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# Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate (Review)

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Vist GE, Bryant D, Somerville L, Birminghem T, Oxman AD.
Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate.
*Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: MR000009.
DOI: 10.1002/14651858.MR000009.pub4.

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[Methodology Review]

# Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate

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**Editorial group:** Cochrane Methodology Review Group.
**Publication status and date:** Unchanged, published in Issue 1, 2010.

**Citation:** Vist GE, Bryant D, Somerville L, Birminghem T, Oxman AD. Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: MR000009. DOI: 10.1002/14651858.MR000009.pub4.



## ABSTRACT

### Background

Some people believe that patients who take part in randomised controlled trials (RCTs) face risks that they would not face if they opted for non-trial treatment. Others think that trial participation is beneficial and the best way to ensure access to the most up-to-date physicians and treatments. This is an updated version of the original Cochrane review published in Issue 1, 2005.

### Objectives

To assess the effects of patient participation in RCTs ('trial effects') independent both of the effects of the clinical treatments being compared ('treatment effects') and any differences between patients who participated in RCTs and those who did not. We aimed to compare similar patients receiving similar treatment inside and outside of RCTs.

### Search methods

In March 2007, we searched The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, The Cochrane Methodology Register, SciSearch and PsycINFO for potentially relevant studies. Our search yielded 7586 new references. In addition, we reviewed the reference lists of relevant articles.

### Selection criteria

Randomized studies and cohort studies with data on clinical outcomes of RCT participants and similar patients who received similar treatment outside of RCTs.

### Data collection and analysis

At least two review authors independently assessed studies for inclusion, assessed study quality and extracted data.

### Main results

We identified 30 new non-randomized cohort studies (45 comparisons): no new RCTs were found. This update now includes five RCTs (yielding 6 comparisons) and 80 non-randomized cohort studies (130 comparisons), with 86,640 patients treated in RCTs and 57,205 patients treated outside RCTs. In the randomised studies, patients were invited to participate in an RCT or not; these comparisons provided

limited information because of small sample sizes (a total of 412 patients) and the nature of the questions they addressed. When the results of RCTs and non-randomized cohorts that reported dichotomous outcomes were combined, there were 98 comparisons; there was also heterogeneity ($P < 0.00001$, $I^2 = 42.2\%$) between studies. No statistical significant differences were found for 85 of the 98 comparisons. Eight comparisons reported statistically significant better outcomes for patients treated within RCTs, and five comparisons reported statistically significant worse outcomes for patients treated within RCTs. There was significant heterogeneity ($P < 0.00001$, $I^2 = 58.2\%$) among the 38 continuous outcome comparisons. No statistically significant differences were found for 30 of the 38 comparisons. Three comparisons reported statistically significant better outcomes for patients treated within RCTs, and five comparisons reported statistically significant worse outcomes for patients treated within RCTs.

**Authors' conclusions**

This review indicates that participation in RCTs is associated with similar outcomes to receiving the same treatment outside RCTs. These results challenge the assertion that the results of RCTs are not applicable to usual practice.

## PLAIN LANGUAGE SUMMARY

**Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate**

This updated review assessed whether there were harmful or beneficial effects from participating in randomized controlled trials (RCTs). The outcomes of patients who participated in RCTs were compared with outcomes of patients who were eligible for the trial and received similar clinical interventions, but did not participate. Comparisons were included both of 'experimental' treatment inside and outside of RCT and of 'control' treatment comparisons. On average, the outcomes of patients participating and not participating in RCTs were similar, suggesting that participation in RCTs, independent of the effects of the clinical interventions being compared, is likely to be comparable.

## BACKGROUND

The efforts of trialists, ethics committees, and funding agencies to inform potential participants (for example, patients) of the risks of participating in randomized controlled trials (RCTs) appear to be motivated in part by the 'conventional wisdom' that those who participate in RCTs face special risks that they would not face if they declined to participate and received their health care in the usual way. Thus we see statements describing trial participants as being 'conscripted' to 'sacrifice' themselves in the service of the 'collective' - 'guinea pigs' to be sacrificed for the benefit of future patients (Sackett 2001). A journal editor expressed her view thus: "If the ethical commitment to protect the participants from the risks of participating in RCTs "is attenuated, even for so good a cause as benefits to future patients, the implicit assumptions of the doctor-patient relationship are violated" (Angell 1984). And the dean of a medical school took up this argument: "The risk of such attenuation by the RCT is great" (Hellman 1991).

Conversely, some researchers and patients believe that participation in RCTs is beneficial, as well as being the most equitable and ethical way to compare the effects of treatments when there is uncertainty. Some patient advocates, especially those with HIV and cancer, demand access to clinical trials.

Anecdotal evidence is sometimes cited to support both of these opposing viewpoints. More often, assumptions are made without reference to empirical evidence. Previous reviews of the evidence of harmful or beneficial effects of participating in RCTs have been limited by the difficulty in identifying and interpreting the available evidence, which, because it comes almost entirely from non-randomized cohort studies, is subject to the same biases as non-randomized cohort studies of clinical interventions.

There are now at least four published reviews of evidence that might help us resolve this disagreement (Stiller 1994; Braunholtz 2001; ECRI 2002; Peppercorn 2004), but their conclusions have varied. Peppercorn and colleagues concluded that the glass is half or more empty: "Despite the widespread belief that enrolment in clinical trials leads to improved outcomes among cancer patients, there are insufficient data to conclude that such a trial effect exists." On the other hand, Braunholtz et al concluded that the glass is at least half full: "While the evidence is not conclusive, it is more likely that clinical trials have a positive rather than a negative effect on the outcome of patients."

Previous reviews have compared all patients treated within trials with all patients treated outside trials, regardless of any differences in the clinical intervention received or differences in patient populations. This previous approach means that we can not know if any differences observed reflect the effects of participating in RCTs (a trial effect), differences in the clinical interventions used within and outside RCTs (treatment effects), or an effect of differences between the patients who participate in RCTs and those who do not.

In this updated review (originally published in Issue 1, 2005) we have built on earlier work by systematically searching for relevant studies, critically appraising them, and abstracting and analysing data for comparisons that can inform judgements about the potential beneficial and harmful effects of participating in RCTs. We will periodically update the resulting review as new data become available and in response to feedback.

## OBJECTIVES

The aim of this review is to address the following question: Do the outcomes of patients who participate in randomized controlled trials differ from those of similar patients, treated similarly, who do not participate? We attempted to control for differences in the clinical interventions that were received by only including analyses that compare patients receiving the same clinical intervention within and outside RCTs. That is, experimental treatment inside an RCT versus similar treatment outside of the RCT, or the control intervention inside an RCT versus similar control treatment outside of the RCT.

This question is addressed through comparisons of participants in RCTs with:
1. patients who choose not to participate, including:
1a. eligible patients who refuse to participate for any reason;
1b. eligible patients who refuse to participate because of a strong preference for one of the interventions being evaluated;
1c. participants in patient preference trials who choose not to be randomized because of a strong preference for one of the interventions being evaluated.
2. patients not invited to participate, including:
2a. uninvited eligible patients of participating clinicians;
2b. eligible patients of non-participating clinicians.
3. patients randomized to be invited/informed that they are participating in a study versus those not invited/informed (including Zelen design where patients are randomized before consent, and then only those who are randomized to the experimental treatment are asked to consent to participate).
4. eligible patients who do not participate and do not fit into one of the above categories. This might include, for example a mixed group where it is not possible to obtain sufficient data to categorise individuals, controls from the same or nearby hospitals that are captured in large health care databases, area-wide population controls, 'not-quite-eligible' patients at the same centres, 'administratively' not eligible patients.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Cohort studies that include at least one of the comparisons specified above. For comparisons 2a, 2b and 4 we included any RCTs that were found in which participation or the possibility of participating in a clinical trial was randomly allocated, including participation in N of 1 trials (individualised and controlled 'trial of therapy') and cluster randomized trials.

#### Types of data

We collected data as reported by investigators for comparisons using concurrent controls. We also attempted to collect or calculate relative risks or hazard ratios.

#### Types of methods

We included comparisons of patient participation in an RCT versus non-participation.

### Types of outcome measures

The main outcome measures of interest were mortality, morbidity (excluding surrogate outcome measures), and clinically important changes in outcomes measured on continuous scales (such as self reported pain, quality of life and function).

## Search methods for identification of studies

In March 2007, we searched:

- MEDLINE, the search strategy is presented in Appendix 1;
- EMBASE, the search strategy is presented in Appendix 2;
- The Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Library Issue 1 2007, the search strategy is shown in Appendix 3;
- PsycInfo, the search strategy is presented in Appendix 4;

We checked the reference lists of the relevant articles that we retrieved. We followed up on abstracts of studies by attempting to find a full report by searching in PubMed.

## Data collection and analysis

Two review authors independently assessed all retrieved citations. Any study that either review author considered potentially relevant was retrieved.

Two review authors independently assessed the relevance of all retrieved articles using the eligibility criteria specified above. Disagreements were resolved by discussion. A third review author was consulted about any disagreements that could not be resolved. We have listed references to all those studies for which there were disagreements or initial uncertainties in the Characteristics of excluded studies table, together with the reasons for our decisions to exclude them.

### Methodological quality

Two review authors using the following criteria independently assessed the validity of the comparisons made in the included studies:

#### *Selection bias*

This criterion was scored as:
Met = concealed random allocation to participate or not in a clinical trial;
Partially met = control for one or more prognostic factors (we noted how many prognostic factors have been controlled for);
No imbalance = no control for prognostic factors because there was no imbalance;
Not met = imbalance in prognostic factors and failure to control for prognostic factors;
Unclear = sufficient information could not be obtained.

#### *Detection bias*

This criterion was scored as:
Met = outcomes measured in the same way in both participants and non-participants;
Partially met = similar standards of measurement for participants and non-participants;
Not met = different standards of measurement for participants and non-participants;
Unclear = sufficient information could not be obtained.

#### *Exclusion bias*

We recorded the number of losses to follow up for each group (loss/total):
Loss in RCT treatment group;
Loss in RCT control group;
Loss in non- participants treatment group;
Loss in non- participants control group;
then grouped them for analysis into:
No losses to follow up;
1% to 20% losses to follow up;
>20% losses to follow up;
unclear if there were any losses to follow up.

#### *Differences in care*

Differences in the care provided to participating and non-participating patients were recorded as a possible explanation for differences in outcomes. We regarded this as reflecting an effect of participating in a trial rather than as a 'performance' bias. Differences in the care provided might be due to differences in adherence to a protocol by participating clinicians; baseline differences between clinicians who participate and do not participate in clinical trials; or a Hawthorne effect (changes in behaviour due to being observed).

We also regarded the possible impact of psychologically mediated effects due to the informed consent process as a possible explanation for differences in outcomes rather than as a bias.

We attempted to control for differences in the clinical interventions received by including only those analyses comparing patients receiving similar treatments.

Because they might explain differences in outcomes, we recorded whether the investigators had noted changes in behaviour attributed to being observed, or different expectations, attributable to the informed consent process.

In addition to recording our assessments of the methodological quality of the included studies, we collected data describing relevant details of the included studies including the study design, types of participating patients, the types of participating clinicians, the clinical interventions that were evaluated and the main outcome measures reported.

Two review authors completed data collection forms independently for all included studies. These were compared and discrepancies were resolved by discussion, including a third review author, when necessary.

### Analysis

We prepared tables summarising the results of all the relevant comparisons included, grouped as described under 'Objectives'. Additionally, comparisons were also grouped based on the risk of selection, detection and exclusion bias into controlled comparisons, partially controlled comparisons and poorly controlled comparisons. The main outcome for each of the included studies was collected, an additional outcome group included mortality only. We have reported the main outcome measures in these summary tables. For each result we recorded or calculated, if possible, a relative risk (RR) or hazard ratio with a 95% confidence interval, using adjusted estimates when these were available. In order to summarise all the dichotomous results in one summary table, we took the natural logarithm of the unadjusted

RR and calculated the associated SE. For similar comparisons and outcomes we conducted a chi-square test of heterogeneity. In order to calculate a pooled estimate for continuous outcomes, the results from individual studies were standardized (in order to return them to the same metric) and a standardized mean difference (SMD) was used to calculate the pooled estimate. For relative risk analysis we used the Mantel-Haenszel approach available in RevMan. We calculated summary statistics using a random-effect model using the inverse of the variance for each study to weigh its treatment effect in the pooled analysis. We did not calculate a pooled estimate if statistically significant heterogeneity was found (defined as $P < 0.10$). For clinically diverse comparisons or statistically heterogeneous results we described the variation in the estimates and key explanatory factors, if possible relating the explanatory factors to observed differences in estimates of the effects of participation. The main explanatory factors that we considered were:

· the risk of selection bias;
· the risk of detection bias;
· the risk of exclusion bias;
· differences in the care provided to patients (including differences between participating and non-participating clinicians, adherence to a protocol by participating clinicians, and a possible Hawthorne effect);
· a possible effect due to the informed consent process;
· differences in the need for skills or experience (e.g. trials of surgical procedures versus drug trials).

We described the number of comparisons and the total number of patients compared from different clinical areas (e.g. cardiology and oncology) and the consistency of the evidence across different clinical areas.

# RESULTS

## Description of studies

The update search identified 7586 potentially relevant references. After an initial screen of titles and abstracts, full articles were obtained for 231 of these. Thirty reported relevant data and a further 51 suggested to us that the investigators might have relevant data.

We identified 30 new non-randomized cohort studies (45 comparisons), no new RCTs were found. This update now includes five RCTs (yielding six comparisons) and 80 non-randomized cohort studies (130 comparisons), with 86,640 patients treated in RCTs and 57205 patients treated outside RCTs. The included studies are described in the Characteristics of included studies table. In each of five randomized studies with a total of 412 patients, investigators randomized patients to be invited to participate in an RCT or not. Based on published data alone, we could include 45 new comparisons. We have listed 51 studies as 'awaiting assessment' because they cannot currently be included or excluded in this review based on the information available to us.

In 38 studies (with 61 comparisons), patients in RCTs were compared with patients who refused to participate in RCTs without a specified reason. In 20 studies (with 34 comparisons), patients in RCTs were compared with patients who refused to participate in RCTs because of treatment preferences. In 11 partially randomized patient preference studies (with 22 comparisons), patients randomized to treatment were compared with patients who chose not to be randomized because of a treatment preference. In six studies (with nine comparisons), patients treated in RCTs were compared with patients who were not invited to participate in the RCTs. In two studies (with two comparisons), patients treated within the context of an RCT were compared with patients treated by other clinicians who did not enter any of their patients to the trial. In one study (with one comparison) non-randomized patients were not invited to the trial because of administrative error or the researcher was absent. In one study (with one comparison) the reason for not including the eligible non-randomized patients in trial is unclear, and finally, in one study (with one comparison) eligible non-randomized patients were given the active treatment to give the clinicians training.

Patients received the following clinical interventions: surgery or other procedures (33 comparisons), drugs (28 comparisons), radiotherapy (15 comparisons), counselling or education (nine comparisons), usual care (45 comparisons), and active monitoring/ watchful waiting (six comparisons).

There were comparisons in the following clinical specialties: oncology (31 comparisons), cardiology (22 comparisons), other internal medicine subspecialties (27 comparisons), obstetrics and gynaecology (29 comparisons), psychology or drug abuse (15 comparisons), and paediatrics (12 comparisons).

Each comparison is represented using the main outcome as reported by the investigators, and this main outcome is noted in the Characteristics of included studies table.

Mortality was reported in 21 studies (with 37 comparisons). In two of these studies (with nine comparisons), mortality was not the main outcome, from these two studies we used the reported main outcome in the summary analysis and the mortality results in the mortality analysis only.

## Risk of bias in included studies

We categorised six randomized comparisons as 'well controlled', 42 comparisons that reported no imbalance or controlled for prognostic factors as 'controlled', 29 comparisons that reported one or two differences as 'partially controlled', and 59 comparisons that reported several statistically significant differences or which did not report characteristics of the patients within and outside the RCTs as 'poorly controlled'.

Outcomes were measured in the same way within and outside the RCTs in 111 comparisons, similarly in twelve comparisons, and differently or not reported in 10 comparisons.

No patients were reported as having been excluded in 55 comparisons. In 49 comparisons, between one and 20% of patients were lost to follow up, and over 20% of patients were lost to follow up in 16 comparisons. It was unclear if there were any losses to follow up in 16 comparisons.

## Effect of methods

### Randomized studies

The five studies (six comparisons) in which patients were randomized to be invited to participate in an RCT or not (Table 1) provide limited information because of their small sample sizes and the nature of the questions they addressed.

Two studies randomized a total of 82 patients to N of 1 trials compared with standard practice (Mahon 1996; Mahon 1999).

One study with 60 patients measured spontaneously reported side effects by patients informed that they were in an RCT compared with those who were not informed (Dahan 1986).

One study with 227 patients reported satisfaction among patients randomized to an RCT compared with patients randomized to a patient preference trial who had a treatment preference (Cooper 1997a; Cooper 1997b).

The fifth study with 43 patients reported pain reduction among patients randomized to an RCT compared with patients who were not invited to participate (Bergmann 1994).

None of these studies found statistically significant differences in outcomes between patients treated within and outside RCTs. Because of the heterogeneity of questions addressed in these studies, we did not consider it appropriate to make a quantitative synthesis of their results.

**Non-randomized cohort studies**

The 80 non-randomized cohort studies (130 comparisons) included a total of 86,362 patients participating in RCTs compared with 57,071 patients treated outside RCTs. Ninety-eight comparisons used dichotomous outcomes, 12 of them with adjusted results, 38 comparisons were of continuous outcomes.

**Main outcome (dichotomous)**

The results of all the comparisons in which dichotomous outcomes were used are summarised and presented in Analysis 1.1. There is statistically significant heterogeneity (overall $P < 0.00001$, and overall $I^2 = 42.2\%$). The summary estimate for the comparisons with dichotomous outcomes is not presented, the confidence interval around the pooled result ranged from 0.93 to 1.06.

In 85 of the 98 comparisons, no statistically significant differences in outcomes were found. The results of the 13 comparisons (two adjusted comparisons and 11 unadjusted comparisons) in which statistically significant differences were found are as follows.

The two adjusted comparisons reported statistically significantly better outcomes for patients treated in RCTs than similar patients receiving similar treatments outside RCTs. One partially controlled adjusted comparison found that lung cancer patients in an RCT had a lower risk of dying inside RCT (RR 0.39, 95% CI 0.18 to 0.83) (Davis 1985). One poorly controlled comparison that adjusted for treatment (total parenteral nutrition or not) found that malnourished surgical patients in the RCT had a lower risk of complications (RR 0.60, 95% CI 0.42 to 0.86) (Williford 1993). Six unadjusted comparisons reported statistically significantly better outcomes for patients treated in RCTs than similar patients receiving similar treatments outside RCTs. Three were partially controlled and found better blood pressure control inside the RCT (RR 0.73, 95% CI 0.56 to 0.97) (Martinez-Amenos1990a), a lower 18 year mortality after a health check without further intervention (RR 0.59, 95% CI 0.45 to 0.78) (Strandberg 1995) and a lower 30 day mortality after surgery in high risk patients (RR 0.23, 95% CI 0.07 to 0.77) (Rigg 2000a). Three poorly controlled comparisons found lower relapse rates for lymphocytic leukaemia in children receiving maintenance chemotherapy (RR 0.27, 95% CI 0.07 to 0.99) (Baum 1979), and more successful pregnancies after oocyte retrieval with different anaesthetics (RR 0.81, 95% CI 0.70 to 0.93 and RR 0.84, CI 0.75 to 0.95) (Rosen 1987a; Rosen 1987b).

Five unadjusted studies reported statistically significant better outcomes outside RCTs. Four were partially controlled comparisons. One found a higher risk of breast cancer recurrence among women who had received mastectomies within an RCT compared with women similarly treated outside the RCT (RR 2.79, 95% CI 1.04 to 7.53) (Blichert-Toft 1988b). One found that medical abortion was more acceptable to women in a preference trial than in the RCT (RR 5.36, 95% CI 1.66 to 17.28) (Henshaw 1993a). One found better satisfaction with the use of nasal tube for endoscopy outside of RCT than inside (RR 1.51, 95% CI 1.22 to 1.87 )(Mori 2006b), one found greater rate of success for treating plantar fascitis (foot disorder) with sham electrohydraulic high-energy shock-wave treatment outside of the RCT than inside the RCT (RR 1.86, 95% CI 1.19 to 2.92) (Ogden 2004).

One poorly controlled unadjusted comparison reported significantly higher satisfaction among women with medical abortion outside of an RCT than women who received medical abortion inside an RCT (RR 1.77, 95% CI 1.12 to 2.80) (Rørbye 2005a).

**Main outcome (continuous)**

The results of the 38 comparisons in which continuous outcomes were used are presented in Analysis 2.1. There was moderate heterogeneity (overall $P < 0.00001$, overall $I^2 = 58.2\%$). The summary estimate for the comparisons with continuous outcomes is not presented, the confidence interval around the pooled SMD ranged from -0.05 to 0.11.

In 30 of the 38 comparisons, no statistically significant differences in outcomes were found. The results of the eight comparisons (five partially and three poorly controlled unadjusted comparisons) in which statistically significant results were found were as follows.

Three partially controlled comparisons reported statistically significant better outcomes for patients treated in RCT than similar patients receiving similar treatment outside of the RCT. One study with two comparisons found that both couples who received pre-IVF counselling and couples who did not receive additional counselling pre-IVF in the RCT had lower anxiety than similar couples given or not given pre-IVF counselling outside of the RCT (SMD -0.37, 95% CI -0.72 to -0.01) (Emery 2003a), (SMD -0.80, 95% CI -1.26 to -0.34) (Emery 2003b). In one study of endoscopy patients who were given sedation inside RCT, they scored less troublesomeness than the patients who were sedated outside of the RCT (SMD -0.85, 95% CI -1.59 to -0.10) (Melchart 2002a).

Two partially controlled comparisons and three poorly controlled comparisons found statistically significant worse outcomes in patients treated in RCTs. In one study the patients found the procedure more troublesome when given a placebo during endoscopy inside the RCT compared with similar patients given nothing during endoscopy outside the RCT (SMD 0.47, 95% CI 0.14 to 0.80) (Abraham 2004b). In one study of young girls who were given growth hormone, they grew more outside the RCT than those who were treated inside the RCT (SMD 1.01, 95% CI 0.05 to 1.97) (McCaughey 1998). In three large, poorly controlled unadjusted studies looking at the effect of acupuncture for osteoarthritis of the knee or hip, or chronic low back pain, or chronic neck pain patients reported less pain, higher reduction in pain and lower WOMAC score when treated with acupuncture outside RCT than similar patients

treated with acupuncture in RCT (osteoarthritis patients, SMD 0.40, 95% CI 0.28 to 0.52) (Witt 2006a) (chronic low back pain, SMD 0.10, 95% CI 0.04 to 0.15) (Witt 2006b) (chronic neck pain, SMD 0.07, 95% CI 0.02 to 0.13) (Witt 2006c). The three acupuncture trials included 22,929 patients and accounted for 79% weight of the total weight of continuous data analysis.

