# Assessing the impact of patient and public involvement (PPI) on enrolment and retention in clinical trials: a systematic review and meta-analysis

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| Complete List of Authors: | Crocker, Joanna; University of Oxford, Nuffield Department of Primary Care Health Sciences<br>Ricci-Cabello, Ignacio; Institut d'Investigació Sanitaria Illes Balears (IdISBa),<br>Parker, Adwoa; University of York, Department of Health Sciences<br>Hirst, Jennifer; University of oxford, Nuffield Department of Primary Care Health Sciences<br>Chant, Alan; NIHR Oxford Biomedical Research Centre<br>Petit-Zeman, Sophie; Formerly NIHR Oxford Biomedical Research Centre<br>Evans, David; University of the West of England<br>Rees, Sian; Oxford Academic Health Science Network |
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## Title

Assessing the impact of patient and public involvement (PPI) on enrolment and retention in clinical trials: a systematic review and meta-analysis

## Authors

Joanna C Crocker[1*], Ignacio Ricci-Cabello[2,3], Adwoa Parker[4], Jennifer A Hirst[5], Alan Chant[6], Sophie Petit-Zeman[7], David Evans[8], Sian Rees[9].

[1] Research Fellow, Health Experiences Research Group, Nuffield Department of Primary Care Health Sciences, University of Oxford, OX2 6GG, UK.

[2] Miguel Servet Research Fellow, Fundació Institut Investigació Sanitària Illes Balears (IdISBa), Mallorca, Spain.

[3] Gerencia de Atención Primaria Mallorca (IB-SALUT), Mallorca, Spain.

[4] Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK.

[5] Senior Researcher, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK.

[6] Patient partner, NIHR Oxford Biomedical Research Centre, Oxford, UK.

[7] Former Director of Patient Involvement, NIHR Oxford Biomedical Research Centre and Unit, Oxford, UK.

[8] Professor in Health Services Research, University of the West of England, UK.

[9] Patient and Public Involvement, Engagement and Experience Theme Lead, Oxford Academic Health Science Network, UK.

*Correspondence to: joanna.crocker@phc.ox.ac.uk

## Abstract

**Objective:** To investigate the impact of patient and public involvement (PPI) on clinical trial enrolment and retention rates, and to explore how this varies with the context and nature of PPI.

**Design:** Systematic review and meta-analysis.

**Data sources:** Ten electronic databases, including Medline, INVOLVE Evidence Library and clinical trial registries.

**Eligibility criteria:** Experimental and observational studies quantitatively evaluating the impact of a PPI intervention, compared with non-PPI intervention(s) or no intervention, on participant enrolment and/or retention rates in a clinical trial or trials.

**Data extraction and analysis:** Two independent reviewers extracted data on enrolment and retention rates, contextual and PPI intervention characteristics, and assessed risk of bias using Cochrane tools. We carried out random effects meta-analyses to determine the average effect of PPI on enrolment and retention in clinical trials, as well as several exploratory subgroup analyses and sensitivity analyses.

**Results:** 26 studies (28 PPI interventions) were included in the review, of which 19 (21 PPI interventions) were eligible for the enrolment meta-analysis and 5 (6 PPI interventions) for the retention meta-analysis. A variety of PPI interventions were identified with different degrees of involvement (one-off, intermittent and full team membership), different numbers and types of PPI contributors (patients vs. lay public) and at different stages of the trial process (designing recruitment and retention strategies, developing patient-facing materials and direct recruitment or follow-up of participants). On average, PPI interventions significantly increased the odds of participant enrolment (OR 1.87; 95% CI 1.31 – 2.68). This finding remained after excluding studies at high risk of bias (including all non-randomised studies) (OR 1.17; 95% CI 1.04 – 1.32; 95% prediction interval 1.01 - 1.36). However, an Egger's test indicated possible publication bias. In exploratory subgroup analyses, the involvement of people with lived experience of the condition under study was significantly associated with improvements in participant enrolment (p=0.017). We did not find evidence that PPI interventions improve retention in clinical trials (OR 1.20; 95% CI 0.68 – 2.12).

**Conclusion:** Our findings add weight to the case for PPI in clinical trials by indicating it is likely to improve participant enrolment, especially if it includes people with lived experience of the health condition under study. Further research is needed to assess cost-effectiveness, the impact of PPI at earlier stages of trial design, and the impact of PPI interventions specifically targeting retention.

**Systematic review registration:** PROSPERO registration number CRD42016043808.

## Lay Summary

Clinical trials are a way of finding out which treatments work best for patients. In most trials one group of patients receives the new treatment and the other group does not. For trials to work, enough people need to agree to take part in the trial (enrolment) and then stay in the trial until it has finished (retention). In reality, both are often big challenges for trialists. Involving patients, carers and the public in designing trials may increase the chances of successful enrolment and retention of participants, but it is unclear how often this leads to such improvements, or by how much. It is also unclear how any benefits might be influenced by the type of patient and public involvement (PPI) and the type of trial.

To try and answer these questions we searched for all published studies which measured the impact of some sort of PPI on the enrolment or retention of participants in trials. We found 26 studies, most of which took place in North America and the UK, and most of which looked at the impact of PPI on enrolment rather than retention. Patients and members of the public were involved at various different stages of the trial process: designing recruitment and retention strategies, developing materials for patients (such as information sheets) and/or direct recruitment or retention of participants.

When we brought together the results of these studies, we found that on average, PPI in clinical trials improved enrolment, especially when the involved people had personal experience of the health condition being studied. However, PPI didn't always lead to improved enrolment, so we need to better understand when and how it works. PPI seemed to have less of an impact on retention, although relatively few studies looked at this. There was also evidence suggesting that some studies showing negative results for PPI may not have been published and therefore would not have been included in this review.

Further research is needed to find out (1) whether PPI reduces the cost of recruiting and retaining participants in trials, (2) the effects of PPI in earlier stages of trial design, and (3) the effects of PPI specifically aimed at improving retention.

## What this paper adds

### What is already known on this subject

- PPI in clinical trials has the potential to improve participant enrolment and retention rates, e.g. by improving trial design, optimising recruitment and retention strategies and patient-facing materials, or directly approaching potential participants.
- We do not know whether, when, or by how much, PPI affects participant enrolment and retention rates.

### What this study adds

- The impact of PPI on trial enrolment and retention varies widely between studies.
- On average, PPI appears to significantly increase the odds of participant enrolment, especially when it includes patients or carers with lived experience of the health condition under study.
- The impact of PPI on retention rates is less clear and requires further primary research evaluating PPI interventions which specifically target retention.

## Introduction

Poor patient recruitment and retention in trials are major sources of research inefficiency because they delay the delivery of research, inflate its costs, and can lead to biased findings.(1, 2) The top inefficiency in trial conduct from recruitment of first participant to publication of results is failure to meet recruitment targets.(3) UK clinical trials unit directors have identified 'research into methods to boost recruitment in trials' and 'methods to minimise attrition' as the top two priorities for trials methodology research.(4) In the UK, only 56% of trials funded by the Health Technology Assessment programme recruit their originally specified target sample size, with 32% receiving an extension.(5, 6) To address these issues a number of initiatives aimed at improving recruitment and retention in clinical trials have been established, including the MRC START research programme(7) and Trial Forge.(8) Recruitment and retention interventions identified as meriting formal evaluation include patient and public involvement (PPI).(9)

PPI in the United Kingdom has been defined as 'research being carried out "with" or "by" members of the public (including patients and carers) rather than "to", "about" or "for" them'.(10) Trials in the UK have experienced a recent surge in PPI activity, partly because the National Institute for Health Research (NIHR) now expects active PPI in the research it funds.(11) PPI roles in trials are primarily in agenda setting, steering committees, ethical review, protocol development and piloting.(12) There are two broad arguments for including PPI in health research: the moral argument (those affected by, or paying for, research should have a say in what and how it is done) and the consequentialist argument (PPI should improve research quality, efficiency and impact).

Because clinical trialists and funders are steeped in a predominantly quantitative, evidence-based culture, the consequentialist argument for PPI in clinical trials (for example, that it increases participant enrolment rates) is likely to play an important role in the adoption of meaningful PPI as routine, widespread practice. Hypotheses regarding how PPI could increase enrolment rates include improved access to potential participants, improved information sheets, improved trial design, more relevant research question, and peer endorsement of research.(13-16) One observational study of 114 trials reported a doubled odds of successful recruitment associated with 'consumer input', but this did not attain statistical significance (OR 2.00 [95% CI 0.36 – 10.05).(17) A more recent observational study reported a statistical association between PPI and recruitment success among UK mental health research studies,(13) but many potential confounding factors could not be controlled for, and there was a lack of information available about the nature of PPI in the included studies. Exploring the effectiveness of PPI practices to improve recruitment and retention of trial participants has been identified as one of the top research priorities for PPI in trials.(18)

This review aimed to measure the impact of PPI interventions on recruitment (specifically participant enrolment) and retention in clinical trials. A secondary objective was to explore how this impact varies according to context (e.g. patient population, recruitment setting, trial treatment/intervention) and the nature of the PPI intervention (e.g. activities, involvement model, PPI contributor characteristics).

## Methods

### Searches

We conducted a systematic review following the PRISMA statement(19) and prospectively registered the review on PROSPERO (registration number CRD42016043808).

We carried out a systematic electronic search in the following databases (last updated October 2017): Medline, Science Citation Index, Social Science Citation Index, Embase, PsychINFO, Cochrane library, CINAHL, Health Expectations journal. The search strategy was constructed by combining keywords within four topic domains: clinical trials, PPI, enrolment or retention of participants, and potential outcomes/change (see Appendix 1). In addition to the electronic database search, we searched the INVOLVE Evidence Library(20) for any papers pertaining to the impact of public involvement on health or public health research, and the ClinicalTrials.gov and WHO ICTRP clinical trial registries.

### Screening and study selection

We conceptualised PPI as a complex intervention,(21) involving human behaviours and often multiple interactive components. We included papers quantitatively evaluating the impact of a PPI intervention, compared with another non-PPI intervention or no intervention, on enrolment and/or retention rates in a clinical trial or trials in any patient population (see Table 1 eligibility criteria). A review restricted to randomised controlled trials would have given an incomplete summary of the impact of PPI, since many types of PPI interventions (for example, PPI in the early stages of trial design) are not amenable to randomisation; we therefore included non-randomised as well as randomised evaluations, with a plan for assessing risk of bias. The evaluation did not have to be the study authors' primary research question. There were no limits on publication date or language.

[Table 1 around here]

Initially, one reviewer (JC) screened all titles and abstracts for potentially eligible papers, and subsequently assessed full-text papers against the eligibility criteria. Another reviewer (SR)

supervised this process and provided advice when there was uncertainty about eligibility. Later, we received funding for a second reviewer (IRC) to independently screen all records in addition to JC. At the end of this process JC and IRC compared their results in terms of studies included and excluded. Discrepancies were discussed and the opinion of a third reviewer (AP) was sought when necessary to achieve consensus. We contacted authors to provide further information when confirmation of eligibility was required.

AP and IRC also carried out forwards and backwards citation searches by hand-searching reference lists of included studies and review articles and using the 'cited by' function in Scopus; any potentially eligible papers were double-screened for eligibility by JC.

**Data extraction**

Using a standardised data extraction form in Microsoft Access, qualitative information about trial context, the nature of PPI interventions, and the nature and findings of evaluations were extracted from each paper by one of three reviewers (JC, AP or IRC). This form was piloted and revised by JC and AP in the early stages. Quantitative data on the primary outcomes (enrolment and retention rates), context and PPI intervention for the meta-analyses were then independently extracted from included papers by two reviewers (JC and IRC) into a standardised Microsoft Excel spreadsheet (Table 2). These variables were chosen because the review team considered them to be potentially influential on enrolment and retention outcomes, they are sometimes or often reported in study publications, and, if categorical, could be split into no more than 2 or 3 categories (due to the small overall sample size). This is consistent with recommendations that systematic reviews of complex interventions include typologies of the structural characteristics of the intervention, and where few or no typologies exist, that face validity for categorisation be provided by experts working in the field.(22) Theories of change underpinning interventions were considered potentially important but could not be appropriately categorised for inclusion in this analysis. We are conducting a realist analysis on the same sample of studies to shed light on the underlying theory and mechanisms of impact of the included interventions (to be published separately).

[Table 2 around here]

Discrepancies between the two data extractors (JC and IRC) were discussed and the opinion of a third reviewer (AP) was sought if necessary to achieve consensus. We sought additional or accompanying papers where necessary to obtain the required data (for example, papers describing the contextual clinical trial or the development of the intervention) and contacted authors to provide further information when there were insufficient data reported in available papers.

**Risk of bias assessment**

Two reviewers (JC and IRC) independently assessed the risk of bias of the studies included in meta-analyses using the Cochrane Risk of Bias tool(23) for randomised studies and the ROBINS-I tool(24) for non-randomised studies (with pre-specified potential confounding domains of time, funder and patient population). Discrepancies were discussed and a third reviewer consulted if necessary to achieve consensus. The studies were assessed for risk of bias in relation to our review question, not the study authors' primary research question (which often differed from ours, particularly for the non-randomised studies).

**Meta-analyses**

The only criterion for carrying out meta-analyses was the availability of raw data to enable us to do so. We took the view that any amount of statistical heterogeneity would be acceptable,(25) and that even in the presence of high heterogeneity, an estimate of the average effect of PPI across studies, and the statistical significance of this effect, was worth reporting. We carried out two separate meta-analyses to determine the average impact of PPI on enrolment and retention. Numbers of participants enrolled and retained with and without PPI were combined using a random effects DerSimonian & Laird meta-analysis to report odds ratios and 95% confidence intervals (CI).We used a random effects model to allow for differences in the effect of PPI interventions from study to study, and generated 95% prediction intervals, which indicate a predicted range for the true effect of PPI in an individual study.(26) Heterogeneity was quantified using the I-squared statistic. We combined randomised and non-randomised studies for the main analysis, but separated them in a subgroup analysis and excluded non-randomised studies in a sensitivity analysis (see below). Where multiple non-PPI recruitment strategies had been employed within a study, the data were pooled for comparison with the PPI recruitment strategy. Where multiple PPI interventions had been compared within a study, both interventions were included as separate comparisons in the meta-analysis and numbers of participants in the comparator group were split equally across the two intervention arms. An Egger's test was carried out for each of the two meta-analyses to assess the risk of publication bias. As only two included studies investigated the cost per participant enrolled of PPI vs. non-PPI interventions, we did not perform a meta-analysis for this outcome.

We used subgroup analyses to explore the influence of context and PPI intervention characteristics on the association between PPI interventions and enrolment or retention rates, and to investigate sources of heterogeneity. These included separation of the randomised and non-randomised studies (due to the high statistical and methodological heterogeneity within our sample, and because non-

randomised studies can sometimes lead to precise but biased estimates of effect(27)), in addition to several pre-planned subgroup analyses (Table 2). We used univariate meta-regression to determine whether differences between subgroups were statistically significant. Sensitivity analyses excluded studies at high risk of bias, non-randomised studies, studies with small sample sizes (N<100), PPI interventions which included additional non-PPI components, and PPI interventions which were formal qualitative research (and therefore not universally classified as PPI).

