing the titles and abstracts.

Although it is important to attempt to identify unreported trials by searching the "grey literature" as this reduces publication bias, it was difficult to know how

many unpublished studies exist and to know how to best access them. A limited attempt at doing this was made. There are currently no guidelines on how this should be done.

The poor quality of most of the included studies limited the generalisability of the results. Potential bias in the studies includes selection bias, bias in how exposure and outcomes were measured as well as confounding and loss to follow up. The inclusion of non-random studies increased the potential for selection bias. Measurement of exposure can be difficult for some recruitment methods such as media, and may differ between studies (e.g. for community presentation, some studies count the number of people attending the meeting, while others approximate the number). Bias in measuring outcomes includes the definition of consent (some studies measure intention to enrol and others measure actual enrolment). As the definition of consent rate varied between studies, standardisation of the measurement was attempted by describing the three types of consent rates – “exposed”, “responder” and “assessed”. Although the “exposed consent rate” most closely reflects the effectiveness of the recruitment method, very few studies described this. “Response” may mean different things in different studies or for different recruitment methods (e.g. someone “responding” and picking up a pamphlet may be compared with a potential participant’s detailed discussion with a health care provider about trial participation). The assessment of recruitment cost for the methods of recruitment was not measured in the same way in each study (e.g. infrastructure and other

costs were not consistently included, resulting in the reported cost of recruitment by health care provide referrals to range from $0 to $868 per participant enrolled).

The heterogeneity of the recruitment methods created a problem for comparing studies, as some studies compared different categories of methods, some variations within one category, and some both. Studies were divided into those evaluating different categories of recruitment methods and those evaluating variations within the same category in an attempt to summarise the data. This resulted in the loss of data for variations within categories for studies that compared different categories of recruitment methods. Because of the heterogeneity between studies, it was inappropriate to combine results to produce a single estimate of effect.

The definition of "effectiveness" was problematic, as it should incorporate consent rates as well as the proportion recruited by each method. For example, a method such as health care provider referral may have 100% consent rate, but if only 2% of the total study population was recruited by that method, it would not be an effective method. In studies evaluating variations of strategies within one category of recruitment method, an attempt was made to combine "exposure consent rates" and proportion enrolled by the method. However, this was difficult to measure in the studies comparing different categories, as there were very few studies where "exposure consent rates" could be derived. In measuring

effectiveness, the time it takes to recruit by the method is also important, as the success of trials also depends on timely recruitment. For example, health care provider referrals may have a high consent rate and low cost, but if it takes years to recruit an adequate number of study participants, this is not an effective method. In the systematic review, no attempt was taken to measure time taken for recruitment.

7.3.2 Paediatricians' attitudes to children's participation in randomised controlled trials (focus group research)

The use of qualitative methods has the limitation that response size cannot be measured. The participants of the focus group discussion for paediatricians were recruited from the Children's Hospital at Westmead, a tertiary referral teaching hospital with a strong research focus located within a large city in Australia. Their responses therefore cannot be generalised to paediatricians outside of that setting. It is postulated, however, that paediatricians outside of that setting are likely to be less research focused, and the results of this study therefore highlight the plight of paediatric clinical research.

Although purposive sampling was employed to ensure that all groups with unique views were presented, the non-attendance by some who were invited to participate may bias the results. Also, participant responses may be influenced by the presence of the researcher who was known to them, despite the attempt

to address this issue by employing a professional facilitator not known to the participants to conduct the groups.

7.3.3 Australian paediatricians' and adult physicians' attitudes to randomised controlled trials (survey)

The relatively low response rate of 60% for the doctors' questionnaire, despite attempts at encouraging survey return by contacting non-responders at least twice to minimise response bias, limits generalisability of the results, as non-responders may answer the questionnaire differently to responders. As participants were randomly selected from the Royal Australasian College of Physicians register, a number were not in active clinical practice, for which the questionnaire is more relevant. Ideally, non-clinicians should have been excluded prior to random selection. This may have increased the participation rate.

The use of the "Physician Oriented Profile" posed some problems in the study context as the questionnaire was initially written for cancer specialists. Some questions that were not relevant to the non-oncology context had to be excluded or altered. Australian doctors also disliked answering binary-option questions, preferring an answer "in between". Although the rationale for using binary-option questions (to ensure that the final score has good predictive value and can be compared with UK and US data) was explained, many chose either to not answer some questions or else to write an alternative answer instead of choosing between available options, while others co-operated. As the mean "POP" score is

derived from the total score divided by the number of questions answered, unanswered questions or questions which did not match one of the options were excluded. This had the potential to bias the outcome (for example, some doctors may not feel comfortable with answering questions that reveal their "clinician orientation" or their "researcher orientation").

Comparison with UK and US data was difficult to interpret because this study was conducted some 5-15 years later and differences in response may partly be due to changes over time. Another factor may be different attitudes to RCTs among different specialties, as the UK and US studies were with cancer specialists, and this questionnaire was applied to physicians from a broad range of subspecialties. Comparison with the subgroup of Australian haematologists/oncologists was difficult to interpret due to the small number (twelve) of Australian haematologists/oncologists who participated.

7.3.4 Parents' attitudes to children's participation in randomised controlled trials (focus group research)

One of the difficulties encountered with parents' focus groups was the poor attendance of some groups of parents. For example, of 46 parents approached for focus group participation, 17 agreed to participate, but none actually attended the focus group. Due to the poor focus group attendance, other suitable parents were approached and interviewed in the ward individually or in pairs. Although

the same prompts were used for the interviews, the group dynamics was lacking which may have influenced responses.

Although purposive sampling was attempted by inviting parents from five different settings (parents from a local primary school, from the hospital oncology unit, renal treatment centre, inpatient wards and research groups), and relevant paediatricians and researchers from the hospital were requested to identify parents who may provide a range of views to participate in the focus groups, most parents attending the groups were in favour of paediatric research. It was not known if there was any selection bias, although it is quite likely, as those less favourable towards paediatric trials were less likely to participate.

The choice of a medical researcher to facilitate the parents' focus groups may not have been ideal, as parents are more likely to respond in a way which they think may please the researcher.

7.4 Implications of findings

The results of the systematic review have implications for researchers designing trials. It is important to consider consent rates as well as proportions enrolled by a method when considering what strategies to employ. The use of health care professional referral is associated with a higher consent rate, but reliance on this method alone may limit the exposure of potential participants. Other methods

where larger numbers of potential participants are exposed to trial information such as mailing may be more cost effective.

The effectiveness of framing trial information in such a way as to emphasise the uncertainty of current best treatment and the need to improve early diagnosis and management is very exciting and has implications for researchers, as this strategy attracts little additional cost and can be incorporated into other methods of recruitment. Consideration should be given to the wording of recruitment information and care must be taken to ensure the method is ethically sound.

When recruiting children for trial participation, researchers should consider the needs and concerns of parents and paediatricians. Suggestions include improving communication between researchers, paediatricians and parents and improving the gains-hazard balance (by increasing incentives while decreasing inconveniences).

This study also has implications for major research institutions that are seeking solutions to the crisis in clinical research in health care. Major reforms in the health care system are needed to address the low priority placed on clinical research by clinicians, such as restructuring clinical research in a setting which is primarily clinically orientated.

7.5 Future research

This thesis suggests a number of possible avenues for future research. The results of the systematic review suggest that there is still a need to assess promising recruitment methods. Uncertainty still remains about the effectiveness of different recruitment methods, which could be tested by a randomised-controlled trial. The effectiveness of the interactive computer programme compared with passively listening to a tape recording of trial material has potential for application where Internet access is readily available. Although Internet recruitment for RCTs is known to occur, this method has never been assessed in a trial setting.

The importance of high consent rates and greater exposure of potential participants to trial information should be incorporated by researchers in the design of effective recruitment strategies. The one study assessing different variations of mailing methods found higher consent rates among people who received recruitment material accompanied by a letter from the trial investigator, even though the letter was identical to the one sent by the director of the health insurance company (141). What is the reason for this response? Do people feel a trial investigator is more personal than the director of an insurance company? How do people identify who they trust? These basic questions can unlock an understanding of the decision making process which can be helpful both to patients and doctors.