**Mortality; subgroup analysis**

In twenty-one studies with 37 comparisons, mortality was reported as an outcome. The mortality results are summarised and presented in Analysis 3.1. There is statistically significant heterogeneity (overall P < 0.03, and overall $I^2$ = 33.7%). The summary estimate for the mortality comparisons is not presented, the confidence interval around the pooled estimate ranged from 0.88 to 1.08.

In 34 of the 37 comparisons, no statistically significant differences in outcomes were found. Three comparisons (one adjusted comparison and two unadjusted comparisons) in which statistically significant differences were found are as follows.

One adjusted mortality comparison found a statistically significant lower risk of dying for patients treated within RCTs (Davis 1985).

Two unadjusted mortality comparisons found a statistically significant lower risk of dying for patients treated within RCTs (Rigg 2000a; Strandberg 1995).

None of the subgroup analyses that we conducted helped to explain the observed heterogeneity in the results of the comparisons we included. We conducted separate analyses for the different types of patients treated outside RCTs (patients who refused to participate in RCTs without a specified reason, patients who refused to participate in an RCT because of a treatment preference, etc.), different types of treatments (surgery or procedures, drugs, etc.), different clinical areas (oncology, cardiology, etc.), and differences in study quality (selection bias, detection bias, and exclusion bias). These subgroup analyses are available from us on request.

Due to insufficient information, we were unable to conduct subgroup analyses examining differences in the clinical care provided to patients or differences in the informed consent process.

## DISCUSSION

Our review does not provide strong evidence of either a harmful or a beneficial trial effect. As we found significant heterogeneity among the results of the included comparisons, which we were not able to explain, these overall findings may not apply to particular circumstances yet to be identified.

The five randomized studies that we found comparing outcomes within and outside RCTs provide limited evidence, but they do demonstrate that it is possible to address questions about the effects of participating in RCTs using randomized designs. Interpretation of the 80 non-randomized cohort studies is limited by the quality and size of the comparisons and the wide variations in participants, clinical interventions and outcomes in these comparisons. Most of the 130 non-randomized cohort comparisons did not yield statistically significant differences, 11 found better outcomes in RCTs and ten found better outcomes outside RCTs.

Do the outcomes of patients who participate in RCTs differ from those of similar patients who do not participate? Three previous reviews have addressed this question. Braunholtz 2001 identified 14 articles reporting data from 21 trials, and concluded that, if anything, randomized trials tend to have beneficial effects rather than harmful effects on the patients who participate in them.

Peppercorn included seven of the 14 articles in the Braunholtz review and an additional 17 (Peppercorn 2004). However, only eight of their studies compared trial patients with non-trial patients who met the same eligibility criteria, and it is only possible to separate treatment effects from trial effects in three of these. As Peppercorn et al. classified studies as 'positive' ("outcomes among trial patients were better with P<0.05") and 'negative (P>0.05), they were unable to distinguish studies that exclude any important trial benefit ('true-negatives') from 'indeterminate' studies that are simply too small to detect either important benefit or important harm.

ECRI 2002 (Emergency Care Research Institute) found 10 comparisons of survival or quality of life between patients treated within and outside RCTs of treatments for life threatening illnesses (eight were cancer treatments). They concluded, "some evidence shows that patients in phase II/III trials survive longer than similar patients who are not in trials. One cannot have great confidence in these results, however, due to the small evidence base."

Our review differs from previous reviews in a number of ways, including the scope, the comprehensiveness of the search, the analysis and, importantly, the question that we asked: Do the outcomes of patients who participate in RCTs differ from those of **similar patients receiving similar treatments** who do not participate? Our results suggest that on average they do not.

An important corollary of this finding is that it counters the suggestions that the results of RCTs cannot be applied to usual clinical practice. Extrapolations of the results from RCTs to patients who are different to the patients who participated in the RCT, or to interventions that are different to those of the RCT, are different issues.

In summary, all of the three previous reviews and our review (now including results from over 140,000 patients) suggest that participating in a randomised controlled trial is likely to result in similar outcomes to having similar treatment outside of the trial. It is likely that there are more relevant studies than those included in this review, as indicated by the number of studies awaiting assessment, and the difficulty we and others have encountered searching for these studies in MEDLINE and other bibliographic databases. Additionally, we did not search dissertation data bases. Twelve of the 30 new studies included in update were published before the previous search data.

What we have attempted in this review and update has been to isolate the 'trial effect' of participating in RCTs. This is a question of effect where only well designed and conducted RCTs will provide conclusive answer. We have only five small randomised controlled trials where patients have been randomised to be asked to participate in a RCT or not. Due to the sparseness of data, we have in an attempt to further inform the issue of trial effect, included cohorts. We have attempted to only compare similar patients inside and outside of the RCTs, and we have attempted to only compare similar interventions inside and outside of the

RCTs. Even so, these cohorts are non-randomized studies and vulnerable to bias. There is an increasing focus on the importance of following patients outside of trials and the number of cohorts that are available for inclusion seems to be increasing. This is a welcome improvement; however, we think that we have now reached the level of information for this particular issue where only new RCTs is likely to give us more confidence in the conclusion. Therefore, updates of this review will only consider RCTs.

It is important to protect people from unnecessary risks and harms and it is essential that people are informed and warned of the risk to which they may be exposed, both in clinical trials and in routine care. When there is collective uncertainty about the effects of clinical interventions, randomised trials provide the best means of resolving that uncertainty (Kunz 2002).

Patients who are given the option of participating in a clinical trial should routinely be told what is known about the potential benefits and harms of the interventions being compared in the trial as well as whatever other options they have.

## AUTHORS' CONCLUSIONS

### Implication for methodological research

Randomized comparisons with adequate sample sizes are needed to provide reliable evidence of potential differences in outcomes of patients who participate in randomised trials compared with similar patients receiving similar interventions who do not participate.

## ACKNOWLEDGEMENTS

We would like to thank Dave Sackett for initiating the effort that has resulted in this review, for his contributions to the protocol and for his generous support. We would like to thank Marit Johansen for the search strategy. We would like to thank Kåre Birger Hagen, PJ Devereraux and Doris Tove Kristoffersen for their contributions to the first (previous) version of this review.

We would like to thank the following for providing additional information about their studies: Albert SM, Antman K, Barrett BJ, Bennett JM, Black SB, Brehm SS, Berglund G, Bergmann JF, Bijker N, Blichert-Toft M, Boros L, Cairncross JG, Carroll KM, Chadwick DW, Chauhan SP, Chilvers C, Clagett GP, Cohen CJ, Collins K, Cooper JS, Cooper KG, Cottin V, Creutzig U, Davis S, DiMagno EP, van Eys J, Ferrone PJ, Forbes GM, Frisell J, Glimelius B, Gluud C, Guillemin F, Hauth JC, Helsing M, Hellberg D, Henderson JM, Hutter AM, Jensen LP, Jonker JJC, Karrison T, King SB, Kjar D, Kronmal RA, Licht RW, Lidbrink E, Liu WF, Madsen JK, Mahon JL, Malangoni MA, Marcocci C, McKay JR, Mourits MP, Moynihan C, Mundy GR, Naylor CD, Neuwirth MG, O'Fallon JR, Paradise JL, Pinchera A, Playforth MJ, Pollock AV, Rokke PD, Rosen MA, Rovers MM, Rychtarik RG, Schmidt B, Schmoor C, Sha BE, Shelhamer JH, Stegmayr BG, Stiller CA, Stone JM, Takolander R, Tannock IF, Vestergaard P, Ward B, Weijer C, Weisdorf DJ, Wyse DG, Yersin B, Yu VL.

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* Indicates the major publication for the study

# CHARACTERISTICS OF STUDIES

## Characteristics of included studies *[ordered by study ID]*

### Abraham 2004a

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The eligible but non-RCT patients were not in the RCT because of patients preference for no sedation (135 patients) or patients refused (27 patients). Adult ambulatory patients scheduled to undergo diagnostic upper endoscopy. There was no losses to follow up. |
| Data | Characteristics of non-RCT patients compared to RCT patients who received the same treatment not presented. 50 RCT patients who received sedation and 27 non-RCT patients who received same treatment. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The Sedation patients received standard parenteral sedation (titrated doses of midazolam and/or meperidine). The placebo group received saline and the non-RCT group nothing. |
| Outcomes | Clinical outcomes were assessed in all patients and they were followed up for 24 hours. Main outcome in this study was patient self reported satisfaction. |
| Notes | |

**Abraham 2004b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The eligible but non-RCT patients were not in the RCT because of patients preference for no sedation (135 patients) or patients refused (27 patients). Adult ambulatory patients scheduled to undergo diagnostic upper endoscopy. There was no losses to follow up. |
| Data | Characteristics of non-RCT patients compared to RCT patients who received the same treatment not presented. 50 RCT patients who received placebo and 135 non-RCT patients who received nothing. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The Sedation patients received standard parenteral sedation (titrated doses of midazolam and/or meperidine). The placebo group received saline and the non-RCT group nothing. |
| Outcomes | Clinical outcomes were assessed in all patients and they were followed up for 24 hours. Main outcome in this study was patient self reported satisfaction. |
| Notes | ? |

**Antman 1985a**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The eligible but non-RCT patients were not in the RCT because of patients refusal (24 patients) or patients not invited by their physician (24 patients). Patients with intermediate or high grade sarcoma. No losses to follow up. |
| Data | Characteristics of non-RCT patients compared to RCT patients who received the same treatment not presented. Twenty RCT patients received doxorubin treatment and 21 non-RCT patients, 7 men and 14 women. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients in a registry. The experimental RCT arm patients were treated with doxorubicin. The control RCT patients were under observation. |
| Outcomes | Clinical outcomes were assessed in all patients. Patients were followed for up to 4 years. Main outcome reported in this study was disease free survival. |
| Notes | No statistically significant difference was shown between the two RCT treatments. |

**Antman 1985b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The eligible but non-RCT patients were not in the RCT because of patients refusal (24 patients) or patients not invited by their physician (24 patients). Patients with intermediate or high grade sarcoma. No losses to follow up. |
| Data | Characteristics of non-RCT patients compared to RCT patients who received the same treatment not presented. Twenty-two RCT patients were under observation and 27 non-RCT patients. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients in a registry. The experimental RCT arm patients were treated with doxorubicin. The control RCT patients were under observation. |
| Outcomes | Clinical outcomes were assessed in all patients. Patients were followed for up to 4 years. Main outcome reported in this study was disease free survival. |
| Notes | No statistically significant difference was shown between the two RCT treatments. |

### Ashok 2005a

| | |
|---|---|
| Methods | Randomised trial with patient preference arm. Patients who refused randomization were treated according to their choice. Women who attend termination of pregnancy at 10-13 weeks gestation. No losses to follow up before discharge from hospital. |
| Data | Characteristics of choice patients presented and compared to RCT patients who received the same treatment were presented in Ashok 2002. RCT medical abortion group were mean (SD) 26 (7) years, 202 women. Preference medical abortion group were mean 29 (7) years, 15 women. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental RCT arm patients underwent medical abortion. The control RCT patients underwent surgical abortion. |
| Outcomes | Clinical outcomes were assessed in all women, they were followed up until discharge from hospital. Main outcome of this study was anxiety after procedure. |
| Notes | The two randomised treatments were not statistically significantly different. |

### Ashok 2005b

| | |
|---|---|
| Methods | Randomised trial with patient preference arm. Patients who refused randomization were treated according to their choice. Women who attend termination of pregnancy at 10-13 weeks gestation. No losses to follow up before discharge from hospital. |
| Data | Characteristics of choice patients presented and compared to RCT patients who received the same treatment were presented in Ashok 2002. RCT surgical abortion group were mean (SD) 25 (7) years, 198 women. Preference medical abortion group were mean 26 (6) years, 71 women. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental RCT arm patients underwent medical abortion. The control RCT patients underwent surgical abortion. |
| Outcomes | Clinical outcomes were assessed in all women, they were followed up until discharge from hospital. Main outcome of this study was anxiety after procedure. |
| Notes | The two randomised treatments were not statistically significantly different. |

### Bain 2001a

| | |
|---|---|
| Methods | Randomised trial with patient preference arm. Patients who refused randomization were treated according to their choice. Women with dysfunctional uterine bleeding suitable for endometrial ablation. No losses to follow up. |
| Data | Characteristics of choice patients presented and compared to RCT patients who received the same treatment. RCT local anaesthesia group were mean (SD) 43 (5) years, 20 women. Preference local anaestesia group were mean 44 (6) years, 32 women. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental RCT arm patients underwent local anaesthesia. The control RCT patients underwent general anaesthesia. |

**Bain 2001a** *(Continued)*

| | |
|---|---|
| Outcomes | Clinical outcomes were assessed in all women, they were followed up until discharge from hospital. The main outcome of this study was pain. |
| Notes | The two randomised treatments were not statistically significantly different. |

**Bain 2001b**

| | |
|---|---|
| Methods | Randomised trial with patient preference arm. Patients who refused randomization were treated according to their choice. Women with dysfunctional uterine bleeding suitable for endometrial ablation. No losses to follow up. |
| Data | Characteristics of choice patients presented and compared to RCT patients who received the same treatment. RCT general anaesthesia group were mean (SD) 42 (3) years, 16 women. Preference general anaesthesia group were mean 43 (5) years, 30 women. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental RCT arm patients underwent local anaesthesia. The control RCT patients underwent general anaesthesia. |
| Outcomes | Clinical outcomes were assessed in all women, they were followed up until discharge from hospital. The main outcome of this study was pain. |
| Notes | The two randomised treatments were not statistically significantly different. |

**Bakker 2000**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The eligible but non-RCT patients were not in the RCT because of patients preference for no medication (31 patients). Patients with panic disorder who had had more than 3 attacks during the last three weeks. Nine (26 %) of the 35 RCT cognitive therapy patients dropped out and seven (23%) of the 31 non-RCT cognitive therapy patients were lost to follow up. |
| Data | Characteristics of non-RCT patients compared to RCT patients who received the same treatment not presented. The majority of patients were female (74% combined groups) and of average age of 34 (SD 8) years. |
| Comparisons | Two RCT arms, the experimental arm was compared with similarly treated non-RCT patients. The experimental group received 12 week of cognitive therapy. The control arm was placebo. |
| Outcomes | Clinical outcomes were assessed in all patients who were followed up. Patients were followed for up for 12 weeks. Main outcome reported in this study was frequency of panic attacks. |
| Notes | ? |

**Balmukhanov 1989a**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. We do not know why the non-RCT patients were not in the RCT. Women with uterine cervix cancer stage II and III. Unclear if there was losses to follow up. |

**Balmukhanov 1989a** *(Continued)*

| | |
|---|---|
| Data | Charateristics of the RCT radiatiotheraphy in combination with metronidazole group were 56 women, age unknown. Non-RCT radiatiotheraphy in combination with metronidazole group were 124 women, age unknown. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental arm patients received rradiatiotheraphy in combination with metronidazole. The control patients received radiation alone. |
| Outcomes | Clinical outcomes were assessed in all patients, patients were followed for 2 weeks after last treatment. Main outcome in this study was lack of clearance. |
| Notes | The experimental arm of the RCT was more effective than control. |

**Balmukhanov 1989b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. We do not know why the non-RCT patients were not in the RCT. Women with uterine cervix cancer stage II and III. Unclear if there was losses to follow up. |
| Data | Characteristics of the RCT radiation alone group were 52 women, age unknown. Non-RCT radiation alone group were 163 women, age unknown. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental arm patients received radiatiotheraphy in combination with metronidazole. The control patients received radiation alone. |
| Outcomes | Clinical outcomes were assessed in all patients, patients were followed for 2 weeks after last treatment. Main outcome in this study was lack of clearance. |
| Notes | The experimental arm of the RCT was more effective than control. |

**Baum 1979**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. Children whose parents or physician refused randomization were treated according to their choice. Children with acute lymphocytic leukemia who had been on continuous chemotherapy for a minimum of three years, regardless of the therapy regimen. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT maintenance chemotherapy children were 22 boys and 22 girls, age uncertain. Non-RCT maintenance chemotherapy patients were 16 boys and 8 girls, age uncertain. |
| Comparisons | Two RCT arms, the experimental arm was compared with similarly treated eligible non-RCT patients. The experimental arm children were given continuation of maintenance chemotherapy for another three years. Chemotherapy was discontinued in the control group. |
| Outcomes | Clinical outcomes were assessed in all the children, they were followed up approximately 25 months. Main outcome in this study was relapse. |
| Notes | The experimental treatment was more beneficial than the control treatment. |

**Bedi 2000a**

| | |
|---|---|
| Methods | Randomised trial with concurrent preference trial outside of the RCT. The non-RCT patients were not in the RCT because they refused randomization, but consented to be followed in a preference trial. 18 to 70 years old primary care patients who meet the Research Diagnostic Criteria for major depression as assessed by the GP. The RCT counseling group lost 8 (23%) patients to follow up, the preference counseling group lost 32 (23%) patients to follow up. |
| Data | Characteristics of preference trial patients presented and compared to RCT patients who received the same treatment. RCT counseling patients were on average approximately 38 years, approximately 23% men. Preference counseling patients were mean 36 (10 SD) years, 36 men and 104 women. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients in a preference trial. The experimental RCT arm the patients were given counseling, the control RCT arm patients were prescribed antidepressants. |
| Outcomes | Clinical outcomes were assessed in all of the patients, they were followed up for 8 weeks. Main outcome in this study was BDI score at 8 weeks. |
| Notes | The two RCT arms were similarly effective. |

**Bedi 2000b**

| | |
|---|---|
| Methods | Randomised trial with concurrent preference trial outside of the RCT. The non-RCT patients were not in the RCT because they refused randomization, but consented to be followed in a preference trial. 18 to 70 years old primary care patients who meet the Research Diagnostic Criteria for major depression as assessed by the GP. The RCT antidepressants group lost 6 (12%) patients to follow up, the preference antidepressants group lost 24 (30%) patients to follow up. |
| Data | Characteristics of preference trial patients presented and compared to RCT patients who received the same treatment. RCT patients prescribed antidepressants were on average approximately 38 years, approximately 23% men. Preference patients prescribed antidepressants were on mean 38 (13 SD) years, 21 men and 59 women. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients in a preference trial. The experimental RCT arm the patients were given counseling, the control RCT arm patients were prescribed antidepressants. |
| Outcomes | Clinical outcomes were assessed in all of the patients, they were followed up for 8 weeks. Main outcome in this study was BDI score at 8 weeks. |
| Notes | The two RCT arms were similarly effective. |

**Berglund 1997**

| | |
|---|---|
| Methods | Randomised trial with eligible non-randomised patients outside of the trial. Patients not in the RCT were not in because they refused randomization, but allowed monitoring. Patients below 75 years of age, curative treatment for a primary tumor and inclusion within 2 months after curative or adjuvant therapy. No patients were lost to follow up in the RCT control group, and 13 patients were lost to follow up in the non-RCT monitoring group. |
| Data | Characteristics of non-randomised patients presented and compared to RCT patients who received the same treatment. RCT control patients were on average 54 years. Non-RCT patients were on average 54 years. |

**Berglund 1997** *(Continued)*

| | |
|---|---|
| Comparisons | Two RCT arms, the control arm patients were compared with similarly treated eligible non-RCT patients. The experimental group took part in a 'starting again' rehabilitation program. The control patients were monitored with survey. |
| Outcomes | Outcomes were assessed in all patients, they were followed up for 1 year. Main outcome in this study was bad quality of life. |
| Notes | |

**Bergmann 1994**

| | |
|---|---|
| Methods | Randomised cross over trial with some patients randomized to not be informed about the trial. Patients with mild or moderate cancer pain which did not need narcotic analgesic. No losses to follow up. |
| Data | Characteristics of RCT informed patients presented and compared to RCT non-informed patients who received the same treatment. RCT informed patients were on average 58 (37 to 82) years, 4 men and 14 women. RCT un-informed patients were on average 63 (42 to 92) years, 10 men and 15 women. |
| Comparisons | Two RCT arms, all patients received both treatment arms and both arms were compared with similarly treated un-informed RCT patients. The experimental arm received naproxen. The control arm received a placebo. Only the experimental arm results are presented. |
| Outcomes | Clinical outcomes were assessed in all patients, they were followed up for 2 days. Main outcome in this study was pain score. |
| Notes | The experimental treatment was more effective than control. |

**Bhattacharya 1998**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not invited to take part in the RCT because they lived more than 20 miles from the hospital. Women with dysfunctional uterine bleeding, <50 years of age and weight < 100 kg. 5 (14%) women were lost to follow up in the RCT inpatient group, 16 (19%) women were lost to follow up in the non-RCT inpatient group. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT patients were mean 41 (5) years. Non-RCT patients were mean 40 (5) years. |
| Comparisons | Two RCT arms, the control arm patients were compared with similarly treated eligible non-RCT patients. The experimental arm patients were treated as day cases and discharged from hospital on the same day. The control patients were treated as inpatients. |
| Outcomes | Clinical outcomes were assessed in all patients, patients were followed for 1 year. Main outcome in this study was severe pain. |
| Notes | No difference was shown between the two RCT treatments. |

**Biederman 1985**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible non-randomised patients outside of the trial. Patients not in the RCT were not in because they refused randomization, but allowed monitoring. Young patiens with anorexia nervose with 19% weight loss. Lossess to follow up not reported. |
| Data | Characteristics of non-randomised patients presented and compared to RCT patients who received the same treatment. The 14 RCT control patients were mean 17 (4) years, 36 (6) kg. The 18 Non-RCT patients were on average 16 (2) years, 36 (7) kg. |
| Comparisons | Two RCT arms, the control arm patients were compared with similarly treated eligible non-RCT patients. The experimental group were given amitriptyline and the control group were given placebo. |
| Outcomes | Clinical outcomes were assessed in all patients, they were followed up for 5 weeks. Main outcome in this study was less than 30% response. |
| Notes | No difference was shown between the two RCT treatments. |

**Bijker 2000a**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients in registry outside of the RCT. The eligible but non-RCT patients were not in the RCT because of patients preference for treatment (41 patients) or physicians preference for treatment (114 patients). Diagnosis of ductal carcinoma in situ, maximum diameter of 5 cm, age < 70 years. 4% loss to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Breast conserving treatment +radiotherapy RCT patients were 133 women, age unknown. Breast conserving treatment +radiotherapy treated non- RCT patients were 29 women, age unknown. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: Breast conserving treatment + radiotherapy. Control: breast conserving treatment. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients in the RCT were followed for an average of 51 months and non-RCT patients were followed for an average of 39 months. Main outcome was number of events. |
| Notes | The experimental treatment was significantly more beneficial than the control treatment. |

**Bijker 2000b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients in registry outside of the RCT. The eligible but non-RCT patients were not in the RCT because of patients preference for treatment (41 patients) or physicians preference for treatment (114 patients). Diagnosis of ductal carcinoma in situ, maximum diameter of 5 cm, age < 70 years. 4% loss to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Breast conserving treatment RCT patients were 135 women, age unknown. Breast conserving treatment non-RCT patients were 93 women, age unknown. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: Breast conserving treatment + radiotherapy. Control: breast conserving treatment. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients in the RCT were followed for an average of 51 months and non-RCT patients were followed for an average of 39 months. Main outcome was number of events. |

**Bijker 2000b** *(Continued)*

| | |
|---|---|
| Notes | The experimental treatment was significantly more beneficial than the control treatment. |

