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Patient and Public Involvement in the Design of Clinical Trials: An Overview of Systematic Reviews

Abstract

Background

Funders encourage lay-volunteer inclusion in research but this is not without controversy or resistance, given concerns of role confusion, exploratory methods and limited evidence about what value this brings to research. This overview explores these elements.

Methods

Eleven databases and gray literature were searched without date or language restrictions for systematic reviews of public involvement in clinical trials design. This systematic overview of patient and public involvement (PPI) included 27 reviews from which areas of good and bad practice were identified. PPI strengths, weaknesses, opportunities and threats were explored through use of meta-narrative analysis.

Results

Inclusion criteria was met by 27 reviews. Confidence in the findings was assessed using Cerqual, Nice-H, CASP for qualitative research and CASP systematic reviews. Quality ranged from high (n=7), medium (n=14) to low (n=6) in the reviews. Four reviews report the risk of bias. Public involvement roles were primarily in agenda setting, steering committees, ethical review, protocol development, and piloting. Research summaries, follow-up, and dissemination contained PPI, with lesser involvement in data collection, analysis, or manuscript authoring. Trialists report difficulty in finding, retaining, and reimbursing volunteers. Respectful inclusion, role recognition, mutual flexibility, advance planning and

sound methods were reported as facilitating public involvement in research. Public involvement was reported to have increased the quantity and quality of patient relevant priorities and outcomes, enrollment, funding, design, implementation and dissemination. Challenges identified include lack of clarity within common language, roles and research boundaries; while logistical needs include extra time, training and funding, Researchers report struggling to report involvement and avoid tokenism.

Conclusions

Involving patients and the public in clinical trials design, can be beneficial but requires resources, preparation, training, flexibility and time. Issues to address include reporting deficits in the areas of risk of bias, study quality and conflicts of interests. There is a need for improved dissemination strategies to increase public involvement and health literacy. Improvements in funding, training, and reporting of PPI are needed to facilitate meaningful and effective PPI.

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PRISMA checklist is available in Appendix-3

Introduction

The requirements for the planning of Patient (or Personal) and Public Involvement (PPI) in research has increased[1] to encourage research that is 'with' or 'by' members of the public and patients rather than 'on,' 'to', 'about' or 'for' them. However, there is no standardized reporting for PPI which makes it difficult to identify in reports of research. Consistent reporting of the design, conduct, analysis, and interpretation of the PPI in clinical trials could facilitate reproducibility and reduce correctable error[2,3]. However, many researchers lack PPI[4] training and experience. In addition impaired communications between patients, clinicians and researchers are well documented and may obstruct meaningful involvement[5,6].

This systematic overview of systematic reviews was undertaken to gather research into a single document to identify available evidence and best practice for PPI in the design of clinical trials[7]. It summarizes what has been found and reported about PPI in clinical trials; identifies the context, methods or processes that facilitate PPI[8]; collates the perceptions of the influence of PPI on the research process, outcomes. and dissemination of results; and promotes the uptake of effective strategies to improve PPI in research and reduce resource costs and that might result from ineffectual PPI.

Why it is important to do this overview

Research in this field varies in quality, scope, size, and focus, making a systematic overview a practical option[8,9]. This enables comparison and critical appraisal of choices made in review selection and can collate, analyze and interpret study results across the separate reviews.

Research Question

What can we learn from existing systematic reviews about involving the public and patients in the design of clinical trials in terms of:

1. How patients and the public are involved in the design of clinical trials
2. What is known about good and bad practice for PPI in the design of clinical trials
3. How the value of PPI is perceived
4. How PPI is reported

Aim

To undertake a systematic overview of systematic reviews of the reporting of PPI in the design of clinical trials.

Objectives

1. Identify existing systematic reviews that examine PPI in trials.
2. Critically appraise these reviews to assess their methodological quality.
3. Extract data from these reviews and use these data to describe how, and to what extent, the public and patients have been involved in trials (other than as participants).
4. Seek examples of what worked and what did not to identify good practice.
5. Identify methods and areas of involvement with positive or negative effects on trial design
6. Identify research gaps in PPI and trials design.
7. Identify good practice in the reporting of PPI.

Methods

Research for consideration

Systematic reviews and overviews published in any language that reviewed existing public or patient involvement in clinical trials (other than as participants) were eligible. The involvement could include but was not limited to, prioritization of the research question, involvement in the design or conduct of the trial, analysis, presentation of results, or dissemination of findings. A review could include quantitative or qualitative or mixed

methods studies. Reviews of PPI in clinical trials were eligible if they searched a minimum two databases, appraised the included studies, provided summary findings and included a synthesis of the data and the information retrieved[10].

Outcome measures

The outcomes of interest were PPI employed in clinical trials design, the impact of PPI on research design and the tensions, barriers, recommendations, and strategies relating to PPI as reported in the studies included in the reviews.

Data Sources and Search Strategy

The following databases were searched from 1995 until December 2015: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R), EMBASE, CINAHL, PsycINFO, Science Citation Index, Cochrane Library, Database of Abstracts of Reviews of Effects, PROSPERO, Global Health Library, Health Technology Assessment, The Joanna Briggs Institute EBP Database, McMaster Knowledge Translation and WHOLIS. There were no restrictions on language or publication status. The general search terms for MedLine Appendix-2 (Table-1) were reviewed by the authors and a medical librarian and adapted for each database.

The PRESS checklist[11] was used to ensure inclusion of essential elements in the search strategy. Reference lists and search terms of reviews captured by the initial searches were searched for additional reviews and topic experts were contacted. We searched Prospero for protocols and followed up conference abstracts identified through the database search that met inclusion criteria to see if they had been subsequently published.

Public Involvement

Volunteers from the Cochrane Task Exchange and Empower-2-Go assisted with screening, data extraction, analysis, prioritizing what to report and editing. The dissemination plan for the overview includes promotion via social media, presentation at conferences, and dissemination to patient advocacy groups. Volunteers were invited to co-create the plain language summary, review the paper for readability and work collaboratively to build an infographic to represent the overview.

Screening and Selection of Reviews

All citations were screened in RAYYAN[12], a free online tool that allows the use of unlimited volunteers, tracking and blind review. To improve screening accuracy, retrieved citations were screened by one author (AP) and then rescreened by her 4 weeks later. This method was described in a published review of systematic reviews of treatment for intracranial aneurysms[13]. A random sample of 6% of titles and abstracts were double screened. Full papers were retrieved for articles that appeared eligible or potentially eligible on the basis of their title and abstract, and for a 1% random sample of those judged to be ineligible to check for correct exclusion[13]. Reviewers were not blinded to author, institution, or journal.

Full Paper Retrieval

Full papers were downloaded to a shared folder and de-duplicated in Mendeley[14], where overview authors could write and share notes, add questions and additional data. Two authors screened the retrieved full papers independently to match them against our eligibility criteria. Papers were categorized as include, exclude or unsure. Papers classified as unsure were discussed and agreement at all stages was reached by consensus of three authors.