All analyses were carried out using Stata 14.0SE (Stata- Corp, College Station, TX, USA), with a threshold of $p<0.05$ to determine statistical significance.

**Patient and Public Involvement in this Review**

The idea for this review emerged from meetings with an advisory panel for JC's research fellowship, which included two patient partners (including author AC). The patient partners were involved in the group in order to ensure that the research was relevant to, and informed by the perspectives of, patients and members of the public. They were chosen because of their long-term experience of PPI and interest in impact assessment. The decision to undertake this review was in part due to our patient partners' desire to quantitatively assess the impact of PPI, particularly on patient recruitment to clinical trials, because "a trial that recruits more quickly will ultimately benefit patients more quickly". While the review was underway, one patient partner retired and a third joined the group. The patient partners provided input at six advisory group meetings and email correspondence in between meetings. As well as helping to decide on the review question, the patient partners helped to decide on our definition of PPI, which contextual and intervention characteristics to explore and how to categorise them, and which potential confounding factors to focus on in the risk of bias assessments. In addition to influencing these decisions, their enthusiasm and belief in the importance of this work helped to maintain JC's motivation through what was a challenging piece of work. PPI has been a wholly positive experience for us and there are no negative outcomes to report.

## Results

**Characteristics of studies included in systematic review**

Our search results yielded 11,856 records. After excluding duplicates, two independent reviewers screened 6939 titles and abstracts, and assessed 134 full-text articles for eligibility. Twenty-six studies met the criteria for inclusion in the review (Figure 1).

[Figure 1 around here]

Table 3 shows the detailed characteristics of all included studies. Most were conducted in the USA or the UK and together covered a wide range of clinical topic areas and trial interventions. The PPI interventions were also diverse. Patients and/or members of the public were involved in different activities: 8 studies(28-35) used PPI in designing recruitment and retention strategies (e.g. as community partners, members of a Community Advisory Board, or focus group participants); 12 studies(29, 32, 36-45) used PPI in developing patient-facing information (e.g. patient information sheets, multimedia and online interventions, recruitment advertisements and verbal messaging) and 10 studies(28, 30, 46-53) used PPI to directly recruit or retain participants (e.g. hiring lay/community workers or asking existing participants to refer friends/relatives). The extent of involvement ranged from one patient advocate acting as a panellist in a one-off educational seminar for recruiting clinicians,(42) to over 80 people helping to develop a patient-friendly online trials registry,(29, 54) or community partners initiating and leading their own recruitment strategies.(30, 35) There were also numerous intended purposes of PPI, including increasing trust between communities and researchers,(28, 30, 47, 49, 50, 53) improving the quality and acceptability of patient-facing information or recruitment messages,(29, 36, 37, 40, 43-45) accessing potential participants via existing participants,(46, 51) and increasing the cultural competence of the research among minority ethnic communities.(33-35, 46, 47, 49, 51-53) Many of the PPI interventions also included non-PPI components, such as the involvement of other stakeholders or experts(29, 33, 34, 41, 43, 50) or novel modes of information delivery which were not a consequence of the PPI.(38, 40, 45, 49, 51-53)

[Table 3 around here]

**Characteristics of studies included in meta-analyses**

Nineteen studies (21 PPI interventions) reporting data from 178,921 participants were included in our enrolment meta-analysis, while 5 studies (6 PPI interventions) reporting data from 6520 participants were included in our retention meta-analysis. Table 4 shows the aggregate characteristics of these studies, including those used in subgroup and sensitivity analyses.

[Table 4 around here]

Six studies could not be included in the enrolment meta-analysis due to insufficient data. Three of these studies reported no significant impact of PPI interventions on enrolment,(41, 42, 50) while the other 3 studies reported an increase in enrolment rates associated with PPI interventions (statistical significance unknown).(32, 34, 45)

**Risk of bias of studies included in meta-analysis**

Of the 12 non-randomised studies, 11 were deemed at 'serious' risk of bias(30, 31, 33, 35, 37, 44, 46, 49, 51-53) and one at 'critical' risk of bias(28) due to potential, uncontrolled confounding by patient population and/or time. Often this was because the study was opportunistic, for example comparing the success of different recruitment strategies, rather than designed specifically to evaluate the impact of PPI vs. non-PPI on enrolment or retention. Of the eight randomised studies, only one was deemed at 'high' risk of bias(29) due to missing outcome data, while two had 'some concerns'(38, 47) and five had 'low' risk of bias.(36, 39, 40, 43, 48) The Egger's test showed evidence of possible publication bias (p=0.001) (see funnel plot in Appendix 5).

**Impact of PPI interventions on enrolment**

Pooling the data in a meta-analysis revealed that, on average, PPI interventions significantly increased the odds of a patient enrolling in a clinical trial compared with no PPI or non-PPI interventions (OR 1.87 [95% CI 1.31 – 2.68]; p=0.001). At the individual study level, results varied considerably ($I^2$ = 95.8%), yielding a 95% prediction interval of OR 0.35 to 9.96 (Figure 2). Half of the PPI interventions (11/21) were associated with significantly higher enrolment rates compared to no PPI or non-PPI interventions,(30, 31, 33, 35, 37, 44, 46, 47, 49, 51, 52) 9 PPI interventions were not significantly associated with enrolment rate,(29, 30, 36, 38-40, 43, 55) and one PPI intervention was associated with significantly lower enrolment (OR 0.41 [95% CI 0.23 – 0.72]).(53) In this study, recruitment of African Americans with diabetes via faith-based organisations (PPI) yielded lower enrolment of patients than recruitment via the health system (non-PPI); the authors stated that this was not surprising, given 'the nature of the provider-patient relationship' and since 'African Americans may be less inclined to have their personal health history known by other members of their church congregation, given the stigma associated with chronic illnesses' (p. 275). Contrast this with Vincent *et al.*'s study, which showed the largest PPI effect size in our sample (OR 13.48 [95% CI 6.07 – 29.95]): here, the PPI contributors (Catholic church partners, some of whom shared a high risk of diabetes with the Mexican American target population) initiated, co-designed and co-delivered a recruitment strategy which was highly successful compared to strategies initiated by the researchers. Note, however, that both of these outlying studies were judged to be at high risk of bias and were excluded from the sensitivity analysis.

[Figure 2 around here]

Exploratory subgroup analyses revealed that the overall positive association between PPI interventions and enrolment substantially increased when at least one PPI contributor had lived experience of the health condition under study (OR 3.14 [2.11 – 4.66]) and all but disappeared when

PPI contributors did not have such lived experience (OR 1.07 [0.83 – 1.37]). Meta-regression confirmed that this effect was statistically significant (p=0.017). Subgroup differences between any of the other variables explored (Appendix 2), including evaluation design (randomised vs. non-randomised; Figure 3), trial intervention type (simple vs. complex), PPI timing (designing recruitment and retention strategies vs. developing patient-facing information vs. direct recruitment or retention of participants) and enrolment rate denominator (pre vs. post eligibility screening) were not found to be statistically significant using meta-regression (p>0.3). Meta-regression was not able to explain the high between-study heterogeneity.

[Figure 3 around here]

The positive overall association between PPI interventions and enrolment remained statistically significant throughout all other sensitivity analyses (see Appendix 3). Exclusion of studies at high risk of bias (including all non-randomised studies and one randomised study) reduced the estimated effect size to OR = 1.17 (95% CI 1.04 – 1.32), removed all of the statistical heterogeneity ($I^2$=0.0%) and produced a 95% prediction interval of 1.01 to 1.36, suggesting that any new, high quality randomised study of a PPI intervention would almost certainly demonstrate a positive impact of PPI on enrolment. The disappearance of the statistical heterogeneity suggests that it may be due to the diverse range of evaluation methods used and the high risk of bias by confounding in non-randomised studies. It could also be explained by heterogeneity of the PPI interventions: almost all of the PPI interventions in the high quality, randomised studies were aimed at improving patient information, while the more complex and more unusual interventions were largely evaluated using poorer quality observational or quasi-experimental methods. Of the two studies reporting the cost per participant enrolled, MacEntee *et al.* reported that a PPI approach involving recruitment at community centres through a local contact person, although more effective, was more than twice the cost per participant of a non-PPI approach involving postal invitations ($23 vs. $11).(49) Chlebowski *et al.* reported that a PPI approach involving recruitment via existing research participants was only one quarter the cost of a non-PPI approach involving the use of commercial mailing lists to send postal invitations ($59 vs. $259).(46)

**Impact of PPI interventions on retention**

Pooling the data in a meta-analysis found that, on average, PPI interventions were not significantly associated with retention of study participants (OR 1.20 [95% CI 0.68 – 2.12]; p=0.519). Again, results varied across studies, with effect estimates ranging from OR=0.38 to OR=3.20 ($I^2$ = 78.3%; 95% prediction interval 0.21 – 6.86) (Figure 4). PPI in developing patient information sheets was not

significantly associated with retention,(36, 39) while using lay Community Health Advisers to support participants (the only PPI intervention specifically targeting retention) led to a significant improvement in retention rates (OR 2.52 [95% CI 1.82 – 3.50]).(48) Apart from this latter example, the PPI interventions primarily targeted enrolment, not retention.

[Figure 4 around here]

We did not perform subgroup analyses for retention outcomes due to the small sample size (only 5 studies / 6 PPI interventions). Sensitivity analyses did not alter the result (Appendix 4) and the Egger's test showed no evidence of publication bias (p=0.772) (Appendix 6).

## Discussion

### Summary of findings

This review identified a variety of PPI interventions aimed at improving participant enrolment and retention in clinical trials, including PPI in the design of recruitment and retention strategies and patient-facing information, identifying and approaching potential participants, and troubleshooting when recruitment was poor. We did not identify any studies which assessed the impact of PPI in developing the trial question or designing the trial itself.

There was considerable statistical heterogeneity between studies (estimated effect sizes varied widely), but on average, PPI interventions significantly increased the odds of a patient enrolling in a clinical trial, relative to no PPI or non-PPI recruitment interventions. This remained statistically significant in sensitivity analyses which removed non-randomised studies and studies at highest risk of bias.

A key exploratory finding was that the effect size was significantly greater for PPI with lived experience of the health condition under study, compared to PPI without such lived experience. This is perhaps unsurprising and is consistent with the view that PPI contributors can benefit research through their role as 'expert in lived experience',(56) though it is unclear how exactly this might happen - something which we are exploring in a complementary realist analysis of the included studies.

Far fewer studies evaluated the impact of PPI interventions on retention of trial participants. Those that did showed, on average, no significant improvement in retention. None of the PPI interventions included people with lived experience of the health condition under study, and most of them primarily targeted enrolment rather than retention.

**Review strengths and limitations**

To our knowledge, this is the first attempt to combine data on the impact of PPI on enrolment and retention in health research, providing a quantitative summary and exploring the influence of contextual and intervention factors. Our results are consistent with previous observational studies which suggested an average positive association between PPI and recruitment success in UK-based health studies.[15, 16] Unlike these previous studies, our review encompassed all geographies and clinical areas and we were able to explore, to some extent, the influence of PPI characteristics and context.

Our review has several limitations. Many of the interventions included non-PPI components and it was impossible to separate out the effects of these from the effects of the PPI components. Nevertheless, PPI was still associated with improved enrolment when interventions including non-PPI components were excluded in a sensitivity analysis. We were unable to explore the influence of many potentially important factors such as underlying programme theory, intervention fidelity and sustainability, the quality of relationships between PPI contributors and researchers, and the attitude of research leaders towards PPI.(22, 57) We are currently undertaking a realist analysis of the included papers to shed more light on these complexities.(22) The framing of PPI as a complex intervention is itself controversial,(58) but we believe that this approach, alongside a range of other perspectives, can usefully contribute to the much broader debate about the impact of PPI on health research.

In addition, Egger's tests indicated possible publication bias in relation to enrolment outcomes. While this could actually be due to poor methodological quality leading to spuriously inflated effects in smaller studies,(59) our main findings with regard to enrolment should be interpreted with caution. We were unable to provide a useful summary of PPI cost-effectiveness because very few studies included an economic impact assessment; thus an 'effective' PPI intervention may not necessarily be cost-effective.

**Implications for clinical trialists and PPI policy makers**

Our findings add support to the case for involving patients and carers in the design and conduct of clinical trials. In the UK, trial funding proposals and protocols are often reviewed by institutional lay panels; our review suggests that ideally, at least some of these reviewers would be patients and carers with lived experience of the health condition under study.

The apparent failure of some PPI interventions to improve enrolment and retention demonstrates that many factors other than PPI also influence these outcomes. In addition, PPI interventions in our

review were often one of several recruitment strategies used by clinical trialists and may not have been sufficient alone; for example, Sanders *et al.* found that although their word-of-mouth PPI strategy was relatively effective at enrolling those it reached, due to limited reach (200 people) it contributed only 2.2% of the total participants, compared with 70.3% for the targeted mail-out strategy (which reached 21,400 people).(51) PPI will not solve all recruitment and retention problems and clinical trialists would be wise to implement multiple additional strategies to minimise the risk of poor enrolment and retention. Furthermore, PPI in the early stages of trial development can sometimes lead researchers to abandon the whole idea of the trial,(60) suggesting that if the target population are not convinced that the trial question is worth answering, PPI in later stages of the trial (such as those seen in this review) may be futile.

**Unanswered questions and future research**

Well-planned, high quality evaluations are needed to improve our understanding of (1) the mechanisms underlying the impact of PPI on enrolment and retention, (2) the cost-effectiveness of PPI interventions (an important part of the drive to improve trial efficiency), (3) the impact of PPI interventions specifically targeting retention (which has received very little attention relative to enrolment), and (4) the impact of PPI at the early stages of trial proposal and design.