**Blichert-Toft 1988a**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT, for part of the study period, a Zelen design were applied where only those randomized to breast preservation were asked to consent. The non-RCT patients were not in the RCT because of preference for one of the treatments. Women with invasive mammary carcinoma of 69 years or younger and with the possibility of a satisfactory cosmetic result by exicion of the tumor. The breast preserving RCT group lost 21 (6%) to follow up, the non-RCT breast preserving group lost 30 (33%) to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Breast preserving RCT patients were 334 women, age unknown. Breast preserving non-RCT patients were 90 women, age unknown. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: breast conservation. Control: Mastectomy. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 6 years. Main outcome was recurrence after 1.75 years. |
| Notes | The two treatments were similarly effective. |

**Blichert-Toft 1988b**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT, for part of the study period, a Zelen design was applied where only those randomized to breast preservation were asked to consent. The non-RCT patients were not in the RCT because of preference for one of the treatments. Women with invasive mammary carcinoma of 69 years or younger and with the possibility of a satisfactory cosmetic result by exicion of the tumor. Mastectomy RCT group lost 22 (7%) to follow up, non-RCT mastectomy group lost 19 (20%) to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Mastectomy RCT patients were 328 women, age unknown. Mastectomy non- RCT patients were 95 women, age unknown. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: breast conservation. Control: Mastectomy. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 6 years. Main outcome was recurrence after 1.75 years. |
| Notes | The two treatments were similarly effective. |

**Boezaart 1998**

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|---|---|
| Methods | Randomised trial with concurrent preference trial outside of the RCT. The non-RCT patients were not in the RCT because they refused randomisation because of preference for treatment. Adult ASA I and II patients who presented for cataract surgery with regional anaesthesia. No lossess to follow up. |

**Boezaart 1998** *(Continued)*

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| Data | Characteristics of non-randomised patients partially presented but not compared to RCT patients who received the same treatment. The 40 patients in the RCT placebo group was compared to the 136 patients in the non-RCT patients who did not want anxiolytic drugs. |
| Comparisons | Six RCT arms, five arms with different anxiolytics and one placebo arm. The placenbo arm was compared with similarly treated eligible patients outside of the trial. |
| Outcomes | Clinical outcomes were assessed in all patients. patients were followed until just after the procedure. Main outcome was anxiety during operation |
| Notes | The RCT treatemtns were not statistically different. |

**CASS 1984a**

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because of patient refusal (28%) and physician refusal (69% patients were not invited) but were followed up in a register. Patients with mild or moderate stable angina pectoris or free of angina but with a documented history of myocardial infarction, both sexes <65 years of age. Outcomes were assessed by cardiologists. The RCT lost 1 patient to follow up, and 10 patients were lost in the nonrandomized groups in total. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Surgery RCT patients were mean 52 (7) years, 353 male and 37 female. Surgery non-RCT patients were mean 51 (8) years, 518 male and 52 female. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: coronary artery bypass surgery. Control: medically treated patients were given medication only. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for an average of 10 years. Main outcome was 5 year mortality. |
| Notes | The two RCT treatment arms were not statistically different. |

**CASS 1984b**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because of patient refusal (28%) and physician refusal (69% patients were not invited) but were followed up in a register. Patients with mild or moderate stable angina pectoris or free of angina but with a documented history of myocardial infarction, both sexes <65 years of age. Outcomes were assessed by cardiologists. The RCT lost 1 patient to follow up, and 10 patients were lost in the nonrandomized groups in total. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Medically treated RCT patients were mean 51 (8) years, 351 male and 39 female. Medically treated non- RCT patients were mean 51 (8) years, 674 male and 71 female. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: coronary artery bypass surgery. Control: medically treated patients were given medication only. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for an average of 10 years. Main outcome was 5 year mortality. |

**CASS 1984b** *(Continued)*

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| Notes | The two RCT treatment arms were not statistically different. |

**Chauhan 1992**

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they refused randomization. Women with singleton pregnancy with intact membranes, AFI equal to or larger than 5.0 cm and no fetal hearth rate tracing abnormalities on admission. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT non infusion patients were on average 22 years. Non-RCT non infusion patients were on average 23 years. |
| Comparisons | Two RCT arms, the control arm patients were compared with similarly treated eligible non-RCT patients. The experimental arm patients were treated with prophylactic saline amnioinfusion. The control patients were not infused. |
| Outcomes | Clinical outcomes were assessed in all women, they were followed up until delivery. Main outcome in this study was incidence of recurrent variable decelerations/bradycardia. |
| Notes | No significant differences were detected between the two RCT arms. |

**Chilvers 2001a**

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| Methods | Randomised trial with patient preference arm. Patients who refused randomization were treated according to their choice. Patients who met research diagnostic criteria for major depression. Missing data for 4 (8%) patients in RCT counseling and 11 (8%) of choice counseling. |
| Data | Characteristics of choice patients presented and compared to RCT patients who received the same treatment. RCT counseling patients were mean 37 (11 SD) years, 16 men and 36 women. Choice counseling patients were mean 36 (10 SD) years, 36 men and 104 women. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The counseling group received 6 sessions of counseling. The other group was given antidepressant drug treatment. |
| Outcomes | Clinical outcomes were assessed in all patients, they were followed up for 1 year. Main outcome in this study was remission. |
| Notes | The two treatments showed similar effectiveness. |

**Chilvers 2001b**

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|---|---|
| Methods | Randomised trial with patient preference arm. Patients who refused randomization were treated according to their choice. Patients who met research diagnostic criteria for major depression. Missing data for 1 (2%) patient in the RCT antidepressant group and 2 (3%) patients in the choice antidepressant group. |
| Data | Characteristics of choice patients presented and compared to RCT patients who received the same treatment. RCT antidepressant patients were mean 38 (12 SD) years, 8 men and 43 women. Choice antidepressant patients were mean 38 (13 SD) years, 21 men and 59 women. |

**Chilvers 2001b** *(Continued)*

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|---|---|
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The counseling group received 6 sessions of counseling. The other group was given antidepressant drug treatment. |
| Outcomes | Clinical outcomes were assessed in all patients, they were followed up for 1 year. Main outcome in this study was remission. |
| Notes | The two treatments showed similar effectiveness. |

**Clagett 1984a**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because of preference for treatment. Patients with asymptomatic cervical bruit and abnormal ocular pneumoplethysmography. No losses to follow up. |
| Data | Characteristics of non-RCT patients not presented and compared to RCT patients who received the same treatment. RCT surgery patients were mean 64 years, 11 men and 4 women. Non-RCT surgery patients were mean 62 years, sex unknown. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental RCT arm patients underwent arteriography and prophylactic carotid endarterectomy if stenotic atherosclerosis was located at the carotid bifurcation. The control RCT patients were given aspirin, 650 mg twice a day. |
| Outcomes | Clinical outcomes were assessed in all patients, they were followed up for an average of 3 years. Main outcome in this study was the sum of all unfavorable outcomes including stroke, death of stroke, major angiographic and perioperative complications, asymptomatic carotid occlusion, and recurrent carotid artery stenosis. |
| Notes | The experimental treatment had resulted in significantly more unfavorable outcomes. |

**Clagett 1984b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because of preference for treatment. Patients with asymptomatic cervical bruit and abnormal ocular pneumoplethysmography. The non-RCT aspirin group lost 2 (14%) patients to follow up, no losses to follow up in the other groups. |
| Data | Characteristics of non-RCT patients not presented and compared to RCT patients who received the same treatment. RCT aspirin patients were mean 63 years, 10 men and 4 women. Non-RCT aspirin patients were mean 65 years, sex unknown. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental RCT arm patients underwent arteriography and prophylactic carotid endarterectomy if stenotic atherosclerosis was located at the carotid bifurcation. The control RCT patients were given aspirin, 650 mg twice a day. |
| Outcomes | Clinical outcomes were assessed in all patients, they were followed up for an average of 3 years. Main outcome in this study was the sum of all unfavorable outcomes including stroke, death of stroke, major angiographic and perioperative complications, asymptomatic carotid occlusion, and recurrent carotid artery stenosis. |
| Notes | The experimental treatment had resulted in significantly more unfavorable outcomes. |

### Clapp 1989

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because parents refused. Babies, 600 to 2000g birth weight, with no major organ malformation or congenital defect. Probably no losses to follow up. |
| Data | Characteristics of non-RCT babies were compared to RCT babies who received the same treatment. RCT babies who received placebo were 31 gestational weeks, weight 1.3 (0.4) kg, 24 boys and 35 girls. The eligible non-RCT babies who were given nothing, were 31 gestational weeks, weight 1.3 (0.4) kg, 48 boys and 37 girls. |
| Comparisons | Two RCT arms, the experiemental arm given intravenously administered immune globulin to prevent nosocomial sepsis and the RCT control arm given placebo. The placebo arm was compard to non-RCT eligible babies given nothing. |
| Outcomes | Clinical outcomes were assessed in all babies, they were followed up until discharge from hospital. Main outcome in this study was mortality. |
| Notes | The experimental treatment was significantly better then control. |

### Cooper 1997a

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|---|---|
| Methods | Randomised trial with patients randomised to a RCT or a patient preference trial. Patients who refused randomization were treated according to their choice. Women attending clinic because of heavy menstrual bleeding. No losses to follow up. |
| Data | Characteristics of choice patients presented and compared to RCT patients who received the same treatment. 31% of RCT transcervical resection patients were under 40 years. 38% of Choice transcervical resection patients were under 40 years. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental group received transcervival surgical resection of the endometrium. The control patients were given medical drug treatment. |
| Outcomes | Clinical outcomes were assessed in all women, they were followed up for 4 months. Main outcome in this study was lack of satisfaction with treatment. |
| Notes | The experimental treatment was more effective than control. |

### Cooper 1997b

| | |
|---|---|
| Methods | Randomised trial with patients randomised to a RCT or a patient preference trial. Patients who refused randomization were treated according to their choice. Women attending clinic because of heavy menstrual bleeding. No losses to follow up |
| Data | Characteristics of choice patients presented and compared to RCT patients who received the same treatment. 33% of RCT medical patients were under 40 years. 37% of Choice medical patients were under 40 years. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental group received transcervival surgical resection of the endometrium. The control patients were given medical drug treatment. |

**Cooper 1997b** *(Continued)*

| | |
|---|---|
| Outcomes | Clinical outcomes were assessed in all women, they were followed up for 4 months. Main outcome in this study was lack of satisfaction with treatment. |
| Notes | The experimental treatment was more effective than control. |

**Creutzig 1993a**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because their parent/s declined randomisation, these patients were treated according to parental choice. The non-RCT patients were followed- up identically to the RCT patients. Previously untreated AML patients less than 17 years of age. Patients were followed for 5 years. No losses to follow up. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. Of the RCT children receiving cranial irradiation 3 were under 2 years, 8 boys and 7 girls. Of the non-RCT children receiving cranial irradiation, none were under 2 years, 6 boys and 7 girls. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: Cranial irradiation. Control: No cranial irradiation. |
| Outcomes | Clinical outcomes were assessed in all the patients. Main outcome was relapse. |
| Notes | The cranial irradiation (experimental) treatment was associated with favorable outcome. |

**Creutzig 1993b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because their parent/s declined randomisation, these patients were treated according to parental choice. The non-RCT patients were followed- up identically to the RCT patients. Previously untreated AML patients less than 17 years of age. Patients were followed for 5 years. No losses to follow up. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. Of the RCT children who did not receive cranial irradiation 1 was under 2 years, 9 boys and 7 girls. Of the non- RCT children who did not receive cranial irradiation 3 were under 2 years, 4 boys and 8 girls. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: Cranial irradiation. Control: No cranial irradiation. |
| Outcomes | Clinical outcomes were assessed in all the patients. Main outcome was relapse. |
| Notes | The cranial irradiation (experimental) treatment was associated with favorable outcome. |

**Dahan 1986**

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| Methods | Randomised trial where half the patients were randomized to not be told about the trial, these patients (No choice) were lead to believe that they were receiving standard practice. The other randomized half of the patients were told that the RCT compared a drug for insomnia and placebo, all the patients were given the same treatment, placebo pills. Patients who were in hospital for more than two days and were suffering from insomnia. No losses to follow up. |

**Dahan 1986** *(Continued)*

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| Data | Characteristics of the patients not presented. 30 placebo RCT patients and 30 no-choice RCT patients. |
| Comparisons | Two RCT arms, both providing the same treatment, but the placebo group consented to take part in a RCT whereas the no-choice group did not know about the trial. |
| Outcomes | Outcomes were assessed in all patients. Patients were followed for one day. Main outcome was # of spontaneously reported side effects. |
| Notes | The no-choice treatment was more effective than the same treatment as placebo for hypnotic activity, results only presented as p value. |

**Davis 1985**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. We do not know why the non-RCT patients were not in the RCT, but their details were recorded in a population based cancer registry. Patients with resected non-small cell lung cancer. Losses to follow up unknown. |
| Data | Characteristics of non-RCT patients compared to RCT patients who received the same treatment not presented but adjusted for in the analysis. |
| Comparisons | Several RCT arms, the control arm patients were compared with similarly treated eligible non-RCT patients. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 1, 2 and 3 years. Main outcome was mortality. |
| Notes | ? |

**Edsmyr 1978**

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. It is unclear why the non-RCT patients were not in the RCT. Diagnosis of prostatic carcinoma and skeletal metastases. No losses to follow up. |
| Data | Some characteristics of non-RCT patients presented next to RCT patients who received the same treatment. RCT patients were on average 68 (55 to 77) years. Ages of the non-RCT patients were not presented. |
| Comparisons | Two RCT arms, the control arm patients were compared with similarly treated eligible non-RCT patients. The experimental arm patients were treated with estramusterine. The control patients and the non-RCT patients were treated with 2.6-cis. |
| Outcomes | Clinical outcomes were assessed in all patients after 1, 2, and 3 months. Main outcome in this study was no improvement in condition after 3 months. |
| Notes | No statistically significant difference was shown between the two RCT treatments. |

**Ekstein 2002a**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they refused. Patients with multivessel coronary artery disease eligible for stenting |

**Ekstein 2002a** *(Continued)*

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| | or bypass surgery based on agreement of cardiologist and surgeon. Unclear if there was any losses to follow up in the RCT group. Three people were lost to follow up in the non-RCT group. |
| Data | Characteristics of the non-RCT patients were presented and compared to RCT patients who received the same treatment. RCT stent patients were 61 (10) years, 462 men, 138 women. Non-RCT stent patietns were 62 (9) years, 40 men and 10 women. |
| Comparisons | Two RCT arms, both arms were compared with eligible non-RCT patients who received similar treatment. The experimental treatment was stent implantation by coronary angioplasty. The control treatment was bypass surgery. |
| Outcomes | Clinical outcomes were measured in all patients. Patients were followed up for 6 months. Main outcome was mortality. |
| Notes | The two RCT treatments were similarly effective. |

**Ekstein 2002b**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they refused. Patients with multivessel coronary artery disease eligible for stenting or bypass surgery based on agreement of cardiologist and surgeon. Unclear if there was any losses to follow up in the RCT group. Two people were lost to follow up in the non-RCT group. |
| Data | Characteristics of the non-RCT patients were presented and compared to RCT patients who received the same treatment. RCT bypass patients were 61 (9) years, 460 men, 145 women. Non-RCT bypass patients were 62 (9) years, 37 men and 9 women. |
| Comparisons | Two RCT arms, both arms were compared with eligible non-RCT patients who received similar treatment. The experimental treatment was stent implantation by coronary angioplasty. The control treatment was bypass surgery. |
| Outcomes | Clinical outcomes were measured in all patients. Patients were followed up for 6 months. Main outcome was mortality. |
| Notes | The two RCT treatments were similarly effective. |

**Elliott 1996**

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| Methods | Randomised population trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they refused. School children 5 to 7.9 years old. Losses to follow up were not reported. |
| Data | Characteristics of the 13463 eligible non-RCT children were not presented and not compared to the 48335 RCT children who recieved similar treatment. |
| Comparisons | Two RCT arms, the control arm children were compared with non-randomised children who did not receive any intervention either. The RCT experimental children were offered testing for diabetes |
| Outcomes | All cases of childhood diabetes were reported to the Department of Paediatrics and records were collected from them. Children were followed up for mean 7.1 years. Main outcome was getting the diagnosis of diabetes. |
| Notes | |

### Emery 2003a

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they refused because of preference for treatment. Couples in in-vitro fertelisation (IVF) program, 1st IVF for the 1st child. |
| Data | Characteristics of the eligible non-RCT patients were not presented or compared to the RCT patients receiving similar treatment. 100 RCT participants received pre-IVF counselling focusing on the narrative capacities of couples, eight were lost to follow up. 24 eligible non-RCT couples received similar treatment, six were lost to follow up. |
| Comparisons | Two RCT arms, both arms were compared with eligible non-randomised couples who received similar treatment. Experimental: pre-IVF counselling focusing on the narrative capacities of couples. Control: no counselling. |
| Outcomes | Outcomes were assessed in all couples. Couples were followed up for 6 weeks. Main outcome was State Trait Anxiety Inventory. |
| Notes | The two RCT arms were not significantly different. |

### Emery 2003b

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they refused because of preference for treatment. Couples in in-vitro fertelisation (IVF) program, 1st IVF for the 1st child. Three RCT control couples were lost to follow up, two non-RCT couples were lost to follow up. |
| Data | Characteristics of the eligible non-RCT patients were not presented or compared to the RCT patients receiving similar treatment. 100 RCT control participants did not receive counselling. 58 eligible non-RCT couples received similar treatment. |
| Comparisons | Two RCT arms, both arms were compared with eligible non-randomised couples who received similar treatment. Experimental: pre-IVF counselling focusing on the narrative capacities of couples. Control: no counselling. |
| Outcomes | Outcomes were assessed in all couples. Couples were followed up for 6 weeks. Main outcome was State Trait Anxiety Inventory. |
| Notes | The two RCT arms were not significantly different. |

### Feit 2000a

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they refused randomisation, but agreed to follow up in a registry. Patients with multivessel coronary artery disease. Losses to follow up unknown. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT percutaneous transluminal coronary angioplasty patients were mean 62 years, 668 men and 247 women. Non-RCT percutaneous transluminal coronary angioplasty patients were mean 61 years, 880 men and 309 women. |

**Feit 2000a** *(Continued)*

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| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients in a registry. The experimental RCT arm patients underwent percutaneous transluminal coronary angioplasty (PTCA). The control RCT patients underwent coronary artery bypass graft surgery (CABG). |
| Outcomes | Clinical outcomes were assessed in all patients, they were followed up for 7 years. Main outcome in this study was mortality. |
| Notes | The experimental treatment resulted in significantly higher mortality than the control treatment. |

**Feit 2000b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they refused randomisation, but agreed to follow up in a registry. Patients with multivessel coronary artery disease. Losses to follow up unknown. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT coronary artery bypass graft surgery patients were mean 61 years, 676 men and 238 women. Non-RCT coronary artery bypass graft surgery patients were mean 63 years, 462 men and 163 women. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients in a registry. The experimental RCT arm patients underwent percutaneous transluminal coronary angioplasty (PTCA). The control RCT patients underwent coronary artery bypass graft surgery (CABG). |
| Outcomes | Clinical outcomes were assessed in all patients, they were followed up for 7 years. Main outcome in this study was mortality. |
| Notes | The experimental treatment resulted in significantly higher mortality than the control treatment. |

**Forbes 2000**

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| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the trial because they refused randomisation. Patients undergoing outpatient colonoscopy. No losses to follow up. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT patients given intravenous were on average 49 (25 to 75) years, 29 male and 17 female. Non-RCT patients given intravenous were on average 52 (18 to 82) years, 29 male and 59 female. |
| Comparisons | Two RCT arms, the control group patients were compared with the non-randomised patients who received similar treatment. Experimental: self-administered inhaled nitrous oxide (Entonox: 50% nitrous oxide, 50% oxygen). Control: intravenous sedation/analgesia (Midazolam and Meperidine). |
| Outcomes | Outcomes were assessed in all patients. The volunteers were followed for a minimum of 30 minutes after colonoscopy. Main outcome was # of adverse events. |
| Notes | The experimental treatment was less effective than control. |

**Forssell 1989**

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|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the trial because they refused randomization (4 patients) and missed randomization (1 patient). Patients undergoing carotid endarterectomy. No losses to follow up. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT general anaesthetic patients were on average 63 (40 to 77) years, 35 male and 20 female. Non-RCT general anaesthetic patients were on average 65 (39 to 75) years, 10 male and 4 female. |
| Comparisons | Two RCT arms, the control arm was compared with the non-randomised patients who received similar treatment. Experimental: local anaesthetic. Control: general anaesthetic. |
| Outcomes | Outcomes were assessed in all patients. Patients were followed for the duration of hospital stay. Main outcome was perioperative neurological deficit. |
| Notes | The two RCT treatments were not statistically different. |

**Helsing 1998a**

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| Methods | Randomised controlled multi-centre trial with some of the centers having problems recruiting patients to the trial, these centers treated patients according to patient choice. Patients with histologically or cytologically proven non-small cell lung cancer, stage IIIB or IV. No losses to follow up. |
| Data | Characteristics of non-RCT patients compared to RCT patients who received the same treatment. Chemotherapy RCT patients were on average 61 (36 to 72) years, 12 male and 10 female. Chemotherapy non-RCT patients were on average 64 (37 to 78) years, 55 male and 42 female. |
| Comparisons | Two RCT arms, both of them were compared with similarly treated eligible non-RCT patients. Experimental: Chemotherapy with carboplatin and etoposide. Control: Best supportive care. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 1 year. Main outcome was mortality. |
| Notes | The experimental treatment was more effective than control. |

**Helsing 1998b**

| | |
|---|---|
| Methods | Randomised controlled multi-centre trial with some of the centers having problems recruiting patients to the trial, these centers treated patients according to patient choice. Patients with histologically or cytologically proven non-small cell lung cancer, stage IIIB or IV. No losses to follow up. |
| Data | Characteristics of non-RCT patients compared to RCT patients who received the same treatment. Basic supportive care RCT patients were on average 65 (44 to 78) years, 18 male and 8 female. Basic supportive care non- RCT patients were on average 72 (66 to 78) years, 3 male and 2 female. |
| Comparisons | Two RCT arms, both of them were compared with similarly treated eligible non-RCT patients. Experimental: Chemotherapy with carboplatin and etoposide. Control: Best supportive care. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 1 year. Main outcome was mortality. |
| Notes | The experimental treatment was more effective than control. |

### Henshaw 1993a

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|---|---|
| Methods | Randomised trial with concurrent eligible patients in a preference trial outside of the RCT. The non-RCT patients were not in the RCT because they refused randomization because of preference for treatment. Women undergoing legal induced abortion at less than nine weeks gestation. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT medical induced patients were mean 25 (6) years. Preference medical induced patients were mean 24 (6) years. |
| Comparisons | Two RCT arms, patients in both arms were compared with similarly treated eligible preference patients. The experimental arm patients had a medical abortion with mifepristone (RU 486) and gemeprost. The control patients had surgical vacuum aspiration. |
| Outcomes | Clinical outcomes were assessed in all women, they were followed up for a mean of 16 days. Main outcome in this study was acceptability of procedure measured by recording the number of women who would not undergo same treatment in future. |
| Notes | The two RCT treatments were not statistically different. |

