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Review

Factors affecting recruitment into depression trials: Systematic review, meta-synthesis and conceptual framework

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ABSTRACT

Background: Depression is common and clinical trials are crucial for evaluating treatments. Difficulties in recruiting participants into depression trials are well-documented, yet no study has examined the factors affecting recruitment. This review aims to identify the factors affecting recruitment into depression trials and to develop a conceptual framework through systematic assessment of published qualitative research.
Methods: Systematic review and meta-synthesis of published qualitative studies. Meta-synthesis involves a synthesis of themes across a number of qualitative studies to produce findings that are "greater than the sum of the parts". ASSIA, CINAHL, Embase, Medline and PsychInfo were searched up to April 2013. Reference lists of included studies, key publications and relevant reviews were also searched. Quality appraisal adopted the "prompts for appraising qualitative research".
Results: 7977 citations were identified, and 15 studies were included. Findings indicate that the decision to enter a depression trial is made by patients and gatekeepers based on the patient's health state at the time of being approached to participate; on their attitude towards the research and trial interventions; and on the extent to which patients become engaged with the trial. Our conceptual framework highlights that the decision to participate by both the patient and the gatekeeper involves a judgement between risk and reward.
Limitations: Only English language publications were included in this review.
Conclusions: Findings from this review have implications for the design of interventions to improve recruitment into depression trials. Such interventions may aim to diminish the perceived risks and increase the perceived rewards of participation.
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Contents

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1. Introduction

Depression is a major health problem and is predicted to become the single leading cause of disease burden worldwide by 2030 (World Health Organization, 2004; World Health Organization, 2013). A significant number of patients do not fully recover despite treatment (National Collaborating Centre for Mental Health, 2009; Torpey and Klein, 2008; Hardeveld et al., 2010). Thus there remains a significant need to develop effective interventions for managing depression.

Whilst clinical trials are the most scientifically rigorous way of comparing alternative treatments, delivery of such trials is limited in a large part by poor recruitment and retention of research participants (Tenhave et al., 2003; Sacks et al., 1982; Barton, 2000). Difficulties with recruiting participants into clinical trials are very common: 45% of publicly funded trials require an extension and 80% of industry trials do not meet enrolment deadlines (Sully et al., 2013; Centerwatch, 2009). To our knowledge there have been no studies establishing the scale of recruitment problems specifically for depression trials, so the exact magnitude of difficulties in this area is unknown. However, there is a general consensus that depression trials experience particular challenges with recruitment, and many fail to recruit their proposed sample of participants to target, or indeed fail altogether (Hunt et al., 2001; Fairhurst and Dowrick, 1996; Woodford et al., 2011; Rendell and Licht, 2007; Hetherton et al., 2004; Garnham et al., 2011; Ruddell et al., 2007; Stek et al., 2007; Katz et al., 2005; Minas et al., 2005; Haberfellner, 2000; Yastrubetskaya et al., 1997). Other consequences of poor recruitment include increased costs and effort, reduction in statistical power, and delays in the generation of evidence and the subsequent adoption of effective interventions (Halpern et al., 2002; Patel et al., 2003; Drüeke et al., 2003).

Historically, recruiting into trials has commonly been considered an "art" rather than a "science", whereby the recruitment experience has been thought to be unique to each trial and each recruiter (Bonvicini, 1998; Baquet et al., 2008; Timmerman, 1996). The importance of recruitment and retention to research, clinical practice and policy received relatively little attention (Froelicher and Lorig, 2002). Whilst a large number of individual interventions to address recruitment difficulties have been reported in the literature, very few of these interventions have robust evidence of effectiveness, leading to the conclusion that "*recruiting for science has not been underpinned by a science of recruitment*" (Bower et al., 2009, p. 393). All systematic reviews undertaken on the topic have called for an urgent need for systematically evaluated recruitment interventions, particularly those that are tested in real-world trials (Foy et al., 2003; Watson and Torgerson, 2006; Woodall et al., 2010; Prescott et al., 1999; Campbell et al., 2007; Mcdonald et al., 2006; Fletcher et al., 2012; Uybico et al., 2007; Caldwell et al., 2010; Johnson et al., 2011; Rendell et al., 2007; Treweek et al., 2013). Furthermore, recruitment is now highlighted as the methodological research priority for clinical trials units in the United Kingdom (Smith et al., 2014).