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## Contributorship statement

Authors JCC, AC, SPZ, DE and SR conceived and designed this review. JCC, IRC and AP undertook searches, record screening and data extraction (supervised by JCC). JH wrote the code for and ran the meta-analyses in Stata. All authors contributed to interpretation of the results. JCC wrote the manuscript and all authors commented on the draft and approved the final version. JCC is the guarantor for this work. The authors are grateful to Michael Osborne (patient contributor), Prof Shaun Treweek and Prof Louise Locock (University of Aberdeen) for providing expert advice throughout this study; Dr Ben Feakins (Medical Statistician, University of Oxford) for providing

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## Competing interests declaration

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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## Transparency declaration

The lead author (study guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

## Tables and Figures



## Appendices

## References


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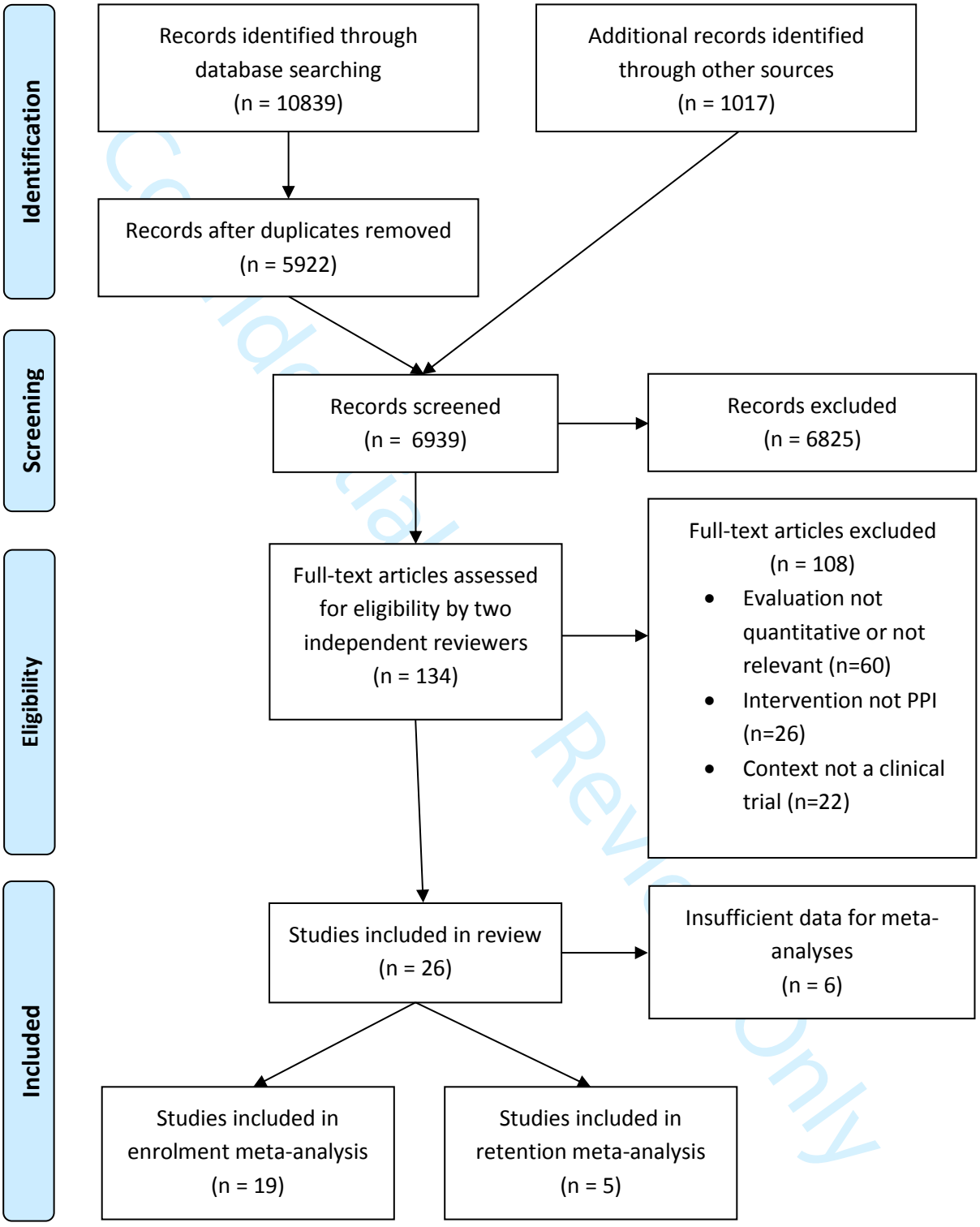
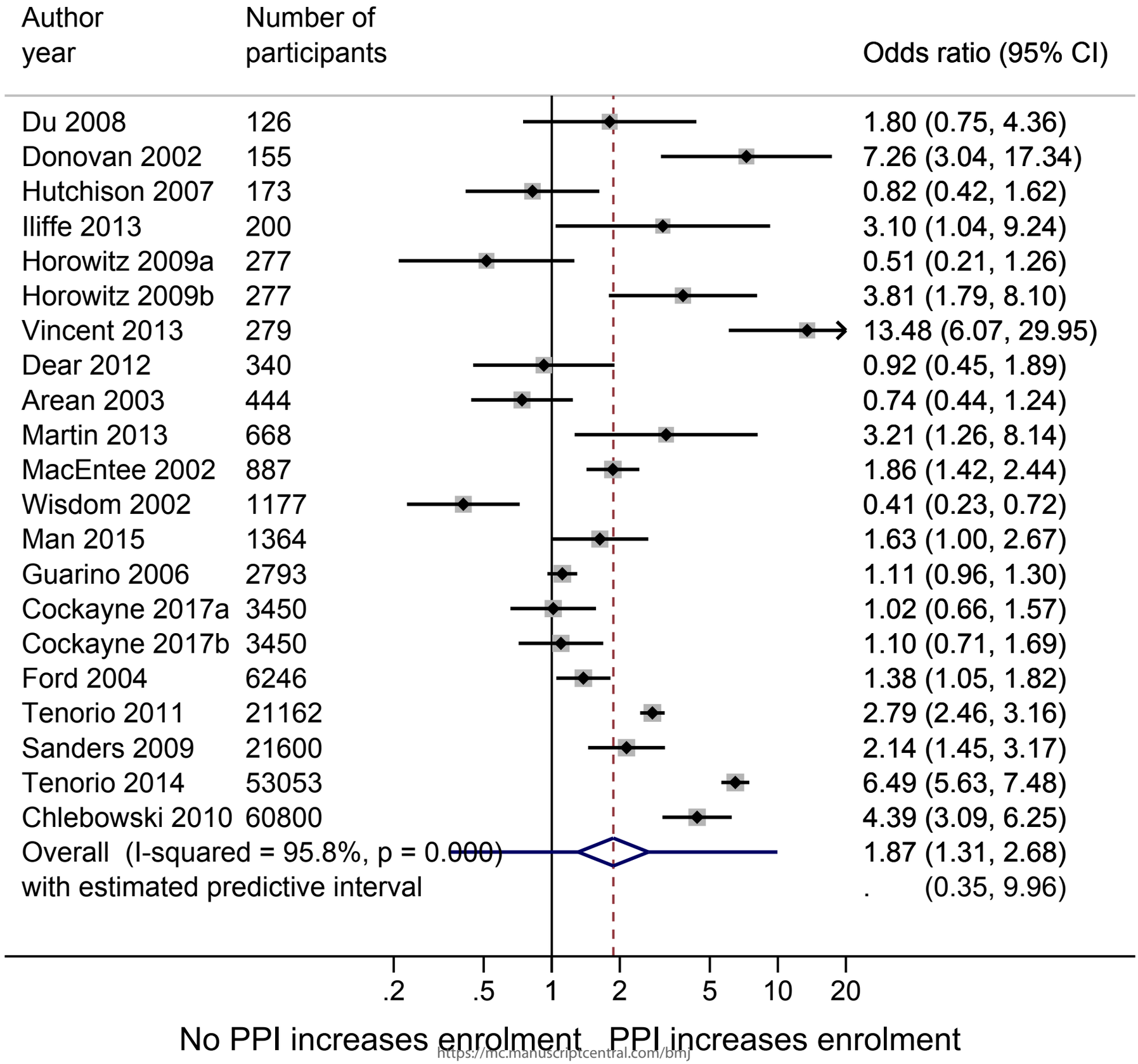
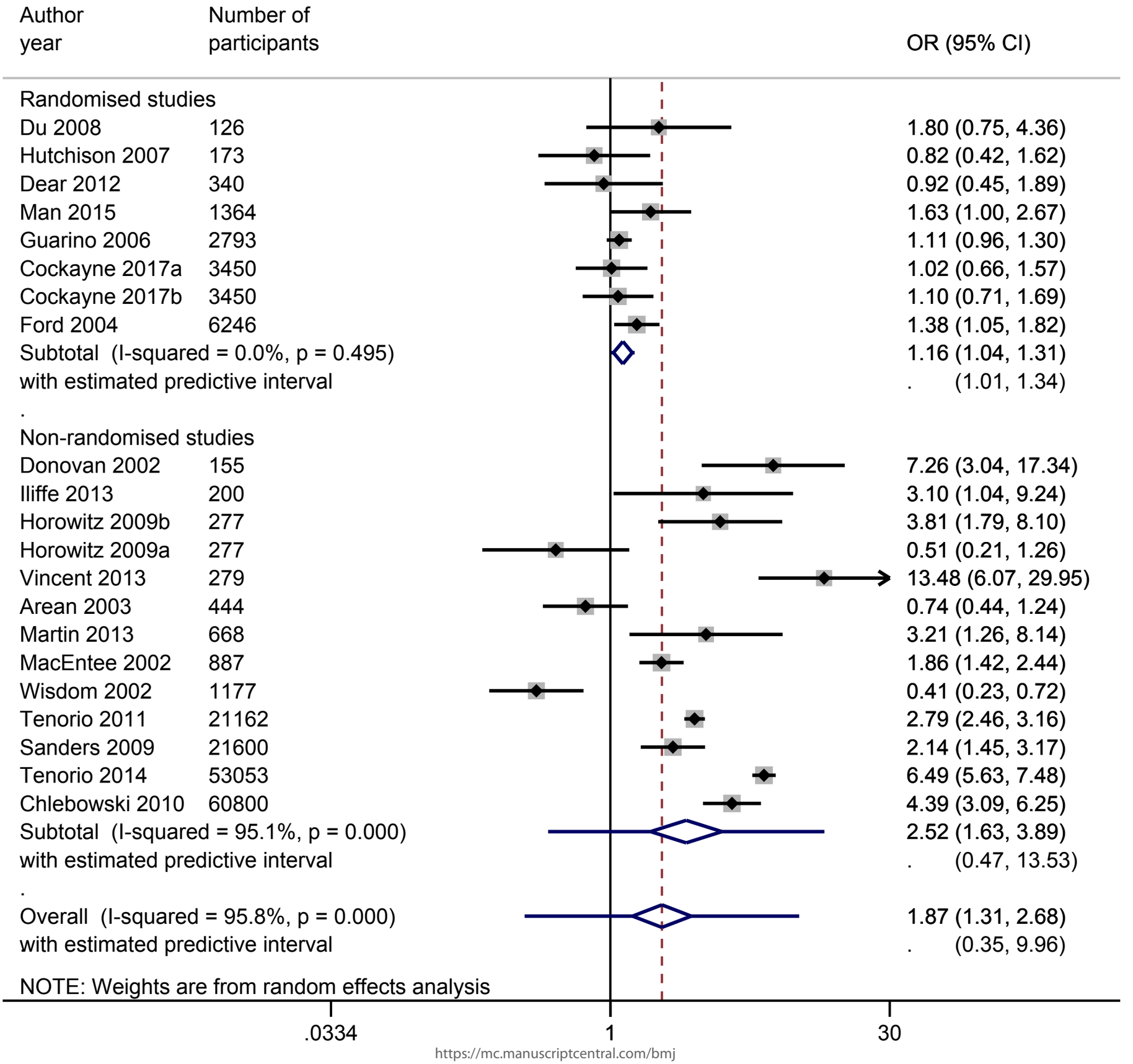
**Figure 1: PRISMA flow diagram of records/studies included at each stage of screening and in the final meta-analyses**




Author year
Number of participants
Odds ratio (95% CI)
Du 2008 126 1.80 (0.75, 4.36)
Donovan 2002 155 7.26 (3.04, 17.34)
Hutchison 2007 173 0.82 (0.42, 1.62)
Iliffe 2013 200 3.10 (1.04, 9.24)
Horowitz 2009a 277 0.51 (0.21, 1.26)
Horowitz 2009b 277 3.81 (1.79, 8.10)
Vincent 2013 279 13.48 (6.07, 29.95)
Dear 2012 340 0.92 (0.45, 1.89)
Arean 2003 444 0.74 (0.44, 1.24)
Martin 2013 668 3.21 (1.26, 8.14)
MacEntee 2002 887 1.86 (1.42, 2.44)
Wisdom 2002 1177 0.41 (0.23, 0.72)
Man 2015 1364 1.63 (1.00, 2.67)
Guarino 2006 2793 1.11 (0.96, 1.30)
Cockayne 2017a 3450 1.02 (0.66, 1.57)
Cockayne 2017b 3450 1.10 (0.71, 1.69)
Ford 2004 6246 1.38 (1.05, 1.82)
Tenorio 2011 21162 2.79 (2.46, 3.16)
Sanders 2009 21600 2.14 (1.45, 3.17)
Tenorio 2014 53053 6.49 (5.63, 7.48)
Chlebowski 2010 60800 4.39 (3.09, 6.25)
Overall (I-squared = 95.8%, p = 0.000) 1.87 (1.31, 2.68)
with estimated predictive interval . (0.35, 9.96)
.2
.5
1
2
5
10
20
No PPI increases enrolment
PPI increases enrolment


Author
year
Number of
participants
OR (95% CI)
Randomised studies
Du 2008 126 1.80 (0.75, 4.36)
Hutchison 2007 173 0.82 (0.42, 1.62)
Dear 2012 340 0.92 (0.45, 1.89)
Man 2015 1364 1.63 (1.00, 2.67)
Guarino 2006 2793 1.11 (0.96, 1.30)
Cockayne 2017a 3450 1.02 (0.66, 1.57)
Cockayne 2017b 3450 1.10 (0.71, 1.69)
Ford 2004 6246 1.38 (1.05, 1.82)
Subtotal (I-squared = 0.0%, p = 0.495) 1.16 (1.04, 1.31)
with estimated predictive interval . (1.01, 1.34)
.
Non-randomised studies
Donovan 2002 155 7.26 (3.04, 17.34)
Iliffe 2013 200 3.10 (1.04, 9.24)
Horowitz 2009b 277 3.81 (1.79, 8.10)
Horowitz 2009a 277 0.51 (0.21, 1.26)
Vincent 2013 279 13.48 (6.07, 29.95)
Arean 2003 444 0.74 (0.44, 1.24)
Martin 2013 668 3.21 (1.26, 8.14)
MacEntee 2002 887 1.86 (1.42, 2.44)
Wisdom 2002 1177 0.41 (0.23, 0.72)
Tenorio 2011 21162 2.79 (2.46, 3.16)
Sanders 2009 21600 2.14 (1.45, 3.17)
Tenorio 2014 53053 6.49 (5.63, 7.48)
Chlebowski 2010 60800 4.39 (3.09, 6.25)
Subtotal (I-squared = 95.1%, p = 0.000) 2.52 (1.63, 3.89)
with estimated predictive interval . (0.47, 13.53)
.
Overall (I-squared = 95.8%, p = 0.000) 1.87 (1.31, 2.68)
with estimated predictive interval . (0.35, 9.96)
NOTE: Weights are from random effects analysis
.0334
1
30