### Henshaw 1993b

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients in a preference trial outside of the RCT. The non-RCT patients were not in the RCT because they refused randomization because of preference for treatment. Women undergoing legal induced abortion at less than nine weeks gestation. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT vacuum aspiration patients were mean 25 (6) years. Preference vacuum aspiration patients were mean 25 (6) years. |
| Comparisons | Two RCT arms, patients in both arms were compared with similarly treated eligible preference patients. The experimental arm patients had a medical abortion with mifepristone (RU 486) and gemeprost. The control patients had surgical vacuum aspiration. |
| Outcomes | Clinical outcomes were assessed in all women, they were followed up for a mean of 16 days. Main outcome in this study was acceptability of procedure measured by recording the number of women who would not undergo same treatment in future. |
| Notes | The two RCT treatments were not statistically different. |

### Heuss 2004

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they refused because of preference for treatment. Patients undergoing an elective colonoscopy as sole endoscopic procedure. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT contol group were 64 (15) years old, 20 men and 9 women. Non-RCT patients were 60 (16) years old, 20 men and 20 women. |
| Comparisons | Two RCT arms, the RCT control patients were compared with eligible non-randomised patietns who received similar treatment. Experimental: self-controlled sedation. Control: nurse-controlled sedation. |

**Heuss 2004** *(Continued)*

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| Outcomes | Clinical outcomes were measured in all patients. Patients were followed up while they were in hospital. Main outcome was tolerability. |
| Notes | The two RCT treatments were equally safe, but the control was preferred. |

**Karande 1998**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients in a preference trial outside of the RCT. The non-RCT patients were not in the RCT because they refused. Newly presenting infertile couples less than 38 years with noprior in-vitro fertelisation and clinically ok. RCT control group lost 13 of the 50 couples to follow up. Non-RCT group lost 18 of the 88 couples to follow up. |
| Data | Characteristics of participants not presented. |
| Comparisons | Two RCT arms, the control arm couples were compared with eligible non-RCT couples who received similar treatment. Experimental: in-vitro fertelisation as first choice treatment. Control: standard infertility treatment. |
| Outcomes | It is unclear for how long couples were followed up. Main outcome was pregnancies. |
| Notes | The control arm of the RCT was better than the experimental treatment. |

**Kendrick 2001a**

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| Methods | Randomised trial with concurrent eligible patients in a preference trial outside of the RCT. The non-RCT patients were not in the RCT because they refused randomization because of preference for treatment. Patients with low back pain on the day of randomisation and for at least 6 weeks prior. 15 RCT patients were lost to follow up and three non-RCT patients were lost to follow up |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT x-ray group were median 39 years old, 90 men and 120 women. Non-RCT x-ray patients were median 38 years old, 22 men and 10 women. |
| Comparisons | Two RCT arms, both arms were compared with eligible non-randomised patients who received similar treatment. Experimental: lumbar spine radiography in addition to usual care. Control: usual care. |
| Outcomes | Patients were followed up for 9 months. Main outcome was number of patients still with back pain. |
| Notes | The control treatment was significantly better then the experimental treatment. |

**Kendrick 2001b**

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| Methods | Randomised trial with concurrent eligible patients in a preference trial outside of the RCT. The non-RCT patients were not in the RCT because they refused randomization because of preference for treatment. Patients with low back pain on the day of randomisation and for at least 6 weeks prior. 12 RCT patients were lost to follow up and , two non-RCT patients were lost to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT non-x-ray group were median 39 years old, 84 men and 127 women. Non-RCT non-x-ray patients were median 39 years old, 12 men and 11 women. |

**Kendrick 2001b** *(Continued)*

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| Comparisons | Two RCT arms, both arms were compared with eligible non-randomised patients who received similar treatment. Experimental: lumbar spine radiography in addition to usual care. Control: usual care. |
| Outcomes | Patients were followed up for 9 months. Main outcome was number of patients still with back pain. |
| Notes | The control treatment was significantly better then the experimental treatment. |

**Kieler 1998**

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they refused randomization. Pregnant women attending the participating antenatal clinics. Loss to follow up unclear for RCT group, 44 (8%) women were lost to follow up in the non-RCT group. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT patients combined were mean 28 (5) years, these data not given for control group only. Non-RCT patients were mean 30 (5) years. |
| Comparisons | Two RCT arms, the control arm patients were compared with similarly treated eligible non-RCT patients. The experimental arm patients were given ultrasound screening. The control patients were not offered ultrasound screening. |
| Outcomes | Clinical outcomes were assessed in all women, they were followed up until delivery. Main outcome in this study was perinatal death. |
| Notes | The experimental treatment was more beneficial. |

**King 1997a**

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients consisted of 97 patients who refused randomizations and 353 patients whose physician did not agree, all non-RCT patients were followed in a registry. Patients with 2- or 3-vessels coronary artery disease, both sexes. Outcomes were assessed by cardiologists. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Bypass treated RCT patients were mean 61 (10) years, 53 women and 141 men. Bypass treated non-RCT patients were mean 63 (10) years, 51 women and 219 men. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Carotid bypass surgery. Percutaneous transluminal coronary angioplasty. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 3 years. Main outcome was 3 years mortality. |
| Notes | The two RCT treatments were not statistically different. |

**King 1997b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients consisted of 97 patients who refused randomizations and 353 patients whose physician did not agree, all non- |

**King 1997b** *(Continued)*

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| | RCT patients were followed in a registry. Patients with 2- or 3-vessels coronary artery disease, both sexes. Outcomes were assessed by cardiologists. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Percutaneous transluminal coronary angioplasty treated RCT patients were mean 62 (10) years, 50 women and 148 men. Percutaneous transluminal coronary angioplasty treated non- RCT patients were mean 60 (11) years, 41 women and 127 men. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Carotid bypass surgery. Percutaneous transluminal coronary angioplasty. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 3 years. Main outcome was 3 years mortality. |
| Notes | The two RCT treatments were not statistically different. |

**King 2000a**

| | |
|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were participants in a patient preference trial who refused to be randomised due to preference.The non-RCT patients were followed up similarly to those in the RCT. Psychology. Patients with depression or depression and anxiety. 27 RCT patients who were given cognitive behavioural therapy were lost to follow up and 15 non-RCT cognitive behavioural therapy treated patients were lost to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Cognitive behavioural therapy RCT patients were mean 35 (11) years, 100 women and 34 men. Cognitive behavioural therapy non-RCT patients were mean 38 (14) years, 63 women and 18 men. |
| Comparisons | Two RCT arms, both arms were compared with eligible non-RCT patients who received similar treatment. The experimental treatment was cognitive behavioural therapy. The control treatment was non-directive counselling. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 12 months. Main outcome was depression measured with Beck Depression Inventory. |
| Notes | The two RCT treatments were not statistically different. |

**King 2000b**

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| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patietns were participants in a patient preference trial who refused to be randomised due to preference.The non-RCT patients were followed up similarly to those in the RCT. Patients with depression or depression and anxiety. 24 RCT patients who were given non-directive counselling were lost to follow up and 14 non-RCT non-directive counselling treated patients were lost to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Non-directive counselling RCT patients were mean 33 (11) years, 91 women and 35 men. Non-directive counselling non-RCT patients were mean 39 (11) years, 43 women and 11 men. |
| Comparisons | Two RCT arms, both arms were compared with eligible non-RCT patients who received similar treatment. The experimental treatment was cognitive behavioural therapy. The control treatment was non-directive counselling. |

**King 2000b** *(Continued)*

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| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 12 months. Main outcome was depression measured with Beck Depression Inventory. |
| Notes | The two RCT treatments were not statistically different. |

**Lansky 1983**

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they refused randomisation. Junior high school children who are 10 % or more overweight. Unclear if there was any losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. The 25 RCT control children were 13 (1) years, 11 boys and 14 girls. The not treated non-RCT children were 13 (1) years old, 26 boys and 33 girls. |
| Comparisons | Two RCT arms, the control arm patients were compared with similarly treated eligible non-RCT patients. The experimental arm patients were given a comprehensive behaviour program. The control patients were not offered anything. |
| Outcomes | Clinical outcomes were measured in all children, who were followed up for 12 weeks. Main outcome was % overweight. |
| Notes | The experimental treatment was more effective than control. |

**Lidbrink 1995**

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| Methods | Randomised screening trial where the women not attending were classed as non-RCT and compared with the RCT control group that were not invited to screening (until after the RCT was completed). The non-RCT patients were not in the RCT because they did not turn up for screening. All cancers are registered with a central cancer registry. Diagnosis of breast cancer, age 40 to 65 years. No losses to follow up. |
| Data | Characteristics of non-RCT patients (non-attenders) presented and compared to RCT control patients. RCT control patients were mean 54 years, 19943 women. Non-RCT patients were mean 54 years, 7785 women. |
| Comparisons | The RCT control arm was compared with the women invited to the RCT who did not participate in the screening (non-RCT patients). |
| Outcomes | For both comparison groups, information was collected from a registry. Patients were followed for an average of 4 years. Main outcome was breast cancer deaths. |
| Notes | The experimental treatment was not significantly different from the control treatment. |

**Link 1991a**

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they declined randomisation, but consented to follow up. Diagnosis of high-grade osteosarcoma of an extremity with no metastases, both sexes, age < 30 years. Outcomes were assessed by oncologists. No losses to follow up. |

**Link 1991a** *(Continued)*

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| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Of the RCT adjuvant chemotherapy children, 10 were over 12 years old, 13 boys and 5 girls. Of the adjuvant chemotherapy non-RCT children, 40 were over 12 years old, 31 boys and 28 girls. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: immediate intensive adjuvant chemotherapy starting two weeks after surgery. Control: observation alone, no adjuvant chemotherapy. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for up to 6 years. Main outcomes were relapse and death. |
| Notes | The experimental treatment was significantly more beneficial than the control treatment. |

**Link 1991b**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they declined randomisation, but consented to follow up. Diagnosis of high-grade osteosarcoma of an extremity with no metastases, both sexes, age < 30 years. Outcomes were assessed by oncologists. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Of the RCT children under observation 12 were over 12 years old, 11 boys and 7 girls. Of the non- RCT observational children, 10 were over 12 years old, 12 boys and 6 girls. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: immediate intensive adjuvant chemotherapy starting two weeks after surgery. Control: observation alone, no adjuvant chemotherapy. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for up to 6 years. Main outcomes were relapse and death. |
| Notes | The experimental treatment was significantly more beneficial than the control treatment. |

**Liu 1998a**

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because of parental refusal (101), obstetrician request (35) or late arrival of the team (27). Infants born through thin meconium, after an otherwise low-risk pregnancy. Outcomes were assessed by respiratory therapists. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT infants under observation were 46 boys and 46 girls. Non- RCT observational infants were 26 boys and 36 girls. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: observation alone, no intubation. Control: intubation, which is 'routine meconium management'. |
| Outcomes | Clinical outcomes were assessed in all the infants. Infants were followed for the duration of the hospital stay. Main outcome was number of respiratory symptoms. |
| Notes | The two treatments were not statistically significantly different. |

**Liu 1998b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because of parental refusal (101), obstetrician request (35) or late arrival of the team (27). Infants born through thin meconium, after an otherwise low-risk pregnancy. Outcomes were assessed by respiratory therapists. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT intubation infants were 41 boys and 36 girls. Non-RCT intubation infants were 53 boys and 48 girls. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: observation alone, no intubation. Control: intubation, which is 'routine meconium management'. |
| Outcomes | Clinical outcomes were assessed in all the infants. Infants were followed for the duration of the hospital stay. Main outcome was number of respiratory symptoms. |
| Notes | The two treatments were not statistically significantly different. |

**MACESG 1992a**

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. We do not know why the non-RCT patients were not in the RCT, but they consented to follow up. Diagnosis of asymptomatic carotid stenosis, both sexes, age 17 to 79 years. Outcomes were assessed by neurologists and surgeons. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. 69% of the surgery RCT patients were over 65 years old, 16 women and 20 men. 63% of the surgery non-RCT patients were over 65 years old, 6 women and 26 men. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: carotid arteriography and endarterectomy, either unilateral or bilateral at the discretion of the surgeon. Control: medically treated patients were given aspirin (80 mg/day orally). All patients received treatment as indicated for other cerebrovascular risk factors. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for an average of 24 months. Main outcome was ischaemic events. |
| Notes | The experimental treatment was significantly less beneficial than the control treatment. |

**MACESG 1992b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. We do not know why the non-RCT patients were not in the RCT, but they consented to follow up. Diagnosis of asymptomatic carotid stenosis, both sexes, age 17 to 79 years. Outcomes were assessed by neurologists and surgeons. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. 71% of the medically treated RCT patients were over 65 years old, 14 women and 21 men. 64% of the medically treated non- RCT patients were over 65 years old, 25 women and 30 men. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: carotid arteriography and endarterectomy, either unilateral or bilateral at the discretion of the |

**MACESG 1992b** *(Continued)*

| | |
|---|---|
| | surgeon. Control: medically treated patients were given aspirin (80 mg/day orally). All patients received treatment as indicated for other cerebrovascular risk factors. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for an average of 24 months. Main outcome was ischaemic events. |
| Notes | The experimental treatment was significantly less beneficial than the control treatment. |

**MacLennan 1985**

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| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because of administrative reasons, there was no relaxin available or the researcher was off duty. Infertile females. No losses to follow up. |
| Data | Characteristics of the patients not presented. RCT placebo group included 45 women, the non-RCT no treatment group included 73 women. |
| Comparisons | Two RCT arms, the control arm women were compared to similarly treated eligible but non-randomised women. The RCT treatment women were treated with pig relaxin gel. The control women were given a placebo. |
| Outcomes | Clinical outcomes were measured in all women, who were followed up for 20 weeks. Main outcome was pregancies. |
| Notes | The two RCT arms were equally effective. |

**Mahon 1996**

| | |
|---|---|
| Methods | N of 1 trial with concurrent eligible patients randomized to standard practice. The non-N of 1 patients were not in the trial because they were randomized to standard practice. Patients with irreversible chronic airflow limitation. N of 1 group lost 2 (14%) patients to follow up, in standard practice 3 (25%) patients were lost to follow up. |
| Data | N of 1 patients were compared to patients randomized to be treated in standard practice. N of 1 patients were mean 68 (7) years. Standard practice patients were mean 71 (8) years. |
| Comparisons | Two RCT arms, patients were randomized to N of 1 trial or standard practice. In the N of 1 trial, patients received theophylline for 10 days and placebo for 10 days in a randomized cross over design. For standard practice patients theophylline was stopped and resumed if their dyspnoea worsened. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 6 months. Main outcome was improvement (6 month distance minus baseline distance) in six minutes walking distance (m). |
| Notes | The walking distance was not significantly different between N of 1 and standard practice. |

**Mahon 1999**

| | |
|---|---|
| Methods | N of 1 trial with concurrent eligible patients randomized to standard practice. The non-N of 1 patients were not in the trial because they were randomized to standard practice. Patients with irreversible chronic airflow limitation. N of 1 group lost 3 (9%) patients to follow up, in standard practice 4 (12%) patients were lost to follow up. |

**Mahon 1999** *(Continued)*

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|---|---|
| Data | N of 1 patients were compared to patients randomized to be treated in standard practice. N of 1 patients were mean 69 (8) years. Standard practice patients were mean 69 (7) years. |
| Comparisons | Two RCT arms, patients were randomized to N of 1 trial or standard practice. In the N of 1 trial, patients received theophylline for 10 days and placebo for 10 days in a randomized cross over design. For standard practice patients theophylline was stopped and resumed if their dyspnoea worsened. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 6 months and 1 year. Main outcome was improvement in six minutes walking distance at 6 months. |
| Notes | The walking distance was not significantly different between N of 1 and standard practice. |

**Marcinczyk 1997**

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| Methods | Retrospective review of a randomised trial with concurrent eligible patients outside of the RCT. The eligible non-RCT patients were not in the RCT because of patient refusal (75), or patients were not referred by clinicians (29). Asymptomatic patients undergoing carotic endarterectomy. Unclear, but unlikely losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients similarly treated. The 54 RCT patients treated with carotid endarterectomy were mean 66 (1) years. The 104 non-RCT patients treated with carotid endarterectomy were mean 67 (1) years. |
| Comparisons | Two RCT arms, the experimental arm patients were compared to similarly treated eligible but non-randomised patients. The experimental treatment was carotid endarterectomy. |
| Outcomes | Clinical outcomes were measured in all patients. Patients were followed up during hospital stay. Main outcome was mortality. |
| Notes | |

**Martinez-Amenos1990a**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because the patients refused. Hypertensive patients attending primary care centers. Losses to follow up unknown. |
| Data | Some characteristics of the patients presented. Individual education RCT patients were mean 60 years, 78 men and 128 women. Individual education non-RCT patients were mean 63 years, 24 men and 45 women. |
| Comparisons | Three RCT arms, two arms were compared with similarly treated eligible non-RCT patients. Experimental not compared: team education. Experimental that was compared: Individual education. Control: the group received no education. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 2 months. Main outcome was lack of blood pressure control. |
| Notes | The RCT treatments were not statistically different. |

**Martinez-Amenos1990b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because the patients refused. Hypertensive patients attending primary care centers. Losses to follow up unknown. |
| Data | Some characteristics of the patients presented. Control RCT patients were mean 61 years, 75 men and 123 women. Control non-RCT patients were mean 65 years, 26 men and 38 women. |
| Comparisons | Three RCT arms, two arms were compared with similarly treated eligible non-RCT patients. Experimental not compared: team education. Experimental that was compared: Individual education. Control: the group received no education. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 2 months. Main outcome was lack of blood pressure control. |
| Notes | The RCT treatments were not statistically different. |

**Masood 2002**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because the patients refused. Patients undergoing prostate biopsy. Unclear, but probably no losses to follow up. |
| Data | Patient characteristics not presented. The 45 patients in the RCT control group were given a mask with only air coming through. The 14 non-RCT patients were not given anything. |
| Comparisons | Two RCT arms, the RCT control arm patients were compared to eligible non-RCT patients who were given similar treatment. Experimental: entonox gas. Control: placebo. |
| Outcomes | Outcomes were assessed in all patients. Patients were followed up for 30 min after the procedure. Main outcome was pain. |
| Notes | The experimental treatment was more effective than control. |

**McCaughey 1998**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they did not consent to randomisation. School entry girls of height 2 SDs or more below the mean height for their age. Two (25%) girls were lost to follow up in the RCT control group, three (14%) girls were lost to follow up in the non-RCT observation group. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT patients were mean 6 (1) years. Non-RCT patients were mean 6 (1) years. |
| Comparisons | Two RCT arms, the control arm patients were compared with similarly treated eligible non-RCT patients. The experimental arm patients were treated with growth hormone. The control patients were not treated. |
| Outcomes | Clinical outcomes were assessed in all girls every 6 months for 6 years. Main outcome in this study was current height minus target height (cm). |
| Notes | The experimental arm of the RCT was more effective than no treatment. |

**McKay 1995a**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients refused randomization because of preference for treatment, but consented to follow up. The non-RCT patients were followed- up identically to the RCT patients. Male alcoholic veterans who sought treatment. In the RCT day care, 7 (29%) patients were lost to follow up. In the non-RCT day care, 13 (20%) patients were lost to follow up. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. RCT patients receiving day care were mean 43 (7) years. Non-RCT patients receiving day care were mean 43 (7) years. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control: Day care. Control: In patients. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 1 year. Main outcome was days of alcohol use during 30 days in the 12th month. |
| Notes | The two RCT treatments were not significantly different. |

**McKay 1995b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients refused randomization because of preference for treatment, but consented to follow up. The non-RCT patients were followed- up identically to the RCT patients. Male alcoholic veterans who sought treatment. In the RCT in patient, 3 (13%) patients were lost to follow up. In the non-RCT in patient, 3 (10%) patients were lost to follow up. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. RCT patients treated as in patients were mean 41 (9) years. Non- RCT patients treated as in patients were mean 38 (8) years. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control: Day care. Control: In patients. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 1 year. Main outcome was days of alcohol use during 30 days in the 12th month. |
| Notes | The two RCT treatments were not significantly different. |

**McKay 1998a**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT in a preference trial. The non-RCT patients were not in the RCT because they did not accept randomisation, these patients were treated according to choice. The non-RCT patients were followed- up identically to the RCT patients. Male veterans with current cocaine use disorder diagnosis who sought treatment. In the RCT day care, 2 (3%) patients were lost to follow up. In the non-RCT day care, 3 (8%) patients were lost to follow up. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. RCT patients receiving day care were mean 34 (6) years. Non-RCT patients receiving day care were mean 36 (6) years. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control: Day care. Control: In patients. |

**McKay 1998a** *(Continued)*

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|---|---|
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 1 year. Main outcome was days of cocaine use during 30 days in the 12th month. |
| Notes | The two treatments were not significantly different. |

**McKay 1998b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT in a preference trial. The non-RCT patients were not in the RCT because they did not accept randomisation, these patients were treated according to choice. The non-RCT patients were followed- up identically to the RCT patients. Male veterans with current cocaine use disorder diagnosis who sought treatment. In the RCT in patient, 6 (11%) patients were lost to follow up. In the non-RCT in patient, 1 (5%) patient was lost to follow up. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. RCT patients treated as in patients were mean 34 (6) years. Non- RCT patients treated as in patients were mean 35 (5) years. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control: Day care. Control: In patients. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 1 year. Main outcome was days of cocaine use during 30 days in the 12th month. |
| Notes | The two treatments were not significantly different. |

**Melchart 2002a**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients refused randomization because of preference for treatment, but consented to follow up. The non-RCT patients were followed- up identically to the RCT patients. Adult patients undergoing endoscopic investigation of upper GI tract. None were lost to follow up in the sedation groups. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT sedation patients were mean 73 (17) years, 7 women, 7 men. Non-RCT sedation patients were mean 67 (16) years, 33 women, 32 men. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: sedation with Midazolam during endoscopy. Control: acupuncture during endoscopy. |
| Outcomes | Clinical outcomes were assessed in all patients. Patients were followed up for 2 hours. Main outcome was patient assessment of troublesomeness. |
| Notes | The experimental arm of the RCT was more effective than no treatment. |

**Melchart 2002b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients refused randomization because of preference for treatment, but consented to follow up. The non-RCT patients were followed- up identically to the RCT patients. Adult patients undergoing endoscopic investigation of upper GI tract. Two (14%) patients were lost to follow up in the RCT sedation group, none were lost to follow up in the non-RCT sedation group. |

**Melchart 2002b** *(Continued)*

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|---|---|
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT acupuncture patients were mean 69 (17) years, 5 women, 7 men. Non-RCT acupuncture patients were mean 62 (16) years, 10 women, 11 men. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: sedation with Midazolam during endoscopy. Control: acupuncture during endoscopy. |
| Outcomes | Clinical outcomes were assessed in all patients. Patients were followed up for 2 hours. Main outcome was patient assessment of troublesomeness. |
| Notes | The experimental arm of the RCT was more effective than no treatment. |

