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

Journal:	*BMJ*
Manuscript ID	BMJ.2018.045186.R1
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	24-Aug-2018
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Keywords:	Patient and public involvement (PPI), Clinical trials, Recruitment, Retention

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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

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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. We define 'PPI' as any form of active patient or lay involvement, including e.g. membership of a trial advisory group, user testing and peer recruitment.

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. PPI interventions could include additional non-PPI components inseparable from the PPI (e.g. other stakeholder involvement).

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: main analysis including randomised studies only, secondary analysis adding non-randomised studies, and several exploratory subgroup and sensitivity analyses.

Results: 26 studies were included in the review; 19 were eligible for enrolment meta-analysis and 5 for retention meta-analysis. Various PPI interventions were identified with different degrees of involvement, different numbers and types of people involved, and input at different stages of the trial process. On average, PPI interventions modestly but significantly increased the odds of participant enrolment in our main analysis (OR 1.16 [95% CI and prediction interval 1.01 – 1.34]). It is possible that non-PPI components of interventions may have contributed to this effect. In exploratory subgroup analyses, the involvement of people with lived experience of the condition under study was significantly associated with improved enrolment (p=0.017). The findings for retention were inconclusive due to the paucity of eligible studies (OR 1.20; 95% CI 0.68 – 2.12 for main analysis).

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 which types of PPI work best in

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particular contexts, the cost-effectiveness of PPI, the impact of PPI at earlier stages of trial design, and the impact of PPI interventions specifically targeting retention.

Systematic review registration: PROSPERO CRD42016043808.

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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 people who run trials. 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 modestly 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. We are uncertain about the effects of PPI on retention because too few studies looked at this.

Further research is needed to find out (1) which types of PPI work best in different situations; (2) whether PPI reduces the cost of recruiting and retaining participants in trials, (3) the effects of PPI in earlier stages of trial design, and (4) the effects of PPI specifically aimed at improving retention.

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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 nature of PPI, and the impact of PPI on trial enrolment and retention, vary widely between studies.
- On average, PPI appears to modestly but significantly increase the odds of participant enrolment. In a hypothetical sample of 1,000 patients where 100 (10%) enrol, a PPI intervention similar to those included in our main meta-analysis would likely lead to between 1 and 30 (average 14) extra patients being enrolled. Our findings suggest that improvements in enrolment may be more likely when involving 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. We also need to understand which PPI interventions work best in different contexts, and the specific effects of PPI in partnership interventions (where the impact of PPI is difficult to separate from the impact of other partners – a limitation of the current review).

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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) Patients and members of the public are primarily involved in agenda setting, steering committees, ethical review, protocol development and piloting.(12) There are many different types of involvement, from one to many individuals or whole patient organisations, one-off involvement in a particular aspect of the trial (e.g. reviewing draft information for patients or recruiting participants from their communities) to involvement throughout the trial (e.g. as members of a Trial Steering Committee), and involvement with no decision making power (e.g. as advisers) to involvement in decision making as equal partners.

There are two broad arguments for involving patients and members of the public 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

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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 and other PPI characteristics).

Methods

Searches

We conducted a systematic literature 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 for further details). We defined 'PPI intervention' as a trial methodology intervention which was, or included as an active component, any form of PPI consistent with the INVOLVE definition of public involvement: 'research being carried out 'with' or 'by' members of the public rather than 'to',

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'about' or 'for' them', where 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.(10) This included interventions not necessarily labelled or conceptualised as 'PPI' by the study authors e.g. user testing, peer recruitment and community-based participatory research. We included interventions in which PPI was integrated with additional components inseparable from the PPI (such as other stakeholder involvement) because this is consistent with the way patients are often involved in practice (e.g. being part of an advisory group). Hereafter we refer to such components as 'non-PPI components' of interventions.

[Table 1 around here]

A review restricted to randomised controlled trials would give an incomplete summary of the impact of PPI, since many types of PPI interventions (for example, patient involvement 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. We accepted all non-randomised study designs (provided there was a direct comparison group), including non-randomised controlled trials, controlled and uncontrolled before-after studies, and observational studies. Comparison groups were patients unexposed to the PPI intervention (e.g. before its introduction) or patients exposed to an alternative intervention with no PPI (e.g. recruitment via healthcare professionals).

The evaluation did not have to be the study authors' primary research question. There were no limits on publication date or language.

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

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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

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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. We used the Hartung-Knapp-Sidik-Jonkman variance correction to calculate 95% confidence intervals reflecting the uncertainty in heterogeneity estimates.(26-28) We examined statistical heterogeneity using the I-squared statistic, and by calculating approximate 95% prediction intervals (which indicate a predicted range for the true effect of PPI in an individual study)(29) using methods reported by Higgins *et al.*(30). Because of high methodological and statistical heterogeneity across non-randomised studies, we made a post-hoc decision to present findings from randomised studies only as our main analysis. We then conducted a secondary analysis including non-randomised as well as randomised studies. Where multiple non-PPI recruitment strategies had been employed within a non-randomised 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.

We carried out pre-planned subgroup analyses on all included studies (randomised and non-randomised combined) 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 (Table 2). We used univariate meta-regression to determine whether differences between subgroups were statistically significant.

Sensitivity analyses were performed on both the main analysis (randomised studies only) and the secondary analysis (randomised and non-randomised studies combined). These excluded studies at high risk of bias, studies with small sample sizes (N<100), PPI interventions which included additional non-PPI components, PPI interventions which were formal qualitative research (and therefore not universally classified as PPI), and studies using a proxy denominator to measure enrolment rate (see Table 2).

Peters' test was carried out to examine small study effects.(31, 32) 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.

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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 involvement in health research and their 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 (MO) retired and a third (RH) 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, they 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 the lead author's motivation through what was a challenging piece of work. Working in partnership with patients has been a very positive experience for the researchers in the team and we have not identified any negative impacts on the research. Our current patient partners (AC and RH) report multiple positive aspects of their involvement including being interested in the topic and endorsing its importance, feeling welcomed and respected as part of the project team, and feeling that their contributions are valued and responded to. Negative aspects have included difficulty following the conversation and contributing during teleconference meetings (sometimes necessary because of the long geographical distance between RH and the lead author) and having only a limited understanding of the mathematics of the meta-analysis.

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).

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[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(33-40) involved patients or lay people in designing recruitment and retention strategies (e.g. as community partners, members of a Community Advisory Board, or focus group participants); 12 studies(34, 37, 41-50) involved patients or lay people in developing patient-facing information (e.g. patient information sheets, multimedia and online interventions, recruitment advertisements and verbal messaging) and 10 studies(33, 35, 51-58) involved patients or lay people in directly recruiting or retaining 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,(47) to over 80 people helping to develop a patient-friendly online trials registry,(34, 59) or community partners initiating and leading their own recruitment strategies.(35, 40) There were also numerous intended purposes of involvement, including increasing trust between communities and researchers,(33, 35, 52, 54, 55, 58) improving the quality and acceptability of patient-facing information or recruitment messages,(34, 41, 42, 45, 48-50) accessing potential participants via existing participants,(51, 56) and increasing the cultural competence of the research among minority ethnic communities.(38-40, 51, 52, 54, 56-58) Many of the PPI interventions also included non-PPI components, such as the involvement of other stakeholders or experts(34, 38, 39, 46, 48, 55) or novel modes of information delivery which were not a direct consequence of the PPI.(43, 45, 50, 54, 56-58)

[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-analyses, while 5 studies (6 PPI interventions) reporting data from 6520 participants were included in our retention meta-analyses. 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-analyses due to insufficient data, despite attempts to contact study authors and identify related papers. Three of these studies reported no significant impact of PPI interventions on enrolment,(46, 47, 55) while the other 3 studies reported

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an increase in enrolment rates associated with PPI interventions (statistical significance unknown).(37, 39, 50)

Risk of bias of studies included in meta-analyses

Of the 8 randomised studies, only one was deemed at 'high' risk of bias(34) due to missing outcome data, while two had 'some concerns'(43, 52) and five had 'low' risk of bias.(41, 44, 45, 48, 53) Of the 12 non-randomised studies, 11 were deemed at 'serious' risk of bias(35, 36, 38, 40, 42, 49, 51, 54, 56-58) and one at 'critical' risk of bias(33) 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.

Impact of PPI interventions on enrolment

Individual study findings

Half of the PPI interventions (11/21) included in our meta-analysis were associated with significantly higher enrolment rates compared to no PPI or non-PPI interventions,(35, 36, 38, 40, 42, 49, 51, 52, 54, 56, 57) 9 PPI interventions were not significantly associated with enrolment rate,(34, 35, 41, 43-45, 48, 60) and one PPI intervention was associated with significantly lower enrolment (OR 0.41 [95% CI 0.23 – 0.72]).(58) In this study, lay community members (faith-based organisations) attempted to directly recruit African Americans with diabetes to the trial; however this yielded a lower enrolment rate 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, lay community members (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 non-randomised and judged to be at high risk of bias.)