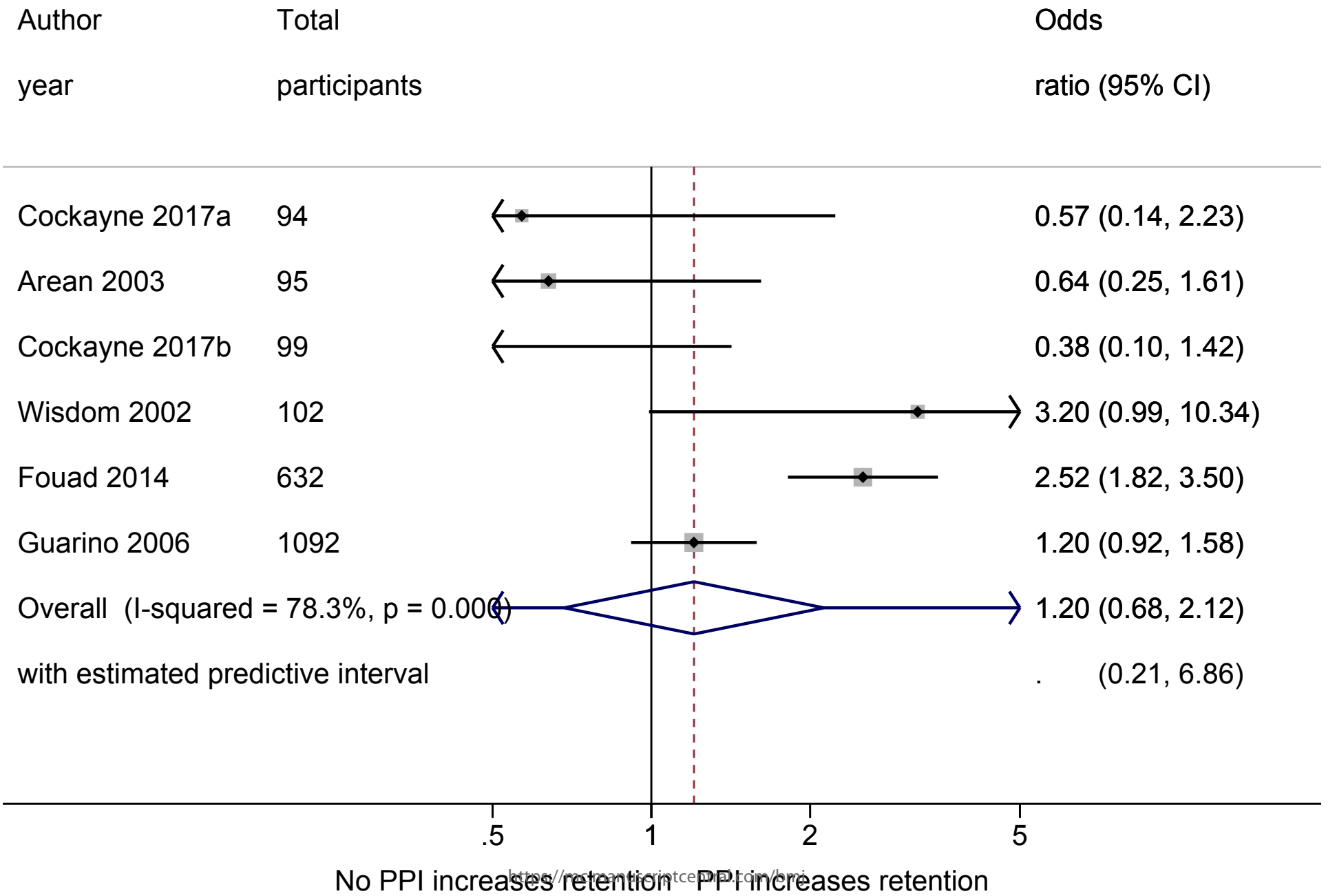


**Table 1: Study eligibility criteria**

| | |
|---|---|
| Population: | Potential clinical trial participants in any patient population. |
| Intervention: | A trial methodological intervention which was, or included as an active component, any of kind PPI consistent with the INVOLVE definition of public involvement: 'research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them.'(10) The term 'public' includes patients, potential patients, carers and people who use health and social care services as well as people from organisations that represent people who use services. The PPI contributor(s) had to be either a patient, carer or lay member of the public; research or healthcare professionals sharing a characteristic with the target population other than health condition (e.g. ethnicity, gender, age) were not classified as PPI. We included qualitative research as a form of patient or public consultation, since this was previously deemed PPI in an INVOLVE report of PPI impact.(16) However, as qualitative research is excluded from many definitions of PPI, we performed a sensitivity analysis without this type of study. |
| Comparator: | A trial methodological intervention with no PPI, or no intervention. We excluded studies with no direct comparison group (e.g. those comparing enrolment and/or retention rates against what might be expected for that patient population). |
| Outcome: | Enrolment and/or retention rate, defined as the proportion of potential participants enrolled and the proportion of enrolled participants retained, respectively. Enrolment included giving consent to take part or being randomised to the trial. We excluded studies which assessed hypothetical participation or willingness to participate in clinical trials, rather than actual enrolment in a trial. Retention included adherence to a treatment program and/or follow-up procedures. At the start of data extraction for our meta-analyses, for pragmatic reasons we decided to exclude studies with no appropriate enrolment rate denominator (e.g. enrolment reported as absolute numbers rather than rates). This led to the retrospective exclusion of some studies which had been included during initial screening. |
| Context: | Clinical trial or trials, defined by the World Health Organization as 'any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes'. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc. This definition includes Phase I to Phase IV trials.'(61) For inclusion in the review, the primary outcome had to be a measure of health status; we excluded studies of trials with a behavioural or other non-clinical primary outcome. |
| Study design: | Observational as well as randomised studies were included, since for many PPI interventions, randomisation would not be practical. |

**Table 2: Variables extracted and included in meta-analysis**

| Variable | Format | Description / additional information |
|---|---|---|
| ***Outcomes data:*** | | |
| Number of individuals invited/approached/reached during recruitment period | Integer | Also included total number of participants, where the intervention was targeting a subgroup within the trial population (e.g. a minority ethnic group) and subgroup proportion with/without the intervention were compared. |
| Number of participants who enrolled in trial | Integer | Included giving consent to take part or being randomised to the trial |
| Number of participants retained in trial | Integer | Where retention was measured at different time points along the treatment or follow-up pathway, the outcome representing the most complete adherence/follow-up was used. |
| Enrolment rate denominator | Pre-eligibility or post-eligibility screening | An intervention might increase the number of recruits, but not necessarily the number of *eligible* recruits, if enrolment was measured before screening for eligibility occurred. Where both pre-screening and post-screening enrolment figures were provided by the authors, both were extracted but only the pre-eligibility figure was used in the primary meta-analysis as this spans a greater period of the recruitment process. Subgroup analyses tested whether there was a difference between pre- and post- eligibility enrolment findings. |
| ***Contextual data:*** | | |
| Trial recruitment setting | Healthcare, community or mixed (both settings) | 'Healthcare' means participants were recruited via contact or association with a healthcare service. |
| Trial intervention type | Simple, complex or multiple | 'Simple' included drugs, other biological products and medical devices; 'Complex' included surgical procedures, behavioural, psychological, educational and health service interventions; Multiple means trials of both types of interventions were included in the study. |
| PPI in choosing research question/topic | Yes or no | PPI in choosing the research question or topic might improve enrolment due to increased relevance/importance to the target population. If not reported in the paper or accompanying papers, and if study authors did not respond to requests for further information, it was assumed that the answer was 'no'. |
| ***PPI intervention characteristics:*** | | |
| Timing/activity | (1) designing recruitment or retention strategy; (2) developing | Timing of the start of PPI intervention / first PPI activity. Earlier involvement might lead to greater improvements for enrolment/retention. |

| | | |
|---|---|---|
| | patient-facing information; (3) directly approaching / recruiting or retaining participants | 'Patient-facing information' included paper and online materials and verbal messaging. |
| Number of the above activities targeted by PPI intervention (1-3). | 1, 2 or 3 | More extensive involvement might lead to greater improvements for enrolment/retention |
| PPI intervention chosen/designed specifically to increase enrolment or retention | Yes or no | An intervention chosen or designed with this specific purpose maybe more effective |
| PPI model | One-off, intermittent or full team membership | 'One-off' = time-limited, single phase or a single task (e.g. a focus group)<br>'Intermittent' = involved periodically during the life of the trial (e.g. an ongoing advisory group)<br>'Full team membership' = PPI contributors considered part of the research team (e.g. a grant co-applicant, co-investigator, research partner or employed recruiter) |
| Number of PPI contributors involved | 1-2 or 3+ | A group of PPI contributors may provide more diverse perspectives than 1 or 2 individuals, the latter being common practice in UK Trial Steering Committees. |
| Lived experience | Yes or no | At least one PPI contributor had lived experience (as patient or carer) of the condition being targeted by the trial. If study authors did not indicate that lay/public contributors were patients or had lived experience of the condition, and did not respond to requests for clarification, we assumed that the answer was 'no'. |
| PPI visible to potential trial participants | Yes or no | This means trial participants would have known about the PPI, either through direct interaction with PPI contributors or information about their involvement in the trial. |

**Table 3. Characteristics of studies included in our review of the impact of PPI on enrolment and retention in clinical trials.**

**(a) Contextual / clinical trial characteristics**

| Study | Participants | Geographical setting | Clinical trial intervention(s) / treatment(s) |
|---|---|---|---|
| Arean *et al.* 2003(28, 55) | Persons aged 65 and older with symptoms of depression, anxiety, and at-risk drinking | San Francisco, USA | Three types of psychosocial intervention for depression; (PPI group); social service model of care delivered in a community geriatric medicine clinic (comparison group) |
| Chlebowski *et al.* 2010(46, 62, 63) | Healthy white men aged 55+ years and healthy black men aged 50+ years | USA (multi-site) | Selenium and vitamin E vs. placebo for prevention of prostate cancer |
| Cockayne *et al.* 2017(36, 64) | People over the age of 65 who had attended a routine podiatry appointment within the past 6 months | UK (multi-site) | Podiatry intervention vs. usual care for prevention of falls in older people |
| Dear *et al.* 2012(29, 54) | Cancer patients consulting with their physician | Australia (multi-site) | Various (multiple trials included) |
| Donovan *et al.* 2002(37, 65) | Men aged 50-69 years diagnosed with localised prostate cancer | UK (multi-site) | Surgery, radiotherapy or monitoring for treatment of localised prostate cancer |
| Du *et al.* 2008(38) | Lung cancer patients aged 21-80 years | Detroit, USA | Various therapeutic and non-therapeutic (multiple trials included) |
| Ford *et al.* 2004(47) | African American men aged 55-74 years | USA (multi-site) | Screening for prostate, lung and colorectal cancers |
| Fouad *et al.* 2014(48, 66) | Minority ethnic, low-income women with low-grade cervical cytologic abnormalities | Jefferson County, Alabama, USA | Immediate colposcopy, triage or conservative management of a cytologic diagnosis of atypical squamous cells of undetermined significance |
| Guarino *et al.* 2006(39, 67) | Gulf War veterans with fatigue, musculoskeletal pain and/or cognitive complaints | USA (multi-site) | Cognitive behavioural therapy, aerobic exercise or both versus usual care for treatment of Gulf War veterans' illnesses |
| Horowitz *et al.* 2009(30, | Adults with pre-diabetes | East Harlem, New York, USA | Community-based, peer-led weight loss program to prevent diabetes |

| | | | |
|---|---|---|---|
| 68) | | | |
| Hutchison *et al.* 2007(40, 69) | Patients diagnosed with colorectal, breast or lung cancer and clinically eligible for entry into a randomised treatment trial | Glasgow, UK | Cancer treatment vs. control/standard treatment or best supportive care |
| Iliffe *et al.* 2013(31, 70, 71) | Patients with moderate to severe Alzheimer's disease who had been treated with donepezil for at least 3 months | UK (multi-site) | Continue donepezil, discontinue donepezil, discontinue donepezil and start memantine, or continue donepezil and start memantine, for treatment of moderate to severe Alzheimer's disease |
| Kass *et al.* 2009(41) | Cancer patients who had been referred for evaluation with an oncologist regarding possible participation in an early-phase clinical trial | USA (multi-site) | Cancer treatments (various early-phase clinical trials) |
| Kimmick *et al.* 2005(42) | Cancer patients aged 65 or older | USA (multi-site) | Cancer treatments (various trials) |
| MacEntee *et al.* 2002(49) | Community-dwelling elders with a poor history of oral care | Vancouver, Canada | Antibacterial mouthwash to reduce tooth loss |
| Man *et al.* 2015(43, 72) | Adult patients with depression | UK (multi-site) | 12-month telehealth intervention vs. usual GP care for treatment of depression |
| Martin *et al.* 2013(44, 73) | New mothers who self-identified as Black/African American or Hispanic/Latina | New York City, USA | Behavioural educational intervention to prevent postpartum depression among Black and Latina women |
| Moinpour *et al.* 2000(50) | Healthy men age 55+ years | USA (multi-site) | Finasteride vs. placebo to prevent prostate cancer |
| Porter *et al.* 2016(32) | Cancer patients registered at one clinical centre | Ohio, USA | Cancer treatments (various trials) |
| Sanders *et al.* 2009(51, 74) | Women aged 70+ years at high risk of falls or fractures | Victoria, Australia | Vitamin D vs. placebo to prevent fractures |
| Tenorio *et al.* 2011(33, 75, 76) | Men and women aged 55-74 years | Denver, USA | Screening vs. routine medical care to reduce mortality from prostate, lung, colorectal and ovarian cancers |
| Tenorio *et al.* 2014(52, 77, 78) | Persons who had smoked at least 30 pack-years of cigarettes | Denver, USA | Computed tomography vs. x-ray screening to diagnose and reduce mortality from lung cancer |
| Vicini *et al.* 2011(34) | Cancer patients diagnosed and treated at one hospital | Michigan, USA | Interventions focused on cancer treatment, prevention, detection, symptom management or cancer control (various clinical trials) |

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| Vincent *et al.* 2013(35, 79) | Spanish-speaking Latinos of Mexican origin at high risk of diabetes | Arizona, USA | Community-based weight loss program to prevent diabetes |
| Wallace *et al.* 2006(45) | Men with early-stage prostate cancer | Toronto, Canada | Surgical prostatectomy vs. interstitial radiation for treatment of early-stage prostate cancer |
| Wisdom *et al.* 2002(53) | African Americans with type 2 diabetes diagnosed after age 30 years | Michigan, USA | Self-management program vs. usual care for treatment of diabetes |

**(b) PPI intervention characteristics**

| Study | Primary aim of intervention | PPI component(s) | Other (non-PPI) components* | Author proposed mechanism |
|---|---|---|---|---|
| Arean *et al.* 2003(28, 55) | To improve recruitment and retention of older minority adults to trial | All recruitment and study procedures were discussed at bimonthly consumer advisory board meetings. A community member was trained by research staff to recruit and screen participants. | A range of other 'consumer-centered' strategies including face-to-face recruitment, personalised mailings and in-home interviews. | Overcoming stigma and mistrust barriers associated with research in minority communities |
| Chlebowski *et al.* 2010(46, 62, 63) | To improve rates of consent to randomisation in trial | Women already participating in a large health research project were asked to recruit their husbands | None | Women participating in clinical studies are altruistic and their husbands share this quality and are willing to participate in a similar clinical trial |
| Cockayne *et al.* 2017(36, 64) | To improve trial recruitment rates | Two different PPI interventions:<br>(a) 'Bespoke user-tested' PIS: Formal user testing of PIS by 30 members of the public.<br>(b) 'Template-developed PIS': Historical non-bespoke user testing; PPI group reviewed PIS and gave feedback. | 'Bespoke user-tested' PIS: Design input by researchers and commercial company<br>'Template-developed PIS': Design input by experienced researchers | Improving the quality and appearance of patient information sheets (PIS) |
| Dear *et al.* 2012(29, 54) | To improve the proportion of patients with whom participation in any clinical trial was discussed | Consumer input into design and content of a consumer-friendly online cancer trials registry | Online cancer trials registry developed by web company with input from staff at Australian New Zealand Clinical Trials Registry | Improving consumer knowledge and understanding of clinical trials; enabling patients to search for local trials they might like to join; providing decision support for patients considering joining a trial. |
| Donovan | To improve rates | In-depth interviews with potential | Qualitative analysis of interviews by | Uncovering information and |