**Moertel 1984**

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| Methods | Zelen trial where those randomized to active treatment but refused were observed, the same as the Zelen control group. Patients with resectable but poor-prognosis gastric carcinoma. Two (8%) patients were lost to follow up in the Zelen control group, no losses to follow up in the other group. |
| Data | Characteristics of Zelen patients who refused are presented and compared to Zelen control patients who received the same treatment. Zelen control patients were on average 56 (41 to 67) years, 17 men and 6 women. Patients who refused were on average 61 (55 to 66) years, 9 men and 1 women. |
| Comparisons | Two Zelen arms, the control arm patients were compared with similarly treated eligible Zelen patients who refused the active treatment. The experimental arm patients were treated with combined 5-Fluorouracil and radiation therapy as a surgical adjuvant. The control patients were not treated. |
| Outcomes | Clinical outcomes were assessed in all patients and they were followed up for 8 years. Main outcome in this study was 5 year mortality. |
| Notes | The experimental Zelen arm was favored over no treatment. |

**Mori 2006a**

| | |
|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were participants in a patient preference trial who refused to be randomised due to preference.The non-RCT patients were followed up similarly to those in the RCT. Patients undergoing endoscopy. None of the oral tube patients were lost to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Oral tube RCT patients were median 62 (22 to 88) years, 31 women and 50 men. Oral tube non-RCT patients were median 62 (22 to 90) years, 157 women and 168 men. |
| Comparisons | Two RCT arms, both arms were compared with eligible non-RCT patients who received similar treatment. The experimental treatment was use of oral tube for endoscopy. The control treatment was nasal tube. |
| Outcomes | Patients were followed up during procedure. Main outcome was satisfaction. |
| Notes | The two RCT treatments were not statistically different. |

**Mori 2006b**

| | |
|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were participants in a patient preference trial who refused to be randomised due to preference.The non-RCT patients were followed up similarly to those in the RCT. Patients undergoing endoscopy. Nine patients were lost to follow up in the RCT nasal tube group. 48 nasal tube non-RCT pateints were excluded during follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Nasal tube RCT patients were median 54 (26 to 79) years, 26 women and 51 men. Nasal tube non-RCT patients were median 57 (16 to 88) years, 179 women and 208 men. |
| Comparisons | Two RCT arms, both arms were compared with eligible non-RCT patients who received similar treatment. The experimental treatment was use of oral tube for endoscopy. The control treatment was nasal tube. |
| Outcomes | Patients were followed up during procedure. Main outcome was satisfaction. |
| Notes | The two RCT treatments were not statistically different. |

**Mosekilde 2000a**

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were participants in a preference trial who refused to be randomized due to preference. Postmenopausal women as close to menopause as possible. In the RCT hormone replacement therapy group 54 (11%) women were lost to follow up, in the hormone replacement therapy choice group 16 (7%) women were lost to follow up. |
| Data | Characteristics of choice patients presented and compared to RCT patients who received the same treatment. Hormone replacement therapy RCT patients were on average 50 (45 to 57) years. Hormone replacement therapy choice patients were on average 50 (45 to 56) years. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: hormone replacement therapy. Control: no hormone replacement therapy. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for an average of 5 years. Main outcome was forearm fractures. |
| Notes | The experimental treatment was significantly more beneficial than the control treatment. |

**Mosekilde 2000b**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were participants in a preference trial who refused to be randomized due to preference. Postmenopausal women as close to menopause as possible. In the RCT no hormone replacement therapy group 55 (11%) women were lost to follow up, in the no hormone replacement therapy choice group 89 (11%) women were lost to follow up. |
| Data | Characteristics of choice patients presented and compared to RCT patients who received the same treatment. No hormone replacement therapy RCT patients were on average 50 (45 to 58) years. No hormone replacement therapy choice patients were on average 51 (45 to 58) years. |
| Comparisons | Two RCT arms, each of them were compared with similarly treated eligible non-RCT patients. Experimental: hormone replacement therapy. Control: no hormone replacement therapy. |

**Mosekilde 2000b** *(Continued)*

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| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for an average of 5 years. Main outcome was forearm fractures. |
| Notes | The experimental treatment was significantly more beneficial than the control treatment. |

**Nagel 1998a**

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they declined randomisation, these patients were treated according to choice. The non-RCT patients were followed- up identically to the RCT patients. Pregnant women requesting early prenatal diagnosis for advanced maternal age. In the RCT early amniocentesis group, one (2%) woman was lost to follow up. In the non-RCT early amniocentesis group, 3 (4%) women were lost to follow up. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. RCT patients receiving early amniocentesis were on average 38 years. Non-RCT patients receiving early amniocentesis were on average 38 years. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control: early amniocentesis. Control: chorionic villus sampling. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 1 year. Main outcome was fetal mortality. |
| Notes | Chorionic villus sampling resulted in much lower fetal mortality than early amniocentesis. |

**Nagel 1998b**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they declined randomisation, these patients were treated according to choice. The non-RCT patients were followed- up identically to the RCT patients. Pregnant women requesting early prenatal diagnosis for advanced maternal age. In the RCT chorionic villus sampling, 10 (17%) women were lost to follow up. In the non-RCT chorionic villus sampling, 3 (12%) women were lost to follow up. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. RCT patients receiving chorionic villus sampling were on average 38 years. Non- RCT patients receiving chorionic villus sampling were on average 38 years. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control: early amniocentesis. Control: chorionic villus sampling. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 1 year. Main outcome was fetal mortality. |
| Notes | Chorionic villus sampling resulted in much lower fetal mortality than early amniocentesis. |

**Nicolaides 1994a**

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients refused randomization because of preference for one of the tests. Women who requested fetal karyotyping with singleton pregnancy at 10 to 23 weeks gestation. One (0.2%) woman in the non-RCT amniocentesis group was lost to follow up. No other losses to follow up. |

**Nicolaides 1994a** *(Continued)*

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|---|---|
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT amniocentesis patients were on average 38 (24 to 45) years. Non-RCT amniocentesis patients were on average 38 (23 to 45) years. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental arm patients were tested with the amniocentesis technique. The control patients were tested with chorionic villus sampling. |
| Outcomes | Clinical outcomes were assessed in all women, they were followed up until delivery. Main outcome in this study was spontaneous fetal death. |
| Notes | The control treatment was safer (fewer spontaneous deaths) than the experimental treatment. |

**Nicolaides 1994b**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients refused randomization because of preference for one of the tests. Women who requested fetal karyotyping with singleton pregnancy at 10 to 23 weeks gestation. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT chorionic villus sampling patients were on average 38 (22 to 46) years. Non-RCT chorionic villus sampling patients were on average 38 (22 to 46) years. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental arm patients were tested with the amniocentesis technique. The control patients were tested with chorionic villus sampling. |
| Outcomes | Clinical outcomes were assessed in all women, they were followed up until delivery. Main outcome in this study was spontaneous fetal death. |
| Notes | The control treatment was safer (fewer spontaneous deaths) than the experimental treatment. |

**Ogden 2004**

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The eligible patients treated outside of the RCT were considered training of the investigating physicians. Patients with chronic plantar fascitis who had failed to respond after at least three attempts of interventional conservative treatment. Four patients were lost to follow up in the RCT sham group, and four patients were lost to follow up in the non-RCT group. |
| Data | Characteristics of patients not presented. 148 RCT sham treatment patients were compared to 51 eligible non-randomised patients who were treated similarly. |
| Comparisons | Two RCT arms, the RCT control arm patients were compared to eligible non-RCT patients who were given similar treatment. Experimental: Electrohydraulic high-energy shock-wave treatment. Control: Sham shock-wave treatment. |
| Outcomes | Patients were followed up for 3 months. Main outcome was success of treatment. |
| Notes | The experimental treatment was more effective than control treatment |

**Paradise 1984a**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because their parent/s declined randomisation, these patients were treated according to parental choice. The non-RCT patients were followed- up identically to the RCT patients. Children severely affected with recurrent throat infection. Children were followed for 3 years. In the RCT, 9 (10%) children were lost to follow up during the first year. In the non-randomised groups, 11 (11%) children were lost to follow up during the first year. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. All children were 15 years or younger. RCT patients receiving tonsillectomy were 21 boys and 22 girls. Non-RCT patients receiving tonsillectomy were 19 boys and 33 girls. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control-T: Tonsillectomy. Control-O: Observation without surgery. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 1, 2 and 3 years. Main outcome was mean number of counting episodes per year. |
| Notes | The surgical treatment showed greater effectiveness than non-surgical treatment. |

**Paradise 1984b**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because their parent/s declined randomisation, these patients were treated according to parental choice. The non-RCT patients were followed- up identically to the RCT patients. Children severely affected with recurrent throat infection. Children were followed for 3 years. In the RCT, 9 (10%) children were lost to follow up during the first year. In the non-randomised groups, 11 (11%) children were lost to follow up during the first year. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. All children were 15 years or younger. RCT patients under observation were 19 boys and 29 girls. Non-RCT patients under observation were 29 boys and 15 girls. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control-T: Tonsillectomy. Control-O: Observation without surgery. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 1, 2 and 3 years. Main outcome was mean number of counting episodes per year. |
| Notes | The surgical treatment showed greater effectiveness than non-surgical treatment. |

**Paradise 1990a**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because their parent/s declined randomisation, these patients were treated according to parental choice. The non-RCT patients were followed- up identically to the RCT patients. Children with persistent and/or recurrent otitis media. In the RCT, 8 (8%) children were lost to follow up during the first year. In the non-randomised groups, 10 (9%) children were lost to follow up during the first year. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. RCT patients receiving adenoidectomy were mean 6 (2) years, 35 boys and 17 girls. Non-RCT patients receiving adenoidectomy were mean 6 (3) years, 29 boys and 18 girls. |

**Paradise 1990a** *(Continued)*

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|---|---|
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control-A: Adenoidectomy. Control-O: Observation without surgery. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 1, 2 and 3 years. Main outcome was weeks per year with otitis media. |
| Notes | The surgical treatment showed greater effectiveness than non-surgical treatment. |

**Paradise 1990b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because their parent/s declined randomisation, these patients were treated according to parental choice. The non-RCT patients were followed- up identically to the RCT patients. Children with persistent and/or recurrent otitis media. In the RCT, 8 (8%) children were lost to follow up during the first year. In the non-randomised groups, 10 (9%) children were lost to follow up during the first year. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. RCT patients under observation were mean 5 (2) years, 33 boys and 14 girls. Non- RCT patients under observation were mean 6 (3) years, 41 boys and 26 girls. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control-A: Adenoidectomy. Control-O: Observation without surgery. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for 1, 2 and 3 years. Main outcome was weeks per year with otitis media. |
| Notes | The surgical treatment showed greater effectiveness than non-surgical treatment. |

**Playforth 1988**

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| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the trial because they were treated by clinicians who were not involved in the RCT and hence, these patients were not invited to take part in the trial. RCT looking at wound infection rates and mortality after colorectal operations in patients undergoing elective colorectal operations. No losses to follow up. |
| Data | Characteristics of the non-RCT patients presented and compared to RCT patients who received the same treatment. RCT patients were mean 60 years, 31 males and 30 females. Non-RCT patients were mean 65 years, 36 males and 47 females. |
| Comparisons | Two RCT arms, the experimental arm patients were compared with similarly treated non-RCT patients. The experimental arm patients received a combined oral and parenteral regimen of antimicrobial prophylaxis whereas the control patients received purely parenteral antimicrobial prophylaxis. |
| Outcomes | Clinical outcomes were measured in all patients. Patients were followed for 30 days. Main outcome in this study was mortality. |
| Notes | The experimental treatment was significantly better then control. |

**Raistrick 2005a**

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|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were participants in a patient preference trial who refused to be randomised due to preference. The non-RCT patients were followed up similarly to those in the RCT. Heroin users receiving treatment at a specialist addiction service. 15 of the 107 RCT patients treated with buprenorphine were lost to follow up. 28 of the 163 eligible non-RCT patients given similar treatment were lost to follow up. |
| Data | Characteristics of non-RCT patients compared to RCT patients who received the same treatment were not presented. 107 RCT patients were treated with buprenorphine, 163 eligible non-RCT patients were given similar treatment. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental arm patients received buprenorphine. The control patients received lofexidine. |
| Outcomes | Clinical outcomes were measured in all patients. Patients were followed up for one month. Main outcome was abstinence at one month. |
| Notes | The two RCT arms were similarly effective. |

**Raistrick 2005b**

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|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were participants in a patient preference trial who refused to be randomised due to preference. The non-RCT patients were followed up similarly to those in the RCT. Heroin users receiving treatment at a specialist addiction service. 21 of the 103 RCT patients treated with lofexidine were lost to follow up. 18 of the 108 eligible non-RCT patients given similar treatment were lost to follow up. |
| Data | Characteristics of non-RCT patients compared to RCT patients who received the same treatment were not presented. 103 RCT patients were treated with lofexidine, 108 eligible non-RCT patients were given similar treatment. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental arm patients received buprenorphine. The control patients received lofexidine. |
| Outcomes | Clinical outcomes were measured in all patients. Patients were followed up for one month. Main outcome was abstinence at one month. |
| Notes | The two RCT arms were similarly effective. |

**Reeves 2004**

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|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the trial because they refused randomization. Patients diagnosed with single vessel disease of the LAD, including urgent patients. Unclear lossess to follow up. |
| Data | Characteristics of non-RCT patients compared to RCT patients who received the same treatment were not presented. 50 RCT percutaneous transluminal coronary angioplasty patients were compared to 25 non-randomised percutaneous transluminal coronary angioplasty patients. |
| Comparisons | Two RCT arms, the control arm patients were compared with similarly treated eligible non-RCT patients. The experimental arm patients received minimally invasive direct coronary artery bypass graft. The control patients received percutaneous transluminal coronary angioplasty. |

**Reeves 2004** *(Continued)*

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| Outcomes | Patients were followed up at 3 months, 1 year, and 3 years. Main outcome was composite endpoint of cardiac-related-deaths at 1 year. |
| Notes | The two RCT arms were similarly effective. |

**Rigg 2000a**

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|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the trial because the patients or their physician refused randomization, but consented to information extraction from medical records. High risk patients in major surgery. It is unclear but unlikely that there were any losses to follow up. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT epidural patients were on average 71 (38 to 90) years, 139 men and 86 women. Non-RCT epidural patients were on average 71 (38 to 90) years, 33 men and 19 women. |
| Comparisons | Two RCT arms, the control arm patients were compared with non-randomised patients who received similar treatment. Experimental: epidural block inserted preoperatively and maintained throughout and for 72 h after surgery, this in addition to general anesthetic during surgery. Control: general anesthetic during surgery and intravenous opioids. |
| Outcomes | Outcomes were assessed in all patients. Patients were followed for 30 days postoperatively. Main outcome was 30 days mortality. |
| Notes | The two RCT treatments were similarly effective. |

**Rigg 2000b**

| | |
|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the trial because the patients or their physician refused randomization, but consented to information extraction from medical records. High risk patients in major surgery. It is unclear but unlikely that there were any losses to follow up. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT control patients were on average 69 (26 to 92) years, 245 men and 177 women. Non-RCT control patients were on average 68 (30 to 93) years, 43 men and 45 women. |
| Comparisons | Two RCT arms, the control arm patients were compared with non-randomised patients who received similar treatment. Experimental: epidural block inserted preoperatively and maintained throughout and for 72 h after surgery, this in addition to general anesthetic during surgery. Control: general anesthetic during surgery and intravenous opioids. |
| Outcomes | Outcomes were assessed in all patients. Patients were followed for 30 days postoperatively. Main outcome was 30 days mortality. |
| Notes | The two RCT treatments were similarly effective. |

**Rosen 1987a**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they declined randomisation. The non-RCT patients were followed- up identically to the RCT patients. Patients undergoing oocyte retrieval via laparoscopy. No losses to follow up. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. Ages unknown. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control-N: Aneasthetic with NOx. Control-O: Anaesthetic without NOx. |
| Outcomes | Clinical outcomes were assessed in all the patients. Length of followed up unknown. Main outcome was number not pregnant. |
| Notes | The two RCT treatments were not statistically different. |

**Rosen 1987b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they declined randomisation. The non-RCT patients were followed- up identically to the RCT patients. Patients undergoing oocyte retrieval via laparoscopy. No losses to follow up. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. Ages unknown. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control-N: Anaesthetic with NOx. Control-O: Anaesthetic without NOx. |
| Outcomes | Clinical outcomes were assessed in all the patients. Length of followed up unknown. Main outcome was number not pregnant. |
| Notes | The two RCT treatments were not statistically different. |

**Rovers 2001a**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because their parent/s declined randomisation, these patients were treated according to parental choice. The non-RCT patients were followed- up identically to the RCT patients. Children with persistent bilateral otitis media with effusion for 4 to 6 months. In the RCT ventilation tube, 3 (3%) children were lost to follow up. In the non-RCT ventilation tube, 8 (22%) children were lost to follow up. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. RCT patients receiving ventilation tube were on average 18 (16 to 25) months, 55 boys and 38 girls. Non-RCT patients receiving ventilation tube were on average 19 (14 to 22) months, 21 boys and 15 girls. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control ventilation tube. Control watchful waiting. |
| Outcomes | Clinical outcomes were assessed in all the patients. Children were followed for 1 year. Main outcome was mean time with effusion. |
| Notes | ? |

**Rovers 2001b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because their parent/s declined randomisation, these patients were treated according to parental choice. The non-RCT patients were followed- up identically to the RCT patients. Children with persistent bilateral otitis media with effusion for 4 to 6 months. In the RCT watchful waiting, 8 (9%) children were lost to follow up. In the non-RCT watchful waiting, 19 (20%) children were lost to follow up. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. RCT patients under observation were on average 19 (14 to 23) months, 55 boys and 39 girls. Non- RCT patients under observation were on average 19 (15 to 26) months, 49 boys and 48 girls. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control ventilation tube. Control watchful waiting. |
| Outcomes | Clinical outcomes were assessed in all the patients. Children were followed for 1 year. Main outcome was mean time with effusion. |
| Notes | ? |

**Rørbye 2005a**

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| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were participants in a patient preference trial who refused to be randomised due to preference.The non-RCT patients were followed up similarly to those in the RCT. Pregnant women with fetus < 63 days gestational age. Nine % losses to follow up. |
| Data | Characteristics of the non-randomised patients compared to RCT patients. Women in the RCT were on average 26 (18 to 44) years, 111 women. Women in the preference trial were on average 27 (18 to 45) years, 922 women. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental arm patients received medical abortion. The control patients received surgical abortion. |
| Outcomes | Women were followed up for 2 weeks. Main outcome was satisfied or very satisfied at two weeks after abortion. |
| Notes | The control arm of the RCT gave more satisfied women compared with the experimental treatment. |

**Rørbye 2005b**

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|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were participants in a patient preference trial who refused to be randomised due to preference.The non-RCT patients were followed up similarly to those in the RCT. Pregnant women with fetus < 63 days gestational age. Nine % loss to follow up. |
| Data | Characteristics of the non-randomised patients compared to RCT patients. Women in the RCT were on average 26 (18 to 44) years, 111 women. Women in the preference trial were on average 27 (18 to 45) years, 922 women. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental arm patients received medical abortion. The control patients received surgical abortion. |
| Outcomes | Women were followed up for 2 weeks. Main outcome was satisfied or very satisfied at two weeks after abortion. |

**Rørbye 2005b** *(Continued)*

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|---|---|
| Notes | The control arm of the RCT gave more satisfied women compared with the experimental treatment. |

**Schmoor 1996a**

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|---|---|
| Methods | Two randomised controlled trials with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the trial because the patients refused randomization because of strong preference for treatment. Women with breast cancer, node-positive patients previously treated with mastectomy. Combined for trials a, b, c and d, losses to follow up were 4% in the RCT group and 12% in the non-RCT group. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT a, 2, 3 x CMF patients were on average 50 (29 to 70) years, 145 women. Non-RCT a, 2, 3 x CMF patients were on average 49 (21 to 76) years, 72 women. |
| Comparisons | Two RCT trials: Trial one including a, b, c and d with four arms, all of them compared with similarly treated non-randomised patients. Trial two including e and f with two arms, both of them compared with similarly treated non-randomised patients. |
| Outcomes | Outcomes were assessed in all patients. Patients were followed for 6 years. Main outcome was relapse + death, and mortality. |
| Notes | ? |

**Schmoor 1996b**

| | |
|---|---|
| Methods | Two randomised controlled trials with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the trial because the patients refused randomization because of strong preference for treatment. Women with breast cancer, node-positive patients previously treated with mastectomy. Combined for trials a, b, c and d, losses to follow up were 4% in the RCT group and 12% in the non-RCT group. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT b, 2, 6 x CMF patients were on average 51 (25 to 80) years, 144 women. Non-RCT b, 2, 6 x CMF patients were on average 51 (27 to 70) years, 104 women. |
| Comparisons | Two RCT trials: Trial one including a, b, c and d with four arms, all of them compared with similarly treated non-randomised patients. Trial two including e and f with two arms, both of them compared with similarly treated non-randomised patients. |
| Outcomes | Outcomes were assessed in all patients. Patients were followed for 6 years. Main outcome was relapse + death, and mortality. |
| Notes | ? |

**Schmoor 1996c**

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|---|---|
| Methods | Two randomised controlled trials with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the trial because the patients refused randomization because of strong preference for treatment. Women with breast cancer, node-positive patients previously treated with mastectomy. Combined for trials a, b, c and d, losses to follow up were 4% in the RCT group and 12% in the non-RCT group. |

**Schmoor 1996c** *(Continued)*

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| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT c, 2, 3 x CMF + tamoxifen patients were on average 58 (33 to 72) years, 93 women. Non-RCT c, 2, 3 x CMF + tamoxifen patients were on average 60 (32 to 79) years, 42 women. |
| Comparisons | Two RCT trials: Trial one including a, b, c and d with four arms, all of them compared with similarly treated non-randomised patients. Trial two including e and f with two arms, both of them compared with similarly treated non-randomised patients. |
| Outcomes | Outcomes were assessed in all patients. Patients were followed for 6 years. Main outcome was relapse + death, and mortality. |
| Notes | ? |

**Schmoor 1996d**

| | |
|---|---|
| Methods | Two randomised controlled trials with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the trial because the patients refused randomization because of strong preference for treatment. Women with breast cancer, node-positive patients previously treated with mastectomy. Combined for trials a, b, c and d, losses to follow up were 4% in the RCT group and 12% in the non-RCT group. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT d, 6 x CMF + tamoxifen patients were on average 58 (34 to 71) years, 91 women. Non-RCT d, 6 x CMF + tamoxifen patients were on average 57 (35 to 80) years, 29 women. |
| Comparisons | Two RCT trials: Trial one including a, b, c and d with four arms, all of them compared with similarly treated non-randomised patients. Trial two including e and f with two arms, both of them compared with similarly treated non-randomised patients. |
| Outcomes | Outcomes were assessed in all patients. Patients were followed for 6 years. Main outcome was relapse + death, and mortality. |
| Notes | ? |

**Schmoor 1996e**

| | |
|---|---|
| Methods | Two randomised controlled trials with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the trial because the patients refused randomization because of strong preference for treatment. Women with breast cancer, node-positive patients previously treated with mastectomy. Combined for group e and f, losses to follow up were 4% in both the RCT and the non-RCT groups. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT e, 6 x CMF patients were on average 55 (28 to 71) years, 101 women. Non-RCT e, 6 x CMF patients were on average 53 (27 to 78) years, 88 women. |
| Comparisons | Two RCT trials: Trial one including a, b, c and d with four arms, all of them compared with similarly treated non-randomised patients. Trial two including e and f with two arms, both of them compared with similarly treated non-randomised patients. |
| Outcomes | Outcomes were assessed in all patients. Patients were followed for 6 years. Main outcome was relapse + death, and mortality. |
| Notes | ? |