Although recruitment data are readily accessible for many trials, these data are not often collected. With the introduction of a centralised trials register in the future, this information should be collected, pooled and analysed to improve our understanding of recruitment. It is therefore important to define stages of recruitment so accurate measurements can be made and compared.

The conclusions from the two studies of paediatricians' attitudes to RCTs suggest personal treatment preferences hinder trial support whereas allocated research time and trial participation by doctors enhance their support. The mandatory research projects of the Australasian College of Physicians for FRACP accreditation are designed to foster research interest. It is currently unclear whether this component has been effective, but should be assessed.

The findings from the parents' focus groups challenge researchers to address the issue of parents' emotional response to their child's participation in a trial and to develop ways of helping parents deal rationally with their reactions (which they acknowledge defy reason). The acknowledgement by parents that how they are approached by doctors and how the trial was explained influenced their decision for trial participation, and the study from the systematic review which demonstrated that informing doctors of the patient's preferences and views about trials improved recruitment suggest that the training of doctors in information giving, particularly for trial participation, is helpful and appreciated by patients.

The challenges encountered by the difficult recruitment for the parents' focus group, and the complete lack of data on this subject has great potential for further study, as qualitative research is increasingly being embraced by the scientific community who has recognised the wealth and depth of information that can be attained using these techniques.

What are children's attitudes to RCTs? Although parents' and paediatricians' responses were explored in this study, it is important to ask the children themselves.

7.6 Conclusion

The randomised-controlled trial provides a scientifically valid and ethically sound technique for assessing the effects of healthcare interventions. However, even the best designed trials depend on recruitment of adequate numbers of study participants for success. The inclusion of children in trials is both necessary and desirable, but is often limited by inadequate recruitment. This thesis systematically reviews previous strategies used for recruiting study participants into RCTs, explores recruitment issues from the perspective of paediatricians and parents (the key gatekeepers for children's RCTs participation) and identifies aspects of the recruitment process that could be modified to improve trial participation for children.

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Appendices

Appendix A: Data extraction form for the systematic review

Data Extraction Form: **Reviewer: ……**

Study details:

First author	
Year	
Country of publication	
Publication type	Journal / Abstract / other (specify)
Name of Journal	

Study Eligibility/Characteristics

	Inclusion Criteria for Systematic Review	**Study**
Type of study	RCT, QRCT, CS, CCS (P), CCS (H), CSA, BAS, ES, DS	yes no unclear
Setting of study (Describe study, incorporating: Participants Source – where pt from Setting of RCT - what is RCT about)		
Types of intervention		
Types of outcome measures mentioned • Accrual rate • Efficiency • Cost per participant • Other		

Methods: Trial Quality (only for RCT/QRCT)

Method of randomisation	
Allocation concealment	Clearly yes, unclear, no
Other method comments	

Participants

	Total	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
#f participants Total exposed							
Responded							
1st screened							
Eligible							
Enrolled							
Randomised							
Ineligible							
Refused							
Lost to follow up							
Efficiency of each method (% enrolled)							
Cost							

Intervention/ Outcome measures (when appropriate: Mean±SD)

Confounders comparable between groups and adjusted for?	
Outcome measured in the same way for groups? Blinding?	
Outcome measured in a valid way?	
Adverse effects mentioned	

Notes • Investigators contacted for more information • Raw data: available/ requested/obtained	

Notes

Appendix B: References to included studies from the systematic review

(1) Aaronson N.K., Visser-Pol E., Leenhout G.H., Muller M.J., van der Schot A.C., van Dam F.S. et al. Telephone based nursing intervention improves the effectiveness of the informed consent process in cancer clinical trials. Journal of Clinical Oncology 1996; 14(3):984-986.

(2) Adams J, Silverman M, Musa D, Peele P. Recruiting older adults for clinical trials. Controlled Clinical Trials 1997; 18(1):14-26.

(3) Anderson LA, Fogler J, Dedrick RF. Recruiting from the community: lessons learned from the diabetes care for older adults project. Gerontologist 1995; 35(3):395-401.

(4) Anonymous. Participant recruitment to the Coronary Primary Prevention Trial. Journal of Chronic Diseases 1983; 36(6):451-465.

(5) Appel LJ, Vollmer WM, Obarzanek E, Aicher KM, Conlin PR, Kennedy BM et al. Recruitment and baseline characteristics of participants in the Dietary Approaches to Stop Hypertension trial. Journal of the American Dietetic Association 1999; 99(8 SUPPL.):S69-S75.

(6) Arnold A, Johnstone B, Stoskopf B, Skingley P, Browman G, Levine M et al. Recruitment for an efficacy study in chemoprevention- the Concerned Smoker Study. Preventive Medicine 1989; 18(5):700-710.

(7) Bell-Syer SEM, Klaber Moffett JA. Recruiting patients to randomized trials in primary care: principles and case study. Family Practice 2000; 17:187-191.

(8) Bjornson-Benson WM, Stibolt TB, Manske KA, Zavela KJ, Youtsey DJ, Buist et al. Monitoring recruitment effectiveness and cost in a clinical trial. Controlled Clinical Trials 1993; 14(2 Suppl):52S-67S.

(9) Brewster WR, Anton-Culver H, Ziogas A, Largent J, Howe S, Hubbell FA et al. Recruitment strategies for cervical cancer prevention study. Gynecologic Oncology 2002; 85:250-254.

(10) Burns PA, Nochajski T, Clesse DP, Pranikoff K. Recruitment experiences in a stress incontinence clinical trial. Neurourology & Urodynamics 1990; 9(1):53-62.

(11) Cambron JA. Recruitment and accrual of women in a randomized controlled trial of spinal manipulation. Journal of Manipulative and Physiological Therapeutics 2001; 24(2):79-83.

(12) Camerini T, De Palo G, Mariani L, Marubini E, Costa A, Veronesi U. Accrual issues for chemoprevention trials: The example of the 4-HPR study for the prevention of contralateral breast cancer. Tumori 1999; 85(4):299-303.

(13) Carew BD, Ahn SA, Boichot HD, Dierenfeldt BJ, Dolan NA, Edens TR et al. Recruitment strategies in the studies of left ventricular dysfunction (SOLVD): strategies for screening and enrollment in two concurrent but separate trials. The SOLVD Investigators. Controlled Clinical Trials 1992; 13(5):325-338.

(14) Chung TD, Park II, Ignacio L, Catchatourian R, Kopnick M, Davison E et al. Television and news print media are effective in recruiting potential participants in a prostate cancer chemoprevention trial. International Journal of Cancer 2000; 90(5):302-304.

(15) Coleman EA, Tyll L, LaCroix AZ, Allen C, Leveille SG, Wallace JI et al. Recruiting African-American older adults for a community-based health promotion intervention: which strategies are effective? American Journal of Preventive Medicine 1997; 13(6 Suppl):51-56.

(16) Connett JE, Bjornson-Benson WM, Daniels K. Recruitment of participants in the Lung Health Study, II: Assessment of recruiting strategies. Controlled Clinical Trials 1993; 14(2 Suppl):38S-51S.

(17) Cooler CY, Finkel SI, Moran MB, Richter EM. Recruitment and enrollment of elderly persons with depression into a clinical drug trial. International Journal of Geriatric Psychopharmacology 1999; 2(1):23-27.

(18) Cosgrove N, Borhani NO, Bailey G, Borhani P, Levin J, Hoffmeier M et al. Mass mailing and staff experience in a total recruitment program for a clinical trial: the SHEP experience. Systolic Hypertension in the Elderly Program. Cooperative Research Group. Controlled Clinical Trials 1999; 20(2):133-148.

(19) Fitzgibbon ML, Prewitt TE, Blackman LR, Simon P, Luke A, Keys LC et al. Quantitative assessment of recruitment efforts for prevention trials in two diverse black populations. Preventive Medicine 1998; 27(6):838-845.

(20) Fleissig A, Jenkins V, Fallowfield L. Results of an intervention study to improve communication about randomised clinical trials of cancer therapy. European Journal of Cancer 2001; 37:322-331.

(21) Folmar S, Oates-Williams F, Sharp P, Reboussin D, Smith J, Cheshire K et al. Recruitment of participants for the Estrogen Replacement and Atherosclerosis (ERA) Trial: A comparison of costs, yields, and participant characteristics from community- and hospital-based recruitment strategies. Controlled Clinical Trials 2001; 22:13-25.