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| *et al.* 2002(37, 65) | of consent to randomisation in trial | participants who had been invited to take part | researchers. Other qualitative research methods including interviews with recruiters and analysis of audio-recorded recruitment appointments. Findings were used to change patient information and train recruiters. | communication issues during recruitment to the trial |
| Du *et al.* 2008(38) | To improve clinical trial enrollment at a large cancer centre | Presentation of a view on clinical trials from the perspectives of patients with diverse ethnic backgrounds and characteristics (in addition to standard care). | Video developed by National Cancer Institute | Positively changing patients' knowledge and attitudes regarding clinical trials |
| Ford *et al.* 2004(47) | To improve rates of recruitment to trial | Church-based project sessions including consent taking, plus enhanced recruitment letter from a prominent local African American man (Arm C of trial) | Screening was conducted by African American interviewers | Addressing four types of barriers (sociocultural, economic, individual and study design) to recruitment of minority groups. |
| Fouad *et al.* 2014(48, 66) | To improve rates of retention in trial and adherence to scheduled appointments | Community Health Advisor (CHA) model, in which community members served as a link between participants and study investigators and provided additional support to participants, in addition to standard retention activities. | None | Providing a trustworthy mentor to help participants overcome personal barriers to retention |
| Guarino *et al.* 2006(39, 67) | To improve informed consent (participants' understanding of the trial) | Focus group of Gulf War veterans reviewed and edited PIS | None | Improving the quality and accessibility of the PIS |
| Horowitz *et al.* 2009(30, 68) | To increase recruitment of black and Latina people into trial | Two different PPI interventions:<br>(a) 'Public events' recruitment strategy: Community members | None | Overcoming barriers to recruitment of minority populations, including fear or mistrust of research, cultural barriers and lack of opportunity to take part |

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| | | recruited participants at public events.<br>(b) 'Partner-led' recruitment strategy: Community advocates designed and led recruitment strategy. | | |
| Hutchison *et al.* 2007(40, 69) | To improve recruitment to cancer clinical trials | In addition to standard written information, patients were given access to audiovisual information which had been designed with input from two cancer patients and was presented by a local actress. | Development of audiovisual patient information was led by professionals. | Improving patients' understanding of clinical trials, including randomisation |
| Iliffe *et al.* 2013(31, 70, 71) | To explore why, in some areas, recruitment rates had been below what was hoped | 2 focus groups with patients with neurological conditions and carers, leading to changes in recruitment strategy | None | Identifying the cause of recruitment problems and suggesting remedial actions |
| Kass *et al.* 2009(41) | To improve patients' understanding of early-phase clinical trials | Intervention included video clips of five actors portraying patients who decided to enroll in a clinical trial (three) or not to enrol (two). The scripts were based on real patient narratives. The overall intervention was modified following feedback from 18 cancer patients and survivors. | Intervention was a self-directed, narrated, computer-based presentation, including suggested questions and video clips of oncologists. Oncologists also gave feedback on the intervention. | Improving patients' understanding of the purpose and benefits of early-phase clinical trials |
| Kimmick *et al.* 2005(42) | To improve accrual of older persons by physicians to cancer treatment | Educational intervention for physicians, including a case discussion seminar with a patient advocate panellist. | The intervention also included standard information, an educational symposium, educational materials, a list of available protocols for use, and a monthly email and mail reminders | Enabling physicians to discuss common issues in geriatric oncology with a panel of experts. |

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| | trials | | for one year (with no patient input). | |
| MacEntee *et al.* 2002(49) | To improve recruitment of ethnic minorities | At least one contact person in each community centre served as a volunteer interpreter and cultural liaison between potential recruits and researchers. | Recruitment by researchers via community centres, including posters and an introductory lecture about the trial | Using active and trusted members of the community to communicate with potential recruits |
| Man *et al.* 2015(43, 72) | To improve recruitment to the trial | PIS underwent 3 rounds of user-testing with members of the public | Input by experts in writing for patients and graphic design (before user-testing) | Improving the readability and presentation of patient information sheets (PIS) |
| Martin *et al.* 2013(44, 73) | To improve recruitment to trial | All women who refused to participate in the trial were asked open-ended questions about their reasons for refusal. Research team used this feedback to improve their recruitment message | Researchers analysed women's feedback and made changes to recruitment message | Identifying and addressing barriers to recruitment |
| Moinpour *et al.* 2000(50) | To improve recruitment of minority ethnic men to the trial | 'Enhanced minority recruitment program' included hiring African American and Hispanic recruiters, several of whom were respected members within their minority communities | The enhanced minority recruitment program included multiple other components e.g. special training in minority recruitment for site staff, consultation with experts in minority recruitment | Reducing the time taken to identify potential participants, establish trust and introduce the trial |
| Porter *et al.* 2016(32) | To achieve a 40% increase in accrual to clinical trials over a 2-year period | The 'comprehensive program' included leadership team informally reaching out to patients at the onset and intermittently during the campaign to increase accrual. A cancer survivor was pictured and quoted on publicity to encourage patients to enquire about clinical trial opportunities. | The program was multi-faceted and included tasking centre leadership with increased oversight of the entire process of patient accrual to trials, education of all stakeholders, increased oversight of the portfolio of clinical trials by Disease-Specific Committees, and optimisation of accrual operations and infrastructure. | Equipping all stakeholders (patients, their families, nurses and staff, physicians, Disease-Specific Committees and centre leadership) with the necessary skills and information to complete the clinical trial accrual process. |
| Sanders *et* | To improve | 'Word of mouth' recruitment | The morning teas provided a social | Giving participants a sense of 'belonging |

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| *al.* 2009(51, 74) | recruitment to the trial | strategy in which the research team organised morning teas for participants and invited them to bring a friend who could potentially enrol in the trial | opportunity for participants and potential participants to meet researchers face-to-face. | and ownership of the project' and providing an opportunity for the friend to enrol in the trial |
| Tenorio *et al.* 2011(33, 75, 76) | To improve recruitment of Hispanic people to the trial | A Hispanic community focus group, including two lay people, advised on recruitment strategies. | The community focus group included healthcare and research professionals. Recruitment strategy was also informed by a literature review of factors affecting recruitment of Hispanic people to clinical trials. | Tailoring the recruitment plan to the Hispanic community; identifying and addressing cultural barriers to recruitment |
| Tenorio *et al.* 2014(52, 77, 78) | To improve recruitment of Hispanic people to the trial | Lay consultants from the Hispanic community approached potential participants | Culturally tailored recruitment strategies including use of bilingual Hispanic staff, bilingual recruitment materials and seminars, announcements at predominantly Hispanic churches. | Overcoming cultural barriers to recruitment of Hispanic people; maximising adherence to Hispanic cultural norms |
| Vicini *et al.* 2011(34) | To decrease ethnic minority health care disparities and increase representation of ethnic minorities in cancer clinical trials | Minority Outreach Program (MOP), involving collaboration with community-based organisations from five major ethnic/minority populations. Hospital representatives worked with community leaders to develop culturally competent programs, leading to a series of forums presented within each ethnic minority community. | The collaboration included hospital representatives. The hospital representatives were available at recruitment forums to inform patients about the clinical trials currently available at the hospital. | Providing culture-specific, bilingual cancer education, prevention and screening information in a culturally competent manner. |
| Vincent *et al.* 2013(35, 79) | To increase recruitment and retention in trial | Catholic church partners suggested a recruitment strategy based on healthy living/diabetes prevention presentations at the churches | None | Minimising cultural and contextual barriers to recruitment; maximising positive relationships, communication, trust and respect, which are particularly important when working with Mexican Americans. |

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| Wallace *et al.* 2006(45) | To improve patients' understanding of the treatment options and facilitate accrual to trial | During a 90-minute patient education session (intervention), a prostate cancer survivor and trial participant shared his (positive) experience of clinical trials with patients | The patient education session also included an informed consent video and a joint presentation by a urologist and radiation oncologist comparing and contrasting their modalities and introducing the concept of a randomised controlled trial | Providing balanced information about the treatment options, thereby increasing patient acceptance of randomisation |
| Wisdom *et al.* 2002(53) | To improve recruitment and retention in trial | Active recruitment of participants by faith-based organisations and churches in the community | As well as pastors, the study Principal Investigator also made regular announcements from the pulpit | Building trust, accessibility, caring, reciprocity and sensitivity, based on two theoretical models to improve recruitment of culturally diverse populations and access to care |

PIS = patient information sheet

*Other non-PPI components implemented before or at the same time as the PPI component. Where the PPI intervention was suggested or led by PPI contributors, it was considered to be 'pure' PPI even if the suggested intervention included other non-PPI aspects.

**(c) Evaluation characteristics**

| Study | Non-PPI comparison group | Enrolment and retention outcomes assessed | Evaluation design |
|---|---|---|---|
| Arean *et al.* 2003(28, 55) | 'Traditional' recruitment model consisting of gate-keeper referral and media advertisements with no design input from consumers | Enrolment: Proportion of potentially eligible minorities identified who were subsequently recruited to trial.<br>Retention: Proportion of minority participants completing 3-month and 6-month follow-up assessment | Observational study |
| Chlebowski *et al.* 2010(46, 62, 63) | Mass mailing of invitation letters to potential participants | Enrolment: Proportion of men targeted for recruitment who were subsequently enrolled in trial; cost per participant enrolled.<br>Retention: Not assessed. | Non-randomised controlled trial |
| Cockayne *et al.* 2017(36, 64) | Original PIS developed for the trial, written in accordance with the standard National Research Ethics Service template | Enrolment: Proportion of participants invited who were subsequently randomised.<br>Retention: Proportion of patients retained in the trial at 3 months post randomisation. | Randomised controlled trial |
| Dear *et al.* 2012(29, 54) | Usual approach to recruitment of trial participants, with no access to consumer-friendly online trials registry | Enrolment: Proportion of eligible patients consulting with a physician who subsequently self-reported consent to take part in a trial.<br>Retention: Not assessed. | Randomised controlled trial |
| Donovan *et al.* 2002(37, 65) | Recruitment according to original trial protocol | Enrolment: Proportion of men invited who subsequently consented to randomisation.<br>Retention: Proportion of men who consented to randomisation and subsequently accepted their allocated treatment. | Uncontrolled before-after study |
| Du *et al.* 2008(38) | Standard care (first visit with medical oncologist) with no access to video. | Enrolment: Proportion of patients who enrolled in therapeutic/non-therapeutic trials following visit with medical oncologist.<br>Retention: Not assessed. | Randomised controlled trial |
| Ford *et al.* 2004(47) | Standard trial recruitment procedures at health site; consent taken by mail; screening conducted by African American and Caucasian interviewers (Arm D of trial) | Enrolment: Proportion of men contacted and found eligible who were randomised to trial.<br>Retention: Not assessed. | Randomised controlled trial |
| Fouad *et al.* 2014(48, 66) | Standard retention activities (reminder calls, cards and incentives) | Enrolment: Not assessed.<br>Retention: Proportion of participants who attended all follow-up visits. | Randomised controlled trial |

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|---|---|---|---|
| Guarino *et al.* 2006(39, 67) | Original PIS designed by researchers | Enrolment: Proportion of patients invited who subsequently refused to take part in trial.<br>Retention: Proportion of participants missing any primary outcome data. | Randomised controlled trial |
| Horowitz *et al.* 2009(30, 68) | Other recruitment strategies: clinical referral, special recruitment events and recruitment via community-based organisations. | Enrolment: Proportion of people approached who were subsequently enrolled in the trial.<br>Retention: Not assessed. | Observational study |
| Hutchison *et al.* 2007(40, 69) | Standard trial-specific written patient information | Enrolment: Proportion of patients invited who were subsequently enrolled into a trial.<br>Retention: Not assessed. | Randomised controlled trial |
| Iliffe *et al.* 2013(31, 70, 71) | Original recruitment strategy prior to focus groups | Enrolment: Proportion of total participants (all regions) recruited in intervention-exposed regions.<br>Retention: Not assessed. | Controlled before-after study |
| Kass *et al.* 2009(41) | Informational pamphlet developed by the National Cancer Institute called "Taking Part in Clinical Trials: What Cancer Patients Need To Know". | Enrolment: Proportion of patients invited to take part in a clinical trial who subsequently decided to enrol in the trial (self-reported).<br>Retention: Not assessed. | Randomised controlled trial |
| Kimmick *et al.* 2005(42) | Standard information only (periodic notification of all existing trials and website access). | Enrolment: Proportion of older cancer patients registered who were subsequently accrued to a cancer treatment trial.<br>Retention: Not assessed. | Randomised controlled trial |
| MacEntee *et al.* 2002(49) | Announcements in newspapers to attract potential recruits | Enrolment: Proportion of initial responders who were subsequently recruited to the trial; cost per recruit.<br>Retention: Not assessed. | Non-randomised controlled trial |
| Man *et al.* 2015(43, 72) | Standard information sheet designed by researchers using National Research Ethics Service guidelines | Enrolment: Proportion of patients who received PIS and were subsequently randomised to trial.<br>Retention: Not assessed. | Randomised controlled trial |
| Martin *et al.* 2013(44, 73) | Original recruitment message (before intervention) | Enrolment: Proportion of women approached who were subsequently randomised to trial.<br>Retention: Not assessed. | Uncontrolled time series |
| Moinpour | Original minority recruitment protocol (before | Enrolment: Proportion of total participants (all ethnicities) who were | Uncontrolled |

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|---|---|---|---|
| *et al.* 2000(50) | enhanced program introduced) | minority ethnic.<br>Retention: Not assessed. | before-after study |
| Porter *et al.* 2016(32) | Original clinical trials accrual program (before comprehensive program introduced) | Enrolment: Annual number of patient accruals, accruals per active trial, and accrual rate (number of patients accrued in a given calendar year divided by number of new analytical cases seen at the cancer centre for that same year).<br>Retention: Not assessed. | Uncontrolled time series |
| Sanders *et al.* 2009(51, 74) | 'Targeted mail out' recruitment strategy consisting of postal invitations to women aged 70+ years listed on government agency databases | Enrolment: Proportion of people invited who were subsequently enrolled in the trial.<br>Retention: Not assessed. | Observational study |
| Tenorio *et al.* 2011(33, 75, 76) | Recruitment plan for general population | Enrolment: Proportion of total participants (all ethnicities) who were Hispanic.<br>Retention: Not assessed. | Controlled before-after study |
| Tenorio *et al.* 2014(52, 77, 78) | Recruitment plan for general population | Enrolment: Proportion of total participants (all ethnicities) who were Hispanic.<br>Retention: Not assessed. | Non-randomised controlled trial |
| Vicini *et al.* 2011(34) | Clinical trial accrual process before introduction of the Minority Outreach Program | Enrolment: Annual number of minority patients accrued, and as a proportion of total patients accrued.<br>Retention: Not assessed. | Uncontrolled time series |
| Vincent *et al.* 2013(35, 79) | Other recruitment strategies: flyers, posters and email announcements; community events; health provider referrals | Enrolment: Proportion of people approached/referred who were subsequently enrolled in trial.<br>Retention: Not assessed. | Observational study |
| Wallace *et al.* 2006(45) | Eligible patients were individually approached by a clinical research associate and invited to view the informed consent video | Enrolment: Proportion of patients attending educational session (intervention) or watching informed consent video (comparator) who subsequently consented to randomisation<br>Retention: Not assessed. | Uncontrolled before-after study |
| Wisdom *et al.* 2002(53) | Recruitment from local healthcare system (via mail) | Enrolment: Proportion of patients contacted who subsequently enrolled in the trial.<br>Retention: Proportion of participants who attended all 7 intervention | Observational study |