Data extracted from included reviews

Two review authors independently extracted key data for included reviews, using a data extraction form in EPPI reviewer[15] that was piloted on a small sample of reviews. Data on public involvement in clinical trials design and preparation was extracted, covering exploration of roles, policy, impact, reporting, interventions, and theoretical frameworks. Relevant data about PPI was included even when the primary focus of the review was not PPI. Table-1 reports the type of review used for the research question as this influences the way the data were collected and how reviews might score in reporting quality checklists. All findings were reviewed and discussed by members of the author team until consensus was reached.

Quality Assessment

The CASP[16] checklists for systematic reviews[17] were used as a preliminary screening tool when assessing systematic reviews for eligibility. The first three questions are general and can be used to include or exclude the review. The NICE Quality Appraisal Guidelines for Qualitative Studies Appendix-H form[18] was used to determine whether the research question(s) and theory underpinning reviews were appropriate for the outcomes sought. The following domains were included when assessing quality: aims, methodology, search quality, recruitment, data collection, data analysis, reflexivity, ethical considerations, findings, and research contributions.

Risk of Bias

Confidence in the Evidence from Reviews of Qualitative Research (CERQual)[19 20] was used to summarize confidence in the findings of the reviews of qualitative research. This is based on four components: limitations of methodology, relevance to the research question, coherence and the adequacy of the data presented. CerQual enables ratings of “high”,

"medium", "low" and "very low" (although this final rating was not needed because such reviews were not eligible). The starting point of 'high confidence' reflects that each review finding is a reasonable representation of the question of interest and is downgraded if there are factors that would weaken this assumption[19]. After assessing all four components, authors agreed on overall confidence in each review finding and the relevance to our research.

NICE, CASP, risk of bias, conflict of interest and CerQual (CQ) were aggregated and reviews were categorized as Low <10.5 Medium>15 High >21 confidence. All measures were pre-specified prior to analysis. The scoring of each review is shown in figure 2.

Thematic Analysis

A strength, weakness, opportunity, and threat (SWOT) framework was used to analyze the findings and organize the data into themes and code them for analysis. This made it possible to identify and agree on methods and areas of involvement with positive or negative effect on trial design and to identify research gaps. The SWOT approach is used in healthcare research[21,22] to help teams to analyze data individually and then reach consensus on how to present their findings.

Descriptions of Information Presentation Forms

We present a summary of each included study in Table 1. The excluded reviews summary contains citations and reason for exclusion and is located in results under the heading full-text screening. All included reviews contained qualitative elements which meant that we need to report their results in a narrative format to describe areas of good and bad practice for PPI in clinical trials and the perceived value of PPI.

Results

Search Report

Figure 1 uses a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram to outline the process of study selection [23].

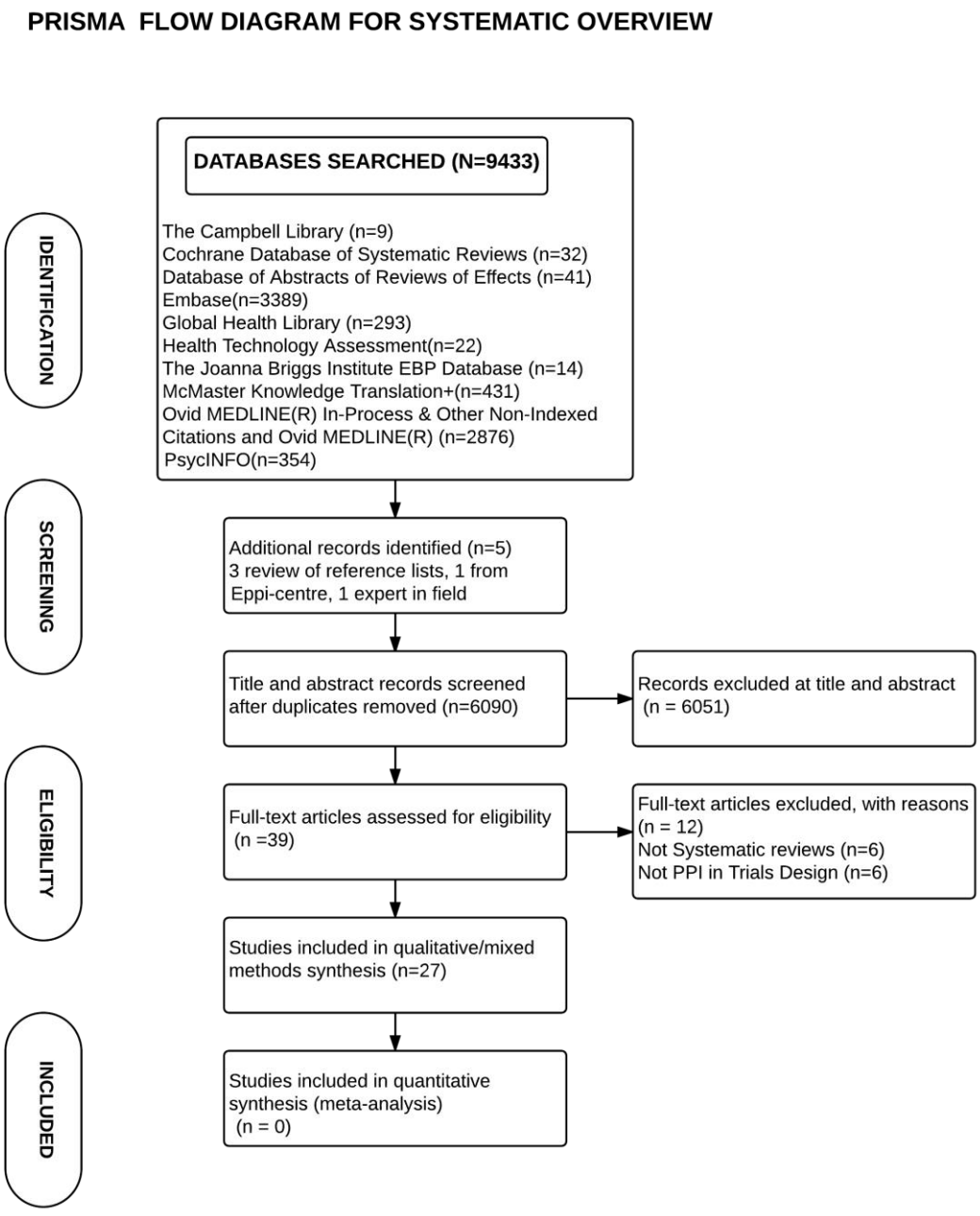

Figure 1 PRISMA Flow Diagram

Our search of 11 databases yielded a total of 9433 records. Three additional records were found by searching the reference lists of included reviews, one more was included from the EPPI Reviewer database and one review was identified by an expert in the field.