(22) Gallo C, Perrone F, De Placido S, Giusti C. Informed versus randomised consent to clinical trials [see comments]. Lancet 1995; 346(8982):1060-1064.

(23) Garcia-Losa M, Dal-Re R, Garcia-Mendez E. Improving patient recruitment in clinical trials: lessons from one multicentre study in asthma [letter]. British Journal of Clinical Pharmacology 1995; 39(2):211-212.

(24) Gill TM, McGloin JM, Gahbauer EA, Shepard DM, Bianco LM. Two recruitment strategies for a clinical trial of physically frail community-living older persons. Journal of the American Geriatrics Society 2001; 49(8):1039-1045.

(25) Goodman GE, Valanis B, Meyskens FLJ, Williams JHJ, Metch BJ, Thornquist MD et al. Strategies for recruitment to a population-based lung cancer prevention trial: the CARET experience with heavy smokers. Beta-Carotene and Retinol Efficacy Trial. Cancer Epidemiology, Biomarkers & Prevention 1998; 7(5):405-412.

(26) Hollis JF, Satterfield S, Smith F, Fouad M, Allender PS, Borhani N et al. Recruitment for phase II of the Trials of Hypertension Prevention. Effective strategies and predictors of randomization. Trials of Hypertension Prevention (TOHP) Collaborative Research Group. Annals of Epidemiology 1995; 5(2):140-148.

(27) Isaacman DJ, Reynolds EA. Effect of a research nurse on patient enrollment in a clinical study. Pediatric Emergency Care 1996; 12(5):340-342.

(28) King AC, Harris RB, Haskell WL. Effect of recruitment strategy on types of subjects entered into a primary prevention clinical trial. Annals of Epidemiology 1994; 4(4):312-320.

(29) Kusek JW, Ahrens A, Burrows PK, Clarke HS, Foster HE, Hanson K et al. Recruitment for a clinical trial of drug treatment for benign prostatic hyperplasia. Urology 2002; 59(1):63-67.

(30) Kusek JW, Coyne T, de Velasco A, Drabik MJ, Finlay RA, Gassman JJ et al. Recruitment experience in the full-scale phase of the Modification of Diet in Renal Disease Study. Controlled Clinical Trials 1993; 14(6):538-557.

(31) Leader MA, Neuwirth E. Clinical research and the noninstitutional elderly: a model for subject recruitment. Journal of the American Geriatrics Society 1978; 26(1):27-31.

(32) Lewis CE, George V, Fouad M, Porter V, Bowen D, Urban N. Recruitment strategies in the Women's Health Trial: Feasibility Study in Minority Populations. Controlled Clinical Trials 1998; 19(5):461-476.

(33) Llewellyn-Thomas HA, Thiel EC, Sem FW, Woermke DE. Presenting clinical trial information: a comparison of methods. Patient Education & Counseling 1995; 25(2):97-107.

(34) Margitic S, Sevick MA, Miller M, Albright C, Banton J, Callahan K et al. Challenges faced in recruiting patients from primary care practices into a physical activity intervention trial. Activity Counseling Trial Research Group. Preventive Medicine 1999; 29(4):277-286.

(35) Martinson BC, Lazovich D, Lando HA, Perry CL, McGovern PG, Boyle RG. Effectiveness of monetary incentives for recruiting adolescents to an intervention trial to reduce smoking. Preventive Medicine 2000; 31:706-713.

(36) Maurer BT, Moreno SI, Pickard AR, Wurst BE, Norden DK, Schumacher HR, Jr. A comparison of recruitment methods for an osteoarthritis exercise study. Arthritis Care & Research 1995; 8(3):161-166.

(37) Miller NL, Markowitz JC, Kocsis JH, Leon AC, Brisco ST, Garno JL. Cost effectiveness of screening for clinical trials by research assistants versus senior investigators. Journal of Psychiatric Research 1999; 33:81-85.

(38) Moon TE, Levine N, Cartmel B, Bangert J, Rodney S, Schreiber M et al. Design and recruitment for retinoid skin cancer prevention (SKICAP) trials. The Southwest Skin Cancer Prevention Study Group. Cancer Epidemiology, Biomarkers & Prevention 1995; 4(6):661-669.

(39) Myles PS, Fletcher HE, Cairo S, Madder H, McRae R, Cooper J et al. Randomized trial of informed consent and recruitment for clinical trials in the immediate preoperative period. Anesthesiology 1999; 91(4):969-978.

(40) Piotrowski NA, Clark HW, Hall SM. Treatment research with crack-cocaine-dependent male veterans: the efficacy of different recruitment strategies. American Journal of Drug & Alcohol Abuse 1994; 20(4):431-443.

(41) Rudick C, Anthonisen NR, Manfreda J. Recruiting healthy participants for a large clinical trial. Controlled Clinical Trials 1993; 14(2 Suppl):68S-79S.

(42) Schoenberger JA. Recruitment experience in the Aspirin Myocardial Infarction Study. Controlled Clinical Trials 1987; 8(4 Suppl):74S-78S.

(43) Silagy CA, Campion K, McNeil JJ, Worsam B, Donnan GA, Tonkin AM. Comparison of recruitment strategies for a large-scale clinical trial in the elderly. Journal of Clinical Epidemiology 1991; 44(10):1105-1114.

(44) Theoret B, Brodeur JM, Perreault M, Seguin L, Boyer G. Recruitment of Montreal women of very low socioeconomical status for a randomised clinical study. Canadian Journal of Public Health 2000; 91(1):60-63.

(45) Tworoger SS, Yasui Y, Ulrich CM, Nakamura H, LaCroix K, Johnston R et al. Mailing strategies and recruitment into an intervention trial of the

exercise effect on breast cancer biomarkers. Cancer Epidemiology, Biomarkers & Prevention 2002; 11:73-77.

(46) Valanis B, Blank J, Glass A. Mailing strategies and costs of recruiting heavy smokers in CARET, a large chemoprevention trial. Controlled Clinical Trials 1998; 19(1):25-38.

(47) Wadland WC, Hughes JR, Secker-Walker RH, Bronson DL, Fenwick J. Recruitment in a primary care trial on smoking cessation. Family Medicine 1990; 22(3):201-204.

(48) Whelton PK, Babnson J, Appel LJ, Charleston J, Cosgrove N, Espeland MA et al. Recruitment in the Trial of Nonpharmacologic Intervention in the Elderly (TONE). Journal of the American Geriatrics Society 1997; 45(2):185-193.

(49) Wragg JA, Robinson EJ, Lilford RJ. Information presentation and decisions to enter clinical trials: a hypothetical trial of hormone replacement therapy. Social Science & Medicine 2000; 51(3):453-462.

(50) Wright JT, Cushman WC, Davis BR, Barzilay J, Colon P, Egan D et al. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT): Clinical Center Recruitment Experience. Controlled Clinical Trials 2001; 22:659-673.

Appendix C: Prompts for paediatricians' focus group discussions

Trials – how does it affect the doctor?

- What do you enjoy about participating in trials?
- What do you see as the advantages of participating in trials? (to you, your patients and the community)
- What do you dislike about participating in trials?
- What do you find difficult about participating in trials?
- What is the difference between trials you have enjoyed participating in and those that you haven't?" (research question, trial factors, investigator factors)
- Are there any trials you would not participate in and why (specifics)?

Perceptions of patient factors

- Do you think some patients/parents are more likely to participate than others? If so…
- Do you think there are some patients/parents who should not be asked to participate in a RCT?
- What do you think would improve the conduct of RCTs?

Appendix D: Demographic questionnaire for the paediatricians' focus groups

"Recruitment of children in randomised controlled trials"
Focus group for paediatricians

The information on this sheet is confidential. It will be used to define the demographics of the participants attending this focus group.