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| | | sessions. | |

PIS = patient information sheet

**Table 4. Aggregate characteristics of studies included in meta-analyses.** (Unless otherwise specified, figures refer to the number of studies with the specified characteristic.)

| Characteristic | Enrolment meta-analysis (N=19) | Retention meta-analysis (N=5) |
|---|---|---|
| *Evaluation features* | | |
| Number of individuals included | Range 126 – 60,800 (median 887) | Range 95 – 4599 (median 632) |
| Year of publication | Range 2002 – 2017 (median 2009) | Range 2002 – 2017 (median 2006) |
| Number of PPI interventions evaluated: | | |
| - One | 17 | 4 |
| - Two | 2 | 1 |
| Enrolment rate denominator: | | N/A |
| - Pre-eligibility screening | 12 | |
| - Post-eligibility screening | 6 | |
| - Unknown | 1 | |
| Study design: | | |
| - Randomised | 7 | 3 |
| - Non-randomised | 12 | 2 |
| Risk of bias*: | | |
| - Low | 4 | 3 |
| - Some concerns | 2 | 0 |
| - High/Serious | 12 | 1 |
| - Critical | 1 | 1 |
| *Context* | | |
| Geographical setting: | | |
| - Australia | 2 | 0 |
| - Canada | 1 | 0 |
| - UK | 5 | 1 |
| - USA | 11 | 4 |
| Clinical trial intervention type: | | |
| - Simple | 7 | 0 |
| - Complex | 9 | 5 |
| - Mixed/both | 3 | 0 |
| Clinical trial recruitment setting: | | |
| - Healthcare | 9 | 2 |
| - Community | 3 | 1 |
| - Mixed/both | 8 | 2 |
| PPI in choosing research question/topic (context) | 3 | 0 |
| *PPI intervention features* | | |
| PPI activity: | | |
| - Recruitment/retention strategies | 6 | 1 |
| - Patient-facing information | 9 | 2 |
| - Direct recruitment/retention | 9 | 3 |
| PPI intervention was chosen/designed specifically to increase recruitment or retention | 18 | 3 |
| PPI model: | | |
| - One-off | 10 | 3 |

| | | |
|---|---|---|
| - Intermittent<br>- Full team membership | 3<br>6 | 1<br>1 |
| Number of PPI contributors involved:<br>- One or two<br>- Three or more<br>- Unknown | <br>1<br>18<br>1 | <br>1<br>5<br>0 |
| PPI contributor(s) had lived experience of condition | 12 | 0 |
| PPI was visible to potential trial participants | 11 | 3 |
| Intervention included some non-PPI components | 14 | 3 |
| PPI was formal qualitative research | 1 | 0 |
| *Findings* | | |
| Impact of PPI intervention on outcome (enrolment/retention rate):<br>- Significant *increase*<br>- No significant impact<br>- Significant *decrease* | <br><br>11<br>8<br>1 | <br><br>1<br>4<br>0 |

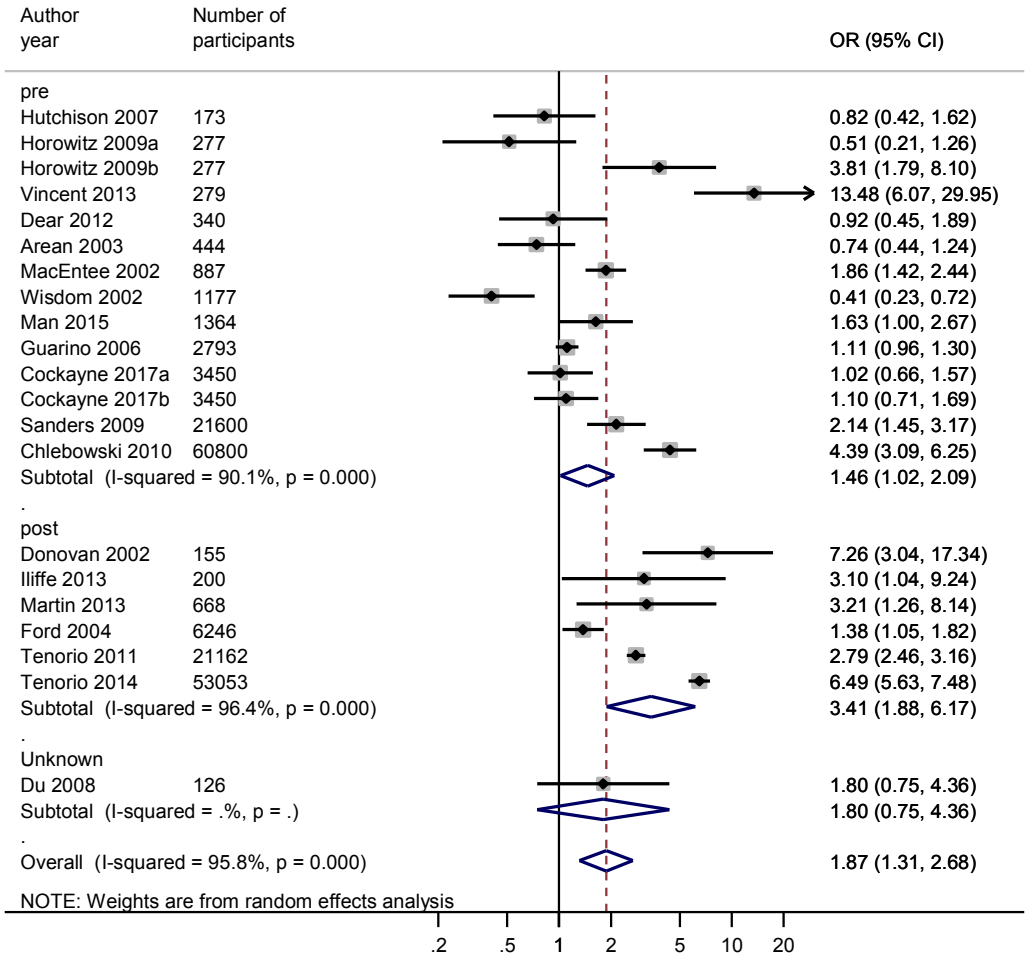
* For randomised studies, the following levels are possible: Low, Some concerns, High. For non-randomised studies, the following levels are possible: Low, Moderate, Serious, Critical. These differences are due to differences in the tools used to assess risk of bias.

## **Appendix 1:** Search strategy

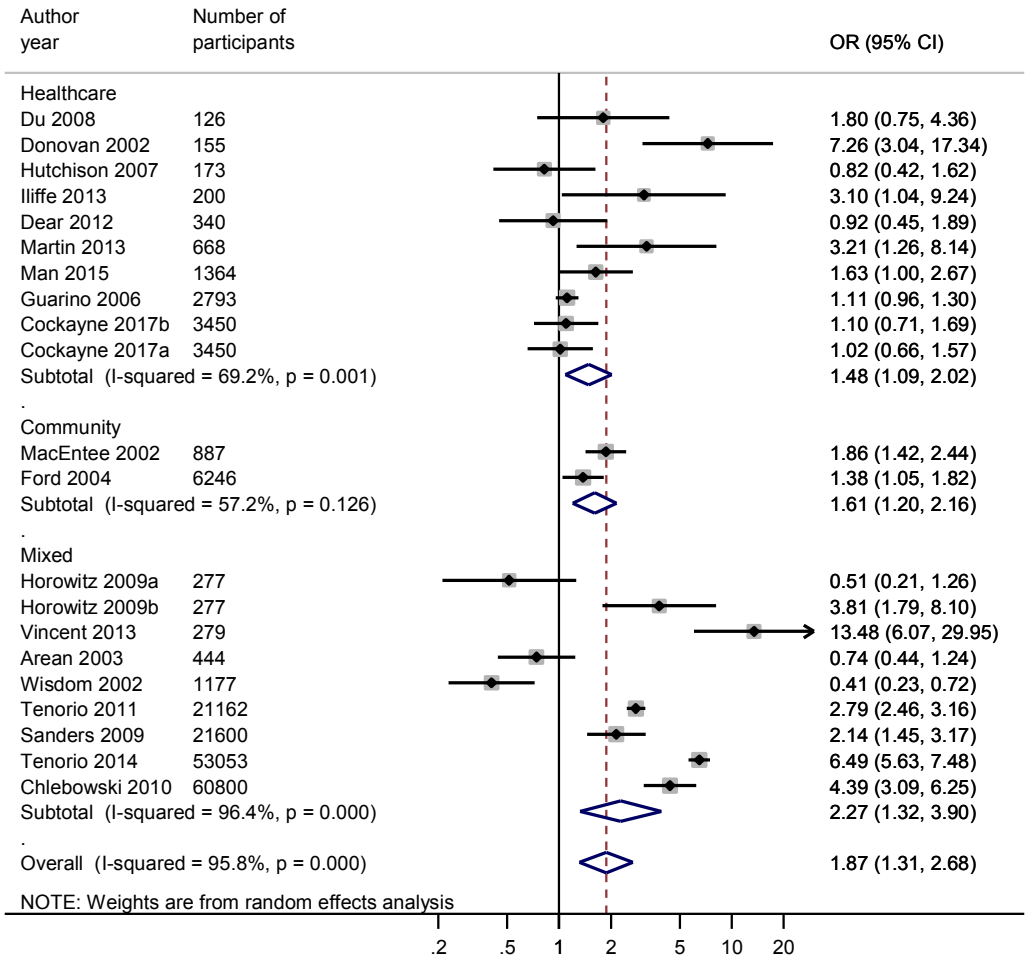
| | **Search domain** | **Search terms** |
|---|---|---|
| 1 | Clinical trials | trial*.mp OR exp Clinical Trial as Topic/ |
| 2 | PPI & recruitment/retention, with focus on PPI | ((consumer? or citizen? or client? or carer? or communit? or lay or patient? or public? or service user? or survivor? or stakeholder? or family or families or relative? or parent?) AND (involv* or collaborat* or engage* or partner* or consult* or advis* or emancipat* or empower* or advocat* or embed* or represent*) OR community-based OR participatory).ti OR *Consumer Participation/ OR *Patient Participation/ OR *Community-Based Participatory Research/ **AND** Patient Selection/ OR exp Informed Consent/ OR Research design/ OR Patient Dropouts/ OR enrol*.ab./freq=2 OR recruit*.ab./freq=2 OR participat*.ab./freq=2 OR enlist*.ab./freq=2 OR consent*.ab/freq=2 OR refus*.ab/freq=2 OR accru*.ab/freq=2 OR retention.ab/freq=2 OR attrition.ab/freq=2 OR followup.ab/freq=2 OR follow-up.ab/freq=2 OR dropout*.ab/freq=2 OR drop-out*.ab/freq=2 OR withdr*.ab/freq=2 |
| 3 | PPI & recruitment/retention, with focus on recruitment/retention | ((consumer? or citizen? or client? or carer? or communit* or lay or patient? or public? or service user? or survivor? or stakeholder? or family or families or relative? or parent?) adj3 (involv* or collaborat* or engage* or partner* or consult* or advis* or emancipat* or empower* or advocat* or embed* or represent*) or community-based or participatory).ab,ti OR Consumer Participation/ OR Patient Participation/ OR Community-Based Participatory Research/ **AND** *Patient Selection/ OR *Informed Consent/ OR *Informed Consent By Minors OR *Research design/ OR *Patient Dropouts/ OR (enrol* OR recruit* OR participat* OR enlist* OR consent* OR refus* OR accru* OR retention OR attrition OR followup OR follow-up OR dropout* OR drop-out* OR withdr*).ti |
| 4 | 2 or 3 | |
| 5 | PPI outcomes | (impact* or effect* or adapt* or modif* or change* or develop* or design* improve* or worse* or increase* or boost* or decreas* or reduc* or differ* or edit* or suggest*).ab,ti |
| 6 | 1 and 4 and 5 | |

**Appendix 2:** Forest plots showing subgroup analyses for enrolment outcome

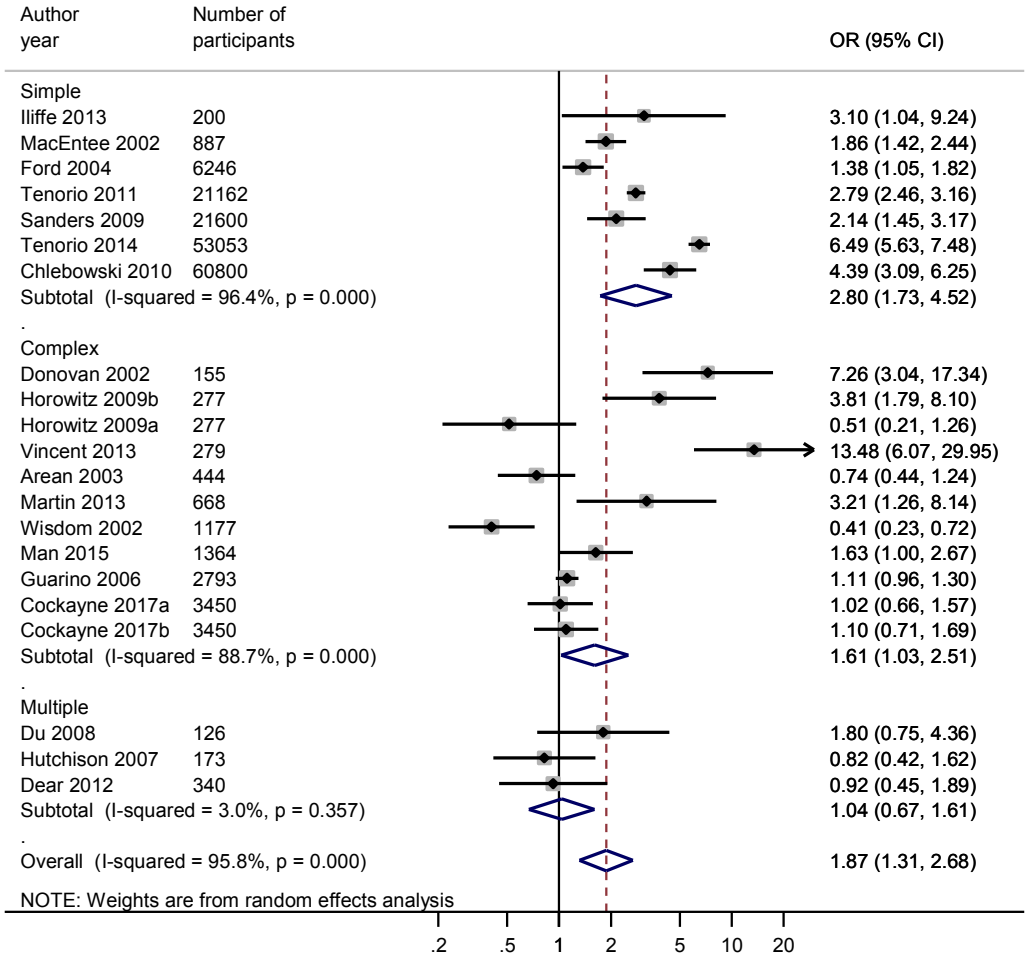
(a) Enrolment rate denominator (pre vs. post eligibility screening)