The MRC Complex Interventions Framework can be adopted to develop and evaluate recruitment interventions using a multi-phased approached (Craig et al., 2008; Tramm et al., 2013). Within the Framework, evidence synthesis and qualitative research are important methodologies in intervention development (Peters, 2010). Here, we use qualitative meta-synthesis to identify and synthesise the evidence base on factors affecting recruitment into depression trials, to assist in the development of interventions aimed at improving recruitment into depression trials.

Systematic reviews provide the most reliable research findings by applying explicit methods that minimise bias (Higgins and Green, 2011; Antman et al., 1992; Oxman and Guyatt, 1993). Systematic reviews of qualitative research aim to apply similar methodology to the exploration of subjective experiences about meanings, processes or interventions (Pettigrew and Roberts, 2006). There have been numerous systematic reviews investigating various aspects of recruitment into clinical trials, and recently two of these reviews have adopted the meta-synthesis approach to investigate reasons for participating in trials in general; and willingness of patients of Chinese heritage to participate in trials (Mccann et al., 2013; Limkakeng et al., 2013). However few have focused on mental health, and of those, the first reviewed barriers to participation in mental health research, focusing on gender, ethnicity and age (Woodall et al., 2010); the second reported on the inclusion of Latinos with obsessive compulsive disorder in clinical trials (Wetterneck et al., 2012); and the third examined barriers to recruiting ethnic minorities to mental health research (Brown et al., 2014). None of these mental health reviews adopted a meta-synthesis approach, nor focused on the specific factors affecting the recruitment of participants into depression trials.

Our aims in undertaking this review were firstly to systematically identify relevant qualitative studies describing factors affecting recruitment of participants into depression trials; and secondly to perform a meta-synthesis to identify common themes that describe factors affecting recruitment into depression trials, to develop a conceptual framework of factors influencing the decision to participate in depression trials.

2. Method

The method we employed was meta-synthesis (Stern and Harris, 1985). Much as meta-analyses for quantitative studies focus on combining results from different studies with the aim of identifying patterns among study results, meta-synthesis attempts to integrate results from a number of different but inter-related qualitative studies to generate new insights. The process involves both induction and interpretation. However, whilst meta-analysis typically aggregates data

to produce a common measure of effect size, meta-synthesis involves reconceptualising themes from across a number of qualitative studies to combine phenomena into a *transformed* whole (Noblit and Hare, 1988). Numerous published high quality systematic reviews of qualitative studies have applied this method, including meta-syntheses on clinical trial recruitment (Limkakeng et al., 2013; Mccann et al., 2013) and depression (Beck, 2002; Khan et al., 2007; Knowles et al., 2014; Lamb et al., 2012; Gask et al., 2011; Malpass et al., 2009); however to our knowledge no study to date has addressed both.

Within meta-synthesis the data comprise the main themes reported in each of the primary studies. These main themes are synthesised across the studies to develop a conceptual framework concerning the factors affecting recruitment into depression trials. Our review and meta-synthesis comprised three stages: systematic literature search; quality appraisal; and synthesis.

2.1. Systematic literature search

This review investigated empirical accounts of factors affecting the recruitment of patients into depression trials. We considered any studies (including those using mixed methods) that reported qualitative empirical findings, including from gatekeepers/professionals as well as from patients with depression. The search strategy identified terms corresponding to clinical trial "recruitment" and "depression" (and their variants) (see Appendix A for Medline search strategy). Electronic bibliographic database searches used a combination of medical subject headings (MeSH) and free text. Test searches were conducted and expert advice from specialists in retrieval was sought to maximise efficiency (Centre for Reviews and Dissemination, 2009). Whilst we aimed to identify qualitative studies, we did not include a "qualitative research" filter in the electronic database searches as our test searches indicated qualitative studies were poorly indexed (Gorecki et al., 2010), whereby a number of studies known to us were not retrieved when the "qualitative" methodological filters were applied. Rather, we read and reviewed study titles and abstracts to increase the likelihood of identifying all suitable qualitative studies.

The following databases were searched from inception: ASSIA (1987 to 8th April 2013), CINAHL (1937 to April 7th 2013), Embase (1974 to 2013 April 05), Medline (1946 to March Week 4, 2013) and PsychInfo (1806 to April Week 1 2013). Manual searches of the reference lists of included studies, key publications and relevant reviews were also undertaken.