Main meta-analysis (randomised studies only)

Seven randomised studies (8 PPI interventions) were included in our main meta-analysis. These interventions all consisted of patient or lay involvement in the design or delivery of patient

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information, with Ford *et al.*'s intervention also including recruitment sessions hosted by churches in the target community.(52) Pooling the data from 7 randomised studies in our main meta-analysis revealed that, on average, PPI interventions modestly but significantly increased the odds of a patient enrolling in a clinical trial compared with no PPI (OR 1.16 [95% CI 1.01 – 1.34]; p=0.035). There was low heterogeneity between studies (I^2 = 0.0%), yielding a 95% prediction interval of OR 1.01 to 1.34 (Figure 2).

[Figure 2 around here]

Secondary meta-analysis and subgroup analyses (randomised and non-randomised studies combined)

Our secondary meta-analysis, combining 19 randomised and non-randomised studies (21 PPI interventions), also found 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 1.25 – 2.80]; p=0.004). There was substantial heterogeneity between studies (I^2 = 95.7%), yielding a 95% prediction interval of OR 0.36 to 9.86 (Figure 3). Exploratory subgroup analyses revealed that the overall positive association between PPI interventions and enrolment substantially increased when at least one involved person had lived experience of the health condition under study (OR 3.14 [1.89 – 5.22]) and all but disappeared when the involved persons had no such lived experience (OR 1.07 [0.74 – 1.53]). Meta-regression confirmed that this effect was statistically significant (p=0.017). Subgroup differences between any of the other variables explored (Appendix 2), including trial intervention type (simple vs. complex), the timing of involvement (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, but 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.

[Figure 3 around here]

Sensitivity analyses and Peters' test

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The positive overall association between PPI interventions and enrolment remained statistically significant throughout all sensitivity analyses except when excluding interventions with non-PPI components from the secondary analysis (see Appendix 3). Although the estimated effect of PPI actually increased in this analysis (OR=2.70), the exclusion of 15/21 studies yielded a very wide 95% confidence interval (0.83 – 8.84). It was not possible to restrict this particular sensitivity analysis to randomised studies because there was only one 'pure' PPI intervention in this subsample.(44)

Peters' test showed no evidence of bias due to small study effects (p=0.924 for main analysis; p=0.592 for secondary analysis).

Cost-effectiveness of PPI

Of the two studies reporting the cost per participant enrolled, MacEntee *et al.* reported that a PPI strategy to recruit participants at community centres through a local contact person, although more effective, was more than twice the cost per participant of a non-PPI strategy which used postal invitations ($23 vs. $11).(54) Chlebowski *et al.* reported that a PPI strategy to recruit trial participants via existing research participants was only one quarter the cost of a non-PPI strategy which used commercial mailing lists to send postal invitations ($59 vs. $259 per participant enrolled).(51)

Impact of PPI interventions on retention

Main meta-analysis (randomised studies only)

Pooling the data from 3 randomised studies (4 PPI interventions) in our main meta-analysis did not find a statistically significant effect of PPI on participant retention (OR 1.16 [95% CI 0.33 – 4.14]; p=0.727). Results varied widely across studies, with effect estimates ranging from OR=0.38 to OR=2.52 (I^2 = 83.5%; 95% prediction interval 0.06 – 22.37; Appendix 4).

Secondary meta-analysis (randomised and non-randomised studies combined)

Our secondary meta-analysis, combining 5 randomised and non-randomised studies (6 PPI interventions), also found no statistically significant effect of PPI interventions on participant retention, compared with no PPI or non-PPI interventions (OR 1.20 [95% CI 0.52 – 2.77]; p=0.590). Again, there was substantial heterogeneity between studies (I^2 = 78.3%), yielding a 95% prediction interval of OR 0.20 to 7.18 (forest plot in Appendix 5). At the individual study level, only one PPI intervention was significantly associated with retention: this constituted using lay Community Health Advisers to support participants (the only PPI intervention specifically targeting retention), leading to

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a significant improvement in retention rates (OR 2.52 [95% CI 1.82 – 3.50]).(53) Apart from this latter example, the PPI interventions primarily targeted enrolment, not retention.

We did not perform subgroup analyses for retention outcomes due to the small sample size.

Sensitivity analyses and Peters' test

Sensitivity analyses did not alter the findings (Appendix 6) and Peters' test showed no evidence of bias due to small study effects (p=0.435 for main analysis; p=0.412 for secondary analysis).

Discussion

Summary of findings

This review identified a variety of PPI interventions aimed at improving participant enrolment and retention in clinical trials. Patients and lay members of the public were involved in designing 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 on enrolment or retention of PPI in developing the trial question or designing the trial itself.

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 regardless of whether non-randomised studies were excluded or included, and in sensitivity analysis which removed studies at highest risk of bias. To illustrate what our main findings could mean in practice: in a hypothetical sample of 1,000 patients, where typically 100 enrol (consistent with the 10% average enrolment rate in our sample of randomised studies), a PPI intervention similar to those included in our main meta-analysis would likely lead to between 1 and 30 (average 14) extra patients being enrolled. As these PPI interventions were mostly restricted to patient or lay involvement in the design or delivery of patient information, the effect size might be even larger for PPI which begins at earlier stages of trial design, since the opportunity to influence patient views and experiences would extend beyond just the provision of information.

A key exploratory finding was that the effect size was significantly greater when involved persons had lived experience of the health condition under study, compared to no such lived experience. This is consistent with the view that patients and carers can benefit research through their role as 'expert in lived experience',(61) though the precise mechanisms linking such expertise with improvements in enrolment and retention are unclear - something which we are exploring in a

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complementary realist analysis of the included studies. This finding, along with all other subgroup analysis and meta-regression findings, should be interpreted with caution due to the potential for study-level confounding.

Far fewer studies evaluated the impact of PPI interventions on retention of trial participants. They showed, on average, a modest but non-significant improvement in retention; the very wide 95% confidence intervals mean we cannot rule out a potentially large increase or decrease in retention associated with PPI. None of the PPI interventions in the retention analysis 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 PPI interventions included non-PPI components and it was impossible to separate out the effects of these from the effects of the PPI components. When interventions including non-PPI components were excluded in a sensitivity analysis of both randomised and non-randomised studies combined, PPI was still associated with improved enrolment, but with reduced certainty due to the decrease in sample size.

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 involved patients and researchers, and the attitude of research leaders towards PPI.(22, 62) 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,(63) 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.

Our 95% prediction intervals should be interpreted with caution because prediction intervals have been reported to be less reliable in meta-analyses with unbalanced study sizes.(64) Finally, we were unable to provide a useful summary of PPI cost-effectiveness because very few studies included an

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economic impact assessment; thus an 'effective' PPI intervention may not necessarily be cost-effective. However, financial modelling of PPI impact in a typical oncology trial suggests that PPI interventions that improve enrolment may add considerable financial value.(65)

Finally, the findings of this study say nothing about the quality or ethical acceptability of PPI in the included studies, or indeed patient views on the importance of the clinical trials being conducted. PPI may improve enrolment, but this does not rule out negative impacts such as an emotional cost to involved patients(66) or patients feeling coerced into enrolling. Should patients assume that all trials are conducted for their benefit, and automatically endorse every trial? Do (and should) involved patients have the necessary skills to assess the risks involved on behalf of their fellow patients? These are important dilemmas which are beyond the scope of this study to address.

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).(56) 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, involving patients in the early stages of trial development can sometimes lead researchers to abandon the whole idea of the trial,(67) 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 the impact of PPI on enrolment and retention in clinical trials, in particular: (1) which types of PPI work best in particular settings and contexts; (2) the mechanisms underlying the impact of PPI on enrolment and retention, (3) the cost-effectiveness of PPI interventions (an important part of the drive to improve

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trial efficiency), (4) the impact of PPI interventions specifically targeting retention (which has received very little attention relative to enrolment), and (5) the impact of PPI at the early stages of trial proposal and design.

Funding

JC, SPZ and JH were funded by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). IRC was funded by the University of Oxford Returning Carers Fund. The funders were not involved in the study design, data collection, analysis or interpretation, or writing the report. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and accuracy of the data analysis. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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 statistical advice at an early stage of this review; Rebecca Harmston (patient contributor) for contributing to the analysis plan and interpretation of results; and Prof Trish Greenhalgh (NIHR Oxford BRC Theme Leader, Partnerships for Health Wealth and Innovation) for providing helpful feedback on an early draft of this paper. We also thank the peer reviewers for their constructive comments which helped to improve this paper.

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.