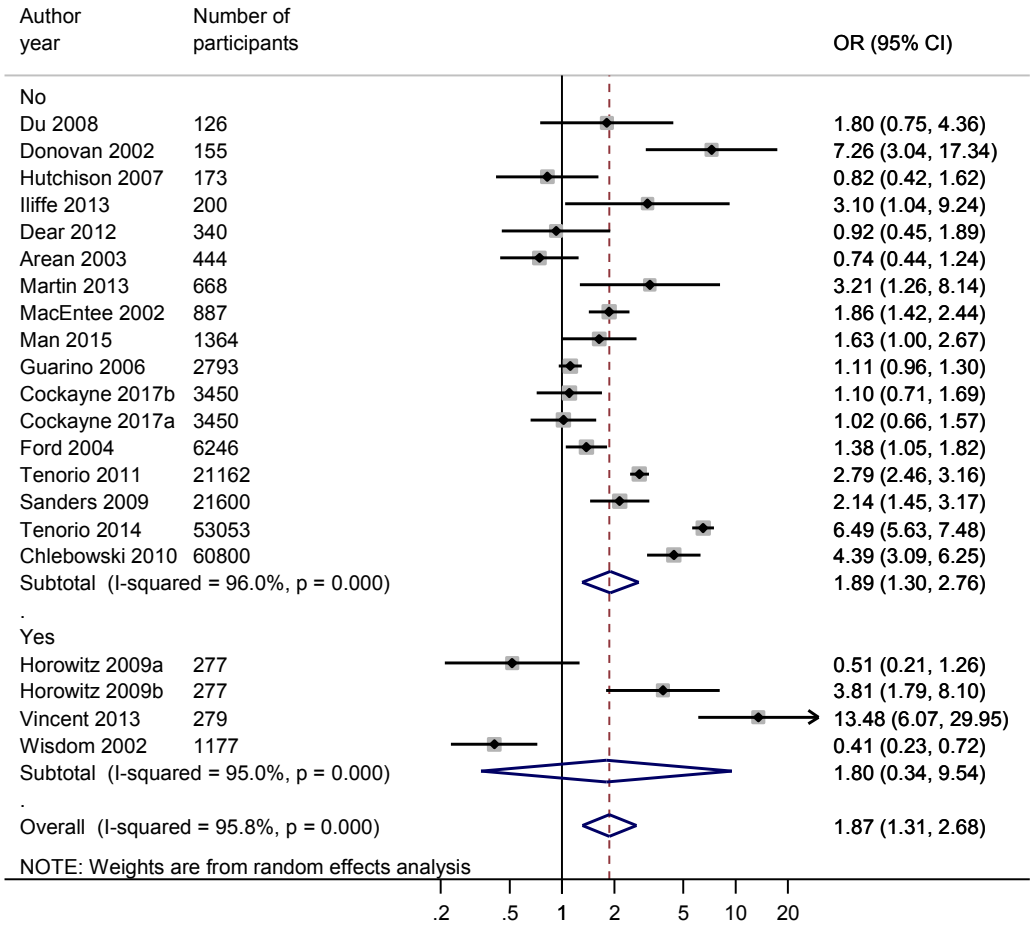
(b) Trial recruitment setting (context)



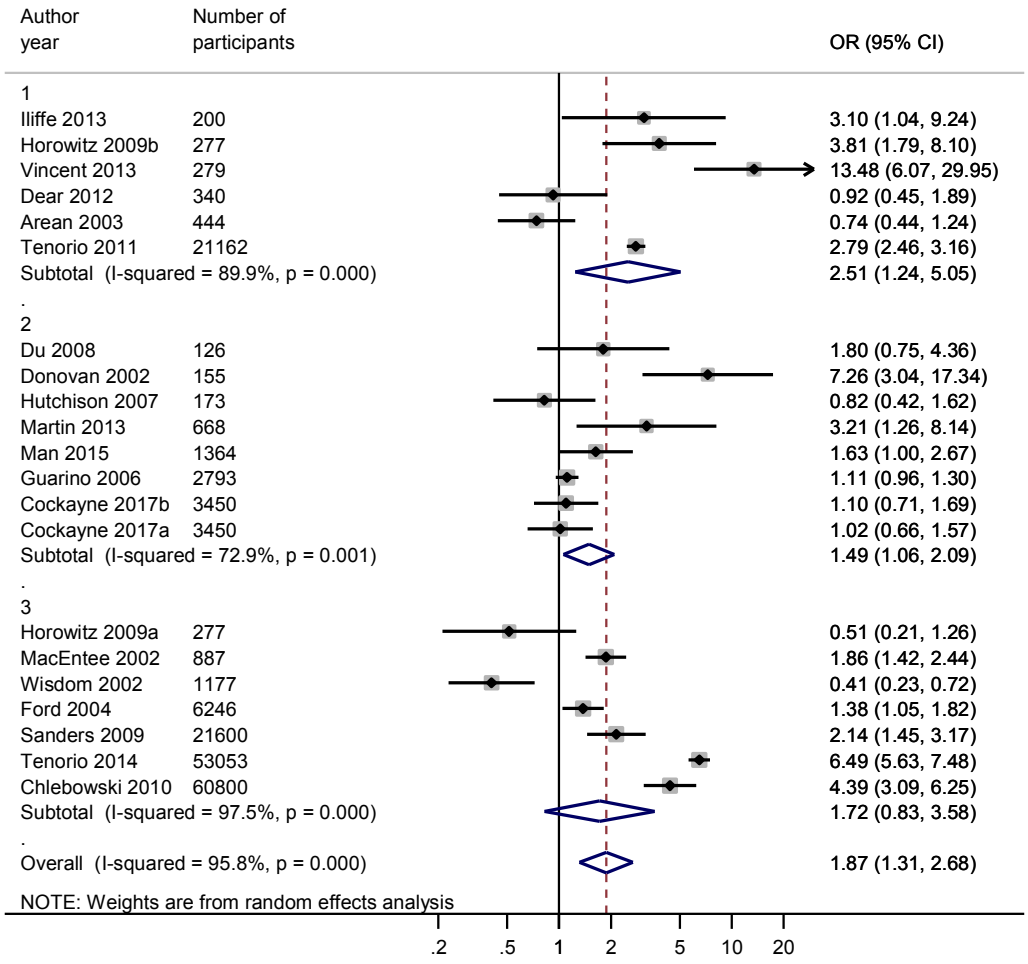
(c) Trial intervention type (context)



(d) PPI in choosing research question/topic (context)



(e) Timing/activity of PPI intervention



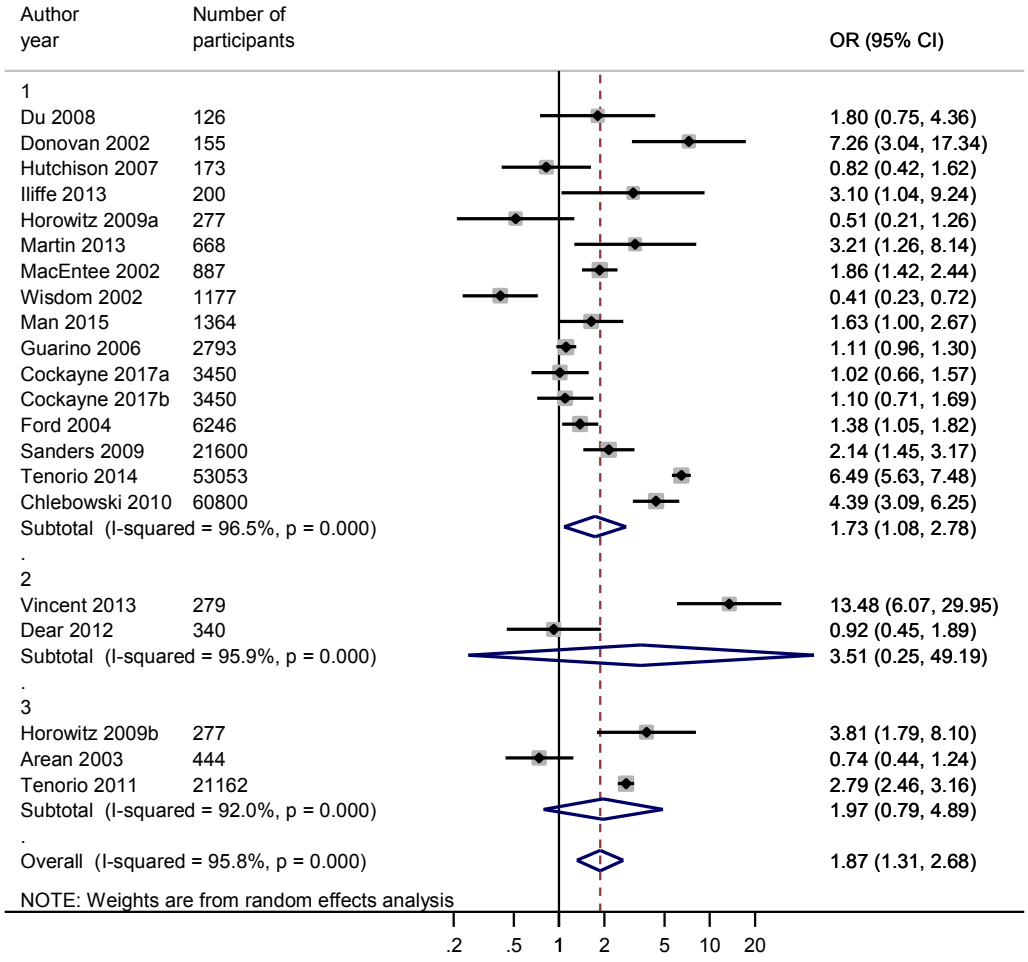

Key:

1 = designing recruitment or retention strategy

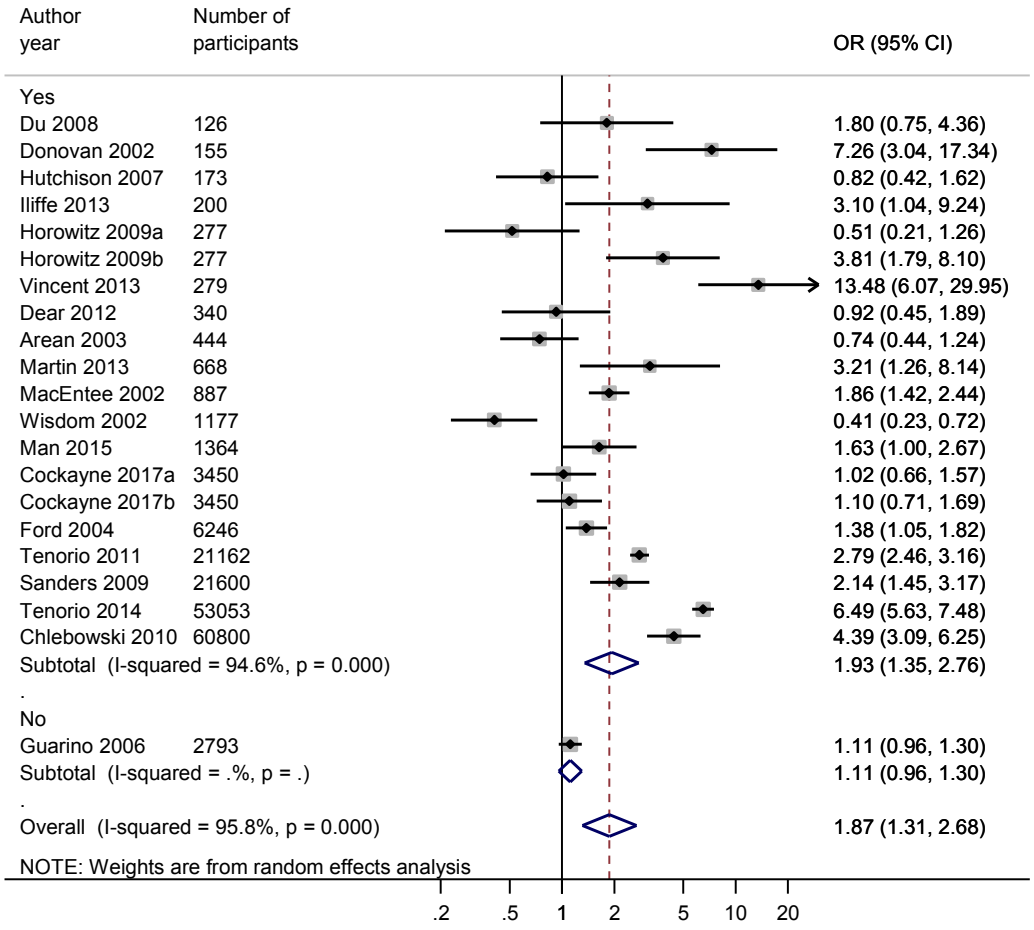
2 = developing patient-facing information

3 = directly approaching / recruiting or retaining participants

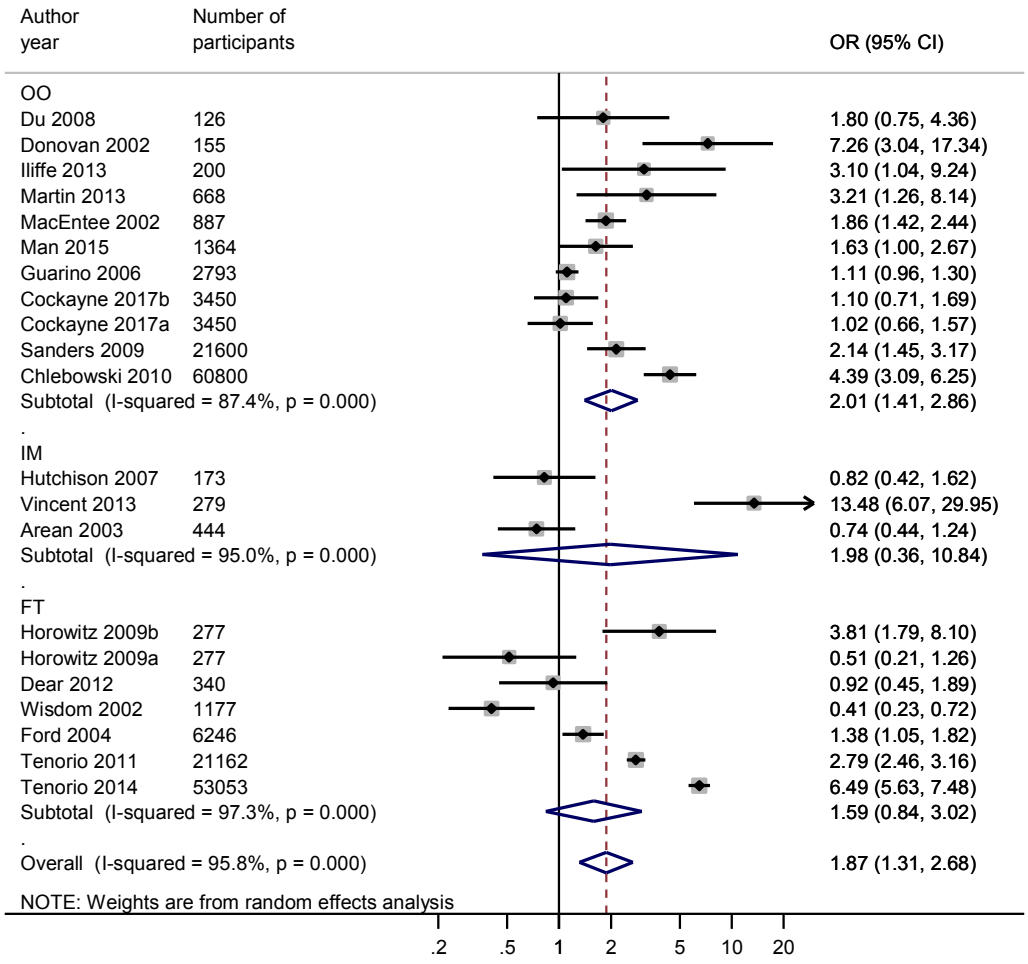
(f) Number of the activities (e) targeted by PPI intervention