Title and Abstract Screening

After de-duplication, 6090 records remained. To improve screening accuracy, retrieved citations were screened by one author (AP) and then rescreened by her 4 weeks later. This method was described in a published review of systematic reviews of treatment for intracranial aneurysms[13]. A random sample of 6% of titles and abstracts were double screened by (AP and LA) and for a 1% random sample of those judged to be ineligible to check for correct exclusion. Full papers were retrieved for articles that appeared eligible or potentially eligible on the basis of their title and abstract. Reviewers were not blinded to author, institution, or journal. The agreement was 100% before discussion and 6051 records were excluded leaving n=39 [24–62] potentially eligible articles for full-text screening.

Full-Text Screening

Two authors, (LA and AP) independently checked the full text of n=39 [24–50] [51–56] [57–62] articles for eligibility, n=12[51–56] [57–62] of which were excluded. Reasons for exclusion were; no public involvement in trials design [51–56] (n=6) and not a systematic review[57–62] (n=6). Twenty-seven reviews [24–50] met inclusion criteria for data extraction and analysis (Appendix-2, Table-5 Excluded Studies). Interrater agreement prior to discussion was Kappa= 0.862 (SE = 0.067, 95% CI= 0.732 - 0.992) and consensus was reached by discussion.

Included Reviews

Table 1 shows the citation number, first author, year of publication, type of review method, research question focus, number of included studies and funding support type for each included review.

Table 1 Included reviews

Citation	**Author reported review design**	**PPI Review Question Focus**	**Studies**	**Funding***
Bailey 2015[24]	Mixed Methods	Disabled children	22	Gov, Priv, Acad
Boote 2010[25]	Narrative & Case Examples	Primary health research design	7	NR
Boote2012[26]	Narrative & Case examples	Organizational approaches to reviews	17	Res
Boote 2015[27]	Bibliometric	Review of PPI literature	683	NR
Brett 2010[28]	Narrative	PPI concepts, measures, outcomes, impact	98	Acad, Priv, Gov
Brett 2014[29]	Mixed Methods	Impact service users, researchers, communities	Not stated	Gov
Brett2014[30]	Mixed Methods	Impact health, social care	66	NR
Concannon 2013[50]	Mixed Methods	Stakeholder involvement in Comparative effectiveness research and PROMs	70	Gov
Degeling 2015[31]	Scoping	Public deliberation health, policy research	78	Gov, Priv
Domecq 2014[32]	Narrative	Patient engagement	7	Gov
Forsythe 2014[33]	Narrative	Rare diseases	35	Gov
Fudge 2007[34]	Qualitative	Older people in health research	35	Priv, Gov
Gysels 2012[35]	Narrative	End of life research participation	20	Gov
Hanney 2013[36]	Mixed Methods	Benefits for healthcare performance	33	Gov
Hubbard 2008[37]	Narrative	Affected by cancer	52	Gov
Jones 2015[38]	Qualitative	Reporting in surgical research	8	Res
Lander 2014[39]	Qualitative	Biomedical research and innovation	46	Acad, Gov
Mockford 2012[40]	Mixed Methods	Impact UK National Health Service (NHS)	28	Gov

Nilsen 2013[41]	Mixed Methods	Development in research healthcare policy, practice guidelines	6	Priv
Oliver 2004[42]	Qualitative	Agenda setting NHS used evidence-based approach	286	Gov
Salvi 2005[49]	Mixed Methods	PPI mental health service users	35	NR
Shippee 2015[43]	Scoping	Research framework for engagement of service user, patient	202	Gov
Smith 2008[44]	Mixed Methods	Nursing, midwifery, health visitor research evidence and practice	416	Gov
Stewart 2011[45]	Qualitative	Effect of patient feedback on clinician research priorities	258	Priv
Stokes 2015[46]	Mixed Methods	Collaboration, coalitions, and partnerships through social media	11	Priv
Tillett 2014[47]	Mixed Methods	Outcome measures psoriatic arthritis	63	Ind
Tong 2015[48]	Qualitative	Research priority setting, kidney disease	16	Gov

** Type of funding is classified as industry (Ind), private foundation/organizations (Priv), governmental (Gov), academic (Acad), researcher (Res) or not reported (NR).*

The total number of studies could not be reported because one review[30] did not report the number of studies reviewed. The total number of studies for the 26 reviews was 2493 (range: 6-683; mean: 104; median: 35). The number of participants per study and PPI roles was not consistently quantified. The use and definition of gray literature was variable.

Twelve [29,32,33,35–37,40,42–44,48,50] included reviews reported government funding, five [24,28,31,34,39] had mixed funding, three [41,45,46] had private funding, two were explicitly funded by the researcher [26,38] and one [47] was funded by industry. Four reviews [25,27,30,49] did not report funding sources. All academic funding reported was combined with other funding. Any impact or influence of direct or indirect industry funding was not reported. For example, it was unclear if academic, private/public foundations, government departments or researchers were indirectly funded,

employed or working on behalf of industry partners (Table 1). Tarpey and Bite (2012) report 75% of industry had no plans for public involvement in research[63] and yet the work of Ehrhardt et al[64] report industry funding was six times more prevalent than other forms of funding for clinical trials.