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Tables and Figures

Appendices

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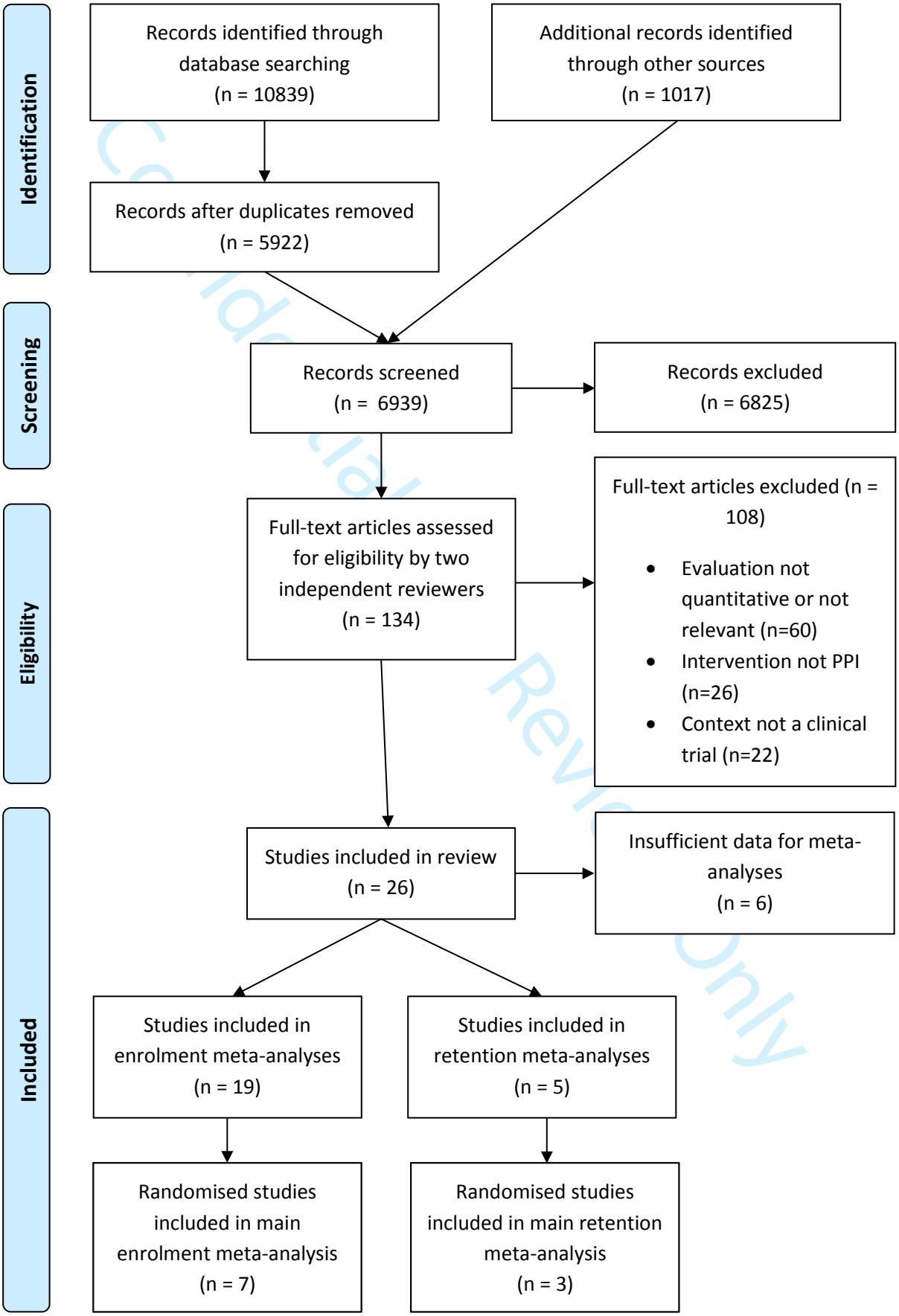
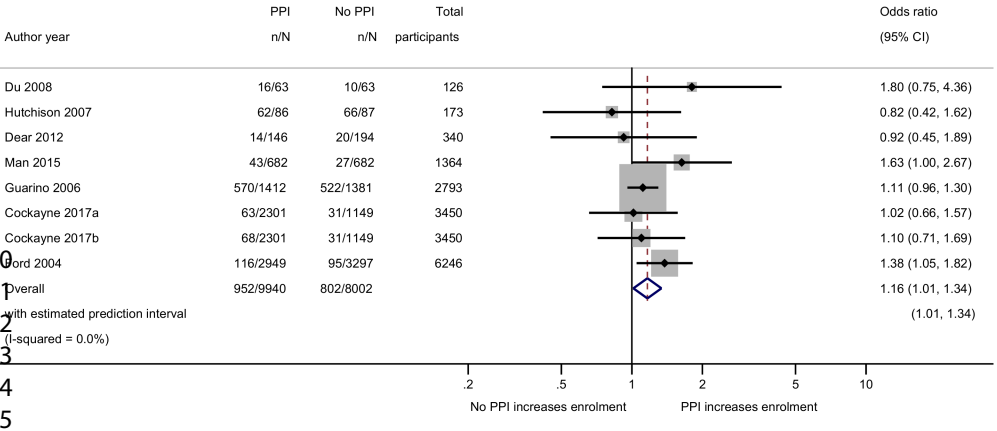
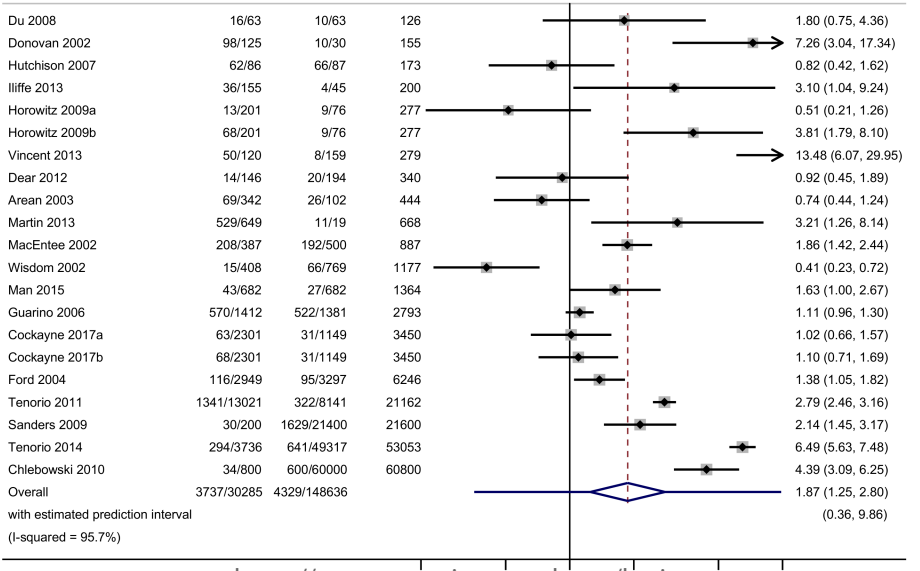
Figure 1: PRISMA flow diagram of records/studies included at each stage of screening and in the final meta-analyses




PPI
No PPI
Total
Odds ratio
Author year
n/N
n/N
participants
(95% CI)
Du 2008 16/63 10/63 126 1.80 (0.75, 4.36)
Hutchison 2007 62/86 66/87 173 0.82 (0.42, 1.62)
Dear 2012 14/146 20/194 340 0.92 (0.45, 1.89)
Man 2015 43/682 27/682 1364 1.63 (1.00, 2.67)
Guarino 2006 570/1412 522/1381 2793 1.11 (0.96, 1.30)
Cockayne 2017a 63/2301 31/1149 3450 1.02 (0.66, 1.57)
Cockayne 2017b 68/2301 31/1149 3450 1.10 (0.71, 1.69)
Ford 2004 116/2949 95/3297 6246 1.38 (1.05, 1.82)
Overall 952/9940 802/8002 1.16 (1.01, 1.34)
with estimated prediction interval (1.01, 1.34)
(I-squared = 0.0%)
.2
.5
1
2
5
10
No PPI increases enrolment
PPI increases enrolment



https://mc.manuscriptcentral.com/bmj

Table 1: Study eligibility criteria

Population	Potential clinical trial participants in any patient population.
Intervention	A trial methodology 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 with the health condition under investigation were included as PPI, but research or healthcare professionals only sharing a characteristic with the target population *other* than health condition (e.g. ethnicity, gender, age) were excluded. 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 methodology 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.'(68) 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.

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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 proxy denominator 'total number of participants', where the intervention was targeting a subgroup within the trial population (e.g. a minority ethnic group or specific geographical region) 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	Timing of the start of PPI intervention / first PPI activity. Earlier involvement

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	retention strategy; (2) developing patient-facing information; (3) directly approaching / recruiting or retaining participants	might lead to greater improvements for enrolment/retention. '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) 'Intermittent' = involved periodically during the life of the trial (e.g. an ongoing advisory group) '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.