2.1.1. Inclusion and exclusion criteria

Table 1 lists the inclusion and exclusion criteria. Due to limited resources we only included papers published in the English language. Unpublished articles, dissertations, non-empirical published articles and book chapters, and conference abstracts without corresponding full text articles were excluded. Studies with a majority (more than 50%) of participants under 18 years of age were also excluded, as paediatric trials can involve specific issues and procedures that are not present in trials involving adults (Caldwell et al., 2004).

2.2. Quality appraisal

There is lack of consensus about quality assessment in qualitative research (Mays and Pope, 2000; Dixon-Woods et al., 2004a). In recognition of this, and arguments that quality in qualitative research does not arise simply from adherence to recommended procedures (Barbour, 2001; Chamberlain, 2000), quality appraisal within this review was therefore adapted from the minimally prescriptive "prompts for appraising qualitative research" (Dixon-Woods et al., 2004b, 2006). The prompts aim to sensitise appraisers to the various dimensions of articles that require evaluation, and include an assessment of whether the aims and objectives of the research were clearly stated; whether the research questions are suited to qualitative methodology; and whether the sampling, data collection and analysis are clearly described and appropriate to the research question (see Table 4). Using these criteria, we critically assessed papers while maintaining a methodologically neutral position, and taking into account methodological rigour, clarity of reporting, as well as our assessment of the overall contribution made by the study.

Although quality assessment can sometimes be used to exclude studies that do not meet certain criteria, this is not standard practice (Centre for Reviews and Dissemination, 2009). Papers were not excluded on the basis of quality assessment, but rather we placed emphasis on contribution, whereby the most relevant and methodologically strong papers were given more weight in the synthesis (Gough, 2007). The objective was to prioritise studies that appeared to be relevant, rather than particular study types or papers that followed particular methodological procedures or standards. This can be described as prioritising "signal" (the "message" of the study, or likely relevance) over "noise" (potential methodological weaknesses) (Dixon-Woods et al., 2006; Edwards et al., 2000). Noise in our review was quantified by a checklist for methodological quality, and signal by an explicit judgement about the value of the findings presented in each study. This has been used effectively in high-quality published reviews (Langer et al., 2013; Dixon-Woods et al., 2006; Marshall et al., 2012; Stack et al., 2012).

One reviewer (AH-M) initially assessed each paper for methodological quality and for contribution. Each included paper was assigned to one of two predetermined categories, using the coding: KP (Key Paper which is conceptually rich and methodologically sound. Papers

Table 1
Study inclusion and exclusion criteria, adapted from SPIDER (Cooke et al., 2012).

Inclusion	Exclusion
Studies: Peer reviewed journal articles or conference papers published anytime up to April 2013.	Unpublished dissertations, book chapters or papers
Articles in English language, published in any country	
Sample: Patients with depression, professionals including clinicians, as well as researchers etc.	Studies with a majority (more than 50%) of participants under 18 years of age
Phenomenon of interest: Recruitment of research participants	Studies that focus on attrition
Design: Qualitative studies, or mixed methods studies containing substantial qualitative components that can make a contribution to the meta-synthesis. As an operational definition, data collected were in the form of semi-structured interviews, focus groups, open ended evaluation forms involving free text responses, observational field notes, or reflective journals. Papers should report some form of thematic or inductive analysis	No qualitative analysis undertaken or primarily quantitative data reported. Questionnaire data were included in this classification
Evaluation: Any type of evaluation/outcome, including patient, clinician or researcher views	Reports that focus on the feasibility of delivering interventions in depression trials, rather than on recruitment
Research type: Qualitative and mixed methods studies that report on factors affecting recruitment into depression trials	Studies of recruitment into depression research studies that are not randomised controlled trials

that in our appraisal of contribution were the most relevant) or SAT (Satisfactory Paper). Where it was unclear about the methodological quality and contribution of a paper, the paper was reviewed by a second author (PB), and then discussed with the first reviewer (PB) to reach agreement. Any disagreement was resolved in discussion with a third reviewer (BY).

2.3. Literature synthesis

To undertake the meta-synthesis, articles were read and re-read, starting with the Key Papers (KP) and continuing through all 15 papers. First and second order constructs were abstracted from the results and discussion sections of papers into a spreadsheet. First-order constructs refer to everyday understandings of the study phenomena (e.g. as conveyed in direct quotes from participants as reported in a paper). Second-order constructs are defined as the authors' interpretations of participants' accounts often expressed as themes or analytical categories within qualitative studies. Based on these first and second order constructs, we developed third order constructs or interpretations, to generate a conceptual framework (Britten et al., 2002; Noblit and Hare, 1988).