Quality Appraisal and Methodological Assessment of Included Reviews

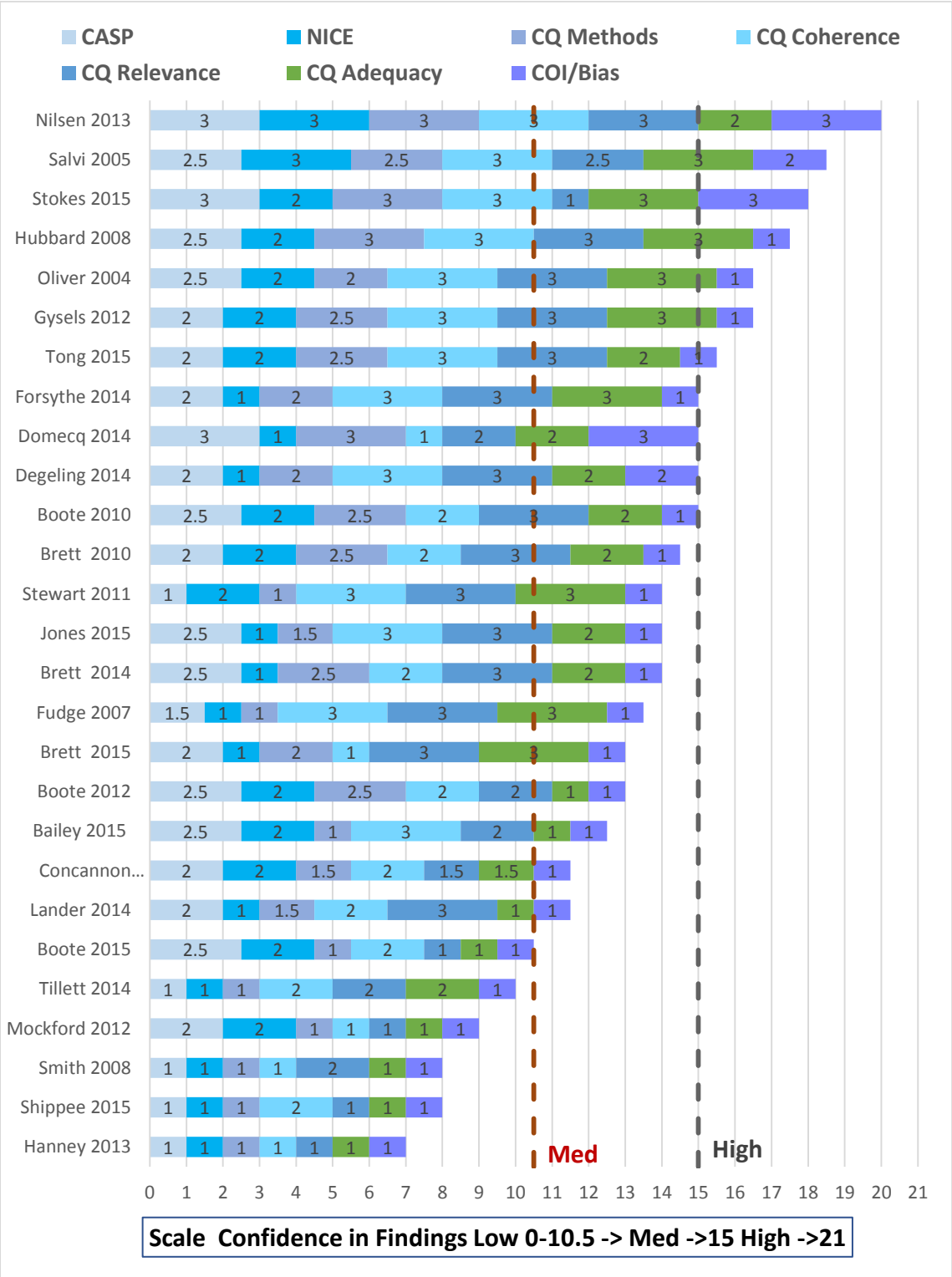

Figure 2 Quality Appraisal using CASP, NICE, Risk of bias (ROB)/conflict of interest (COI) and Critical appraisal by CerQual (CQ) appraising four sectors; quality of methodology, coherence, relevance and adequacy and reporting of bias or conflict of interest with scores each ranging from 1-3, low-high for a composite score of 21.

After the assessment of confidence in the findings for our review question by two reviewers and a lay volunteer, the included reviews were categorized as low [27,36,40,43,44,47] (n=6), moderate[24–26,28–34,38,39,45,50] (n=14) high[35,37,41,42,46,48,49] (n=7) Conflicts of interest and risk of bias were reported for the included studies[32,41,46,49] in four of the included reviews. In two reviews this was referred to but not reported by individual study[31,49]. As expected, although some reviews might have been good enough to answer their research question, they were a substandard source of evidence for our research question. For example, three scoping reviews [27,31,43] scored low on quality because they looked only at abstracts and case studies but these still contained some useful information for our research questions. Likewise, studies seeking impact across research fields[28] contained valuable background information but this was peripheral to the overview aim. The quantitative data reported was descriptive, heterogeneous and scattered across reviews making it a poor fit for meta-analysis and of relatively little relevance to our overview.

Extent of PPI involvement

PPI was more frequent in the form of researchers asking members of the public and patients for feedback on the trial design or citizen to citizen interaction such as moderating forums and recruiting participants, rather than in active participation for hands-on research tasks such as study design, ethical review, policy, recruiting, analysis and dissemination. PPI impact was reported in 14 reviews using many formats. Four reviews[28–30,40] written by authors working together on the question of impact investigated the reporting of impact and have proposed reporting guidelines[61], however, these reviews were hampered by inconsistent reporting within individual studies. Figure 2 shows how PPI was reported across the reviews and the methods of public involvement for various tasks. It shows surveys and focus groups were dominant methods of involvement, yet all 27 reviews reported the use of multiple tasks and methods.

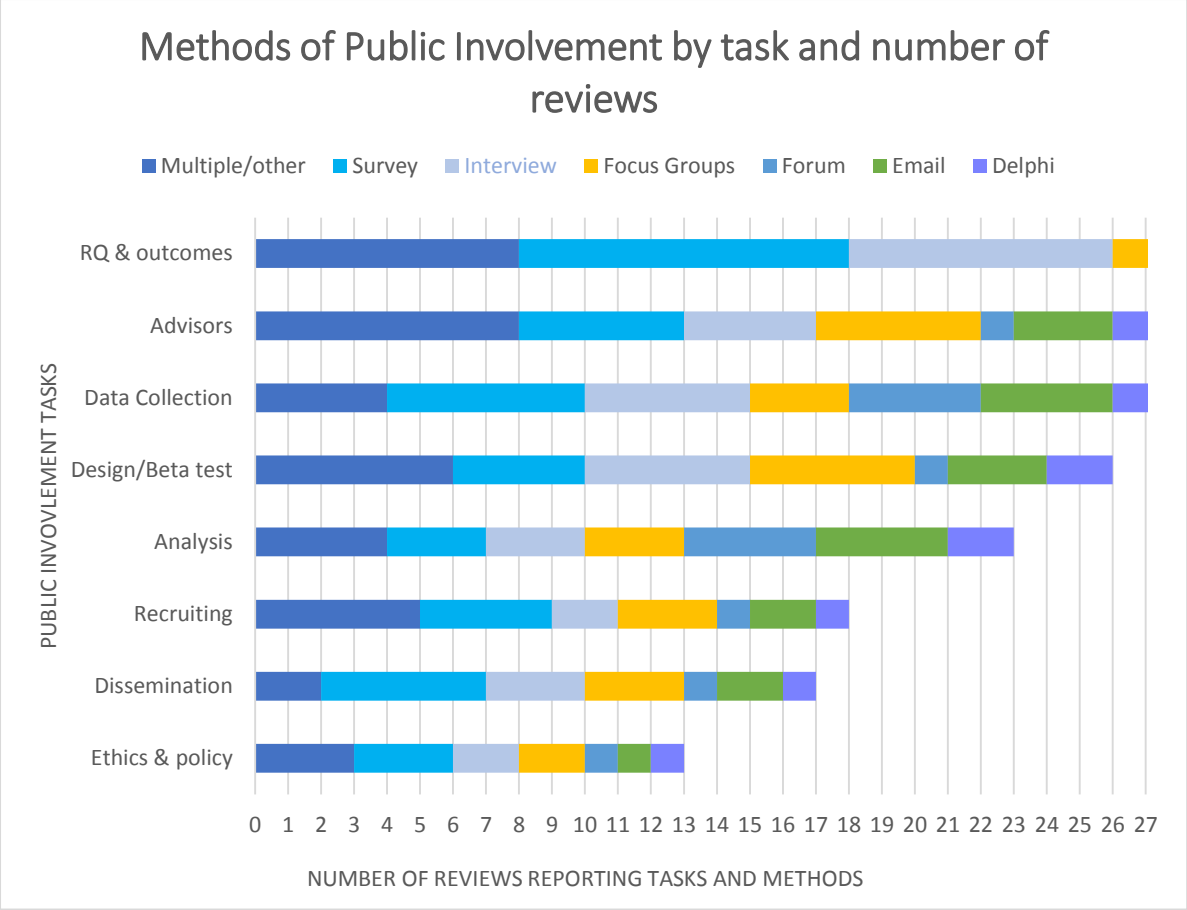

Figure 3 PPI in reviews (n=27) grouped by task and method, RQ (research question), combination (multiple PPI tasks and methods reported), Multiple/other refers to multiple tasks and other methods such as peer to peer interviewing/support, administering interventions.