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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(33, 60)	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(51, 69, 70)	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(41, 71)	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(34, 59)	Cancer patients consulting with their physician	Australia (multi-site)	Various (multiple trials included)
Donovan *et al.* 2002(42, 72)	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(43)	Lung cancer patients aged 21-80 years	Detroit, USA	Various therapeutic and non-therapeutic (multiple trials included)
Ford *et al.* 2004(52)	African American men aged 55-74 years	USA (multi-site)	Screening for prostate, lung and colorectal cancers
Fouad *et al.* 2014(53, 73)	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(44, 74)	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(35,	Adults with pre-diabetes	East Harlem, New York, USA	Community-based, peer-led weight loss program to prevent diabetes

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75)			
Hutchison *et al.* 2007(45, 76)	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(36, 77, 78)	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(46)	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(47)	Cancer patients aged 65 or older	USA (multi-site)	Cancer treatments (various trials)
MacEntee *et al.* 2002(54)	Community-dwelling elders with a poor history of oral care	Vancouver, Canada	Antibacterial mouthwash to reduce tooth loss
Man *et al.* 2015(48, 79)	Adult patients with depression	UK (multi-site)	12-month telehealth intervention vs. usual GP care for treatment of depression
Martin *et al.* 2013(49, 80)	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(55)	Healthy men age 55+ years	USA (multi-site)	Finasteride vs. placebo to prevent prostate cancer
Porter *et al.* 2016(37)	Cancer patients registered at one clinical centre	Ohio, USA	Cancer treatments (various trials)
Sanders *et al.* 2009(56, 81)	Women aged 70+ years at high risk of falls or fractures	Victoria, Australia	Vitamin D vs. placebo to prevent fractures
Tenorio *et al.* 2011(38, 82, 83)	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(57, 84, 85)	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(39)	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(40, 86)	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(50)	Men with early-stage prostate cancer	Toronto, Canada	Surgical prostatectomy vs. interstitial radiation for treatment of early-stage prostate cancer
Wisdom *et al.* 2002(58)	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(33, 60)	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(51, 69, 70)	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(41, 71)	To improve trial recruitment rates	Two different PPI interventions: (a) 'Bespoke user-tested' PIS: Formal user testing of PIS by 30 members of the public. (b) 'Template-developed PIS': Historical non-bespoke user testing; PPI group reviewed PIS and gave	'Bespoke user-tested' PIS: Design input by researchers and commercial company 'Template-developed PIS': Design input by experienced researchers	Improving the quality and appearance of patient information sheets (PIS)

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		feedback.		
Dear *et al.* 2012(34, 59)	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 *et al.* 2002(42, 72)	To improve rates of consent to randomisation in trial	In-depth interviews with potential participants who had been invited to take part	Qualitative analysis of interviews by 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.	Uncovering information and communication issues during recruitment to the trial
Du *et al.* 2008(43)	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(52)	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(53, 73)	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

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Guarino *et al.* 2006(44, 74)	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(35, 75)	To increase recruitment of black and Latina people into trial	Two different PPI interventions: (a) 'Public events' recruitment strategy: Community members recruited participants at public events. (b) 'Partner-led' recruitment strategy: Community advocates designed and led recruitment strategy.	None	Overcoming barriers to recruitment of minority populations, including fear or mistrust of research, cultural barriers and lack of opportunity to take part
Hutchison *et al.* 2007(45, 76)	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(36, 77, 78)	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(46)	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	Intervention was a self-directed, narrated, computer-based presentation, including suggested questions and video clips of oncologists. Oncologists also gave	Improving patients' understanding of the purpose and benefits of early-phase clinical trials

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		patient narratives. The overall intervention was modified following feedback from 18 cancer patients and survivors.	feedback on the intervention.	
Kimmick *et al.* 2005(47)	To improve accrual of older persons by physicians to cancer treatment trials	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 for one year (with no patient input).	Enabling physicians to discuss common issues in geriatric oncology with a panel of experts.
MacEntee *et al.* 2002(54)	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(48, 79)	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(49, 80)	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(55)	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.*	To achieve a 40% increase in	The 'comprehensive program' included leadership team	The program was multi-faceted and included tasking centre leadership	Equipping all stakeholders (patients, their families, nurses and staff, physicians,

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2016(37)	accrual to clinical trials over a 2-year period	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.	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.	Disease-Specific Committees and centre leadership) with the necessary skills and information to complete the clinical trial accrual process.
Sanders *et al.* 2009(56, 81)	To improve recruitment to the trial	'Word of mouth' recruitment 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	The morning teas provided a social opportunity for participants and potential participants to meet researchers face-to-face.	Giving participants a sense of 'belonging and ownership of the project' and providing an opportunity for the friend to enrol in the trial
Tenorio *et al.* 2011(38, 82, 83)	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(57, 84, 85)	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(39)	To decrease ethnic minority health care disparities and increase representation of ethnic minorities	Minority Outreach Program (MOP), involving collaboration with community-based organisations from five major ethnic/minority populations. Hospital representatives worked with community leaders to	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.

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	in cancer clinical trials	develop culturally competent programs, leading to a series of forums presented within each ethnic minority community.		
Vincent *et al.* 2013(40, 86)	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.
Wallace *et al.* 2006(50)	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(58)	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	Total number of participants	Evaluation design
Arean *et al.* 2003(33,	'Traditional' recruitment model consisting of gate-keeper referral and media advertisements with no design	Enrolment: Proportion of potentially eligible minorities identified who were subsequently recruited to trial. Retention: Proportion of minority participants completing	Enrolment: 444 Retention: 95	Observational study

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60)	input from consumers	3-month and 6-month follow-up assessment		
Chlebowski *et al.* 2010(51, 69, 70)	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. Retention: Not assessed.	Enrolment: 60,800 Retention: N/A	Non-randomised controlled trial
Cockayne *et al.* 2017(41, 71)	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. Retention: Proportion of patients retained in the trial at 3 months post randomisation.	Enrolment: 6,900 Retention: 193	Randomised controlled trial
Dear *et al.* 2012(34, 59)	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. Retention: Not assessed.	Enrolment: 340 Retention: N/A	Randomised controlled trial
Donovan *et al.* 2002(42, 72)	Recruitment according to original trial protocol	Enrolment: Proportion of men invited who subsequently consented to randomisation. Retention: Proportion of men who consented to randomisation and subsequently accepted their allocated treatment.	Enrolment: 155 Retention: 108	Uncontrolled before-after study
Du *et al.* 2008(43)	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. Retention: Not assessed.	Enrolment: 126 Retention: N/A	Randomised controlled trial
Ford *et al.* 2004(52)	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. Retention: Not assessed.	Enrolment: 6,246 Retention: N/A	Randomised controlled trial
Fouad *et al.* 2014(53, 73)	Standard retention activities (reminder calls, cards and incentives)	Enrolment: Not assessed. Retention: Proportion of participants who attended all follow-up visits.	Enrolment: N/A Retention: 632	Randomised controlled trial
Guarino *et al.*	Original PIS designed by researchers	Enrolment: Proportion of patients invited who subsequently refused to take part in trial.	Enrolment: 2,793 Retention: 1,092	Randomised controlled trial

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2006(44, 74)		Retention: Proportion of participants missing any primary outcome data.		
Horowitz *et al.* 2009(35, 75)	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. Retention: Not assessed.	Enrolment: 554 Retention: N/A	Observational study
Hutchison *et al.* 2007(45, 76)	Standard trial-specific written patient information	Enrolment: Proportion of patients invited who were subsequently enrolled into a trial. Retention: Not assessed.	Enrolment: 173 Retention: N/A	Randomised controlled trial
Iliffe *et al.* 2013(36, 77, 78)	Original recruitment strategy prior to focus groups	Enrolment: Proportion of total participants (all regions) recruited in intervention-exposed regions before vs. after intervention. Retention: Not assessed.	Enrolment: 200 Retention: N/A	Controlled before-after study
Kass *et al.* 2009(46)	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). Retention: Not assessed.	Enrolment: 130 Retention: N/A	Randomised controlled trial
Kimmick *et al.* 2005(47)	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. Retention: Not assessed.	Enrolment: 3,032 Retention: N/A	Randomised controlled trial
MacEntee *et al.* 2002(54)	Announcements in newspapers to attract potential recruits	Enrolment: Proportion of initial responders who were subsequently recruited to the trial; cost per recruit. Retention: Not assessed.	Enrolment: 887 Retention: N/A	Non-randomised controlled trial
Man *et al.* 2015(48, 79)	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. Retention: Not assessed.	Enrolment: 1,364 Retention: N/A	Randomised controlled trial
Martin *et al.* 2013(49, 80)	Original recruitment message (before intervention)	Enrolment: Proportion of women approached who were subsequently randomised to trial. Retention: Not assessed.	Enrolment: 668 Retention: N/A	Uncontrolled time series
Moinpour	Original minority recruitment protocol	Enrolment: Proportion of total participants (all	Enrolment: 18,882	Uncontrolled