(g) PPI intervention chosen/designed specifically to increase recruitment or retention



(h) PPI model



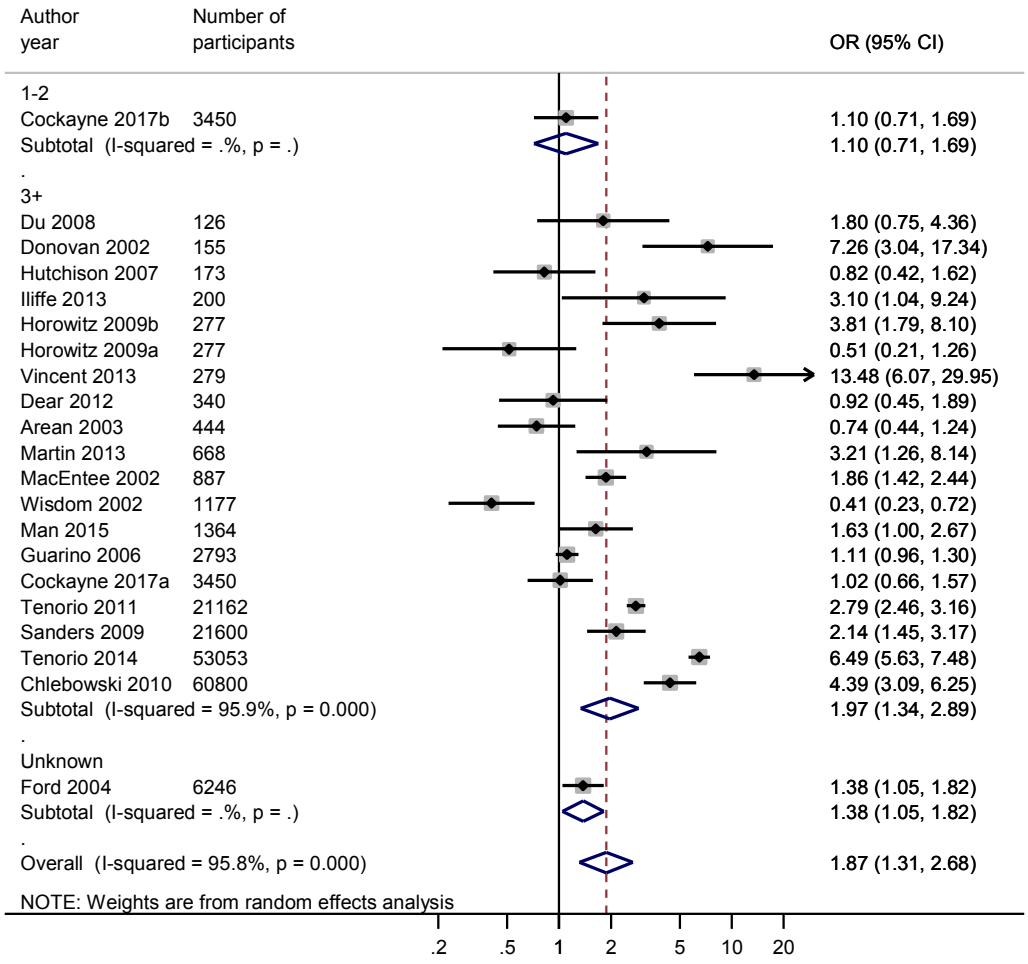

Key:

OO = One-off

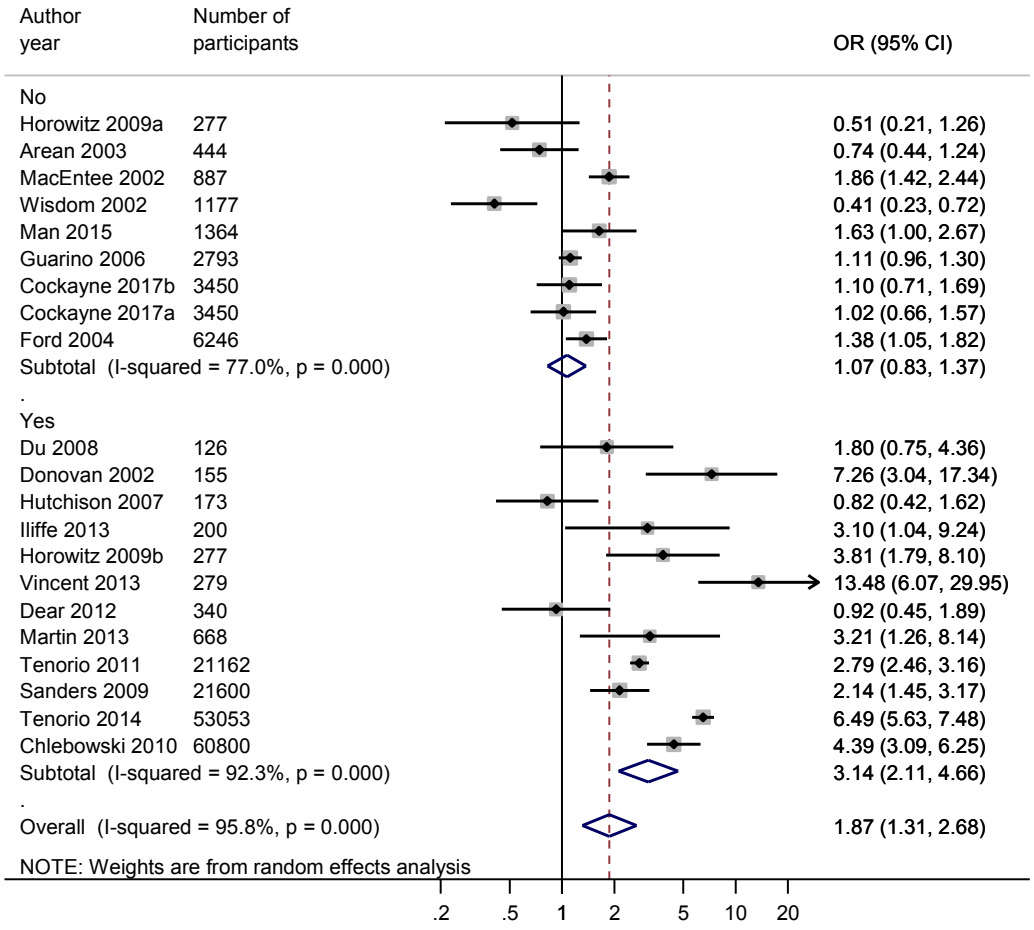
IM = Intermittent

FT = Full team membership

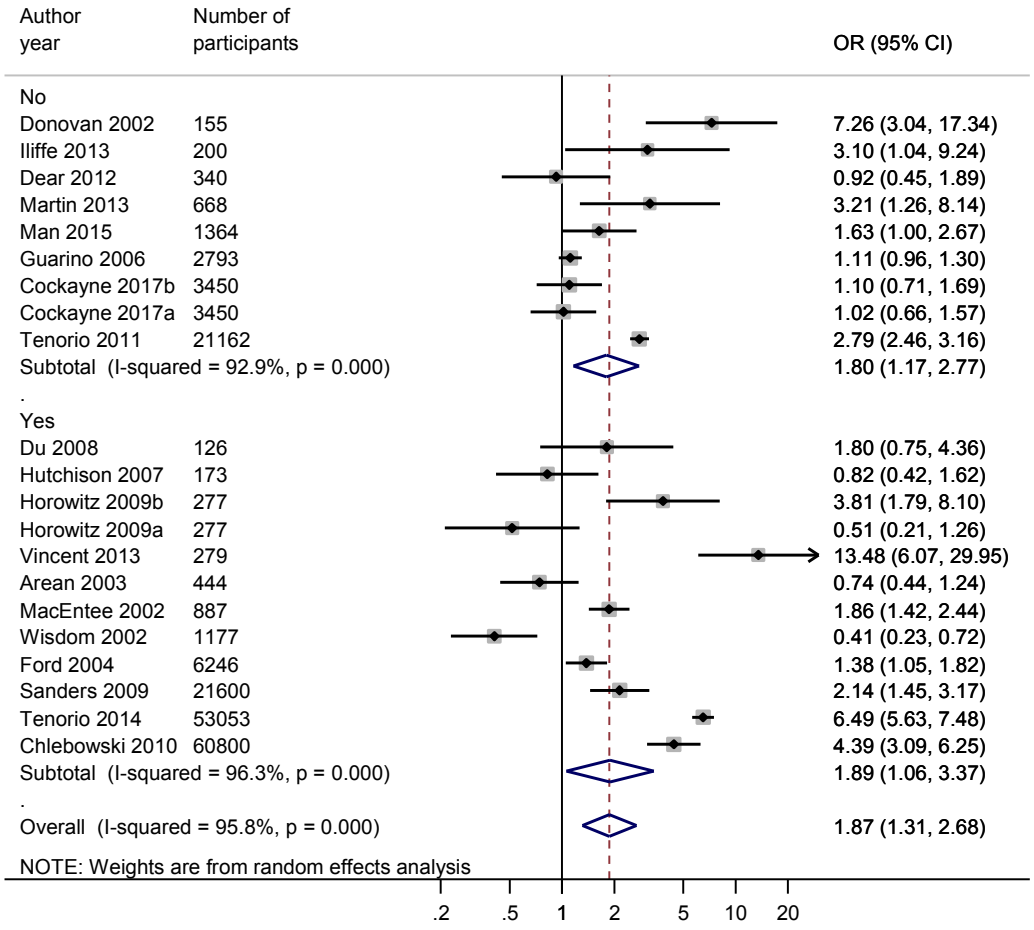
(i) Number of PPI contributors involved



(j) Lived experience



(k) PPI visible to potential trial participants



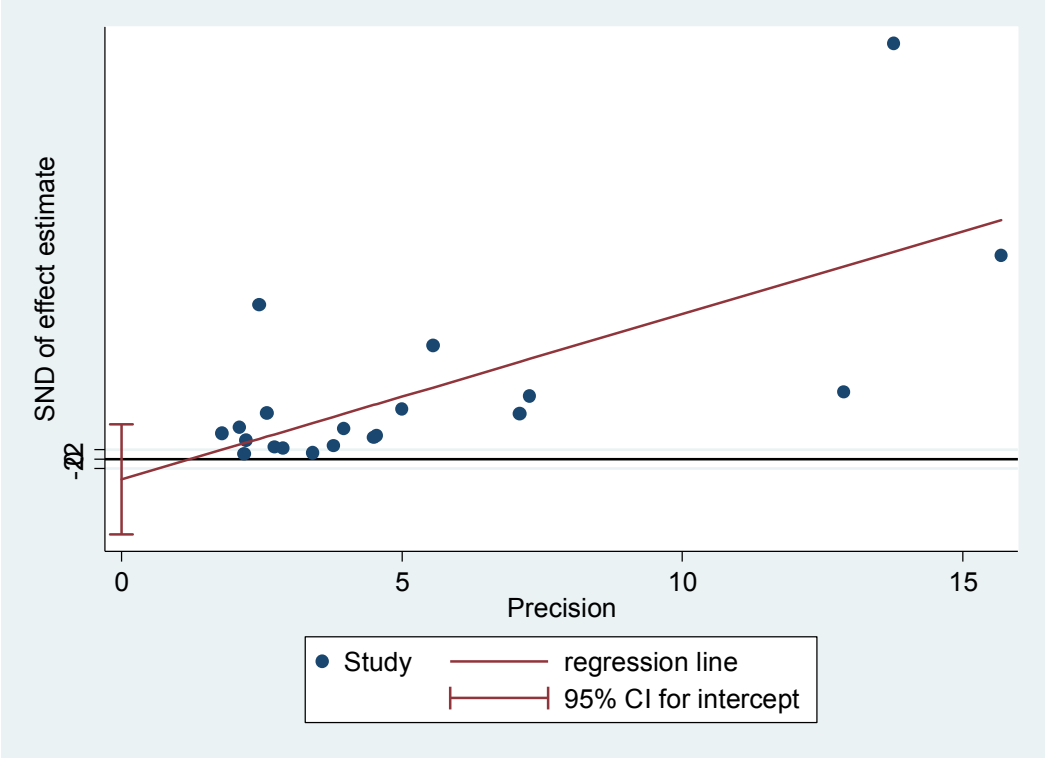
**Appendix 3:** Results of sensitivity analyses for enrolment outcome

| Studies excluded | Number of comparisons | Estimated OR (95% CI) | p-value |
|---|---|---|---|
| High risk of bias | 7 | 1.17 (1.04 – 1.32) | 0.007 |
| Non-randomised studies | 8 | 1.16 (1.04 – 1.31) | 0.009 |
| Small samples (N<100) | 21 | 1.87 (1.31 – 2.68) | 0.001 |
| Interventions with non-PPI components | 6 | 2.70 (1.14 – 6.38) | 0.023 |
| Formal qualitative research | 20 | 1.77 (1.23 – 2.54) | 0.002 |

**Appendix 4:** Results of sensitivity analyses for retention outcome

| Studies excluded | Number of comparisons | Estimated OR (95% CI) | p-value |
|---|---|---|---|
| High risk of bias | 4 | 1.16 (0.59 – 2.28) | 0.657 |
| Non-randomised studies | 4 | 1.16 (0.59 – 2.28) | 0.657 |
| Small samples (N<100) | 5 | 1.36 (0.74 – 2.50) | 0.323 |
| Interventions with non-PPI components | 2 | 1.73 (0.84 – 3.57) | 0.137 |
| Formal qualitative research | 6 | 1.20 (0.68 – 2.12) | 0.519 |

**Appendix 5:** Funnel plot for enrolment meta-analysis



**Appendix 6:** Funnel plot for retention meta-analysis