Reviewers' use of PPI in their review

We recorded how review authors reported public involvement in their own reviews to supplement the inconsistent reporting of the numbers of studies or participants involved in tasks. This information builds a unique value statement about whether talking about PPI encourages practice. Fourteen reviews did not report any PPI in the review and activities were frequently passive. For example, the public was updated by review authors and then were invited to advise or comment on the review, rather than engaging the public directly with the data. This is shown in Figure 4, where 11 reviews report the use of an advisory board. PPI extended to collaborative screening of the literature in three reviews, and analysis and study design roles were largely advisory as recorded in the multiple/other category with

seven reviews. The reviews report lack of funding as a barrier to PPI, and two reviews reported offering compensation for PPI.

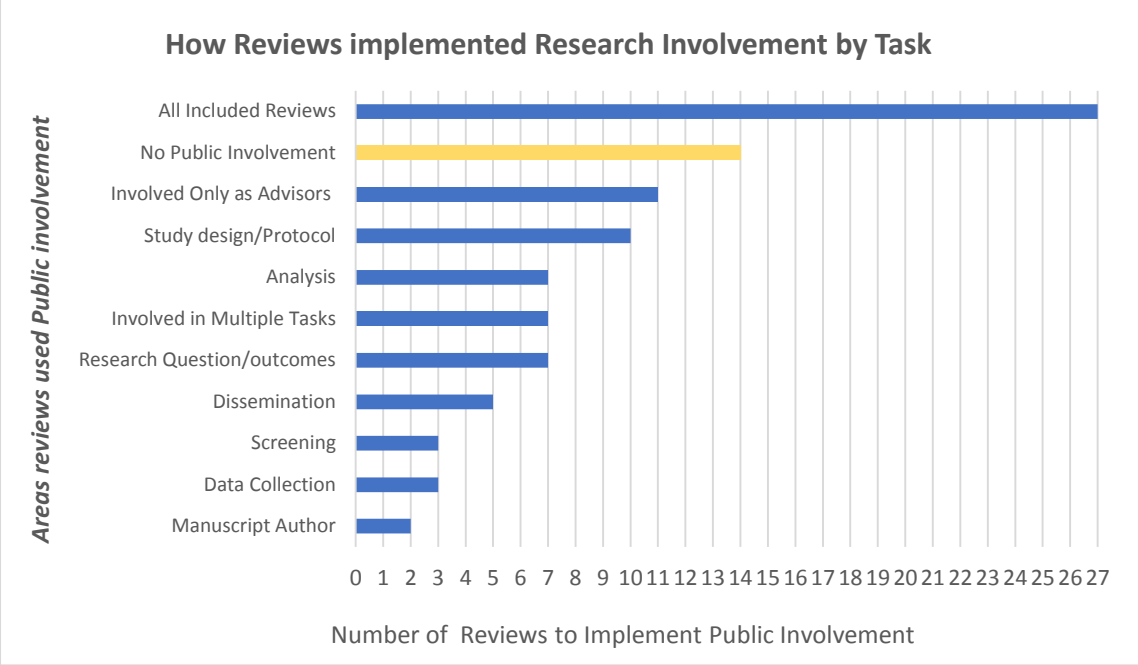

Figure 4 Number of included reviews (n=27) and ways the review authors incorporated public involvement

Our PPI for this Systematic Overview

One volunteer from the Cochrane Task Exchange and three volunteers from Empower-2-Go assisted with screening, data extraction, analysis, synthesis, prioritizing what to report, and editing. One lay volunteer and co-author underwent treatment with chemotherapy and radiation for lung cancer and other volunteers completed her tasks. Volunteers will help with dissemination planning, conduct and implementation of the overview and are working with us to prepare teaching materials. They co-created the plain language summary, suggested improvements for the tables and figures, reviewed the paper for readability and will work collaboratively to build an infographic to represent the overview.

Thematic Analysis with Review Authors and Citizen Collaborators

In this section, we report what was learned from existing systematic reviews of primary research for involving the public and patients in the design of clinical trials through a SWOT analysis. This allowed us to code the narratives to answer our objectives.

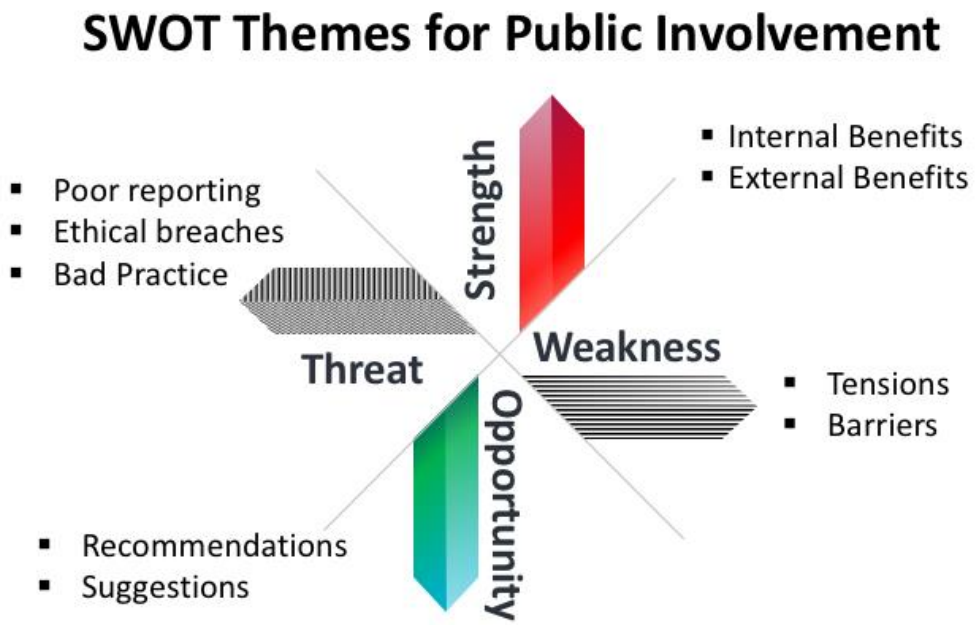

Figure 5 provides an outline of the SWOT with the themes used for analysis

Strengths of Public Involvement

Strengths were coded using themes of internal and external benefits. Twenty reviews contributed to these themes [24–26,28–34,37–42,46–49,57]

Internal Benefits

Shared internal benefits of PPI include knowledge of conditions, interventions and expanding of perspectives. Negative stereotypes and power imbalances were lessened through working together and were replaced by mutual respect. Researchers were encouraged by volunteers' resiliency, innovation and tenacity and report newly acquired motivation and inspiration to

work towards solutions. Patients cite greater confidence, research literacy, hope, trust and a sense of community. They felt participating gave their lives purpose, meaning, and identity. Patients also report learning more about their condition during trials, helping them to feel valued, empowered and validated.