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et al. 2000(55)	(before enhanced program introduced)	ethnicities) who were minority ethnic. Retention: Not assessed.	Retention: N/A	before-after study
Porter *et al.* 2016(37)	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). Retention: Not assessed.	Enrolment: 35,853 Retention: N/A	Uncontrolled time series
Sanders *et al.* 2009(56, 81)	'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. Retention: Not assessed.	Enrolment: 21,600 Retention: N/A	Observational study
Tenorio *et al.* 2011(38, 82, 83)	Recruitment plan for general population	Enrolment: Proportion of total participants (all ethnicities) who were Hispanic before vs. after intervention. Retention: Not assessed.	Enrolment: 21,162 Retention: N/A	Controlled before-after study
Tenorio *et al.* 2014(57, 84, 85)	Recruitment plan for general population	Enrolment: Proportion of total participants (all ethnicities) who were Hispanic before vs. after intervention. Retention: Not assessed.	Enrolment: 53,053 Retention: N/A	Non-randomised controlled trial
Vicini *et al.* 2011(39)	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. Retention: Not assessed.	Enrolment: 3,056 Retention: N/A	Uncontrolled time series
Vincent *et al.* 2013(40, 86)	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. Retention: Not assessed.	Enrolment: 279 Retention: N/A	Observational study
Wallace *et al.* 2006(50)	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 Retention: Not assessed.	Enrolment: 290-324 (exact figure unknown due to data discrepancies) Retention: N/A	Uncontrolled before-after study
Wisdom *et*	Recruitment from local healthcare	Enrolment: Proportion of patients contacted who	Enrolment: 1,177	Observational

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al. 2002(58)	system (via mail)	subsequently enrolled in the trial. The denominator for the PPI-exposed group is the estimated number of faith-based organisation participants with diabetes shown in the Table 3 footnote, since the comparator intervention (recruitment via health system) targeted only patients with diabetes. Retention: Proportion of participants who attended all 7 intervention sessions.	Retention: 102	study

PIS = patient information sheet

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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)
Study design:		
- Randomised	7	3
- Non-randomised	12	2
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	
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

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- Intermittent - Full team membership	3 6	1 1
Number of PPI contributors involved: - One or two - Three or more - Unknown	 1 18 1	 1 5 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): - Significant *increase* - No significant impact - Significant *decrease*	 11 8 1	 1 4 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.

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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	

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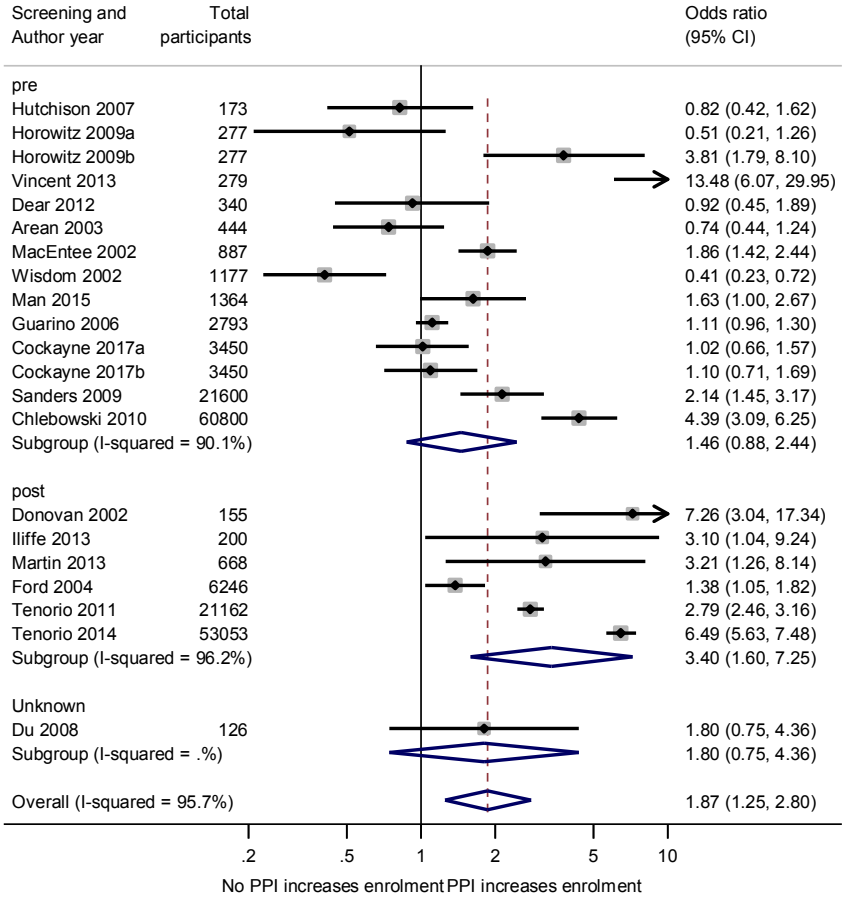
Appendix 2: Forest plots showing subgroup analyses for enrolment outcome

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



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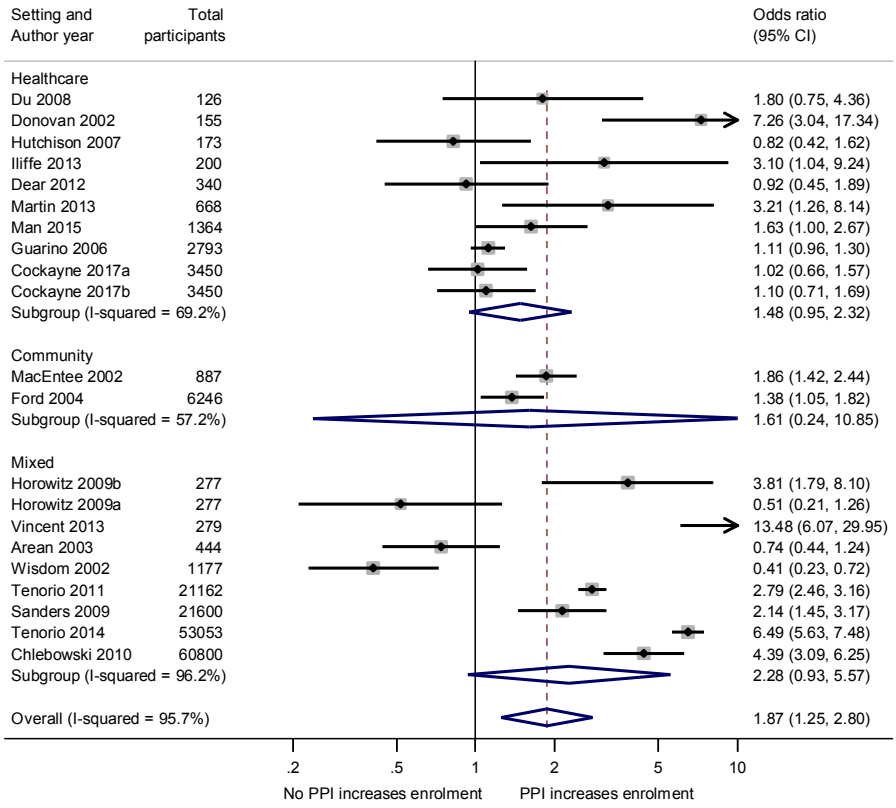
(b) Trial recruitment setting (context)



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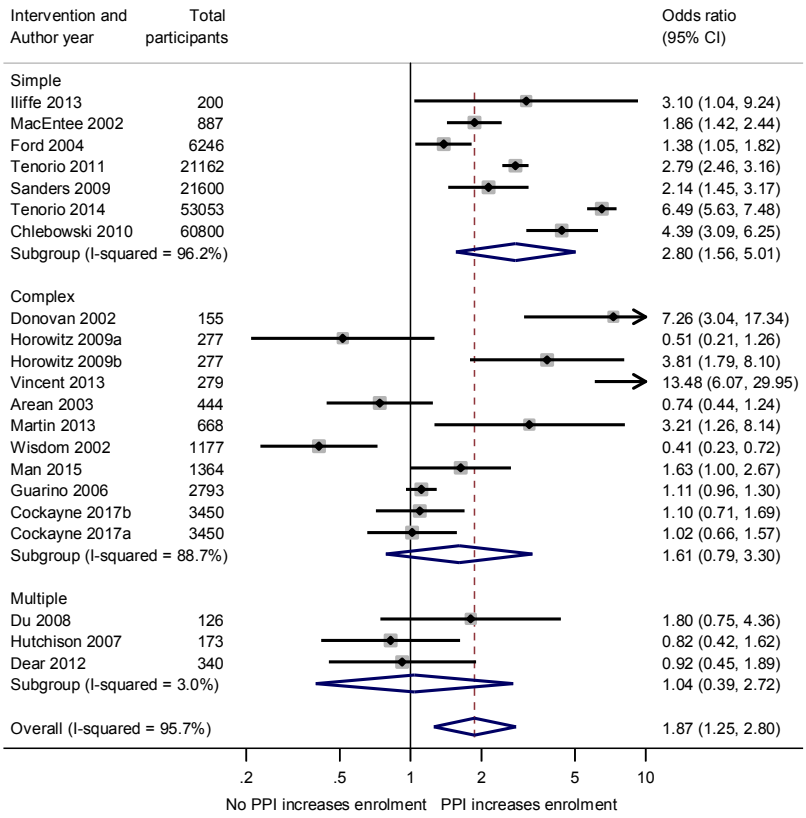
(c) Trial intervention type (context)