Two reviewers (AHM, NS) reviewed the spreadsheet independently and categorised the first order constructs to identify emerging themes. Second-order constructs were reviewed to see how they compared and translated across papers. Review of the constructs also paid attention to any differences in perspective between patients and gatekeepers. Reviewers independently sifted the second order constructs, developing new third order constructs to offer new insights and understanding. Discussion with a third, independent reviewer (PB) then refined these constructs until a consensual understanding was reached.

Duplicated papers were removed before screening. Titles and abstracts were screened for relevance by one reviewer (AH-M). 10% of retrievals were reviewed by a second reviewer (NS). Full-text retrievals were assessed by two reviewers (AH-M and BY). Where it was unclear whether to include or exclude a paper, the full text was obtained and discussed between all authors. Disagreements were dealt with via discussion.

3. Results

3.1. Search results

The search initially identified 9932 citations, and 15 studies were eligible for inclusion in the review. The flowchart summary of literature search and outcome is presented in the PRISMA diagram (Fig. 1) (Moher et al., 2009). Appendix B outlines the studies excluded at full-text review and reasons for exclusion.

Table 2 summarises and Table 3 details the characteristics of the 15 included papers (Barnes et al., 2012; Bartlam et al., 2012; Carey et al., 2001; Cramer et al., 2011; Dowrick et al., 2007; Fairhurst and Dowrick, 1996; Hetherton et al., 2004; Hinton et al., 2006; Mason et al., 2007; Mendel et al., 2011; Schroer et al., 2009; Shellman and Mokel, 2010; Tallon et al., 2011; Van Der Weele et al., 2012; Chew-Graham et al., 2007).