Please tick appropriate boxes

1. What is your position? VMO - general paediatrician
   AMO - general paediatrician (Staff Specialist)
   AMO - subspecialist (Staff Specialist)
   Fellow
   Registrar

2. What is your age?

3. What is your sex? male female

4. What is your country of origin? _____
   (i.e. with what culture do you identify?)

5. Do you have children? no
   yes
   If yes, do any of them fall within the following age brackets?
   0-5 6-12 13-18 19+

6. Do you have grandchildren? no
   yes
   If yes, do any of them fall within the following age brackets?
   0-5 6-12 13-18 19+

7. How many years have you worked as a doctor? years

8. Regarding your previous experience with children participating in randomised controlled trials (RCTs):
   I have referred one or more of my patients to a RCT in the past
   I have participated in conducting a RCT in the past
   I have referred one or more of my patients to a RCT <u>in the last year</u>
   I have participated in conducting a RCT <u>in the last year</u>

Thank you for completing this survey

Appendix E: Physician and paediatrician's questionnaire

"Attitudes of physicians and paediatricians to randomised controlled trials"

The information on this sheet is confidential.

Please tick appropriate boxes

Some of the questions in this questionnaire force you to choose between only two options and you may feel your true response falls somewhere in between. We acknowledge that such choices can be hard; however, the questionnaire was designed this way to ensure that the final score has good predictive value. The scale has been completed previously in Europe and America by thousands of clinicians, and our capacity to compare data cross-culturally would be lost if we changed the questionnaire. Please choose the answer that most closely matches your true response.

1. Age
2. Sex: Male Female
3. Specialty: Adult Physician Paediatrician
4. Subspecialty: No Yes (please specify)_____
5. (a) Primary setting for clinical practice:

   Private practice Teaching hospital Non teaching hospital

   Other (please specify)_____

   (b) Location of practice:

   Urban Rural
6. Appointment:

   VMO Staff Specialist Academic

   Other (please specify)_____
7. How many patients do you see each week?

   0 1-20 21-50 51-100 >100
8. Have you ever enrolled patients in randomised controlled trials?

   Yes No
9. How many of your patients participated in a randomised controlled trial in the last year?

   0 1-10 >10

10. How much time do you devote to research?

None <30% research 30-50% research

50-70% research >70% research

11. How many articles have you published in the last year?

0 1 2 3 >3

12. Although many doctors are expected to perform both tasks, as a doctor my *primary* commitment is to:

future generations of patients (society)

present patients (individual)

13. When there is controversy in the literature as to which treatment is best:

I enter the patient in a clinical trial if one exists

I personally select a treatment for the patient

14. If I had to choose, I would say my primary task is:

caring for individual patients

contributing to scientific knowledge

15. In my hospital, doctors are given more reward for:

clinical skills with patients

contributing to scientific knowledge

16. If written informed consent was not required, I would approach more patients to enter clinical trials

true

makes no difference

17. When making critical and controversial decisions, I usually:

seek major input from my patients

do not seek major input from my patients

18. Ideally I would like to refer or enter the following proportion of my potentially eligible patients into randomised clinical trials:

    none some half most all

19. The time I devote to publications, lectures and research commitments, compared to clinical work, is relatively:

    totally devoted to clinical work

    mainly devoted to clinical work

    devoted equally to clinical work and research

    mainly devoted to research

    totally devoted to research

20. My income is:

    dependent on my research activities

    not dependent on my research activities

21. I would like to assess how successful I was as a physician by:

    my research contribution

    how I helped individual patients

22. I would rather be somewhat:

    too involved with my patients

    too detached from my patients

23. If a patient refuses to participate in a randomised clinical trial, I would:

    treat the patient off the study

    refer the patient to another doctor

24. I would rather be known for:

    my interpersonal skills with patients

    my research accomplishments

25. Overall I feel the quality of patient care:

    increases when a patient is in a clinical trial

    decreases when a patient is in a clinical trial

    does not change when a patient is in a clinical trial

26. When published data and my clinical judgement conflict, I am more likely to rely on:

    my clinical experience

    published data

27. Randomised clinical trials restrict my ability to individualise patient care

    true

    makes no difference

28. In my hospital the pressure to participate in a randomised clinical trial is relatively:

    low

    high

29. The need for detailed monitoring of my management of trial patients by trial staff deters me from participating in randomised clinical trials:

    no

    yes

30. The increased paperwork involved in treating patients on trials deters me from participating in randomised clinical trials:

    no

    yes

31. When a potentially eligible patient chooses not to enrol on a trial that I have suggested, I:

    often feel disappointed

    seldom feel disappointed

32. Frequent publications are important to my career advancement:

agree

disagree

33. When a protocol includes a treatment that is more aggressive than I would usually give to similar non-trial patients:

I am often reluctant to participate

it makes no difference

34. When a protocol includes a treatment that is less aggressive than I would usually give to similar non-trial patients:

I am often reluctant to participate

it makes no difference

35. I am reluctant to participate in a trial that may randomise the patient to a 'no treatment' group:

agree

disagree

36. The opinions of the patient's usual doctor regarding randomised clinical trials affects my decision to approach an eligible patient:

true

false

37. The thought of having to spell out all the details of a trial to eligible patients discourages me from approaching them to participate:

true

false

38. A major reason for my participation in randomised clinical trials is that it financially benefits my institution or department:

agree

disagree

39. Overall, involvement in randomised clinical trials:

    enhances my reputation

    does not enhance my reputation

40. When I am personally uncertain as to which treatment is best, I am likely to:

    enter the patient in a randomised clinical trial if I am aware one exists

    personally select a treatment

41. If research activities were to enhance my income, I would enter more patients in randomised clinical trials:

    agree

    disagree

42. I am more likely to attend a conference that focuses on:

    clinical issues

    research issues

43. I think the patient's right to select treatment options is always more important than the advancement of scientific knowledge:

    true

    false

44. When I participate in a randomised clinical trial, it is more likely that I:

    increase my patient population

    lose patients I might otherwise keep

    it makes no difference to my patient population

Thank you for completing this survey. Your help is greatly appreciated.

Comments:

Appendix F: Prompts for parents' focus group on "Attitudes to children's participation in randomised controlled trials"

General attitudes to clinical research

- What do you think about medical research that involves people?
- What do you think about research involving children?
- Should parents be informed about trials being conducted, which may be relevant to their child's condition?
- Should doctors decide whether to tell parents about trials that may be relevant to their child's condition?
- How much should children be involved in the decision about participating in a trial?

Knowledge of research

- Do you know about the different types of research? (Questionnaires, RCTs)

Randomised controlled trials

- What do you know about randomised controlled trials?

(An explanation of randomised controlled trial is given by facilitator:
A randomised controlled trial is a special study which can find out what is the best treatment, when it is not clear which treatment is best. When a randomised controlled trial is conducted, nobody, not even the doctors or scientists, know which is the better treatment. What is known is that all of the treatments used are effective in treating the disease. Preliminary studies have also been done to prove that all the treatments are safe and any new treatments are not going to be worse than the standard treatments. If it was not safe, the trial would not be conducted. There are usually two treatments being compared, and the treatment each child receives is decided by chance. It is necessary to decide the treatment by chance to make sure that at the beginning of the study, both groups of children are very similar. Therefore we know that any differences at the end of the study will be due to the treatment alone. For example, if someone, like the doctor, decided which treatment each child would have, he or she might give some children (say the older children) one treatment, and the younger children the other – then differences at the end might be due to age, rather than the treatment itself.

- How do you feel about the child's treatment being allocated by chance?

There are some trials that compare 2 medications. For example, there are asthma trials that compare Medicine A with Medicine B, and each child will receive either Medicine A or Medicine B

- What questions might you have if your child was invited a trial like this?

Sometimes, randomised controlled trials involve the use of a placebo, which is a nonactive medication. It is used when testing whether using a particular treatment is better than not using anything. Each child will receive either the treatment being tested or the placebo.

- How would it be different if your child was invited to an asthma trial, which compared Medicine A with a placebo (compared with a trial that compared 2 treatments)?

In the treatment of childhood cancers, one combination of drugs is often compared with another combination.

- What questions might you have if your child was invited to participate in cancer trials, which compared one combination of drugs with another?

Motivators and Barriers

- What do you think are some of the benefits for children being involved in a randomised controlled trial?
- What do you think are some of the problems with children being involved in a randomised controlled trial?
- Why do you think some parents might be reluctant or keen for their children to be involved in a randomised controlled trial?
- Would you feel differently if it were you rather than your child who was asked to participate in a randomised controlled trial? Why?