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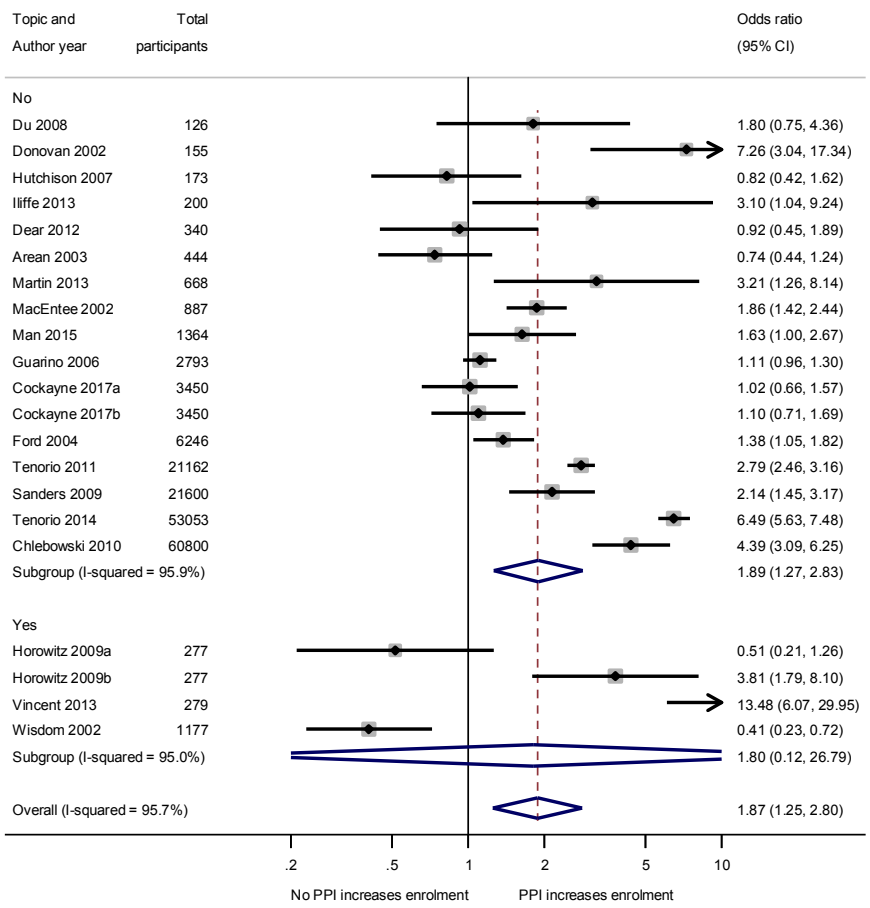
(d) PPI in choosing research question/topic (context)



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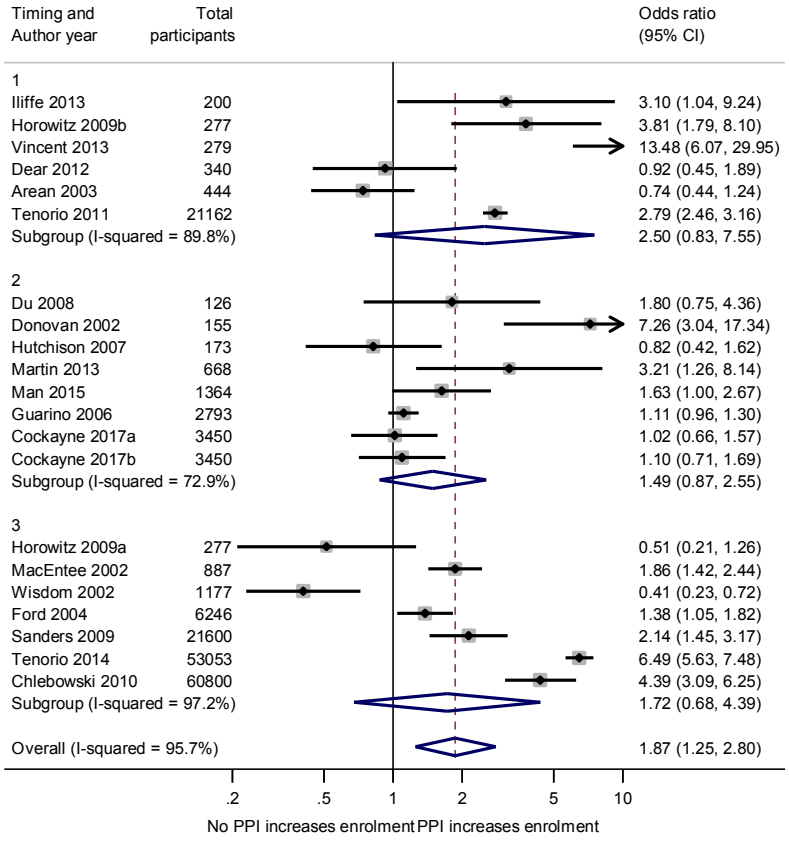
(e) Timing/activity of PPI intervention



Key:

1 = designing recruitment or retention strategy

2 = developing patient-facing information

3 = directly approaching / recruiting or retaining participants

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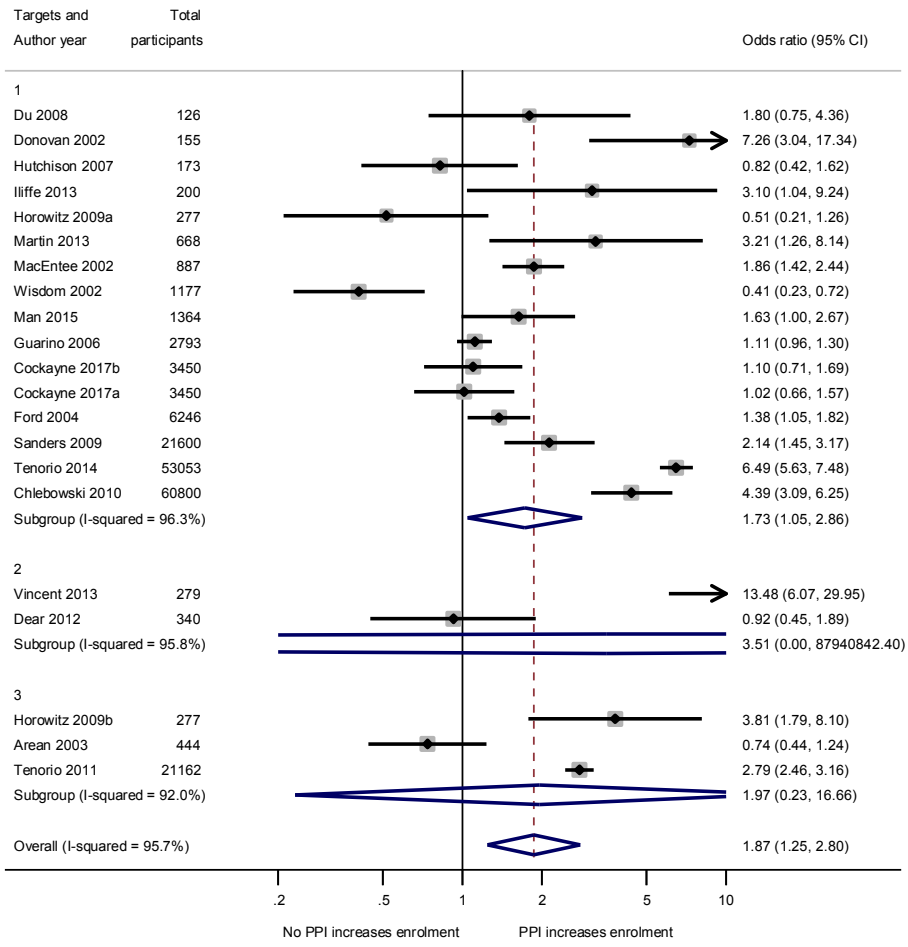
(f) Number of the activities (e) targeted by PPI intervention