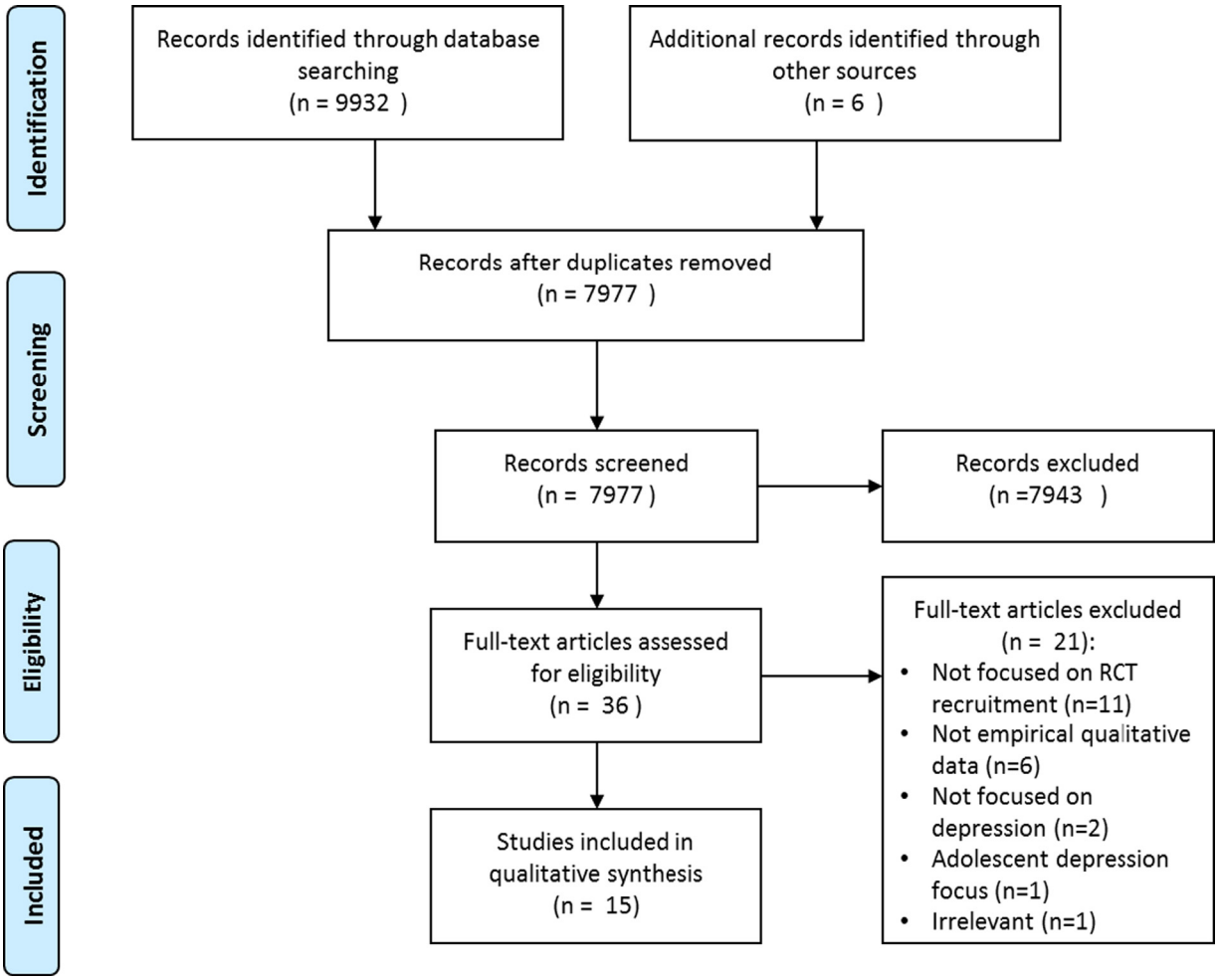

Fig. 1. Summary of literature search, adapted from PRISMA (Moher, 2009).

Table 2
Summary of included studies.

	Number of studies (%)
Country:	
UK	9 (60%)
USA	4 (27%)
Netherlands	1 (7%)
Multinational	1 (7%)
Context:	
Primary care	10 (67%)
Outpatient psychiatry	1 (7%)
Hospital and community	1 (7%)
Ethnic minorities/underserved communities only	1 (7%)
Older ethnic minority adults	1 (7%)
Primary and secondary care	1 (7%)
Perspective:	
Gatekeepers/providers/staff only	7 (47%)
Patients with depression only	6 (40%)
Both Gatekeepers/providers/staff and patients	2 (13%)
Data collection:	
Qualitative interviews only	8 (53%)
Mixed[a] qualitative methods	5 (33%)
Focus groups	1 (7%)
Free text responses	1 (7%)
Analysis method:	
Thematic analysis	5 (33%)
Framework	4 (27%)
Constant comparison	2 (13%)
Content analysis	1 (7%)
Immersion/crystallisation technique	1 (7%)
Inductive	1 (7%)
Mixed (thematic analysis, constant comparison, framework approach)	1 (7%)

[a] Mixed methods combined interviews with the following: questionnaires, conversations, focus groups, open ended evaluation forms, field notes, journals and observations.

3.2. Quality appraisal outcome

Table 4 presents the outcome of the quality and contribution assessment for each of the 15 included papers. Based on overall contribution and conceptual richness, in addition to satisfying each of the prompt questions, eight papers out of the 15 included papers were judged to be Key Papers. Overall therefore, the majority of included studies were judged to be of generally good quality. Seven papers were judged to be Satisfactory Papers; compared to the Key Papers, Satisfactory Papers lacked conceptual richness and made a lesser contribution to the synthesis, and/or demonstrated limitations in the reporting of findings. Common weaknesses within the 15 included studies were mainly around the presentation of findings, and included: lack of a clear description of analysis method; insufficient raw data to support interpretations; and limited contextual information about sampling and participants.

3.3. Literature synthesis: analysis and results

45 emerging themes and analytical categories were initially identified and furnished with first and second-order quotes extracted from individual studies, which we reviewed and consolidated into 11 sub-themes.

Firstly, we categorised these sub-themes into either "facilitators to participation" or "barriers to participation" in depression trials; these were concepts directly adopted from use in several of the included papers (Bartlam et al., 2012; Hinton et al., 2006; Mason et al., 2007; Mendel et al., 2011; Shellman and Mokel, 2010) (Tables 5 and 6).

The seven sub-themes around barriers were

- *Expression of depression symptoms* (which includes presentation, endorsement and impact of depression symptoms)
- *Risk of trial to mental health* (that participation would be depressing or anxiety provoking)
- *Stigma* (including perceived stigma, self-stigma, and double stigma – "weakness" or "vulnerability" associated with mental illness, as well as that associated with severe mental illness or "craziness")
- *Protecting the vulnerable patient* (such as clinician concerns about capacity of depressed patients to provide valid informed consent, concerns about welfare of patients as well as patients being perceived to be "too depressed")
- *Presenting depression trials to patients* (including the particular difficulties introducing research in a depression consultation, clinician skill, confidence and experience in introducing the trial to patients)
- *Treatment preferences* (such as strong patient preferences for particular trial treatments, or negative views about treatment options and objections to randomisation)
- *Views of trial processes and procedures* (such as inconvenience posed by participation).