External Benefits

Consultation with volunteers contributed to salient, pragmatic study designs and raised issues that researchers would not otherwise have anticipated. Volunteers improved recruiting, interviews, influenced policy setting, and accessed funding for research. In addition, there was community influence where PPI was considered a factor in de-stigmatizing mental health, age issues, disease stereotypes, and cultural challenges.

The external benefits of PPI were reported from early stages in the design of a clinical trial, including in protocol consultation, setting user-focused research objectives and finalizing research questions; developing questionnaires, interview schedules, and consent processes; planning data analysis, user testing, and implementation and dissemination. Volunteers were also reported as helping with practical problem-solving skills, depth, and perspective.

PPI contributions to recruitment and follow-up timing, strategy, lay materials and protocols, funding applications, and research manuscripts were reported to increase relevance and add research value. Progress was noted for research awareness, literacy, transparency, and training materials. This resulted in increased recruitment, retention, favorable policy integration and community trust. These benefits were more frequent when there was bidirectional communication, collective decision-making, and research intervention delivery training available to support the volunteers.

Weaknesses of Public Involvement

Weaknesses were coded by tensions and barriers. Shared tensions and barriers were followed by those specific to volunteers, researchers, and organizations. Ten reviews contributed to these themes[24,26,29,31,33,34,37,38,41,57].

Tensions in Public Involvement

Shared tensions revolved around unclear roles, absent or ill-fitting reporting guidelines, tokenism, exclusion, framework limitations, resource allocation and administrative boundaries. Research questions posed by patients were not articulated in ways they could be applied. Jargon was blamed for exclusion and confusion. Tensions were balanced by an overarching desire to carve out a mutually agreed path.

Volunteers reported needing early involvement to propose constructive changes. They welcomed frequent updates and specific feedback with opportunities for reflection and shared decision making about the fate of the research. Volunteers indicated that provision for their physical limitations was suboptimal. They worried about inappropriate conclusions from composite outcomes but lacked opportunity to share these concerns and noted they would benefit from research methods training.

Researchers worried about maintaining methodological rigor and focus while adapting research design for patients and report personal lobbying by volunteers for pet causes. Instances were reported where group dynamics changed and overly aggressive patients and those without respect for rules of confidentiality or data protection harmed the research. Researchers hesitated to involve people who were ill, who might slow the research pace and compromise deadlines that might be related to funding.

Organizations reacted to potential “scope creep” where research-irrelevant community concerns increase costs, time and threatened feasibility. Accountability was compromised when researchers added PPI in grants but failed to report this in research.

Barriers to Public Involvement

Shared barriers included those imposed by cultures, values, and power hierarchies. There was limited co-creation of knowledge or community engagement for health via coalitions, collaborations, and partnerships. Some trialists took positions that PPI was a specialist area and not scalable across research disciplines.

Patients reported that involving them too late in a trial meant that the design was already funded and fixed and that the priorities and outcomes were not reversible, leaving them with only user experience to contribute. They were vulnerable to negative attitudes or dismissive behavior and felt overloaded when drawn into internal strife.

Researchers struggled to identify a lead for public involvement, a lack of relevant recruiting networks, difficulties with information about structured, practical methods of involvement, and insufficient time to plan for PPI.

Organizational or gatekeeper barriers ranged from concerns about data being hijacked by opinion rather being centered by evidence. Organizations struggled between tensions of protecting vulnerable patients and appearing paternalistic due to legal and ethical constraints.

Opportunities for Public Involvement

Opportunities were represented by themes of recommendations and strategies. Nineteen reviews contributed to these themes [24–26,28–31,33,34,36–40,42,48–50,57].

Recommendations

A focus on triangulation of teams and clear direction by senior research team members can reduce assumptions. Transparency with time for questions led to better outcomes and good research practice. Research methods and PPI training increased parity between researchers and volunteers. Participatory designs enabled inclusion of participants and cultures across research designs. Using flexible responsive approaches to tasks increased the efficiency and quality of involvement. Researchers suggested combining interviews and focus groups to reduce scheduling conflicts and manage costs. Reviews suggest engaging volunteers in post-study reflection.

Suggestions

These suggestions were developed as a result of findings for good and bad practice in PPI and all the included reviews contributed to this theme. PCORI USA[65], SPOR Canada[66], INVOLVE UK[67] materials were reviewed for suggestions. The table was developed with feedback from volunteers and review authors. The tables are used in informal researcher/volunteer training Amy Price developed for The BMJ[68,69] and for Tabula Rasa an asynchronous online medical support learning network[70]. The tables were adapted for use in an interactive workshop at The Cochrane Canada Symposium 2017[71] and as an element of the course structure at the FORCE11 Scholarly Communication Institute (FSCI) 2017[72]

Table 2 Suggestions for Patient, Personal and Public Involvement

Getting ready for Public Involvement
1. Train everyone on the team who will work with volunteers. It builds community and transparency to train researchers and volunteers together or to train them separately and then bring them together to discuss the training.
2. Use interactive learning, problem-solving and keep it positive.
3. Training materials and ideas for involvement can be found at INVOLVE, PCORI, and SPOR or accessed through university research involvement teams
4. It is more about making the journey pleasant than doing everything right. Volunteers are mostly forgiving and flexible.
5. Bring in volunteers when you have planned for them so they can operate optimally and not be shaken by constant changes or disorganization.
From the Beginning
1. Involve members of the public at every decision-making level.
2. Introduce the patient caregiver and family perspective to each meeting.
3. Provide consistent oversight, task-specific feedback, and support.
Find and Cultivate
1. Identify partners through social media, advocacy groups, word-of-mouth, universities, within the community, schools, and forums.
2. Consider cultivating patient and advocacy groups to work with you.
3. Think about how you will fund the PPI and what the needs are, build this into your funding proposals. If you don't have money, consider what you can you offer of value to volunteer research partners, be transparent and ask volunteer partners for ideas.
Setting the Scene
1. Use advance planning to build capacity and training, coordinate your resources and share your work plan and time structure with volunteers.
2. Develop a climate for open communication of public and patient experiences.
3. Change language from "patients are involved" to "patients are partners".
Making PI Functional
1. Have lay volunteers choose their levels of involvement, be realistic and adapt expectations as they may be ill or have other jobs. For example, they might be fine for part of your research and then have a health crisis.
2. Honor your volunteers on the level to which they can commit and respect their time.
3. Keep tasks flexible, make time for training and questions.
4. Develop strategies for when volunteers are ill, have mental health, or cognitive challenges, need to be replaced or want to come back after recovery.
5. Consider involvement from the research, to dissemination, to implementation, to further development, or refining the intervention and for long-term follow-up
6. Integrate research volunteers into all research processes with a sensitivity to their ability and capacities, do not assume because they are members of the public that they are unable to contribute.
7. Use a Plan>Build>Test>Reflect>Refine approach and pilot everything with feedback.