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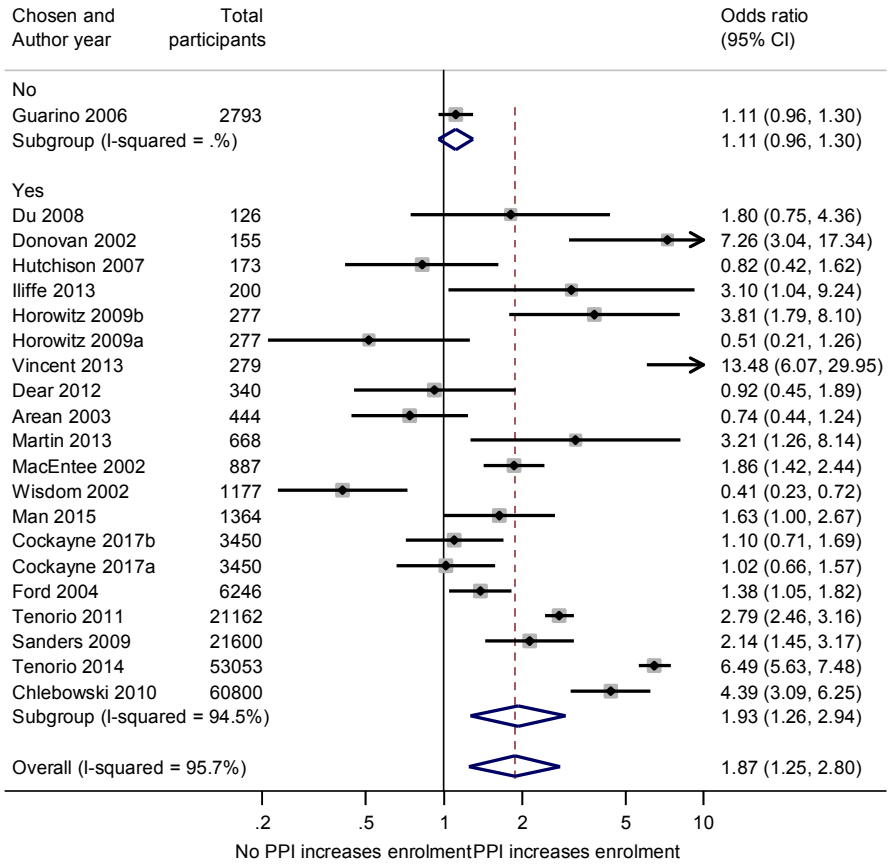
(g) PPI intervention chosen/designed specifically to increase recruitment or retention



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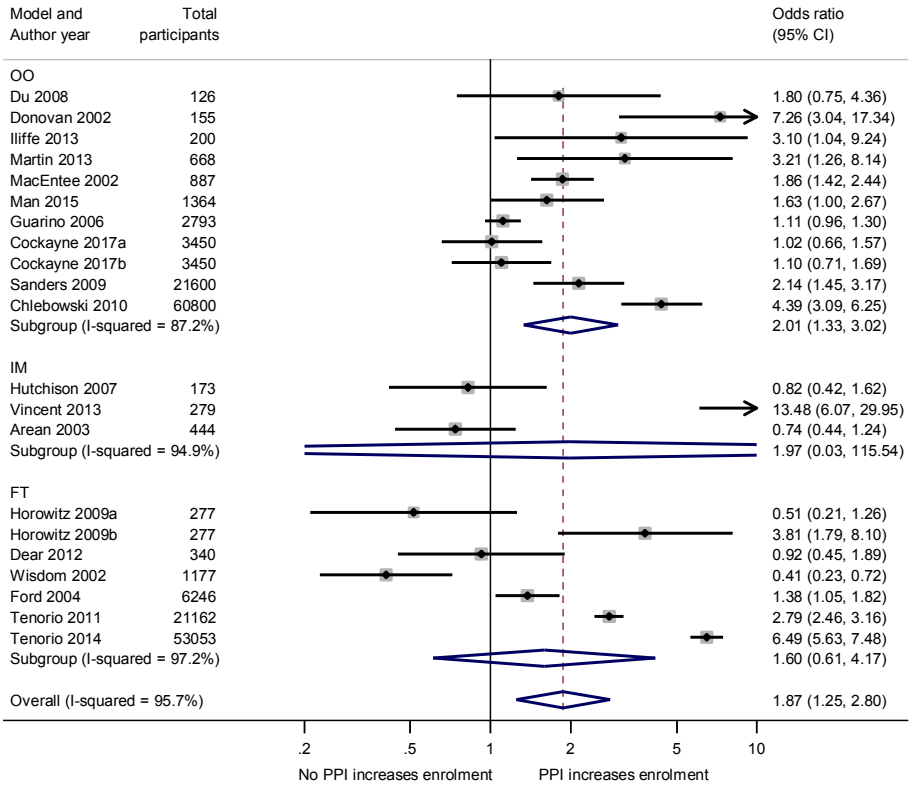
(h) PPI model



Key:

OO = One-off

IM = Intermittent

FT = Full team membership

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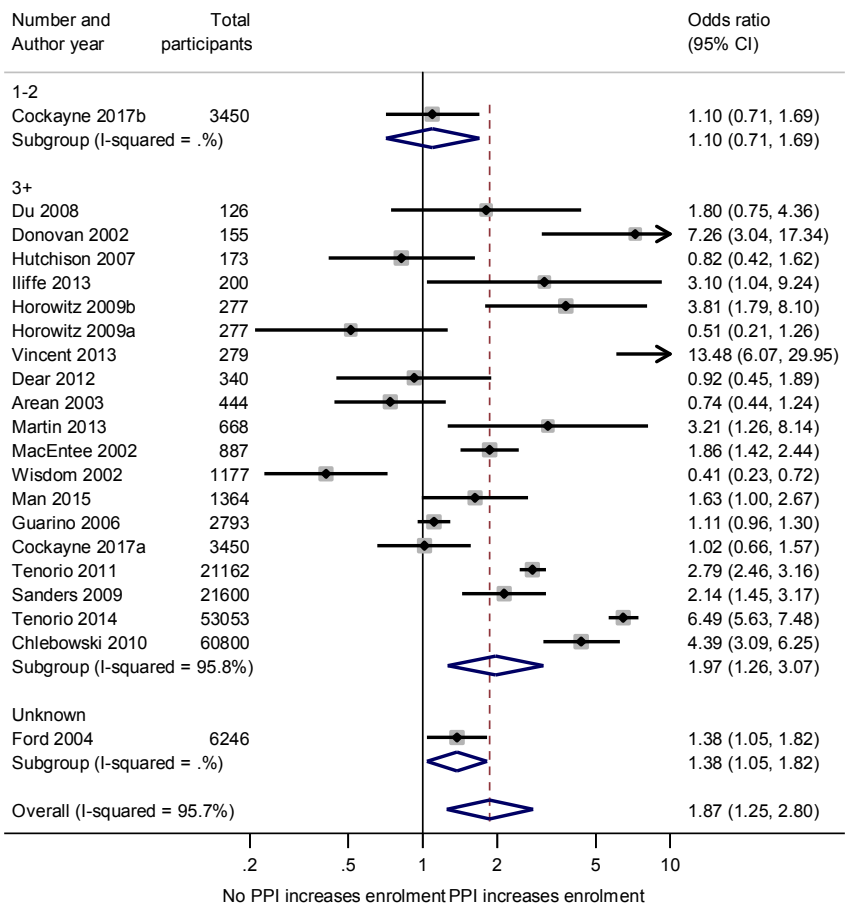
(i) Number of PPI contributors involved



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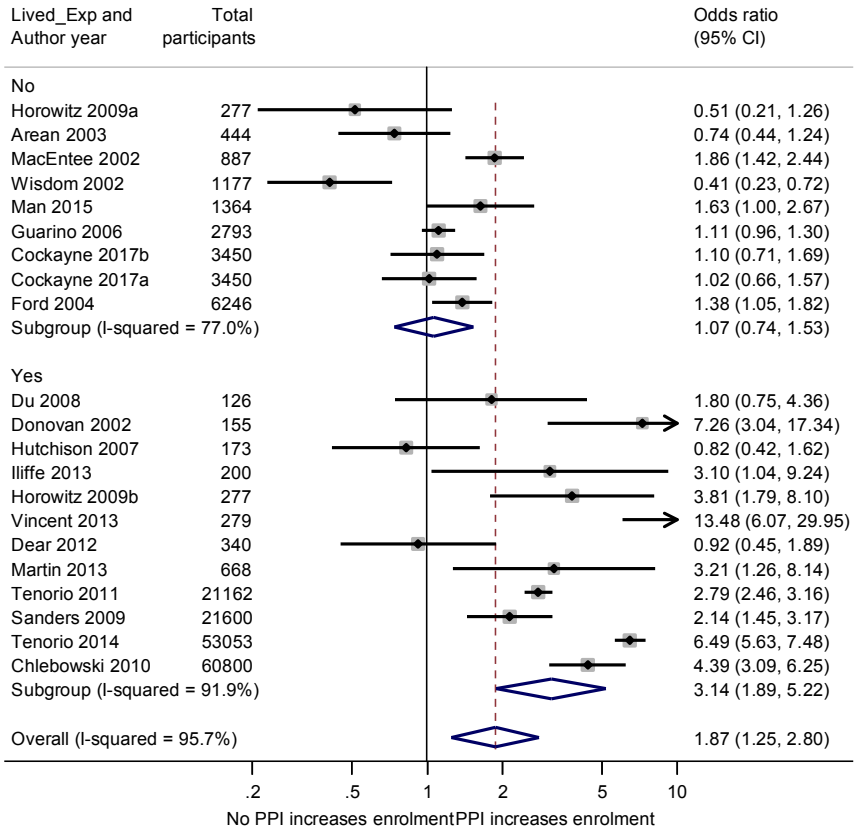
(j) Lived experience