Future

- How can we help parents to understand more about randomised controlled trials?
- From the parents and patients' point of view, what do you think are some of the things that researchers need to think of when they design research?
- How can we improve research involving children in the future?

Appendix G: Demographic questionnaire for parents' focus groups
"Attitudes to children's participation in randomised controlled trials"

Focus group for Parents

The information on this sheet is confidential. It will be used to define the participants attending this focus group.

Please tick appropriate boxes

1. Who are you in relationship to the child?

Father	Step-Father	Male guardian
Mother	Step-Mother	Female guardian

2. How old are you?

3. How many children are currently living in your household?

4. What is the postcode of your place of residence?

5. What is your level of education?

   School Certificate (up to year 10)

   High School Certificate (year 12)

   Tertiary

6. What is your country of origin? _____
   (i.e. with what culture do you identify?)

7. Have you or any of your children ever participated in a randomised controlled trial in the past?

   yes no

Thank you for completing this survey. Your help is greatly appreciated.
……

If you would like feedback about this research, please fill in your name and address below.

Yes, I would like feedback about this research.
Name: _____
Address: _____
_____

Bibliography

(1) NHMRC. How to review the evidence: systematic identification and review of the scientific literature - Handbook series on preparing clinical practice guidelines. 1999.

(2) Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. BMJ 2000; 321(7256):255-256.

(3) Sackett DL, Rosenberg WMC, Gray JAM, Harnes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996; 312:71-72.

(4) Eden T. Evidence based medicine. Archives of Disease in Childhood 2000; 82(4):275-277.

(5) Medical Research Council Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment of pulmonary tuberculosis. BMJ 1948;(ii):769-783.

(6) Kerridge I, Lowe M, Henry D. Ethics and evidence based medicine. BMJ 1998; 316(7138):1151-1153.

(7) Chessells JM. Treatment of childhood acute lymphoblastic leukemia: present issues and future prospects. Blood Reviews 1992; 6:193-203.

(8) Shuster E. Fifty years later: the significance of the Nuremburg Code. New England Journal of Medicine 1997; 337(20):1436-1440.

(9) World Medical Association Declaration of Helsinki: Recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997; 277(11):925-926.

(10) Weijer C, Shapiro SH, Cranley GK. For and against: clinical equipoise and not the uncertainty principle is the moral underpinning of the randomised controlled trial. BMJ 2000; 321(7263):756-758.

(11) Beauchamp TL, Childress JF. Principles of biomedical ethics. New York: Oxford University Press, 1994.

(12) Segelov E, Tattersall MHN, Coates AS. Redressing the balance - The ethics of not entering an eligible patient on a randomised clinical trial. Annals of Oncology 1992; 3:103-105.

(13) Peart N. Health research with children: the New Zealand experience. Current Legal Issues 2000; 3:421-439.

(14) Smyth RL. Research with children. Paediatric practice needs better evidence--gained in collaboration with parents and children. BMJ 2001; 322(7299):1377-1378.

(15) Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. BMJ 1998; 316:343-345.

(16) Lamprill J. Trials of Paediatric Medicines. Clinical Research Focus 1999; December.

(17) Nahata MC. Licensing of medicines for children in the USA. Pediatric and Perinatal Drug Therapy May 1997. 1997. Priory Lodge Education Ltd.

(18) Smyth RL, Weindling AM. Research in children: ethical and scientific aspects. Lancet 1999; 354((suppl II)):2124.

(19) Kauffman RE et al. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics 1995; 95(2):286-294.

(20) Broome ME. Children's assent to clinical trial participation: a unique kind of informed consent. http://cancertrials.nci.nih.gov/understanding/indepth/protections/assent/index.html . 2001.

(21) Simar MR. Pediatric drug development: The international conference on harmonization focus on clinical investigations in children. Drug Information Journal 2000; 34(3):809-819.

(22) Botstein P. Why FDA is encouraging drug testing in children. FDA consumer special report. http://www.fda.gov/fdac/special/newdrug/kidmed.html. 1995.

(23) Food and Drug Administration. Best Pharmaceuticals for Children Act. www.fda.gov/opacom/laws/pharmkids/contents.html . 2002.

(24) National Institute of Health. NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. http.//grants.nih.gov/grants/guide/notice-files/not98-204.html. 1998.

(25) Royal College of Paediatrics and Child Health: Ethics Advisory Committee. Guidelines for the ethical conduct of medical research involving children. Archives of Disease in Childhood 2000; 82:177-182.

(26) NHMRC. Human Research Ethics Handbook - Commentary on the National Statement on Ethical Conduct in Research Involving Humans. 2001.

(27) International Conference on Harmonisation; E11 Clinical Investigation of Medicinal Products in the Paediatric Population. http://eudra.org/emea.html 2000.

(28) Peart N, Holdaway D. Legal and Ethical Issues of Health Research with Children. Childrenz Issues Journal 1998; 2(2):42-46.

(29) Choonara I. Clinical trials of medicines in children. BMJ 2000; 321:1093-1094.

(30) Ceci A. Clinical trials in children in Europe. BMJ 2000; Nov.

(31) Cruzan SM. Pediatric Rule (Communication with FDA Media Relations Staff) 301-827-6248. Caldwell PHY. 2002.

(32) Gottlieb S. Testing of drugs on children ruled unlawful by US judge. BMJ 2002; 325(7370):920.

(33) World summit against cancer for the new millenium charter of Paris, Article III. Paris: 2000.

(34) Ellis PM, Butow PN, Simes RJ, Tattersall MHN, Dunn SM, MacLeod C. Doctors' participation in randomized trials of adjuvant systemic therapy in breast cancer: How does it relate to their recommendations for standard therapy in breast cancer? Breast 1999; 8(4):182-187.

(35) Vist GE, Hagen KB, Devereaux PJ, Oxman AD. Outcomes of patients who participate in randomised controlled trials versus those of similar patients who do not participate (Protocol for a Cochrane Methodology Review). Cochrane Library [4]. 2001.

(36) Schmidt B, Gillie P, Caco C, Roberts J, Roberts R. Do sick newborn infants benefit from participation in a randomized clinical trial? Journal of Pediatrics 1999; 134(2):151-155.

(37) Davis S, Wright PW, Schulman SF, Hill LD, Pinkham RD, Johnson LP et al. Participants in prospective, randomized clinical trials for resected non-small cell lung cancer have improved survival compared with nonparticipants in such trials. Cancer 1985; 56(7):1710-1718.

(38) Janofsky J, Starfield B. Assessment of risk in research on children. Journal of Pediatrics 1981; 98(5):842-846.

(39) McCarthy A, Richman L, Hoffman RP, Rubenstein L. Psychological screening of children for participation in nontherapeutic invasive research. Archives of Pediatrics & Adolescent Medicine 2001; 155:1197-1203.

(40) Swanson GM, Ward AJ. Recruiting minorities into clinical trials: toward a participant-friendly system. Journal of the National Cancer Institute 1995; 87(23):1747-1759.

(41) Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S et al. Factors that limit the quality, number and progress of randomised controlled trials. Health Technology Assessment (Washington DC) 1999; 3(20):iii-139.

(42) Hunninghake DB, Darby CA, Probstfield JL. Recruitment experience in clinical trials: literature summary and annotated bibliography. Controlled Clinical Trials 1987; 8(4 Suppl):6S-30S.

(43) Lovato LC, Hill K, Hertert S, Hunninghake DB, Probstfield JL. Recruitment for controlled clinical trials: literature summary and annotated bibliography. Controlled Clinical Trials 1997; 18(4):328-352.

(44) Walson PD. Patient recruitment: US perspective. Pediatrics 1999; 104(3 Pt 2):619-622.

(45) Campbell H, Surry SAM, Royle EM. A review of randomised controlled trials published in Archives of Disease in Childhood from 1982-96. Archives of Disease in Childhood 1998; 79:192-197.

(46) Taylor KM. Integrating conflicting professional roles: physician participation in randomized clinical trials. Social Science & Medicine 1992; 35(2):217-224.

(47) Morrow GR, Hickok JT, Burish TG. Behavioral aspects of clinical trials. An integrated framework from behavior theory. Cancer 1994; 74(9 Suppl):2676-2682.