The four sub-themes around facilitators were

- *Access to services to meet mental health need* (gaining additional resources and trial being perceived as offering a service)
- *Altruism*
- *Marketing* (active promotion of trial to patients and gatekeepers)
- *Trust* (in research teams and in referrers, as well as endorsement by valued individuals and organisations).

The second step was to apply a line-of-argument synthesis based on the themes around barriers and facilitators (Noblit and Hare, 1988). Line-of-argument synthesis is fundamentally about inference, and uses both similarities and differences across the studies to build up a picture, or a "whole" that makes sense of the parts. Our reading of the included studies showed consistent themes but also different perspectives, particularly those between

Table 3
Characteristics of included studies.

Reference and setting	Study objectives	Sample	Method of data collection	Analysis	Context
1. Barnes et. al. (2012) United Kingdom	To explore patients' reasons for declining to be contacted about a study of the effectiveness of cognitive behavioural therapy as a treatment for depression	Patients responding to an initial invitation to participate in research involving a talking therapy ($n=25$)	Questionnaire and semi-structured telephone interviews	Thematic analysis	Primary care
2. Bartlam et. al. (2012) Nine countries: the Czech Republic, Israel, Italy, Lithuania, Holland, Poland, Romania, Spain and the UK	Concern over the inappropriate exclusion of older people from clinical trials is longstanding. To investigate the extent of exclusion of older people in clinical trials, and to explore the views of those directly involved	Older people and carers living with conditions commonly affecting older people: hypertension, cancer, dementia, heart failure, stroke and depression ($n=285$)	Focus groups ($n=42$)	Constant comparison	Hospital and community
3. Carey et. al. (2001) USA	To provide information regarding the experiences of 45 outpatients who recently completed their participation in a trial that was designed to promote healthier behaviours among adults with a SPMI	Outpatients with severe and persistent mental illness (SPMI) who had participated in a trial ($n=45$)	Semi-structured [exit] interviews	Content analysis	Outpatient psychiatric clinics
4. Chew-Graham et. al. (2007) United Kingdom	To presents experience of recruiting patients into the PRIDE trial which was carried out in one Primary Care Trust (PCT)	General practice staff, general practitioners, practice nurses and community nurses ($n=15$)	Conversations and semi-structured interviews	Constant comparison	Primary care
5. Cramer et. al. (2011) United Kingdom	To examine the feasibility and acceptability of a trial of a group intervention based on CBT principles for women with depression in primary care	Women aged 30–55 years ($n=75$)	Interviews	Thematic analysis, constant comparison method and framework approach	Primary care
6. Dowrick et. al. (2007) United Kingdom	To ascertain views of potential study participants of the ethics and pragmatics of various balanced placebo designs, in order to inform the design of future antidepressant drug trials	GPs, psychiatrists and patients with depression ($n=48$)	Focus groups and in-depth interviews	Thematic analysis using Framework	Primary and secondary care
7. Fairhurst and Dowrick (1996) United Kingdom	To evaluate the effectiveness of counselling in the management of minor psychiatric morbidity in general practice, and to explore the reasons for difficulties in recruiting patients to such an evaluation	General practitioners ($n=8$)	Semi-structured telephone interviews	Inductive	Primary care
8. Hetherton et. al. (2004) United Kingdom	To describe the study, the problems that were encountered when GPs agreed to recruit participants during consultations and to outline possible solutions to these problems	General practitioners ($n=3$)	Questionnaire, qualitative interview	Thematic analysis	Primary care
9. Hinton et. al. (2006) USA	To examine gender differences in recruitment, depression presentation, and depression treatment history in a large effectiveness trial; and to use qualitative data to generate hypotheses about reasons for observed gender differences	Referring physicians, depression care managers, and study recruiters ($n=30$)	Qualitative interviews	Thematic analysis	Primary care
10. Mason et. al. (2007) United Kingdom	To investigate the perceived barriers among GPs towards introducing participation in trials to patients presenting with depression during consultations	General practitioners ($n=41$)	Semi-structured interviews	Thematic analysis using framework approach	Primary care
11. Mendel et. al. (2011) USA	To evaluate one of a number of community engagement strategies employed in the Community Partners in Care (CPIC) study, the first randomized controlled trial of the role of community engagement in adapting and implementing evidence-based depression care	Administrators, providers, psychologists, licensed therapists, social workers, psychiatrists, physicians, registered nurses, drug treatment counsellors, case managers ($n=187$)	Open-ended evaluation forms, qualitative observation field notes	Thematic analysis	Community engagement/ Inclusion of ethnic minorities in RCTs
12. Schroer et. al. (2009) United Kingdom	To identify subgroups of patients with depression who could be the focus of effectiveness trials	Acupuncture patients, acupuncturists, physicians ($n=30$)	In-depth interviews	Thematic analysis using the framework approach	Primary care
13. Shellman and Mokel (2010) USA	To describe barriers and strengths of a study testing the effects of reminiscence on depressive symptoms in community-dwelling older African Americans	Research assistants, senior centre directors, pastors, church group leaders ($n=$not reported)	Reflective journals, participant observations, and key informant interviews	Immersion/ crystallisation technique	Older adults/ Research with ethnic minority communities Primary care