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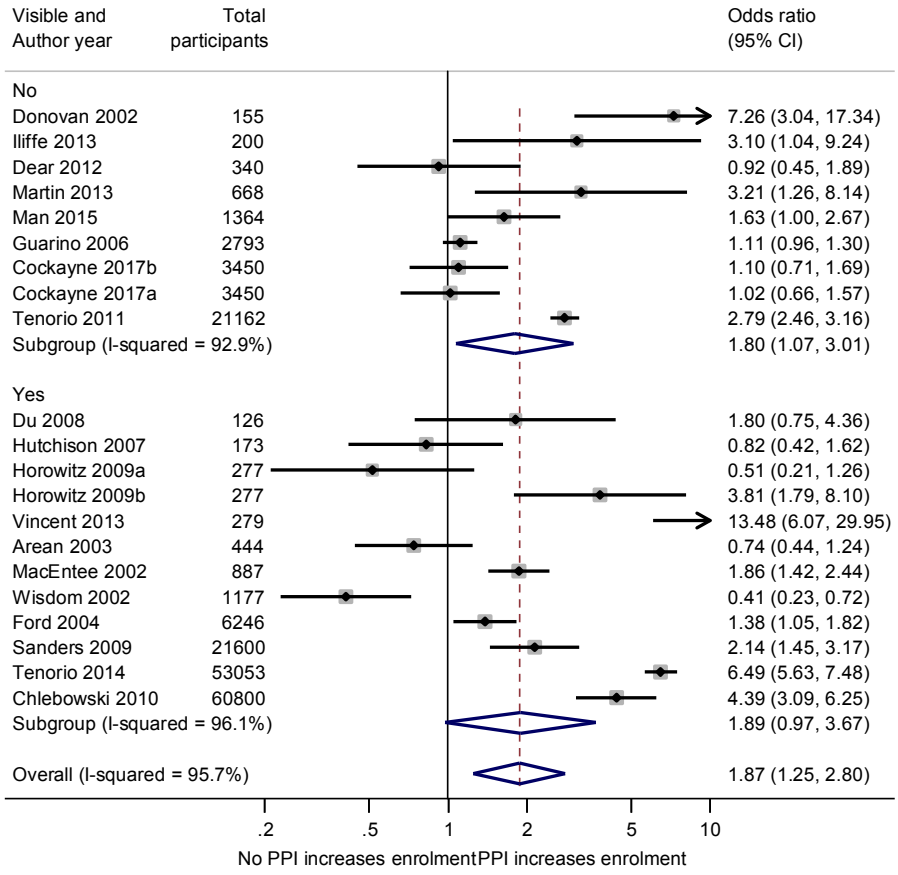
(k) PPI visible to potential trial participants



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Appendix 3: Results of sensitivity analyses for enrolment outcome

a) Main analysis (randomised studies only)

Sensitivity analysis	Number of comparisons remaining (out of total 8)	Estimated OR (95% CI)	p-value
Excluding studies high risk of bias	7	1.17 (1.01-1.35)	0.036
Excluding small studies (N<100)	8	1.16 (1.01-1.34)	0.035
Excluding PPI interventions with non-PPI components	1	-	-
Excluding formal qualitative research interventions	8	1.16 (1.01-1.34)	0.035
Excluding studies using a proxy denominator to measure enrolment rate	8	1.16 (1.01-1.34)	0.035

b) Secondary analysis (randomised and non-randomised studies combined)

Sensitivity analysis	Number of comparisons remaining (out of total 21)	Estimated OR (95% CI)	p-value
Excluding studies high risk of bias	7	1.17 (1.01 – 1.32)	0.036
Excluding small studies (N<100)	21	1.87 (1.25 – 2.80)	0.004
Excluding PPI interventions with non-PPI components	6	2.70 (0.83 – 8.84)	0.084
Excluding formal qualitative research interventions	20	1.77 (1.18 – 2.64)	0.008
Excluding studies using a proxy denominator to measure enrolment rate	18	1.63 (1.06 – 2.52)	0.029

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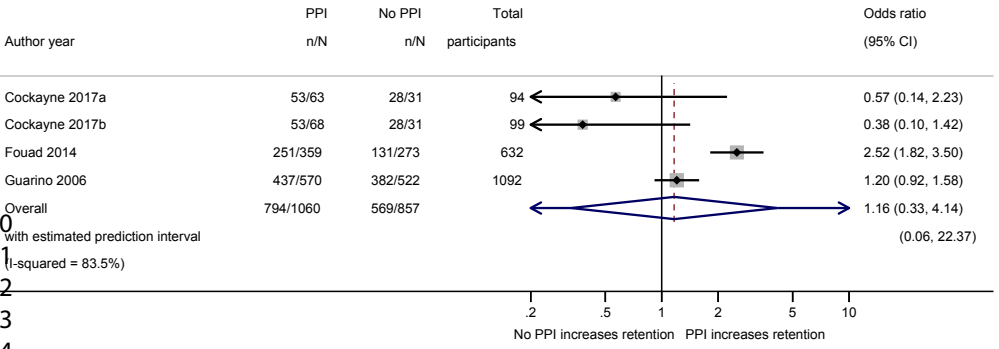
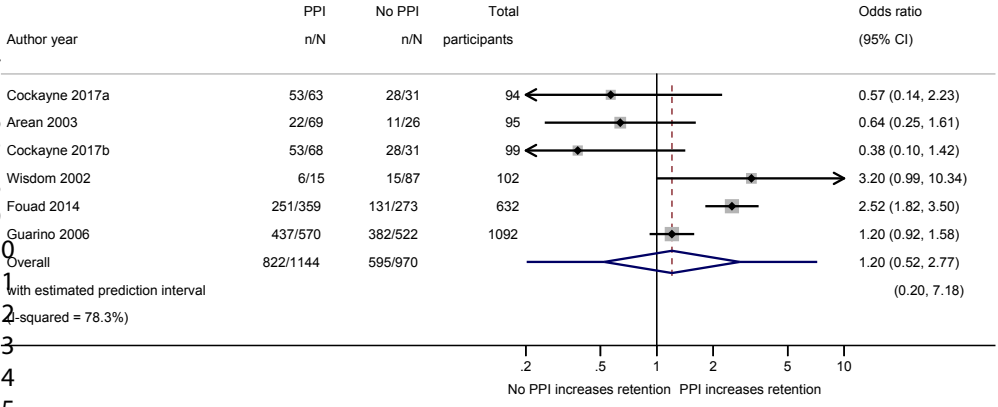

PPI
No PPI
Total
Odds ratio
Author year
n/N
n/N
participants
(95% CI)
Cockayne 2017a 53/63 28/31 94 0.57 (0.14, 2.23)
Cockayne 2017b 53/68 28/31 99 0.38 (0.10, 1.42)
Fouad 2014 251/359 131/273 632 2.52 (1.82, 3.50)
Guarino 2006 437/570 382/522 1092 1.20 (0.92, 1.58)
Overall 794/1060 569/857 1.16 (0.33, 4.14)
with estimated prediction interval (0.06, 22.37)
(I-squared = 83.5%)
.2
.5
1
2
5
10
No PPI increases retention
PPI increases retention


PPI
No PPI
Total
Odds ratio
Author year
n/N
n/N
participants
(95% CI)
Cockayne 2017a
53/63
28/31
94
0.57 (0.14, 2.23)
Arean 2003
22/69
11/26
95
0.64 (0.25, 1.61)
Cockayne 2017b
53/68
28/31
99
0.38 (0.10, 1.42)
Wisdom 2002
6/15
15/87
102
3.20 (0.99, 10.34)
Fouad 2014
251/359
131/273
632
2.52 (1.82, 3.50)
Guarino 2006
437/570
382/522
1092
1.20 (0.92, 1.58)
Overall
822/1144
595/970
1.20 (0.52, 2.77)
with estimated prediction interval
(0.20, 7.18)
d-squared = 78.3%)
.2
.5
1
2
5
10
No PPI increases retention
PPI increases retention

Appendix 6: Results of sensitivity analyses for retention outcome

a) Main analysis (randomised studies only)

Sensitivity analysis	Number of comparisons remaining (out of 4 total)	Estimated OR (95% CI)	p-value
Excluding studies at high risk of bias	4	1.16 (0.33 – 4.14)	0.727
Excluding small studies (N<100)	4	1.16 (0.33 – 4.14)	0.727
Excluding PPI interventions with non-PPI components	2	1.73 (0.02 – 188.33)	0.377
Excluding formal qualitative research interventions	4	1.16 (0.33 – 4.14)	0.727

b) Secondary analysis (randomised and non-randomised studies combined)

Sensitivity analysis	Number of comparisons remaining (out of 6 total)	Estimated OR (95% CI)	p-value
Excluding studies at high risk of bias	4	1.16 (0.33 – 4.14)	0.727
Excluding small studies (N<100)	5	1.36 (0.50 – 3.73)	0.445
Excluding PPI interventions with non-PPI components	2	1.73 (0.02 – 188.33)	0.377
Excluding formal qualitative research interventions	6	1.20 (0.52 – 2.77)	0.590

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