(48) Taylor KM, Kelner M. Interpreting physician participation in randomized clinical trials: the Physician Orientation Profile. Journal of Health & Social Behavior 1987; 28(4):389-400.

(49) Fallowfield L, Ratcliffe D, Souhami R. Clinicians' attitudes to clinical trials of cancer therapy. European Journal of Cancer 1997; 33(13):2221-2229.

(50) Kinney AY, Richards C, Vernon SW, Vogel VG. The effect of physician recommendation on enrollment in the Breast Cancer Chemoprevention Trial. Preventive Medicine 1998; 27(5 Pt 1):713-719.

(51) Siminoff LA, Zhang A, Colabianchi N, Sturm CM, Shen Q. Factors that predict the referral of breast cancer patients onto clinical trials by their surgeons and medical oncologists. Journal of Clinical Oncology 2000; 18(6):1203-1211.

(52) Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. Journal of Clinical Epidemiology 1999; 52(12):1143-1156.

(53) Taylor KM. Physician participation in a randomized clinical trial for ocular melanoma. Annals of Ophthalmology 1992; 24(9):337-344.

(54) Taylor KM. The doctor's dilemma: physician participation in randomized clinical trials. Cancer Treatment Reports 1985; 69(10):1095-1100.

(55) Taylor KM, Margolese RG, Soskolne CL. Physicians' reasons for not entering eligible patients in a randomized clinical trial of surgery for breast cancer. New England Journal of Medicine 1984; 310(21):1363-1367.

(56) Ellis PM, Butow PN, Simes RJ, Tattersall MHN, Dunn SM. Barriers to participation in randomized clinical trials for early breast cancer among Australian cancer specialists. Aust New Zealand J Surgery 1999; 69:486-491.

(57) McCaskill-Stevens W, Pinto H, Marcus AC, Comis R, Morgan R, Plomer K et al. Recruiting minority cancer patients into cancer clinical trials: a pilot project involving the Eastern Cooperative Oncology Group and the National Medical Association. Journal of Clinical Oncology 1999; 17(3):1029-1039.

(58) Peto V, Coulter A, Bond A. Factors affecting general practitioners' recruitment of patients into a prospective study. Family Practice 1993; 10(2):207-211.

(59) Aaronson N.K., Visser-Pol E., Leenhout G.H., Muller M.J., van der Schot A.C., van Dam F.S. et al. Telephone based nursing intervention improves the effectiveness of the informed consent process in cancer clinical trials. Journal of Clinical Oncology 1996; 14(3):984-986.

(60) Benson AB, Pregler JP, Bean JA, Rademaker AW, Eshler, Anderson K. Oncologists' reluctance to accrue patients onto clinical trials: an Illinois Cancer Center study. Journal of Clinical Oncology 1991; 9(11):2067-2075.

(61) Anonymous. Viability of cancer clinical research: patient accrual, coverage, and reimbursement. American Medical Association Council on Scientific Affairs. Journal of the National Cancer Institute 1991; 83(4):254-259.

(62) Taylor KM, Shapiro M, Soskolne CL, Margolese RG. Physician response to informed consent regulations for randomized clinical trials. Cancer 1987; 60(6):1415-1422.

(63) Chang RW, Falconer J, Stulberg SD, Arnold WJ, Dyer AR. Prerandomization: an alternative to classic randomization. The effects on recruitment in a controlled trial of arthroscopy for osteoarthrosis of the knee. Journal of Bone & Joint Surgery - American Volume 1990; 72(10):1451-1455.

(64) Taylor KM, Feldstein ML, Skeel RT, Pandya KJ, Ng P, Carbone PP. Fundamental dilemmas of the randomized clinical trial process: results

of a survey of the 1,737 Eastern Cooperative Oncology Group investigators. Journal of Clinical Oncology 1994; 12(9):1796-1805.

(65) Harth SC, Thong YH. Parental perceptions and attitudes about informed consent in clinical research involving children. Social Science & Medicine 1995; 41(12):1647-1651.

(66) Henzlova MJ, Blackburn BH, Bradley EJ, Rogers WJ. Patient perception of a long-term clinical trial: Experience using a close-out questionnaire in the Studies of Left Ventricular Dysfunction (SOLVD) trial. Controlled Clinical Trials 1994; 15(4):284-293.

(67) Cassileth BR, Lusk EJ, Miller DS, Hurwitz S. Attitudes toward clinical trials among patients and the public. JAMA 1982; 248:968-970.

(68) Harth SC, Thong YH. Sociodemographic and motivational characteristics of parents who volunteer their children for clinical research: a controlled study. BMJ 1990; 300:1372-1375.

(69) Lara PN, Higdon R, Lim N, Kwan K, Tanaka M, Lau DHM et al. Prospective evaluation of cancer clinical trial accrual patterns: Identifying potential barriers to enrollment. Jounal of Clinical Oncology 2001; 19(6):1728-1733.

(70) Langley GR, Sutherland HJ, Wong S, Minkin S, Llewellyn-Thomas HA, Till JE. Why are (or are not) patients given the option to enter clinical trials? Controlled Clinical Trials 1987; 8(1):49-59.

(71) Yeomans-Kinney A, Vernon SW, Frankowski RF, Weber DM, Bitsura JM, Vogel et al. Factors related to enrollment in the breast cancer prevention trial at a comprehensive cancer center during the first year of recruitment. Cancer 1995; 76(1):46-56.

(72) Holden G, Rosenberg G, Barker K, Tuhrim S, Brenner B. The recruitment of research participants: a review. Social Work in Health Care 1993; 19(2):1-44.

(73) Snowdon C, Garcia J, Elbourne D. Making sense of randomization; responses of parents of critically ill babies to random allocation of treatment in a clinical trial. Social Science & Medicine 1997; 45(9):1337-1355.

(74) Welton AJ, Vickers MR, Cooper JA, Meade TW, Marteau TM. Is recruitment more difficult with a placebo arm in randomised controlled trials? A quasirandomised, interview based study. BMJ 1999; 318(7191):1114-1117.

(75) Bleyer WA. Re: recruiting minorities into clinical trials: toward a participant-friendly system. Journal of the National Cancer Institute 1996; 88(6):377.

(76) Collet JP, Floret D, Cochat P, Gillet J, Cogan-Collet J, David L et al. Group meetings for recruitment of children in a clinical trial. Therapie 1991; 46(2):139-142.

(77) Chessells JM, Bailey C, Richards SM. Intensification of treatment and survival in all children with lymphoblastic leukemia:results of UK Medical Research Council trial UKALL X. Lancet 1995; 345(14348).

(78) Ross JA, Severson RK, Pollock BH, Robison LL. Childhood Cancer in the United States: A Geographical Analysis of Cases from the Pediatric Cooperative Clinical Trials Groups. Cancer 1996; 77:201-207.

(79) Murphy SB. The National Impact of Clinical Cooperative Group Trials for Pediatric Cancer. Medical & Pediatric Oncology 1995; 24:279-280.

(80) Ellis P. Improving recruitment to cancer clinical trials. Cancer Forum 1999; 23(3):153-155.

(81) Simone JV, Lyons J. The Evolution of Cancer Care for Children and Adults. Journal of Clinical Oncology 1998; 7:2904-2905.

(82) Mansour EG. Barriers to clinical trials. Part III: Knowledge and attitudes of health care providers. Cancer 1994; 74(9 Suppl):2672-2675.

(83) Walterspiel JN. Informed consent: influence on patient selection among critically ill premature infants. Pediatrics 1990; 85(1):119-121.

(84) Tercyak KPJ, Johnson SB, Kirkpatrick KA, Silverstein JH. Offering a randomized trial of intensive therapy for IDDM to adolescents. Reasons for refusal, patient characteristics, and recruiter effects. Diabetes Care 1998; 21(2):213-215.

(85) Langley JM, Halperin SA, Mills EL, Eastwood B. Parental willingness to enter a child in a controlled vaccine trial. Clinical & Investigative Medicine - Medecine Clinique et Experimentale 1998; 21(1):12-16.

(86) Anonymous. Recruitment of participants in the childhood Asthma Management Program (CAMP). I. Description of methods: Childhood Asthma Management Program Research Group. Journal of Asthma 1999; 36(3):217-237.