Table 3 Suggestions for Getting the Best from Public Involvement

Ongoing Support and Implementation
1. Develop your publication and implementation strategy early. Consider asking volunteers to help with plain language translation of your research findings and in the general knowledge translation of your work. 2. Volunteers with the necessary skills can build posters, infographics, presentations, peer-to-peer meetings, recruitment materials and can edit documents for clarity and ease of reading. 3. Volunteers can be trained to conduct interviews or focus groups with their peers. 4. Involve volunteers in both quantitative and qualitative research. This will help them to identify good research questions that are scientifically valid.
Training/Mentoring/Capacity Building
1. Provide training in research literacy and ethics, drawing on the many training programs that are available. 2. At every meeting have a jargon bin, when an unfamiliar term comes up, define it and use this to build glossaries. This will also make people aware of when they are speaking in jargon (even after they have understood the term). 3. Nurture a reciprocal learning relationship, letting volunteers know that you have made a long-term commitment to patient and public partnership in research. 4. Foster realistic expectations in volunteers and researchers and manage relationships with respect.
Inclusion Process
1. Involve volunteers at multiple levels. 2. Invest in building informed leadership and decision-making. Avoid silos. 3. Build together. 4. Use peer-to-peer mentoring and training. 5. Evaluate in an ongoing way. Is it working for everyone? What can we do better?
Building Trust and Community
1. Build community through shared understanding and cooperation. 2. Explore and take risks together. 3. Be transparent. Keep volunteers informed. 4. Support collaborative research from the top.
Reinforce Value and Validate
1. Give specific targeted, frequent feedback. A generic “thank you” is not as effective. **2.** Let volunteers know how you are implementing their suggestions and why some suggestions will not work. Be transparent, respectful and kind. **3.** Adopt “promise back” mechanisms.

Threats to public involvement

Themes identified as threats are poor reporting, data contamination, ethical breaches, and bad practice. All included reviews contributed to this theme.

Poor Reporting

Threats centered around poor reporting and inadequate quality appraisal of studies and the absence of pre-study published protocols. Conflicts of interest revolved around patient-provider relationships, industry and undue influence of advocacy organizations.

Ethical Breaches

Volunteers reported fear to speak out due to threats of blacklisting or exclusion. Patients without training in ethics or research methods report feeling ill prepared to sit on ethics boards, decide policy or provide good quality PPI because they may inadvertently breach confidentiality or patient safety. Cases of premature exposure of data on social media or prepublication leaks by volunteers were reported.

Bad Practice

Planning, training, and information deficits hindered volunteers' ability to contribute. Unpublished methods were lost opportunities for learning. Potential harms of PPI need to be balanced against potential benefits with the caveat that patients and carers might be vulnerable populations. Mixed methods studies without registered protocols could be used to pander influence or exalt experience above evidence. PPI reporting relegated only to supplementary files and not reported or linked in the research made methods difficult to replicate. Supplemental files are valuable for reviewing and learning from the research as they can contain a level of detail that may not be available in the main paper however if they

are inaccessible or not linked to the paper their use is limited at best. Research students without support are inappropriate for troubleshooting and managing volunteers.

Discussion

Public involvement was reported as beneficial for volunteers, researchers, and systems in a variety of settings, including different stages of trial design, cultures and disease states. The best impact was obtained where resources, preparation, training, flexibility and time were designated for PPI and where communication channels were transparent. The identified tensions and challenges are not uncommon in emergent research fields and may be mitigated by testing and modification of current methods and improved research reporting. Common language and research reporting needs could be agreed by use of a Delphi process[73]. This could be piloted by testing a multi-use protocol with built-in reporting mechanisms for PPI. Methods could be tested by using a study within a trial (SWAT)[74] and reported for others to replicate, improve, and validate.

As patients become research collaborators, provide recruiting testimonials, conduct interviews with participants and exert cultural change through social media declaring all conflicts of interest would be best practice[75]. However, standard conflict of interests declarations are insufficient to address relationships leading to unintentional bias or deliberate manipulation, as noted in an analysis of power relations and society/individual agency during research triangulation[76]. Disclosing prior roles between patients, researchers and referring clinicians can reduce the risk of bias[50] and identify indirect financial benefits in the form of industry influence[77] including medical device or intervention choices[78]. Agreed standardized declarations, started from protocol stages, introduced in reporting guidelines, and adopted by journal publishers may reduce the impact of conflicts of interest and bias, and increase reporting quality.

The overlap across reviews in impact appraisal, research prioritization and choice of outcomes may contribute to an overstatement of equality between researchers and citizens. At present, well-meaning efforts including reporting of the impact of PPI in reports of trial could introduce selection bias and increase imbalances of power. Researchers are not evaluated as performance partners within research manuscripts, but their research is evaluated after peer reviewed publication and impact is evaluated by external parties. Research prioritization and the development of core outcome sets[79] as stand-alone exercises[45,80] hinders widespread usage. DUETS UK[81] previously provided a platform where those navigating public preferences, priorities and research questions could find common ground[82] but DUETS was subsumed by NICE and not maintained[83,84]. PCORI USA[65] and SPOR Canada[66] are investing in platforms to store priority setting results, core outcome sets and evaluation materials for PPI. In the interim, COMET[85] has produced a free to access online database of core outcome sets to promote their uptake. Kirkham and colleagues have defined a methodological approach for assessing the uptake of core outcome sets from findings of randomized controlled trials of rheumatoid arthritis listed on using ClinicalTrials.gov. This method may also prove useful for tracking the uptake of PPI and research prioritization[86].

Limitations of this research

The absence of dedicated funding for this systematic overview limited double screening to a sample of citations. Unspecified MESH terms at the time of the search may have compromised search sensitivity and specificity. Rogers et al have since independently conceptualized and validated the terms to prepare a MEDLINE search filter to identify PPI in health research[87]. The deficits in standardized language, research methods and reporting of

PPI provided challenges for identifying search terms, assessing quality and risk of bias and this impacted our interpretation of data and scope of comparisons for the overview.

Differences between protocol and review

References in the protocol to quantitative methods, effect sizes, meta-analysis, GRADE[88], and AMSTAR[89] were not relevant to the final systematic overview because all included reviews were reported qualitatively. We changed the emphasis to "value reported" rather than "impact reported" because the term impact was based on differing cultural assumptions across disciplines.