**Schmoor 1996f**

| | |
|---|---|
| Methods | Two randomised controlled trials with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the trial because the patients refused randomization because of strong preference for treatment. Women with breast cancer, node-positive patients previously treated with mastectomy. Combined for group e and f, losses to follow up were 4% in both the RCT and the non-RCT groups. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT f, 6 x CMF + radiotherapy patients were on average 55 (29 to 69) years, 98 women. Non-RCT f, 6 x CMF + radiotherapy patients were on average 51 (33 to 75) years, 41 women. |
| Comparisons | Two RCT trials: Trial one including a, b, c and d with four arms, all of them compared with similarly treated non-randomised patients. Trial two including e and f with two arms, both of them compared with similarly treated non-randomised patients. |
| Outcomes | Outcomes were assessed in all patients. Patients were followed for 6 years. Main outcome was relapse + death, and mortality. |
| Notes | ? |

**Strandberg 1995**

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|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they refused randomization. Helsinki businessmen. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT control patients were on average 48 (40 to 55) years. Non-RCT patients were on average 47 (40 to 55) years. |
| Comparisons | Two RCT arms, the control arm patients were compared with similarly treated eligible non-RCT patients. The experimental arm patients took part in a cardiovascular primary prevention. The control patients were given health checks without intervention. |
| Outcomes | The population was followed for 18 years. The main outcome in this study was mortality. |
| Notes | The experimental treatment was more beneficial. |

**Sullivan 1982a**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. We do not know why the non-RCT patients were not in the RCT. Children of age <18 years with proven Hodgkin's disease of pathologic I or II, no prior radiotherapy or chemotherapy. 15 (29%) children were lost to follow up in the RCT involved-field radiotherapy group, in the non-RCT involved-field radiotherapy group 8 (50%) children were lost to follow up. |
| Data | Characteristics of patients were not presented. |
| Comparisons | Three RCT arms, each arm were compared with similarly treated eligible non-RCT patients. Involved-field radiotherapy, involved-field radiotherapy + chemotherapy, extended-field radiotherapy. |
| Outcomes | Clinical outcomes were assessed in all the children. Patients were followed for 208 weeks. Main outcomes were death and relapse. |

**Sullivan 1982a** *(Continued)*

| | |
|---|---|
| Notes | Significant differences were found between the RCT treatments. |

**Sullivan 1982b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. We do not know why the non-RCT patients were not in the RCT. Children of age <18 years with proven Hodgkin's disease of pathologic I or II, no prior radiotherapy or chemotherapy. 43(39%) children were lost to follow up in the RCT involved-field radiotherapy + chemotherapy group, in the non-RCT involved-field radiotherapy + chemotherapy group 3 (38%) children were lost to follow up. |
| Data | Characteristics of patients were not presented. |
| Comparisons | Three RCT arms, each arm were compared with similarly treated eligible non-RCT patients. Involved-field radiotherapy, involved-field radiotherapy + chemotherapy, extended-field radiotherapy. |
| Outcomes | Clinical outcomes were assessed in all the children. Patients were followed for 208 weeks. Main outcomes were death and relapse. |
| Notes | Significant differences were found between the RCT treatments. |

**Sullivan 1982c**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. We do not know why the non-RCT patients were not in the RCT. Children of age <18 years with proven Hodgkin's disease of pathologic I or II, no prior radiotherapy or chemotherapy. 21 (34%) children were lost to follow up in the RCT extended-field radiotherapy group, in the non-RCTextended-field radiotherapy group 10 (45%) children were lost to follow up. |
| Data | Characteristics of patients were not presented. |
| Comparisons | Three RCT arms, each arm were compared with similarly treated eligible non-RCT patients. Involved-field radiotherapy, involved-field radiotherapy + chemotherapy, extended-field radiotherapy. |
| Outcomes | Clinical outcomes were assessed in all the children. Patients were followed for 208 weeks. Main outcomes were death and relapse. |
| Notes | Significant differences were found between the RCT treatments. |

**Urban 1999**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because of physician preference for an early invasive approach. Patients who developed clinical cardiogenic shock within 48 hours of the onset of acute myocardial infarction. Unclear if losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT patients were mean 66 (10) years, 23 men and 9 women. Non-RCT patients were mean 60 (16) years, 15 men and 9 women. |

**Urban 1999** *(Continued)*

| | |
|---|---|
| Comparisons | Two RCT arms, the experimental arm patients were compared with similarly treated eligible non-RCT patients. The experimental arm patients underwent emergency angiography followed immediately by revascularization when indicated. The control patients received initial medical management. |
| Outcomes | Clinical outcomes were assessed in all patients, patients were followed for 1 month. Main outcome in this study was death. |
| Notes | No difference was shown between the two RCT treatments. |

**Villamaria 1997a**

| | |
|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the trial. The non-RCT patients were not in the trial because they refused randomisation. Cardiac surgery patients. RCT forced-air warming group lost one (3%) patient to follow up. Non-RCT forced-air warming lost two (25%) patients to follow up. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT forced air warming patients were on average 68 (51 to 89) years, 23 men and 7 women. Non-RCT forced air warming patients were on average 63 (54 to 81) years, 6 men and 2 women. |
| Comparisons | Two RCT arms, both arms were compared with non-randomised patients who received similar treatment. Experimental: forced air warming. Control: usual care with warm blankets and overhead heat lamps. |
| Outcomes | Outcomes were assessed in all patients. Patients were followed for 3 years. Main outcome was postoperative temperature at 6 hours. |
| Notes | The two experimental treatments were not significantly different. |

**Villamaria 1997b**

| | |
|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the trial. The non-RCT patients were not in the trial because they refused randomisation. Cardiac surgery patients. RCT usual care lost two (7%) patients to follow up, non-RCT usual care lost three (19%) patients to follow up. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT usual care patients were on average 69 (51 to 82) years, 23 men and 7 women. Non-RCT usual care patients were on average 62 (46 to 81) years, 13 men and 2 women. |
| Comparisons | Two RCT arms, both arms were compared with non-randomised patients who received similar treatment. Experimental: forced air warming. Control: usual care with warm blankets and overhead heat lamps. |
| Outcomes | Outcomes were assessed in all patients. Patients were followed for 3 years. Main outcome was postoperative temperature at 6 hours. |
| Notes | The two experimental treatments were not significantly different. |

**Waard 2002a**

| | |
|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were participants in a patient preference trial who refused to be randomised due to preference. The non-RCT patients were followed up similarly to those in the RCT. Women with early fetal demise or incomplete miscarriage at a gestational age of < 16 completed weeks. RCT group lost 31 women to follow up. Non-RCT group lost 85 women to follow up. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT expected management patients were mean 32 years, 64 women. Non-RCT preference expectant management women were on average 33 years, 126 women. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental arm patients received expectant management. The control patients received surgery. |
| Outcomes | Women were followed up for 6 weeks and 12 weeks. Main outcome was success at 6 weeks. |
| Notes | The two experimental treatments were not significantly different. |

**Waard 2002aa**

| | |
|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. The non-RCT patients were participants in a patient preference trial who refused to be randomised due to preference. The non-RCT patients were followed up similarly to those in the RCT. Women with early fetal demise or incomplete miscarriage at a gestational age of < 16 completed weeks. RCT group lost 26 women to follow up. Non-RCT group lost 124 women to follow up. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT surgery patients were mean 33 years, 58 women. Non-RCT preference surgery women were on average 32 years, 179 women. |
| Comparisons | Two RCT arms, both arms were compared with similarly treated eligible non-RCT patients. The experimental arm patients received expectant management. The control patients received surgery. |
| Outcomes | Women were followed up for 6 weeks and 12 weeks. Main outcome was success at 6 weeks. |
| Notes | The two experimental treatments were not significantly different. |

**Walker 1986**

| | |
|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the RCT. It is unclear why the eligible non-RCT patients did not participate in the trial. Patients undergoing cardio-pulmonary bypass procedures. No losses to follow up. |
| Data | Characteristics of non-RCT patients compared with RCT patients who received similar treatment are not presented. 50 patients were randomised the control group. 37 eligible non-RCT patients received similar treatment. |
| Comparisons | Two RCT arms, the RCT control patients were compared to similarly treated eligible non-RCT patients.There was 50 RCT patients and 37 non-RCT patients. Experimental adjuvant use of preincisional presternal antibiotic infiltration. Control: usual care. |
| Outcomes | Clinical outcomes were assessed in all patients. Follow up was until at least 24 hours post operation. Main outcome was wound colonisation. |

**Walker 1986** *(Continued)*

| | |
|---|---|
| Notes | The experimental treatment was more effective than the control treatment. |

**Wallage 2003**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because the patients refused because of preference for treatment. Women undergoing endometrial ablation. Six randomized women were lost to follow up and four non-randomized women were lost to follow up |
| Data | Characteristics of non-RCT patients compared with RCT patients who received similar treatment are not presented. 97 women were randomised to local anaesthesia. 32 non-RCT women received local anaesthesia due to preference. |
| Comparisons | Two RCT arms, both arms compared to eligible women similarly treated outside of the trial. Complete results only presented for the experimental group. Experimental treatment: Local anaesthesia during endometrial ablation. Control: General anaesthesia during endometrial ablation. |
| Outcomes | Clinical outcomes were assessed in all women. Follow up was until discharge from hospital. Main outcome was acceptability measured as how many would have the procedure done again. |
| Notes | The two experimental treatments were not similarly effective. |

**Wetzner 1979**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. We do not know why the non-RCT patients were not in the RCT. Patients who would benefit from view of the gallbladder. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. Cerultide RCT patients were between 29 and 83 years, 1 woman and 16 men. Ceruletide non-RCT patients were between 19 and 71 years, 21 women and 43 men. The measuring times were different for the RCT patients and the eligible non-RCT patients. |
| Comparisons | Two RCT arms, the experimental treatment was compared with similarly treated eligible non-RCT patients. Experimental: ceruletide-assisted cholecystography. Control: fatty meal- assisted cholecystography. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients in the RCT were followed for 40 min, patients in the non-RCT group were followed for 30 min. Main outcome was lack of reduction in gallbladder area at 20 min. |
| Notes | The experimental treatment was more effective than control. |

**Wikdahl 1992**

| | |
|---|---|
| Methods | Randomised controlled trial with concurrent eligible patients outside of the trial. The non-RCT patients were not in the trial because of patient refusal of randomisation because of strong preference for treatment. No losses to follow up. |

**Wikdahl 1992** *(Continued)*

| | |
|---|---|
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT integrated disconnect system patients were mean 57 years, 12 men and 6 women. Non-RCT integrated disconnect system patients were mean 44 years, 7 men. |
| Comparisons | Two RCT arms, the experimental treatment was compared with non-randomised patients who received similar treatment. Experimental: integrated disconnect system, Control: UV-box system. |
| Outcomes | Outcomes were assessed in all patients. RCT patients were followed for mean 11 months, non-RCT patients were followed for mean 8 months. Main outcome was peritonitis. |
| Notes | The experimental RCT treatment was more effective than control. |

**Williford 1993**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because the patients refused. Malnourished surgical patients who required nonemergency laparotomy or noncardiac thoractomy. Losses to follow up unknown. |
| Data | Characteristics of the RCT patients presented and compared to the eligible non-randomised patients. RCT patients were mean 63 (10) years, 391 men and 4 women. Non-RCT patients were mean 62 (10) years, 196 men and 3 women. |
| Comparisons | Two RCT arms, both arms were combined and compared with eligible non-RCT patients with analysis adjusted for treatment. Experimental: Total parenteral nutrition. Control: this group received no perioperative total parenteral nutrition. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients in were followed for 90 days. Main outcome was number of complications at 90 days. |
| Notes | The two RCT treatments showed similar effectiveness. |

**Witt 2006a**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because the patients refused . Patients with pain due to osteoarthritis of the knee or the hip. RCT group lost 57 patients to follow up. Non-RCT group lost 285 patients to follow up. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT acupuncture patients were mean 61 (10) years, 183 women, 139 men. Non-RCT acupuncture patients were on mean 62 (11) years, 1788 women, 1133 men. |
| Comparisons | Two RCT arms, the RCT experimental arm patients were compared to similarly treated eligible non-RCT patients. Experimental treatment: Acupuncture. Control: delayed start of acupuncture. |
| Outcomes | Patient were followed up for three months. Main outcome was WOMAC severity score. |
| Notes | The experimental treatment was more effective than the control treatment. |

**Witt 2006b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because the patients refused. Patients with chronic neck pain. RCT group lost 262 patients to follow up. Non-RCT group lost 1150 patients to follow up. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT acupuncture patients were mean 50 (13) years, 1225 women, 528 men. Non-RCT acupunture patients were mean 51 (13) years, 7006 women, 3389 men. |
| Comparisons | Two RCT arms, the RCT experimental arm patients were compared to similarly treated eligible non-RCT patients. Experimental treatment: Acupuncture. Control: delayed start of acupuncture. |
| Outcomes | Patient were followed up for three months. Main outcome was % reduction in neck pain. |
| Notes | The experimental treatment was more effective than the control treatment. |

**Witt 2006c**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because the patients refused. Patients with chronic low back pain. RCT group lost 88 patients to follow up. Non-RCT group lost 770 patients to follow up. |
| Data | Characteristics of the non-randomised patients compared to RCT patients who received the same treatment. RCT acupuncture patients were mean 53 (14) years, 847 women, 614 men. Non-RCT acupuncture patients were mean 53 (14) years, 5061 women, 3476 men. |
| Comparisons | Two RCT arms, the RCT experimental arm patients were compared to similarly treated eligible non-RCT patients. Experimental treatment: Acupuncture. Control: delayed start of acupuncture. |
| Outcomes | Patient were followed up for three months. Main outcome was % less pain. |
| Notes | The experimental treatment was more effective than the control treatment. |

**Yamamoto 1992a**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because some endoscopists were uncomfortable randomizing as they had considerable experience with one of the dilators. The non-RCT patients were followed-up identically to the RCT patients. Patients with newly diagnosed peptic strictures, both sexes, age 23 to 91 years. Outcomes were assessed by endoscopists at hospital. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT patients with Eder-Puestow dilator were mean 65 (18) years, 4 women and 12 men. Non-RCT patients with Eder-Puestow dilator were mean 65 (12) years, 23 women and 35 men. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control-EP: Eder-Puestow dilator. Control-b: balloon dilator. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for as long as 4 years. Main outcome was recurrence of dysphagia. |
| Notes | The two RCT treatments were not significantly different. |

**Yamamoto 1992b**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because some endoscopists were uncomfortable randomizing as they had considerable experience with one of the dilators. The non-RCT patients were followed-up identically to the RCT patients. Patients with newly diagnosed peptic strictures, both sexes, age 23 to 91 years. Outcomes were assessed by endoscopists at hospital. No losses to follow up. |
| Data | Characteristics of non-RCT patients presented and compared to RCT patients who received the same treatment. RCT patients with balloon dilator were mean 69 (11) years, 7 women and 8 men. Non- RCT patients with balloon dilator were mean 67 (12) years, 15 women and 19 men. |
| Comparisons | Two RCT arms, each in common use, and each of them were compared with similarly treated eligible non-RCT patients. Control-EP: Eder-Puestow dilator. Control-b: balloon dilator. |
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for as long as 4 years. Main outcome was recurrence of dysphagia. |
| Notes | The two RCT treatments were not significantly different. |

**Yamani 2005**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the trial because they refused participation. Cardiac transplant patients with hypogammaglobulinemia. No losses to follow up. |
| Data | Characteristics of non-RCT patiens presented and compared to RCT patients who received the same treatment. The 10 RCT control patients were mean 55 (6) years, eight men and two women.The 33 non-randomised patients were mean 54 (10) years, 27 men and six women. |
| Comparisons | Two RCT arms, the control arm patients were compared with similarly treated eligible non-RCT patients. The experiemental treatment was 150 mg/kg CytoGam intravenously over 4 hours. The control patients were monitored. |
| Outcomes | Clinical outcomes were assessed in all the patients, patients were followed for six months. Main outcome was cytomegalovirus infection. |
| Notes | The two RCT treatments were not significantly different. |

**Yersin 1996**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because they did not accept randomisation, these patients were treated according to choice. The non-RCT patients were followed- up identically to the RCT patients. Patients in a general medical ward with alcohol problems. In the RCT abstinence counseling group 9 (47%) patients were lost to follow up. In the non-RCT abstinence counseling group, 6 (38%) patients were lost to follow up. |
| Data | Non-RCT patients were compared to RCT patients who received the same treatment. RCT patients receiving abstinence counseling were on average 57 (33 to 65) years, 16 men and 3 women. Non-RCT patients receiving abstinence counseling were on average 53 (40 to 68) years, 12 men and 4 women. |
| Comparisons | Two RCT arms individualized referral (experimental) and simple abstinence counseling (control) which was compared with similarly treated eligible non-RCT patients. |

**Yersin 1996** *(Continued)*

| | |
|---|---|
| Outcomes | Clinical outcomes were assessed in all the patients. Patients were followed for approximately 1 year. Main outcome was lack of abstinence. |
| Notes | The experimental treatment was more effective than control. |

**Young 1996**

| | |
|---|---|
| Methods | Randomised trial with concurrent eligible patients outside of the RCT. The non-RCT patients were not in the RCT because of parental refusal (21 children), timing (22 children) and 3 others. Infants with congenital nasolacrimal duct obstruction. No losses to follow up in the RCT group, 4 eyes lost to follow up in the non-RCT group. |
| Data | Characteristics of the patients not presented. Watchful waiting RCT patients included 16 affected eyes. Watchful waiting non-RCT patients included 37 affected eyes. |
| Comparisons | Two RCT arms, the control treatment was compared with similarly treated eligible non-RCT patients. Experimental: probing. Control: Watchful waiting. |
| Outcomes | Clinical outcomes were assessed in all the infants. Patients were followed 15 and 24 months. Main outcome was problem unresolved at 1 year. |
| Notes | The experimental treatment was more effective than control at 1 year. |

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Akaza 1995 | All patients were trial participants |
| Albert 1997 | Different inclusion criteria across trials and for the non-participating group of patients |
| Amadori 1993 | Required additional information not available |
| Ashok 2002 | Patients included in Ashok 2005 |
| Azurin 1971 | Not same treatment in RCT and outside of RCT |
| Bahit 2003 | Not same treatment in RCT and outside of RCT |
| Banach 2000 | Required additional information not available |
| Bangstad 1992 | Not same treatment in RCT and outside of RCT |
| Barnett 1992 | Required additional information not available |
| Bartalena 1983 | RCT and non-RCT patients not treated concurrently |
| Behar 1975 | Required additional information not available |
| Bertelsen 1991 | Required additional information not available |
| Bertelsen 1994 | Required additional information not available |

| Study | Reason for exclusion |
|---|---|
| Bifano 1994 | Required additional information not available |
| Birch 1992 | Not same treatment or patient diagnosis in RCT and outside of RCT |
| Black 1993 | Required additional information not available |
| Boros 1985 | Non-participants were not evaluated according to RCT inclusion criteria |
| Bouchet 1996 | Not same treatment inside RCT and outside RCT |
| Brower 2000 | Required additional information not available |
| Brown 1981 | Required additional information not available |
| Brown 1999 | Required additional information not available |
| Browne 1990 | Required additional information not available |
| Canfield 1977 | Required additional information not available |
| Caplan 1984 | Required additional information not available |
| Carroll 1999 | RCT eligibility criteria not applied to non-research patients, no information about similarity of treatment |
| Chadwick 1991 | Non-RCT patients were not followed up |
| Chaitman 1986 | Patients already included in CASS 1984 |
| Chaitman 1990 | Patients already included in CASS 1984 |
| Chen 2000 | Required additional information not available |
| Clemens 1992 | Not same treatment in RCT and outside of RCT |
| Cohen 1983 | Non-participants were a different patient population to the RCT included patients |
| Cooper 1999 | RCT and non-RCT patients were not treated concurrently |
| Cottin 1999 | Information regarding eligibility criteria and treatment not available for non-participants |
| Cunningham 1989 | Required additional information not available |
| Cutlip 2001 | Required additional information not available |
| Dahlberg 1999 | Required additional information not available |
| Davis 1988 | Patients already included in CASS 1984 |
| Decensi 2003 | Not same treatment in RCT and outside of RCT |
| Detre 1999 | Patients already included in Feit 2000 |
| Deuschle 2004 | Treatments were not concurrent |

| Study | Reason for exclusion |
|---|---|
| Devine 1973 | Required additional information not available |
| Diehl 1995 | Required additional information not available |
| Exner 1999 | Required additional information not available |
| Fossa 2002 | Required information not presented |
| Franz 1995 | Not same treatment in RCT and outside of RCT |
| Frazee 1996 | Required additional information not available |
| Frucht-Pery 2006 | Not same treatment in RCT and outside of RCT |
| GBSG 1995 | Patients already included in Schmoor 1996 |
| Gonwa 2002 | Patients outside of trial were not eligible |
| Gossop 1986 | Required additional information not available |
| Groff 2004 | Different patients inside and outside of trial |
| Haberkern 1997 | Required additional information not available |
| Hauth 1983 | Not same treatment in RCT and outside of RCT |
| Hertegard 2002 | Patients outside of trial were not eligible |
| Hjorth 1992 | Required additional information not available |
| Hoh 1998 | Not same treatment in RCT and outside of RCT |
| Holubkov 1999 | Patients already included in Feit 2000 |
| Jack 1990 | Required additional information not available |
| Jensen 1996 | The same patients both inside RCT and outside RCT |
| Jeremic 1999 | Patients outside of trial were not eligible |
| Jha 1996 | No information about eligibility criteria and treatment for non-participants |
| Julien 2000 | Patients already included in Bijker 2000 |
| Kahan 2000 | Data not available because industry sponsored |
| Kamal 2006 | Not same treatment in RCT and outside of RCT |
| Karande 1997 | Patients included in Karande 1998 |
| Kober 1995 | Required additional information not available |
| Kober 2000 | Not same treatment in RCT and outside of RCT |
| Korvick 1992 | Required additional information not available |

| Study | Reason for exclusion |
|---|---|
| Lechner 1983 | Required additional information not available |
| Lennox 1979 | Required additional information not available |
| Libman 2000 | Not same treatment in RCT and outside of RCT |
| Licht 1997 | Not same treatment inside RCT and outside RCT |
| Link 1986 | Patients already included in Link 1991 |
| Madsen 1993 | Not same treatment inside RCT and outside RCT |
| MAGPIE 1995 | Required additional information not available |
| Marsa-Vila 1991 | RCT patients and non-RCT patients not treated concurrently |
| Mayers 2001 | Unknown if the patients outside the RCTs were eligible |
| McAfee 2006 | Treatments were not concurrent |
| McCusker 1982 | Unknown if the patients outside of RCT were eligible or received similar treatment |
| Meade 2000 | Required additional information not available |
| Meier 1985 | RCT patients and patients outside of RCT were not treated concurrently |
| Mendonca 1983 | Choice effect, not RCT effect |
| Merlino 2001 | Not same treatment inside RCT and outside RCT |
| Millat 1993 | Required additional information not available |
| Mourits 2000 | Additional information required on the patients outside of RCT not available |
| Moynihan 1998 | Required additional information not available |
| Mundy 1983 | Required additional information not available |
| Narayan 1998 | Not same treatment in RCT and outside of RCT |
| NASCET 1991 | Required additional information not available |
| Naukkarinen 1989 | Patients outside of trial were not eligible |
| Neill 1991 | Required additional information not available |
| Newman 2002 | Not same treatment in RCT and outside of RCT |
| Olschewski 1992 | Patients already included in CASS 1984 |
| Peterson 2006 | Not same treatment in RCT and outside of RCT |
| Phillips 1975 | Patients outside of trial were not eligible |
| Powles 1997 | Required additional information not available |

| Study | Reason for exclusion |
|---|---|
| Quoix 1986 | Required additional information not available |
| Ravindranath 1996 | Required additional information not available |
| Regan 2006 | All the patients agreed to be in an experiment, and the treatments were not concurrent |
| Rock 1992 | Patients outside of trial were not eligible |
| Rogers 1995 | Patients already included in Feit 2000 |
| Rokito 1996 | Additional information required not available |
| Rokke 1999 | Additional information required not available |
| Rychtarik 1998 | Not same treatment inside RCT and outside RCT |
| Schmidt 1999 | Not same treatment inside RCT and outside RCT |
| Sha 1995 | Not same treatment inside RCT and outside RCT |
| Sharp 2004 | Treatments were not concurrent |
| Singh 1995 | Required additional information not available |
| Singhal 2003 | Patients outside of trial were not eligible |
| Smith 1990 | Not same treatment inside RCT and outside RCT |
| Sterling 1997 | Treatments were not concurrent |
| Stiller 1989 | Not same treatment inside RCT and outside RCT |
| Stiller 1994 | Not same treatment inside RCT and outside RCT |
| Stiller 1999 | Not same treatment inside RCT and outside RCT |
| Stockle 1995 | Required additional information not available |
| Stone 1994 | Treatment of the non-RCT patients unknown, they were not followed up |
| Straatsma 2003 | Not same treatment in RCT and outside of RCT |
| Swartz 2001 | Not the same patient diagnosis |
| Thomas 1990 | Additional information required not available |
| Thompson 2000 | Required additional information not available |
| Tuppurainen 1998 | Not same treatment in RCT and outside of RCT |
| van Bergen 1995 | Not same treatment inside RCT and outside RCT |
| van Eys 1987 | Additional information required not available |
| Vassilopoulou-Sellin 1995 | Required additional information not available |

| Study | Reason for exclusion |
|---|---|
| Verdonck 1995 | Required additional information not available |
| Waard 2002b | Patients included in Waard 2002 |
| Ward 1992 | Required additional information not available |
| Warren 1982 | Additional information required not available |
| Weijer 1996 | Additional information required not available |
| Weijmar Schultz 1996 | Required additional information not available |
| Weisdorf 1997 | Additional information required not available |
| Welt 1981 | Not same treatment in RCT and outside of RCT |
| Westerberg 2000 | Required additional information not available |
| Whitehouse 2006 | Not same treatment in RCT and outside of RCT |
| Wilhelmsen 1976 | Required additional information not available |
| Winger 1989 | Not same treatment inside RCT and outside RCT |
| Winters 1981 | Required additional information not available |
| Woodcock 2001 | Patients outside of trial were not eligible |
| Woodhouse 1995 | Not same treatment in RCT and outside of RCT |
| Wyse 1991 | Not same treatment inside RCT and outside RCT |