(87) Hayman RM, Taylor CT, Peart NS, Galland BC, Sayers RM. Participation in research: informed consent, motivation and influence. Journal of Pediatrics and Child Health 2001; 37:51-54.

(88) Zupancic JAF, Gillie P, Streiner DL, Watts JL, Schmidt B. Determinants of parental authorization for involvement of newborn infants in clinical trials. Pediatrics 1997; 99(1).

(89) Constantine WL, Haynes CW, Spiker D, Kendall-Tackett K, Constantine NA. Recruitment and retention in a clinical trial for low birth

weight, premature infants. Journal of Developmental & Behavioral Pediatrics 1993; 14(1):1-7.

(90) Thong YH, Harth SC. The social filter effect of informed consent in clinical research. Pediatrics 1991; 87(4):568-569.

(91) Wiley FM, Ruccione K, Moore IM, McGuire-Cullen P, Fergusson J, Waskerwitz MJ et al. Parents' perceptions of randomization in pediatric clinical trials. Cancer Practice 1999; 7(5):248-256.

(92) Tarnowski K.J, Allen D.M., Mayall C., Kelly P.A. Readability of pediatric biomedical research informed consent forms. Pediatrics 1990; 85(1):58-62.

(93) Spry VM, Hovell MF, Sallis JG, Hofsteter CR, Elder JP, Molgaard CA. Recruiting survey respondents to mailed surveys: controlled trials of incentives and prompts. American Journal of Epidemiology 1989; 130(1):166-172.

(94) Cartmel B, Moon TE. Study of strategies for the recruitment of elders including the use of community volunteers. Journal of the American Geriatrics Society 1992; 40(2):173-177.

(95) Tai SS, Nazareth I, Haines A, Jowett C. A randomized trial of the impact of telephone and recorded delivery reminders on the response rate to research questionnaires. Journal of Public Health Medicine 1997; 19(2):219-221.

(96) Panser LA, Chute CG, Girman CJ, Guess HA, Oesterling JE, Lieber MM et al. Effect of several recruitment strategies on response rates at baseline in a prospective cohort investigation. The Olmsted County Study of Urinary Symptoms and Health Status among Men. Annals of Epidemiology 1994; 4(4):321-326.

(97) Koepsell TD, McGuire V, Longstreth WTJ, Nelson LM, van Belle G. Randomized trial of leaving messages on telephone answering machines for control recruitment in an epidemiologic study. American Journal of Epidemiology 1996; 144(7):704-706.

(98) Pirkis JE, Jolley D, Dunt DR. Recruitment of women by GPs for pap tests: a meta-analysis. British Journal of General Practice 1998; 48(434):1603-1607.

(99) Hunt JM, Gless GL, Straton JA. Pap smear screening at an urban aboriginal health service: report of a practice audit and an evaluation of recruitment strategies. Australian & New Zealand Journal of Public Health 1998; 22(6):720-725.

(100) Clover KA, Redman S, Forbes JF, Sanson-Fisher RW, Dickinson JA. Promotion of attendance for mammographic screening through general practice: a randomised trial of two strategies. Medical Journal of Australia 1992; 156(2):91-94.

(101) Turnbull D, Irwig L. Ineffective recruitment strategies for screening mammography: letterbox drops and invitations for friends. Australian Journal of Public Health 1992; 16(1):79-81.

(102) Garton MJ, Torgerson DJ, Donaldson C, Russell IT, Reid DM. Recruitment methods for screening programmes: trial of a new method within a regional osteoporosis study. BMJ 1992; 305(6845):82-84.

(103) Lando HA, Hellerstedt WL, Pirie PL, McGovern PG. Brief supportive telephone outreach as a recruitment and intervention strategy for smoking cessation. American Journal of Public Health 1992; 82(1):41-46.

(104) Lowe JB, Windsor RA, Post KL. Effectiveness of impersonal versus interpersonal methods to recruit employees into a worksite quit smoking program. Addictive Behaviors 1987; 12(3):281-284.

(105) Wadland WC, Hughes JR, Secker-Walker RH, Bronson DL, Fenwick J. Recruitment in a primary care trial on smoking cessation. Family Medicine 1990; 22(3):201-204.

(106) Diaz T, Chu SY, Sorvillo F, Mokotoff E, Davidson AJ, Samuel MC et al. Differences in participation in experimental drug trials among persons with AIDS. JAIDS: Journal of Acquired Immune Deficiency Syndromes 1995; 10(5):562-568.

(107) Gimble JG, Kline L, Makris N, Muenz LR, Friedman LI. Effects of new brochures on blood donor recruitment and retention. Transfusion 1994; 34(7):586-591.

(108) Bolgiano DC, Smith S, Slichter SJ. Strategies to recruit plateletpheresis donors from a registry of HLA-typed, unrelated, bone marrow donors. Transfusion 1993; 33(8):675-678.

(109) Gries JA, Black DR, Coster DC. Recruitment to a university alcohol program: evaluation of social marketing theory and stepped approach model. Preventive Medicine 1995; 24(4):348-356.

(110) Gerace TA, George VA, Arango IG. Response rates to six recruitment mailing formats and two messages about a nutrition program for women 50-79 years old. Controlled Clinical Trials 1995; 16(6):422-431.

(111) Coleman EA, Tyll L, LaCroix AZ, Allen C, Leveille SG, Wallace JI et al. Recruiting African-American older adults for a community-based health promotion intervention: which strategies are effective? American Journal of Preventive Medicine 1997; 13(6 Suppl):51-56.

(112) Zifferblatt SM. Recruitment in large-scale clinical trials. pp 187-95. In: Weiss SM, ed 1900; Proceedings of the National Heart and Lung Institute Working Conference on health behavior. Bethesda, NIH, 1975. WG 200 N279p 1975.

(113) Bjornson-Benson WM, Stibolt TB, Manske KA, Zavela KJ, Youtsey DJ, Buist et al. Monitoring recruitment effectiveness and cost in a clinical trial. Controlled Clinical Trials 1993; 14(2 Suppl):52S-67S.

(114) Hollis JF, Satterfield S, Smith F, Fouad M, Allender PS, Borhani N et al. Recruitment for phase II of the Trials of Hypertension Prevention. Effective strategies and predictors of randomization. Trials of Hypertension Prevention (TOHP) Collaborative Research Group. Annals of Epidemiology 1995; 5(2):140-148.

(115) Leader MA, Neuwirth E. Clinical research and the noninstitutional elderly: a model for subject recruitment. Journal of the American Geriatrics Society 1978; 26(1):27-31.

(116) Stephenson T, Walker DA. Gaining patients' consent. Telling parents all relevant details might reduce recruitment of children to trials. BMJ 1996; 313(7053):362-363.

(117) Simes RJ, Tattersall MHN, Coates AS, Rains KT, Solomon HJ, Smartt H. Randomised comparison of procedures for obtaining informed consent in clinical trials of treatment of cancer. BMJ 1986; 293:1065-1068.

(118) Myles PS, Fletcher HE, Cairo S, Madder H, McRae R, Cooper J et al. Randomized trial of informed consent and recruitment for clinical trials in the immediate preoperative period. Anesthesiology 1999; 91(4):969-978.

(119) Zelen M. A new design for randomized clinical trials. New England Journal of Medicine 1979; 300:1242-1245.

(120) Snowdon C, Elbourne D, Garcia J. Zelen randomization: Attitudes of parents participating in a neonatal clinical trial. Controlled Clinical Trials 1999; 20(2):149-171.

(121) Levene M, Wright I, Griffiths G. Is informed consent in neonatal randomised controlled trials ritual? Lancet 1996; 347:475.

(122) Wendler D, Rackoff JE, Emanuel EJ, Grady C. The ethics of paying for children's participation in research. J Pediatr 2002; 141:166-171.

(123) Dobson R. Lump sums for children taking part in research may distort parents' judgement. BMJ 2002; 325(7368):796.

(124) Swanson GM, Ward AJ. Recruiting minorities into clinical trials: toward a participant-friendly system. Journal of the National Cancer Institute 1995; 87(23):1747-1759.

(125) Lovato LC, Hill K, Hertert S, Hunninghake DB, Probstfield JL. Recruitment for controlled clinical trials: literature summary and annotated bibliography. Controlled Clinical Trials 1997; 18(4):328-352.