Conclusions

PPI was wide-ranging and innovative in the reviews we identified. Active public involvement in the decision-making process of designing trials was less common than consultation on what was already decided. PPI initiated at the protocol stage was identified with best practice as was resource acquisition for training, planning, and compensation. Involving lay volunteers for problem-solving provided insights, enhanced research design and served to identify weaknesses and barriers. Contingency plans were useful for adapting to disease progression and competing priorities. Short term tasks based on volunteer strengths, helped volunteers proceed with dignity and reduced guilt when task fulfilment was truncated by disability. Threats to research integrity might be averted through reporting personal conflicts of interest and appraisal of bias in mixed methods or non-quantitative research. The reporting of PPI in the methods section of clinical trial reports could aid replication and make methods available for others to adapt and refine. The use of PPI in dissemination planning, design, implementation, and distribution could increase public involvement, contribute to health literacy and expand knowledge for patient values and preferences. Evaluating PPI impact as a standalone process is ill advised as it is an integral part of the research process, like a

statistician, or trials manager and internal evaluation for external validation is not god practice. Research is evaluated externally by peer review. The addition of patient reviewers by journals may contribute to health literacy and provide insights for future participatory research practice.

Author Contributions

Amy Price drafted and wrote the protocol, manuscript and completed the analysis for this systematic overview with feedback from co-authors and research volunteers. She is the guarantor for this research. The search terms were developed in collaboration with Nia Roberts. Loai Albarqouni, and Amy Price jointly screened, data extracted and completed the analysis. All authors satisfy COPE recommendations for authorship, commented on the manuscript and approved the final version.

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Declarations of interest

The authors have no financial conflicts of interest to declare.

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Appendix-1

Table 4 Overview search terms for MedLine

#	SEARCH TERMS
1	1 (research adj2 (involv* or participat* or engag* or collaborat* or cooperat* or co-operat*)).ti,ab.
2	consumer participation/ or patient participation/
3	((public or patient? or citizen? or survivor? or volunteer? or consumer? or user? or stakeholder?) adj3 (involv* or participat* or engag* or collaborat* or cooperat* or co-operat*)).ti,ab.
4	(expert adj (patient? or user? or consumer?)).ti,ab.
5	((public or patient? or citizen? or survivor? or volunteer? or consumer? or user? or stakeholder?) adj (panel? or group?)).ti,ab.
6	(advisory adj (panel? or group?)).ti,ab.
7	2 or 3 or 4 or 5 or 6
8	exp Biomedical Research/
9	Research Personnel/
10	Research Subjects/
11	exp Clinical Trials as Topic/
12	Research Design/
13	((health or healthcare or clinical or biomedical or medical or gene or genetic or genomic or social care) adj research*).ti.
14	(trial? or study).ti.
15	researcher?.ti.
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	7 and 16
18	1 or 17
19	medline.ti,ab.
20	(systematic and review).ti,ab.
21	meta-analysis.pt.
22	(meta-synthesis or metasynthesis or meta-ethnography or metaethnography or meta-study or meta study).ti,ab.
23	(evidence synthesis or realist synthesis or realist review).ti,ab.
24	19 or 20 or 21 or 22 or 23
25	18 and 24
26	(overview and systematic).ti.
27	meta-review.ti.
28	"review of reviews".ti.
29	"review of systematic reviews".ti.
30	umbrella.ti. and (review or systematic).mp.
31	(policy and brief and evidence).ti.
32	26 or 27 or 28 or 29 or 30 or 31
33	18 and 32

Appendix-2

Table 5 Excluded Studies

Author	Citation	Reason
Evans 2103	Evans D, Coad J, Cottrell K, *et al.* Public involvement in research: assessing impact through a realist evaluation. *Health Services and Delivery Research* 2014;**7**:1–128. doi:10.3310/hsdr02360	Not PPI
Sarrami-Foroushani 2014	Sarrami-Foroushani P, Travaglia J, Debono D, *et al.* Key concepts in consumer and community engagement: a scoping meta-review. *BMC Health Services Research* 2014;**14**:250. doi:10.1186/1472-6963-14-250	Not PPI
Sarrami-Foroushani 2104	Sarrami-Foroushani P, Travaglia J, Debono D, *et al.* Implementing strategies in consumer and community engagement in health care: results of a large-scale, scoping meta-review. *BMC Health Services Research* 2014;**14**:402. doi:10.1186/1472-6963-14-402	Not PPI
Simpson 2002	Simpson EL, House A. Involving users in the delivery and evaluation of mental health services: systematic review. BMJ. 2002 Nov 30;325(7375):1265–1265.	Not PPI
Tempfer 2011.	Tempfer CB, Nowak P. Consumer participation and organizational development in health care: A systematic review. *Wiener Klinische Wochenschrift* 2011;**123**:408–14. doi:10.1007/s00508-011-0008-x	Not PPI
Ward 2012	Ward J, de Motte C, Bailey D. Service user involvement in the evaluation of psycho-social intervention for self-harm: a systematic literature review. *Journal of Research in Nursing* 2013;**18**:114–30. doi:10.1177/1744987112461782	Not PPI
Higginson 2013.	Higginson IJ, Evans CJ, Grande G, *et al.* Evaluating complex interventions in End of Life Care: the MORECare Statement on good practice generated by a synthesis of transparent expert consultations and systematic reviews. *BMC Medicine* 2013;**11**:111. doi:10.1186/1741-7015-11-111	Not systematic review
Jagosh 2012	Jagosh M, Macaulay A, Pluye P, *et al.* Uncovering the Benefits of Participatory Research: Implications of a Realist Review for Health Research and Practice. *Milbank Quarterly* 2012;**90**:311–46. doi:10.1111/j.1468-0009.2012.00665.x	Not systematic review
Jamshidi 2014	Jamshidi E, Morasae EK, Shahandeh K, *et al.* Ethical Considerations of Community-based Participatory Research: Contextual Underpinnings for Developing Countries. *International Journal of Preventive Medicine* 2014;**5**:1328–36.	Not systematic review
Oliver 2008	Oliver SR, Rees RW, Clarke-Jones L, *et al.* A multidimensional conceptual framework for analysing public involvement in health services research. *Health Expectations* 2008;**11**:72–84. doi:10.1111/j.1369-7625.2007.00476.x	Not systematic review
Staniszewska 2011	Staniszewska S, Brett J, Mockford C, *et al.* The GRIPP checklist: Strengthening the quality of patient and public involvement reporting in research. *International Journal of Technology Assessment in Health Care* 2011;**27**:391–9. doi:10.1017/S0266462311000481	Not systematic review
Wilson 2015	Wilson, P. et al., 2015. ReseArch with Patient and Public invOlvement: a RealisT evaluation – the RAPPORT study. Health Services and Delivery Research, 3(38), p.1-176. Available at: http://www.journalslibrary.nihr.ac.uk/hsdr/volume-3/issue-38.	Not systematic review

Appendix-3 PRISMA

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, systematic overview meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, **as applicable:** background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	37 A-1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	15
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. Thematic and descriptive analysis	14-27
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	13-14
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14-27
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14-27
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	28-29
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	29
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	30
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	31

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097