## DATA AND ANALYSES

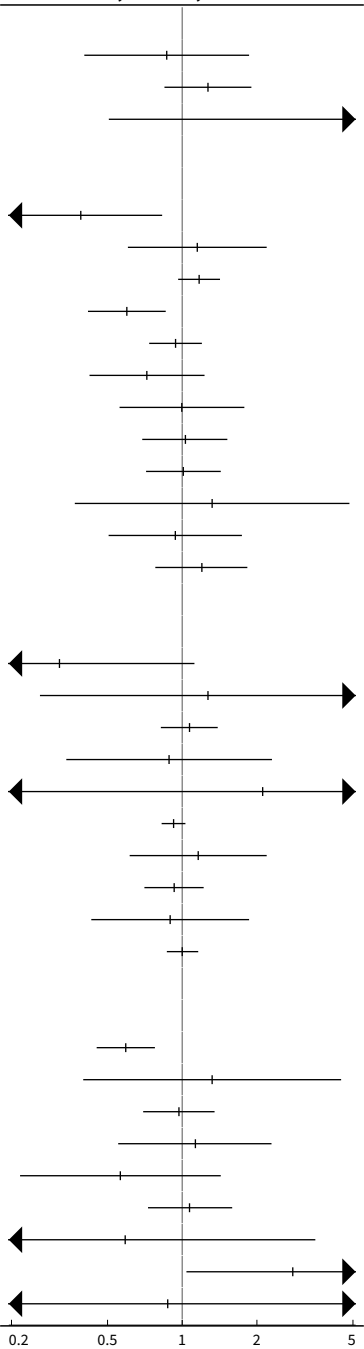
### Comparison 1. All in RCTs versus all out of RCTs, dichotomous

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Main outcome, dichotomous | 98 | | Relative Risk (Random, 95% CI) | Totals not selected |
| 1.1 Randomized | 3 | | Relative Risk (Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.2 Adjusted results | 12 | | Relative Risk (Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.3 Controlled comparisons | 10 | | Relative Risk (Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.4 Partially controlled comparisons | 36 | | Relative Risk (Random, 95% CI) | 0.0 [0.0, 0.0] |

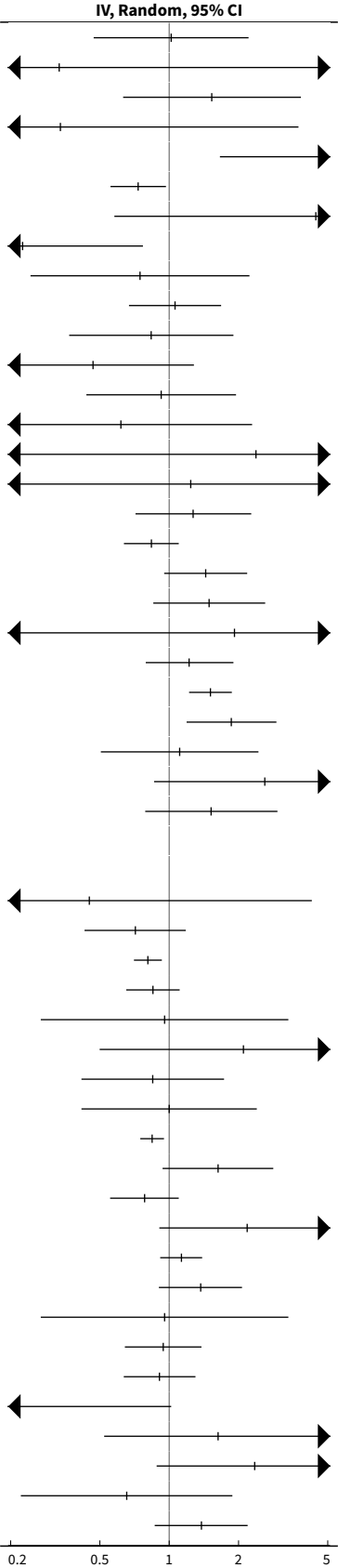
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.5 Poorly controlled comparisons | 37 | | Relative Risk (Random, 95% CI) | 0.0 [0.0, 0.0] |

## Analysis 1.1. Comparison 1 All in RCTs versus all out of RCTs, dichotomous, Outcome 1 Main outcome, dichotomous.

| Study or subgroup | Inside RCT N | Outside RCT N | log[Relative Risk] (SE) | Relative Risk IV, Random, 95% CI | Relative Risk IV, Random, 95% CI |
|---|---|---|---|---|---|
| **1.1.1 Randomized** | | | | | |
| Cooper 1997b | 1 | 1 | -0.1 (0.39) | | 0.87[0.4,1.86] |
| Cooper 1997a | 1 | 1 | 0.2 (0.205) | | 1.27[0.85,1.9] |
| Dahan 1986 | 1 | 1 | 2.2 (1.469) | | 9[0.51,160.07] |
| **1.1.2 Adjusted results** | | | | | |
| Davis 1985 | 1 | 1 | -0.9 (0.385) | | 0.39[0.18,0.83] |
| Mosekilde 2000a | 1 | 1 | 0.1 (0.329) | | 1.15[0.6,2.19] |
| Feit 2000a | 1 | 1 | 0.2 (0.099) | | 1.17[0.96,1.42] |
| Williford 1993 | 1 | 1 | -0.5 (0.184) | | 0.6[0.42,0.86] |
| Feit 2000b | 1 | 1 | -0.1 (0.125) | | 0.94[0.74,1.2] |
| Schmoor 1996c | 1 | 1 | -0.3 (0.272) | | 0.72[0.42,1.23] |
| Schmoor 1996f | 1 | 1 | -0 (0.295) | | 1[0.56,1.78] |
| Schmoor 1996a | 1 | 1 | 0 (0.202) | | 1.03[0.69,1.52] |
| Schmoor 1996b | 1 | 1 | 0 (0.176) | | 1.01[0.72,1.43] |
| Mosekilde 2000b | 1 | 1 | 0.3 (0.65) | | 1.32[0.37,4.72] |
| Schmoor 1996d | 1 | 1 | -0.1 (0.316) | | 0.94[0.5,1.74] |
| Schmoor 1996e | 1 | 1 | 0.2 (0.219) | | 1.2[0.78,1.83] |
| **1.1.3 Controlled comparisons** | | | | | |
| Nicolaides 1994b | 1 | 1 | -1.1 (0.64) | | 0.32[0.09,1.12] |
| Nagel 1998a | 1 | 1 | 0.2 (0.796) | | 1.27[0.27,6.06] |
| Link 1991b | 1 | 1 | 0.1 (0.134) | | 1.07[0.82,1.39] |
| Bhattacharya 1998 | 1 | 1 | -0.1 (0.487) | | 0.89[0.34,2.3] |
| Nagel 1998b | 1 | 1 | 0.7 (1.531) | | 2.11[0.1,42.37] |
| Helsing 1998b | 1 | 1 | -0.1 (0.057) | | 0.92[0.83,1.03] |
| Nicolaides 1994a | 1 | 1 | 0.1 (0.324) | | 1.16[0.61,2.19] |
| Helsing 1998a | 1 | 1 | -0.1 (0.141) | | 0.93[0.7,1.22] |
| Link 1991a | 1 | 1 | -0.1 (0.374) | | 0.89[0.43,1.86] |
| MacLennan 1985 | 1 | 1 | 0 (0.075) | | 1[0.87,1.16] |
| **1.1.4 Partially controlled comparisons** | | | | | |
| Strandberg 1995 | 1 | 1 | -0.5 (0.138) | | 0.59[0.45,0.78] |
| Rigg 2000b | 1 | 1 | 0.3 (0.61) | | 1.32[0.4,4.37] |
| Martinez-Amenos1990b | 1 | 1 | -0 (0.169) | | 0.97[0.7,1.35] |
| Creutzig 1993b | 1 | 1 | 0.1 (0.363) | | 1.13[0.55,2.29] |
| Forbes 2000 | 1 | 1 | -0.6 (0.475) | | 0.56[0.22,1.43] |
| CASS 1984b | 1 | 1 | 0.1 (0.199) | | 1.07[0.73,1.59] |
| Henshaw 1993b | 1 | 1 | -0.5 (0.901) | | 0.59[0.1,3.44] |
| Blichert-Toft 1988b | 1 | 1 | 1 (0.506) | | 2.79[1.04,7.53] |
| Liu 1998b | 1 | 1 | -0.1 (0.9) | | 0.87[0.15,5.11] |



| Study or subgroup | Inside RCT N | Outside RCT N | log[Relative Risk] (SE) | Relative Risk IV, Random, 95% CI | Relative Risk IV, Random, 95% CI |
|---|---|---|---|---|---|
| Chauhan 1992 | 1 | 1 | 0 (0.395) | | 1.02[0.47,2.21] |
| Clagett 1984b | 1 | 1 | -1.1 (1.59) | | 0.33[0.01,7.52] |
| Blichert-Toft 1988a | 1 | 1 | 0.4 (0.453) | | 1.53[0.63,3.73] |
| Liu 1998a | 1 | 1 | -1.1 (1.214) | | 0.34[0.03,3.64] |
| Henshaw 1993a | 1 | 1 | 1.7 (0.597) | | 5.36[1.66,17.28] |
| Martinez-Amenos1990a | 1 | 1 | -0.3 (0.142) | | 0.73[0.56,0.97] |
| Creutzig 1993a | 1 | 1 | 1.5 (1.028) | | 4.33[0.58,32.48] |
| Rigg 2000a | 1 | 1 | -1.5 (0.614) | | 0.23[0.07,0.77] |
| Clagett 1984a | 1 | 1 | -0.3 (0.559) | | 0.75[0.25,2.23] |
| CASS 1984a | 1 | 1 | 0.1 (0.235) | | 1.06[0.67,1.68] |
| Antman 1985a | 1 | 1 | -0.2 (0.418) | | 0.84[0.37,1.9] |
| Antman 1985b | 1 | 1 | -0.8 (0.513) | | 0.47[0.17,1.28] |
| Biederman 1985 | 1 | 1 | -0.1 (0.381) | | 0.92[0.44,1.95] |
| Clapp 1989 | 1 | 1 | -0.5 (0.669) | | 0.62[0.17,2.29] |
| Ekstein 2002a | 1 | 1 | 0.9 (1.43) | | 2.38[0.14,39.14] |
| Ekstein 2002b | 1 | 1 | 0.2 (1.017) | | 1.24[0.17,9.08] |
| Elliott 1996 | 1 | 1 | 0.2 (0.295) | | 1.27[0.71,2.27] |
| Karande 1998 | 1 | 1 | -0.2 (0.14) | | 0.84[0.64,1.1] |
| Kendrick 2001a | 1 | 1 | 0.4 (0.212) | | 1.44[0.95,2.18] |
| Kendrick 2001b | 1 | 1 | 0.4 (0.285) | | 1.49[0.85,2.61] |
| Marcinczyk 1997 | 1 | 1 | 0.7 (1.993) | | 1.92[0.04,95.32] |
| Mori 2006a | 1 | 1 | 0.2 (0.223) | | 1.22[0.79,1.9] |
| Mori 2006b | 1 | 1 | 0.4 (0.11) | | 1.51[1.22,1.87] |
| Ogden 2004 | 1 | 1 | 0.6 (0.23) | | 1.86[1.19,2.92] |
| Walker 1986 | 1 | 1 | 0.1 (0.402) | | 1.11[0.51,2.44] |
| Wallage 2003 | 1 | 1 | 1 (0.564) | | 2.6[0.86,7.86] |
| Yamani 2005 | 1 | 1 | 0.4 (0.337) | | 1.52[0.79,2.95] |
| **1.1.5 Poorly controlled comparisons** | | | | | |
| Edsmyr 1978 | 1 | 1 | -0.8 (1.135) | | 0.45[0.05,4.16] |
| Lidbrink 1995 | 1 | 1 | -0.3 (0.259) | | 0.71[0.43,1.18] |
| Rosen 1987a | 1 | 1 | -0.2 (0.071) | | 0.81[0.7,0.93] |
| Yamamoto 1992b | 1 | 1 | -0.2 (0.136) | | 0.85[0.65,1.11] |
| Forssell 1989 | 1 | 1 | -0 (0.631) | | 0.95[0.28,3.29] |
| MACESG 1992b | 1 | 1 | 0.7 (0.733) | | 2.1[0.5,8.81] |
| King 1997b | 1 | 1 | -0.2 (0.363) | | 0.85[0.42,1.73] |
| Yersin 1996 | 1 | 1 | 0 (0.447) | | 1[0.42,2.4] |
| Rosen 1987b | 1 | 1 | -0.2 (0.06) | | 0.84[0.75,0.95] |
| Berglund 1997 | 1 | 1 | 0.5 (0.282) | | 1.63[0.94,2.83] |
| Yamamoto 1992a | 1 | 1 | -0.2 (0.175) | | 0.78[0.55,1.1] |
| Bijker 2000b | 1 | 1 | 0.8 (0.449) | | 2.18[0.91,5.25] |
| Chilvers 2001b | 1 | 1 | 0.1 (0.107) | | 1.13[0.91,1.39] |
| Moertel 1984 | 1 | 1 | 0.3 (0.212) | | 1.37[0.9,2.07] |
| Kieler 1998 | 1 | 1 | -0 (0.631) | | 0.95[0.28,3.29] |
| Young 1996 | 1 | 1 | -0.1 (0.196) | | 0.94[0.64,1.38] |
| Balmukhanov 1989b | 1 | 1 | -0.1 (0.182) | | 0.91[0.63,1.3] |
| Sullivan 1982b | 1 | 1 | -2.6 (1.336) | | 0.07[0.01,1.02] |
| Playforth 1988 | 1 | 1 | 0.5 (0.582) | | 1.63[0.52,5.1] |
| Wetzner 1979 | 1 | 1 | 0.9 (0.501) | | 2.35[0.88,6.28] |
| Bijker 2000a | 1 | 1 | -0.4 (0.54) | | 0.65[0.23,1.88] |
| Urban 1999 | 1 | 1 | 0.3 (0.236) | | 1.38[0.87,2.19] |



| Study or subgroup | Inside RCT N | Outside RCT N | log[Relative Risk] (SE) | Relative Risk IV, Random, 95% CI | Relative Risk IV, Random, 95% CI |
|---|---|---|---|---|---|
| MACESG 1992a | 1 | 1 | -0.5 (0.598) | | 0.59[0.18,1.91] |
| King 1997a | 1 | 1 | 0.3 (0.389) | | 1.28[0.6,2.75] |
| Sullivan 1982c | 1 | 1 | 0.4 (1.045) | | 1.46[0.19,11.35] |
| Wikdahl 1992 | 1 | 1 | -0 (0.708) | | 0.97[0.24,3.9] |
| Baum 1979 | 1 | 1 | -1.3 (0.66) | | 0.27[0.07,0.99] |
| Balmukhanov 1989a | 1 | 1 | -0.9 (0.752) | | 0.4[0.09,1.76] |
| Sullivan 1982a | 1 | 1 | 1.9 (1.387) | | 6.75[0.45,102.39] |
| Chilvers 2001a | 1 | 1 | -0.1 (0.111) | | 0.93[0.75,1.16] |
| Raistrick 2005a | 1 | 1 | -0.1 (0.104) | | 0.89[0.72,1.09] |
| Raistrick 2005b | 1 | 1 | 0 (0.107) | | 1.04[0.84,1.29] |
| Reeves 2004 | 1 | 1 | -0.5 (0.554) | | 0.6[0.2,1.78] |
| Rørbye 2005a | 1 | 1 | 0.6 (0.234) | | 1.77[1.12,2.8] |
| Rørbye 2005b | 1 | 1 | -0.3 (0.584) | | 0.72[0.23,2.26] |
| Waard 2002a | 1 | 1 | -0.1 (0.14) | | 0.92[0.7,1.21] |
| Waard 2002aa | 1 | 1 | -0.1 (0.641) | | 0.93[0.26,3.25] |
| | | | Favors in RCT | 0.2 0.5 1 2 5 | Favors outside RCT |

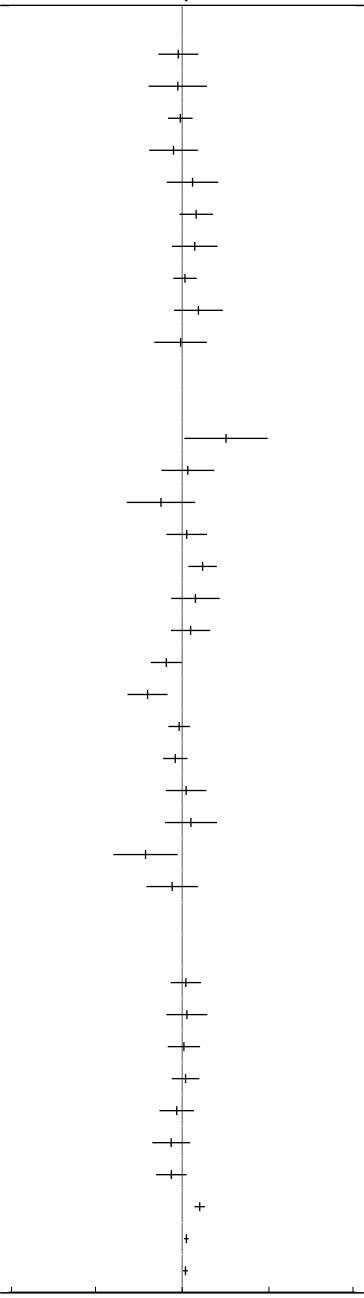
## Comparison 2. All in RCTs versus all out of RCTs, continuous

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Main outcome, continuous scale | 38 | | Std. Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 1.1 Randomized | 3 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.2 Controlled comparison | 10 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.3 Partially controlled comparison | 15 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.4 Poorly controlled comparison | 10 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |

### Analysis 2.1. Comparison 2 All in RCTs versus all out of RCTs, continuous, Outcome 1 Main outcome, continuous scale.

| Study or subgroup | In RCTs N | In RCTs Mean(SD) | Out of RCTs N | Out of RCTs Mean(SD) | Std. Mean Difference Random, 95% CI | Std. Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|
| **2.1.1 Randomized** | | | | | | |
| Mahon 1999 | 31 | 7 (65) | 30 | -8 (63) | | 0.23[-0.27,0.74] |
| Bergmann 1994 | 18 | -22.1 (31) | 25 | -5.3 (34) | | -0.5[-1.12,0.11] |
| Mahon 1996 | 12 | -12 (29) | 9 | -3 (53) | | -0.21[-1.08,0.66] |
| | | | | Favors in RCT | -4 -2 0 2 4 | Favors outside RCT |

| Study or subgroup | In RCTs N | In RCTs Mean(SD) | Out of RCTs N | Out of RCTs Mean(SD) | Std. Mean Difference Random, 95% CI | Std. Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|
| **2.1.2 Controlled comparison** | | | | | | |
| McKay 1998a | 49 | 1.6 (4.3) | 29 | 2 (4.1) | | -0.09[-0.55,0.37] |
| McKay 1995b | 18 | 6.9 (9.1) | 16 | 7.9 (10) | | -0.1[-0.78,0.57] |
| Rovers 2001b | 94 | 70 (24.7) | 97 | 71 (20.1) | | -0.04[-0.33,0.24] |
| McKay 1995a | 16 | 3.4 (5.7) | 52 | 4.9 (7.9) | | -0.2[-0.76,0.36] |
| McKay 1998b | 41 | 2.6 (4.4) | 15 | 1.6 (3.4) | | 0.24[-0.36,0.83] |
| Rovers 2001a | 93 | 36 (19.7) | 36 | 30 (15.3) | | 0.32[-0.07,0.71] |
| Ashok 2005a | 202 | 3.3 (2.7) | 15 | 2.5 (2.5) | | 0.29[-0.24,0.81] |
| Ashok 2005b | 198 | 2.2 (2.2) | 71 | 2.1 (2.1) | | 0.06[-0.21,0.33] |
| Bain 2001a | 20 | 1.5 (1.2) | 32 | 1.1 (1.1) | | 0.37[-0.19,0.94] |
| Bain 2001b | 16 | 0.9 (1.5) | 30 | 1 (1.6) | | -0.04[-0.64,0.57] |
| **2.1.3 Partially controlled comparison** | | | | | | |
| McCaughey 1998 | 6 | 10.6 (4.3) | 20 | 5.1 (5.5) | | 1.01[0.05,1.97] |
| Villamaria 1997b | 30 | -37.3 (0.6) | 16 | -37.4 (0.8) | | 0.13[-0.48,0.74] |
| Villamaria 1997a | 30 | -37.6 (0.7) | 8 | -37.2 (0.7) | | -0.49[-1.28,0.3] |
| Abraham 2004a | 50 | 1.6 (1.2) | 27 | 1.5 (1.2) | | 0.1[-0.37,0.57] |
| Abraham 2004b | 50 | 2.6 (2.7) | 135 | 1.3 (2.7) | | 0.47[0.14,0.8] |
| Bakker 2000 | 26 | 2.8 (8.4) | 24 | 0.9 (1.4) | | 0.3[-0.25,0.86] |
| Emery 2003a | 86 | 37.8 (12.7) | 24 | 35.4 (10.8) | | 0.19[-0.26,0.65] |
| Emery 2003b | 82 | 33.9 (11.6) | 49 | 38.7 (15) | | -0.37[-0.72,-0.01] |
| Heuss 2004 | 38 | 1 (2) | 40 | 2.7 (2.2) | | -0.8[-1.26,-0.34] |
| King 2000a | 107 | 12.5 (12.1) | 147 | 13.3 (10.7) | | -0.07[-0.32,0.18] |
| King 2000b | 102 | 12.8 (9.9) | 94 | 14.4 (9.9) | | -0.16[-0.44,0.12] |
| Lansky 1983 | 25 | 2.4 (7.6) | 59 | 1.5 (11.3) | | 0.09[-0.38,0.56] |
| Masood 2002 | 45 | 5.7 (1.6) | 14 | 5.4 (0.9) | | 0.2[-0.4,0.8] |
| Melchart 2002a | 12 | 3 (26.5) | 21 | 31 (35.1) | | -0.85[-1.59,-0.1] |
| Melchart 2002b | 14 | 18 (36.3) | 51 | 24 (21.9) | | -0.23[-0.83,0.36] |
| **2.1.4 Poorly controlled comparison** | | | | | | |
| Bedi 2000b | 51 | 14.8 (10.1) | 80 | 14 (9.3) | | 0.08[-0.27,0.43] |
| Paradise 1984b | 35 | 2.7 (2.3) | 34 | 2.4 (2.3) | | 0.11[-0.36,0.58] |
| Paradise 1990b | 47 | 13.8 (9.2) | 67 | 13.4 (9.8) | | 0.04[-0.33,0.41] |
| Bedi 2000a | 52 | 15.2 (11.6) | 140 | 14.4 (9.8) | | 0.08[-0.24,0.4] |
| Paradise 1990a | 52 | 10.2 (8.4) | 46 | 11.2 (7.2) | | -0.13[-0.52,0.27] |
| Paradise 1984a | 38 | 0.8 (1) | 44 | 1.1 (1.2) | | -0.25[-0.69,0.18] |
| Boezaart 1998 | 40 | 0.7 (1.3) | 136 | 1.1 (2) | | -0.25[-0.61,0.1] |
| Witt 2006a | 300 | 30.5 (1) | 2636 | 30.3 (0.4) | | 0.4[0.28,0.52] |
| Witt 2006b | 1618 | -28.9 (26.7) | 9245 | -31.7 (29.4) | | 0.1[0.04,0.15] |
| Witt 2006c | 1363 | -37 (35.8) | 7767 | -39.4 (31.5) | | 0.07[0.02,0.13] |



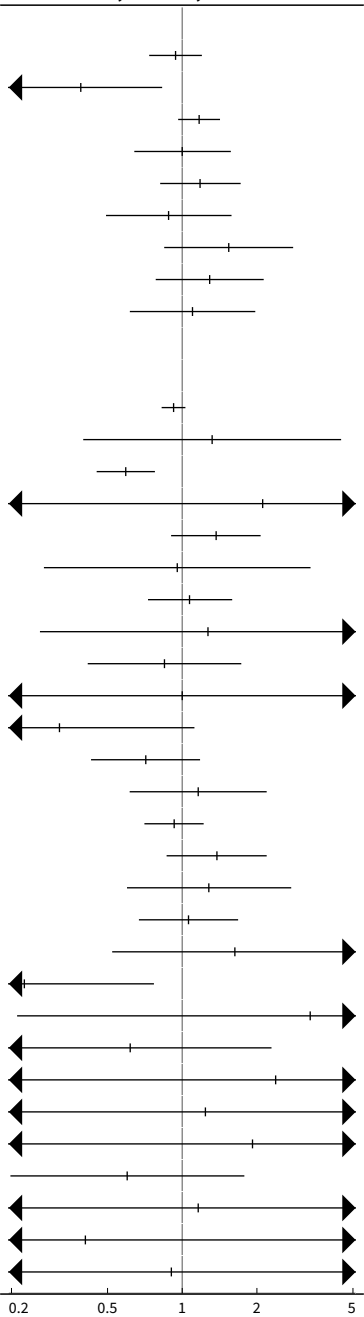

## Comparison 3. Mortality

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mortality | 37 | | Relative Risk (Random, 95% CI) | Totals not selected |
| 1.1 Adjusted mortality | 9 | | Relative Risk (Random, 95% CI) | 0.0 [0.0, 0.0] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.2 Unadjusted mortality | 28 | | Relative Risk (Random, 95% CI) | 0.0 [0.0, 0.0] |

## Analysis 3.1. Comparison 3 Mortality, Outcome 1 Mortality.

| Study or subgroup | Inside RCT N | Outside RCT N | log[Relative Risk] (SE) | Relative Risk IV, Random, 95% CI | Relative Risk IV, Random, 95% CI |
|---|---|---|---|---|---|
| **3.1.1 Adjusted mortality** | | | | | |
| Feit 2000a | 1 | 1 | -0.1 (0.125) | | 0.94[0.74,1.2] |
| Davis 1985 | 1 | 1 | -0.9 (0.385) | | 0.39[0.18,0.83] |
| Feit 2000b | 1 | 1 | 0.2 (0.099) | | 1.17[0.96,1.42] |
| Schmoor 1996a | 1 | 1 | 0 (0.228) | | 1[0.64,1.57] |
| Schmoor 1996b | 1 | 1 | 0.2 (0.19) | | 1.18[0.81,1.72] |
| Schmoor 1996c | 1 | 1 | -0.1 (0.297) | | 0.88[0.49,1.58] |
| Schmoor 1996d | 1 | 1 | 0.4 (0.305) | | 1.54[0.85,2.8] |
| Schmoor 1996e | 1 | 1 | 0.3 (0.256) | | 1.29[0.78,2.13] |
| Schmoor 1996f | 1 | 1 | 0.1 (0.297) | | 1.1[0.62,1.97] |
| **3.1.2 Unadjusted mortality** | | | | | |
| Helsing 1998b | 1 | 1 | -0.1 (0.057) | | 0.92[0.83,1.03] |
| Rigg 2000b | 1 | 1 | 0.3 (0.61) | | 1.32[0.4,4.37] |
| Strandberg 1995 | 1 | 1 | -0.5 (0.138) | | 0.59[0.45,0.78] |
| Nagel 1998b | 1 | 1 | 0.7 (1.531) | | 2.11[0.1,42.37] |
| Moertel 1984 | 1 | 1 | 0.3 (0.212) | | 1.37[0.9,2.07] |
| Kieler 1998 | 1 | 1 | -0 (0.631) | | 0.95[0.28,3.29] |
| CASS 1984b | 1 | 1 | 0.1 (0.199) | | 1.07[0.73,1.59] |
| Nagel 1998a | 1 | 1 | 0.2 (0.796) | | 1.27[0.27,6.06] |
| King 1997b | 1 | 1 | -0.2 (0.363) | | 0.85[0.42,1.73] |
| Link 1991b | 1 | 1 | 0 (1.973) | | 1[0.02,47.78] |
| Nicolaides 1994b | 1 | 1 | -1.1 (0.64) | | 0.32[0.09,1.12] |
| Lidbrink 1995 | 1 | 1 | -0.3 (0.259) | | 0.71[0.43,1.18] |
| Nicolaides 1994a | 1 | 1 | 0.1 (0.324) | | 1.16[0.61,2.19] |
| Helsing 1998a | 1 | 1 | -0.1 (0.141) | | 0.93[0.7,1.22] |
| Urban 1999 | 1 | 1 | 0.3 (0.236) | | 1.38[0.87,2.19] |
| King 1997a | 1 | 1 | 0.3 (0.389) | | 1.28[0.6,2.75] |
| CASS 1984a | 1 | 1 | 0.1 (0.235) | | 1.06[0.67,1.68] |
| Playforth 1988 | 1 | 1 | 0.5 (0.582) | | 1.63[0.52,5.1] |
| Rigg 2000a | 1 | 1 | -1.5 (0.614) | | 0.23[0.07,0.77] |
| Link 1991a | 1 | 1 | 1.2 (1.388) | | 3.28[0.22,49.81] |
| Clapp 1989 | 1 | 1 | -0.5 (0.669) | | 0.62[0.17,2.29] |
| Ekstein 2002a | 1 | 1 | 0.9 (1.43) | | 2.38[0.14,39.14] |
| Ekstein 2002b | 1 | 1 | 0.2 (1.017) | | 1.24[0.17,9.08] |
| Marcinczyk 1997 | 1 | 1 | 0.7 (1.993) | | 1.92[0.04,95.32] |
| Reeves 2004 | 1 | 1 | -0.5 (0.554) | | 0.6[0.2,1.78] |
| Sullivan 1982a | 1 | 1 | 0.2 (1.502) | | 1.16[0.06,22.1] |
| Sullivan 1982b | 1 | 1 | -0.9 (1.484) | | 0.41[0.02,7.47] |
| Sullivan 1982c | 1 | 1 | -0.1 (1.601) | | 0.9[0.04,20.82] |



## ADDITIONAL TABLES

**Table 1. Patients randomized to trial participation or not**

| Study id | Patients | Outcome measure | Inside trial (n) | Outside trial (n) | RR or SMD |
|---|---|---|---|---|---|
| Bergmann 1994 | Oncology patients | Pain score on a 100 point scale after given pain killer | mean -22 (31), n=18 | mean -5 (34), n=25 | SMD -0.5 (-1.12 to 0.11) |
| Cooper 1997a | women w/heavy menstrual bleeding | Lack of satisfaction with surgical resection treatment | 23 of 93 | 6 of 21 | RR 0.87 (0.40 to 1.86) |
| Cooper 1997b | Women w/heavy menstrual bleeding | Lack of satisfaction with medical treatment | 69 of 94 | 11 of 19 | RR 1.27 (0.85 to 1.90) |
| Dahan 1986 | Insomnia patients | # spontaneously reported side effects after placebo pills | 4 of 30 | none of 30 | RR 9.0 (0.51 to 160.2) |
| Mahon 1996 | Patients with irreversible chronic airflow limitation | Change in 6 min walk distance (m) | 12 (29) m, n=12 | 3 (53) m, n=9 | SMD-0.21 (-1.08 to 0.66) |
| Mahon 1999 | Patients with irreversible chronic airflow limitation | Change in 6 min walk distance (m) | 7 (65)m, n=31 | 8 (63) m, n=30 | SMD 0.23 (-0.27 to 0.74) |

## APPENDICES

### Appendix 1. MEDLINE search strategy

| |
|---|
| Randomized Controlled Trials/ |
| Random Allocation/ |
| random$.tw. |
| or/1-3 |
| (outside adj3 (trial? or randomi?ed or rct? or program)).tw. |
| ((nonentry or non entry or nonenter$ or non enter$ or "not enter$" or nonenrol$ or non enrol$ or "not enrol$" or nonparticip$ or non particip$ or "not particip$") adj3 (trial? or randomi?ed or rct?)).tw. |
| ((nonentry or non entry or nonenter$ or non enter$ or "not enter$" or nonenrol$ or non enrol$ or "not enrol$" or nonparticip$ or non particip$ or "not particip$") adj3 patient?).tw.<br>8. ((nonrandom$ or non random$) adj3 (patient? or group? or case? or serie? or study or studies or trial?)).tw.<br>((nonentry or non entry or nonenter$ or non enter$ or "not enter$" or nonenrol$ or non enrol$ or "not enrol$" or nonparticip$ or non particip$ or "not particip$") adj3 patient?).tw.<br>8. ((nonrandom$ or non random$) adj3 (patient? or group? or case? or serie? or study or studies or trial?)).tw. |

*(Continued)*

| |
|---|
| (exclud$ adj3 randomi?ation).tw. |
| ((non participant? or nonparticipant?) adj3 group?).tw. |
| (patient? adj3 prefer$).tw. |
| ((treatment or method?) adj3 prefer$).tw. |
| (treatment adj3 (select$ or choose or chose or chosen or choice)).tw. |
| ((own or patient? or by) adj choice).tw. |
| ((standard or usual) adj practice).tw. |
| ((refus$ or decline$) adj3 (participat$ or random$)).tw. |
| ((non or "not" or lack$ or withh$ or without or refus$ or decline$) adj3 consent).tw. |
| (follow up adj3 register?).tw. |
| 19. or/5-18 |
| zelen.tw. |
| (4 and 19) or 20 |
| clinical trial.pt. |
| controlled clinical trial.pt. |
| randomized controlled trial.pt. |
| comparative study.pt. |
| Cohort Studies/ |
| (preference adj (stud$ or trial?)).tw. |
| (cohort adj (stud$ or trial? or analysis)).tw. |
| or/22-28 |
| Humans/ |
| Animals/ |
| 31 not (30 and 31) |
| editorial.pt. |
| letter.pt. |
| comment.pt. |
| or/33-35 |

*(Continued)*

| |
|---|
| 29 not (32 or 36) |
| 21 and 37 |

## Appendix 2. EMBASE search strategy

| |
|---|
| Randomized Controlled Trial/ |
| Randomization/ |
| random$.tw. |
| or/1-3 |
| Refusal to Participate/ |
| (outside adj3 (trial? or randomi?ed or rct? or program)).tw. |
| ((nonentry or non entry or nonenter$ or non enter$ or "not enter$" or nonenrol$ or non enrol$ or "not enrol$" or nonparticip$ or non particip$ or "not particip$") adj3 (trial? or randomi?ed or rct?)).tw. |
| ((nonentry or non entry or nonenter$ or non enter$ or "not enter$" or nonenrol$ or non enrol$ or "not enrol$" or nonparticip$ or non particip$ or "not particip$") adj3 patient?).tw. |
| ((nonrandom$ or non random$) adj3 (patient? or group? or case? or serie? or study or studies or trial?)).tw. |
| (exclud$ adj3 randomi?ation).tw. |
| ((non participant? or nonparticipant?) adj3 group?).tw. |
| (patient? adj3 prefer$).tw. |
| ((treatment or method?) adj3 prefer$).tw. |
| (treatment adj3 (select$ or choose or chose or chosen or choice)).tw. |
| ((own or patient? or by) adj choice).tw. |
| ((standard or usual) adj practice).tw. |
| ((refus$ or decline$) adj3 (participat$ or random$)).tw. |
| ((non or "not" or lack$ or withh$ or without or refus$ or decline$) adj3 consent).tw. |
| (follow up adj3 register?).tw. |
| or/5-19 |
| zelen.tw. |
| (4 and 20) or 21 |

*(Continued)*

| |
|---|
| Major Clinical Study/ |
| Controlled Study/ |
| Clinical Trial/ |
| Clinical Article/ |
| Randomized Controlled Trial/ |
| Cohort Analysis/ |
| (preference adj (stud$ or trial?)).tw. |
| (cohort adj (stud$ or trial? or analysis)).tw. |
| or/23-30 |
| Nonhuman/ |
| letter.pt. |
| editorial.pt. |
| 31 not (32 or 33 or 34) |
| 22 and 35 |
| limit 36 to em=2001$ |
| limit 36 to em=2002$ |
| limit 36 to em=2003$ |
| limit 36 to em=2004$ |
| limit 36 to em=2005$ |
| limit 36 to em=2006$ |
| limit 36 to em=2007$ |
| or/37-43 |

## Appendix 3. CENTRAL search strategy

| |
|---|
| MeSH descriptor Randomized Controlled Trials, this term only |
| MeSH descriptor Random Allocation, this term only |
| (random*):ti or (random*):ab |

*(Continued)*

| |
|---|
| (outside NEAR/3 (trial* or randomized or randomised or rct* or program)):ti or (outside NEAR/3 (trial* or randomized or randomised or rct* or program)):ab |
| (nonentry or non NEXT entry or nonenter* or non NEXT enter* or not NEXT enter* or nonenrol* or non NEXT enrol* or not NEXT enrol* or nonparticip* or non NEXT particip* or not NEXT particip*) NEAR/3 (trial* or randomized or randomised or rct*):ti or (nonentry or non NEXT entry or nonenter* or non NEXT enter* or not NEXT enter* or nonenrol* or non NEXT enrol* or not NEXT enrol* or nonparticip* or non NEXT particip* or not NEXT particip*) NEAR/3 (trial* or randomized or randomised or rct*):ab |
| (nonentry or non NEXT entry or nonenter* or non NEXT enter* or not NEXT enter* or nonenrol* or non NEXT enrol* or not NEXT enrol* or nonparticip* or non NEXT particip* or not NEXT particip*) NEAR/3 patient*:ti or (nonentry or non NEXT entry or nonenter* or non NEXT enter* or not NEXT enter* or nonenrol* or non NEXT enrol* or not NEXT enrol* or nonparticip* or non NEXT particip* or not NEXT particip*) NEAR/3 patient*:ab |
| (nonrandom* or non NEXT random*) NEAR/3 (patient* or group* or case* or serie* or study or studies or trial*):ti or (nonrandom* or non NEXT random*) NEAR/3 (patient* or group* or case* or serie* or study or studies or trial*):ab |
| (exclud* NEAR/3 (randomization or randomisation)):ti or (exclud* NEAR/3 (randomization or randomisation)):ab |
| (non NEXT participant* or nonparticipant*) NEAR/3 group*:ti or (non NEXT participant* or nonparticipant*) NEAR/3 group*:ab |
| (patient* NEAR/3 prefer*):ti or (patient* NEAR/3 prefer*):ab |
| (treatment or method*) NEAR/3 prefer*:ti or (treatment or method*) NEAR/3 prefer*:ab |
| (treatment NEAR/3 (select* or choose or chose or chosen or choice)):ti or (treatment NEAR/3 (select* or choose or chose or chosen or choice)):ab |
| (own or patient* or by) NEXT choice:ti or (own or patient* or by) NEXT choice:ab |
| (standard or usual) NEXT practice:ti or (standard or usual) NEXT practice:ab |
| (refus* or decline*) NEAR/3 (participat* or random*):ti or (refus* or decline*) NEAR/3 (participat* or random*):ab |
| (non or lack* or with* or without or refus* or decline*) NEAR/3 consent:ti or (non or lack* or with* or without or refus* or decline*) NEAR/3 consent:ab |
| (follow NEXT up) NEAR/3 register*:ti or (follow NEXT up) NEAR/3 register*:ab |
| (zelen):ti or (zelen):ab |
| (#1 OR #2 OR #3) |
| (#4 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17) |
| (( #19 AND #20 ) OR #18) |

## Appendix 4. PsycInfo search strategy

| |
|---|
| random$.tw. |
| (outside adj3 (trial? or randomi?ed or rct? or program)).tw. |

*(Continued)*

| |
|---|
| ((nonentry or non entry or nonenter$ or non enter$ or "not enter$" or nonenrol$ or non enrol$ or "not enrol$" or nonparticip$ or non particip$ or "not particip$") adj3 (trial? or randomi?ed or rct?)).tw. |
| ((nonentry or non entry or nonenter$ or non enter$ or "not enter$" or nonenrol$ or non enrol$ or "not enrol$" or nonparticip$ or non particip$ or "not particip$") adj3 patient?).tw. |
| ((nonrandom$ or non random$) adj3 (patient? or group? or case? or serie? or study or studies or trial?)).tw. |
| (exclud$ adj3 randomi?ation).tw. |
| ((non participant? or nonparticipant?) adj3 group?).tw. |
| (patient? adj3 prefer$).tw. |
| ((treatment or method?) adj3 prefer$).tw. |
| (treatment adj3 (select$ or choose or chose or chosen or choice)).tw. |
| ((own or patient? or by) adj choice).tw. |
| ((standard or usual) adj practice).tw. |
| ((refus$ or decline$) adj3 (participat$ or random$)).tw. |
| ((non or "not" or lack$ or withh$ or without or refus$ or decline$) adj3 consent).tw. |
| (follow up adj3 register?).tw. |
| or/2-15 |
| zelen.tw. |
| (1 and 16) or 17 |
| Clinical Trials/ |
| Cohort Analysis/ |
| "Treatment Outcome/Clinical Trial".md. |
| (preference adj (stud$ or trial?)).tw. |
| (cohort adj (stud$ or trial? or analysis)).tw. |
| or/19-23 |
| 18 and 24 |
| 2001$.up. |
| 2002$.up. |
| 2003$.up. |
| 2004$.up. |

(Continued)

| |
|---|
| 2005$.up. |
| 2006$.up. |
| 2007$.up. |
| or/26-32 |
| 25 and 33 |

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 16 February 2009 | Amended | Reference corrected |

## HISTORY

Protocol first published: Issue 4, 2001
Review first published: Issue 1, 2005

| Date | Event | Description |
|---|---|---|
| 15 May 2008 | New citation required but conclusions have not changed | The list of authors has changed. |
| 15 May 2008 | New search has been performed | This review has been updated (new search in March 2007) from a previously published review (Vist 2005). Thirty new studies with 45 comparisons have been included in this update. A total of 85 studies with 136 comparisons are included. These studies report on 86,640 patients who have been randomised to treatment within RCTs compared with 57,205 similar patients who received similar treatment outside of the trial. |
| 22 February 2007 | Amended | Converted to new review format |

## CONTRIBUTIONS OF AUTHORS

Gunn Elisabeth Vist: study selection, data extraction, statistical analysis, drafting of written submissions, protocol and review development.
Dianne Bryant: study selection, data extraction, statistical analysis, drafting of written submissions, and review development.
Lyndsay Somerville: study selection, data extraction, statistical analysis, drafting of written submissions, review development.
Trevor Birmingham: study selection, data extraction, drafting of written submissions.
Andrew David Oxman: statistical analysis, drafting of written submissions, protocol and review development.

## DECLARATIONS OF INTEREST

None known

## SOURCES OF SUPPORT

### Internal sources

- Norwegian Knowledge Centre for the Health Services, Norway.
- University of Western Ontario, London, Canada.

### External sources

- The Nuffield Trust, UK.
- Department of Health, UK.

## INDEX TERMS

### Medical Subject Headings (MeSH)

*Patient Acceptance of Health Care; *Process Assessment, Health Care; *Refusal to Participate; Cohort Studies; Randomized Controlled Trials as Topic [*adverse effects] [mortality]; Risk Assessment; Treatment Outcome

### MeSH check words

Humans