(126) Baines CJ. Impediments to recruitment in the Canadian National Breast Screening Study: response and resolution. Controlled Clinical Trials 1984; 5(2):129-140.

(127) Mapstone J, Elbourne D, Roberts I. Strategies to improve recruitment to research studies (Protocol for a Cochrane Review). The Cochrane Library [4]. 2002.

(128) Willis NS, Mitchell R, Craig JC Renal Group. In: *The Cochrane Library*, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

(129) Schulz KF, Chalmers I, Hayes RJ, Altman, DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273(5):408-412.

(130) Stroup DF, Berlin J, Morton S, Olkin I. Meta-analysis of Observational Studies in Epidemiology. JAMA 2000; 283(15):2008-2012.

(131) Egger M, Smith GD, Schneifer M. Systematic reviews of observatonal studies. In: Egger M, Smith GD, Altman DG, editors. Systematic reviews in health care: Meta-analysis in context. London: BMJ, 2001: 211-227.

(132) Egger M, Schneider M, Smith GD. Meta-analysis Spurious precision? Meta-analysis of observational studies. BMJ 1998; 316:140-144.

(133) Review Manager (RevMan) [Computer program]. Version 4.2 for Windows. Oxford, England: The Cochrane Collaboration, 2002, CD-ROM and Internet.

(134) Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Annals of Internal Medicine 1997; 127(9):820-826.

(135) Isaacman DJ, Reynolds EA. Effect of a research nurse on patient enrollment in a clinical study. Pediatric Emergency Care 1996; 12(5):340-342.

(136) Carew BD, Ahn SA, Boichot HD, Dierenfeldt BJ, Dolan NA, Edens TR et al. Recruitment strategies in the studies of left ventricular dysfunction (SOLVD): strategies for screening and enrollment in two concurrent but separate trials. The SOLVD Investigators. Controlled Clinical Trials 1992; 13(5):325-338.

(137) Moon TE, Levine N, Cartmel B, Bangert J, Rodney S, Schreiber M et al. Design and recruitment for retinoid skin cancer prevention (SKICAP) trials. The Southwest Skin Cancer Prevention Study Group. Cancer Epidemiology, Biomarkers & Prevention 1995; 4(6):661-669.

(138) Wragg JA, Robinson EJ, Lilford RJ. Information presentation and decisions to enter clinical trials: a hypothetical trial of hormone replacement therapy. Social Science & Medicine 2000; 51(3):453-462.

(139) Martinson BC, Lazovich D, Lando HA, Perry CL, McGovern PG, Boyle RG. Effectiveness of monetary incentives for recruiting adolescents to an intervention trial to reduce smoking. Preventive Medicine 2000; 31:706-713.

(140) Llewellyn-Thomas HA, Thiel EC, Sem FW, Woermke DE. Presenting clinical trial information: a comparison of methods. Patient Education & Counseling 1995; 25(2):97-107.

(141) Valanis B, Blank J, Glass A. Mailing strategies and costs of recruiting heavy smokers in CARET, a large chemoprevention trial. Controlled Clinical Trials 1998; 19(1):25-38.

(142) Fleissig A, Jenkins V, Fallowfield L. Results of an intervention study to improve communication about randomised clinical trials of cancer therapy. European Journal of Cancer 2001; 37:322-331.

(143) Gallo C, Perrone F, De Placido S, Giusti C. Informed versus randomised consent to clinical trials [see comments]. Lancet 1995; 346(8982):1060-1064.

(144) Lilford RJ. Ethics of clinical trials from a bayesian and decision analytic perspective: whose equipoise is it anyway? BMJ 2003; 326:980-981.

(145) Kinney AY, Richards C, Vernon SW, Vogel VG. The effect of physician recommendation on enrollment in the Breast Cancer Chemoprevention Trial. Preventive Medicine 1998; 27(5 Pt 1):713-719.

(146) Taylor KM, Margolese RG, Soskolne CL. Physicians' reasons for not entering eligible patients in a randomized clinical trial of surgery for breast cancer. New England Journal of Medicine 1984; 310(21):1363-1367.

(147) Taylor KM, Feldstein ML, Skeel RT, Pandya KJ, Ng P, Carbone PP. Fundamental dilemmas of the randomized clinical trial process: results of a survey of the 1,737 Eastern Cooperative Oncology Group investigators [see comments]. Journal of Clinical Oncology 1994; 12(9):1796-1805.

(148) Collet JP, Floret D, Cochat P, Gillet J, Cogan-Collet J, David L et al. [Group meetings for patient recruitment in clinical trial in pediatrics]. [French]. Therapie 1991; 46(2):139-142.

(149) Hoppu K. Patient recruitment--European perspective. Pediatrics 1999; 104(3 Pt 2):623-626.

(150) Vollmer WM, Hertert S, Allison MJ. Recruiting children and their families for clinical trials: a case study. Controlled Clinical Trials 1992; 13(4):315-320.

(151) Langley JM, Halperin SA, Mills EL, Eastwood B. Parental willingness to enter a child in a controlled vaccine trial. Clinical & Investigative Medicine - Medecine Clinique et Experimentale 1998; 21(1):12-16.

(152) Bender DE, Ewbank D. The focus group as a tool for health research: issues in design and analysis. Health Transition Review 1994; 4(1):63-80.

(153) Pope C, Ziebland S, Mays N. Qualitative research in health care. Analysing qualitative data. BMJ 2000; 320(7227):114-116.

(154) Strauss A, Corbin J. Basics of qualitative research: grounded theory procedures and techniques. 1990.

(155) McCaskill-Stevens W, Pinto H, Marcus AC, Comis R, Morgan R, Plomer K et al. Recruiting minority cancer patients into cancer clinical trials: a pilot project involving the Eastern Cooperative Oncology Group and the National Medical Association. Journal of Clinical Oncology 1999; 17(3):1029-1039.

(156) Stone VE, Mauch MY, Steger KA. Provider attitudes regarding participation of women and persons of color in AIDS clinical trials. JAIDS: Journal of Acquired Immune Deficiency Syndromes 1998; 19(3):245-253.

(157) Anonymous. Viability of cancer clinical research: patient accrual, coverage, and reimbursement. American Medical Association Council on Scientific Affairs. Journal of the National Cancer Institute 1991; 83(4):254-259.

(158) Caldwell PHY, Butow PN, Craig JC. Paediatricians' attitudes to randomized controlled trials involving children. Journal of Pediatrics 2002; 141(6):798-803.

(159) Dent O. Clinical Workforce Surveys 2001: Clinical workforce in internal medicine and paediatrics in Australia 2001. The Royal Australasian College of Physicians, editor. 3-19. 2001. Sydney, Australia, The Royal Australasian College of Physicians.

(160) Association of American Medical Colleges. Clinical Research: A National Call to Action. http://www.aamc.org/research/calltoaction.html. 2000.

(161) NHMRC. Health and Medical Research Strategic Review - Implementation of the government's response. 19-20. 2001. Canberra, AustInfo.

(162) Peart N, Holdaway D. Ethical Guidelines for Health Research with Children. New Zealand Bioethics Journal 2000; 1(3):3-9.

(163) Giacomini M, Cook D. Users' guide to the medical literature: Qualitative research in health care - Are the results of the study valid? JAMA 2000; 284(3):357-362.

(164) Kjoergaard LL, Kruse AY, Krogsgaard K, Gluud CN, Mortensen EL, Gottschau A et al. Outpatients' knowledge about and attitude towards clinical research and randomized clinical trials. Danish Medical Bulletin 1998; 45(4):439-443.

(165) Passamani E. Clinical trials - are they ethical? New England Journal of Medicine 1991; 324(22):1589-1591.

(166) Snowdon C, Garcia J, Elbourne D. Reactions of participants to the results of a randomised controlled trial: exploratory study. BMJ 1998; 317(7150):21-26.

(167) Snowdon C, Garcia J, Elbourne D. Making sense of randomization; responses of parents of critically ill babies to random allocation of treatment in a clinical trial. Social Science & Medicine 1997; 45(9):1337-1355.

(168) Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. New England Journal of Medicine 1995; 333(22):1456-1461.