Table 3 (*continued*)

Reference and setting	Study objectives	Sample	Method of data collection	Analysis	Context
14. Tallon et. al. (2011) United Kingdom	To investigate patients' views on participating in a primary care trial comparing two antidepressant drugs	Patients with depression who had participated in a trial ($n=601$)	Cross-sectional survey involving free text responses	Thematic analysis using framework approach	
15. Van Der Weele et. al. (2012) The Netherlands	To explore limiting and motivating factors in accepting an offer to join a "coping with depression" course, and perceived needs among persons aged $>/=75$ years who screened positive for depressive symptoms in general practice	Patients with depression offered a "coping with depression" course ($n=23$)	Interviews	Thematic analysis	Primary care

Table 4
Quality appraisal using the prompts, adapted from Dixon-Woods et al. (2007).

Source paper	Are the aims and objectives of the research clearly stated?	Are the research questions suited to qualitative enquiry?	Are the following clearly described?			Are the following appropriate to the research question?			Are claims supported by sufficient evidence?	Are the data, interpretations and conclusions clearly integrated?	Does the paper make a useful contribution?	Rating
			Sampling	*Data collection*	*Analysis*	*Sampling*	*Data collection*	*Analysis*				
1. Barnes et. al. (2012)	√	√	√	√	√	√	√	√	√	√	√	KP
2. Bartlam et. al. (2012)	√	√	√	√	√	√	√	√	√	√	√	KP
3. Carey et. al. (2001)	√	√	√	√	√	√	√	√	√	√	√	KP
4. Chew-Graham et. al. (2007)	√	√	√	√	√	√	√	√	√	√	√	KP
5. Cramer et. al. (2011)	√	√	√	√	√	√	√	√	√	√	√	SAT
6. Dowrick et. al. (2007)	√	√	√	√	√	√	√	√	√	√	√	SAT
7. Fairhurst and Dowrick (1996)	√	√	√	√	√	√	√	√	√	√	√	KP
8. Hetherton et. al. (2004)	√	√	√	√	X	√	√	√	√	√	√	SAT
9. Hinton et. al. (2006)	√	√	√	√	√	√	√	√	√	√	√	KP
10. Mason et. al. (2007)	√	√	√	√	√	√	√	√	√	√	√	KP
11. Mendel et. al. (2011)	√	√	√	√	X	√	√	√	X	√	√	SAT
12. Schroer et. al. (2009)	√	√	√	√	√	√	√	√	√	√	√	SAT
13. Shellman (2010)	√	√	X	√	√	√	√	√	√	√	√	SAT
14. Tallon et. al. (2011)	√	√	√	√	√	√	√	√	√	√	√	KP
15. Van Der Weele et. al. (2012)	√	√	√	√	√	√	√	√	√	√	√	SAT

KP: Key Paper, to be included in systematic review, SAT: Satisfactory Paper, to be included in systematic review.

patients and gatekeepers. The line-of-argument approach was utilised to make sense of apparent contradictions in the data and to integrate the emergent themes and derive new insights. This synthesis revealed three key constructs which are discussed with direct quotations extracted from original interviews:

1. Health state
2. Attitudes towards research and trial interventions
3. Engaging the patient.

Table 7 provides examples of first- and second-order constructs and third-order synthesised themes. These core themes enabled us to develop a conceptual framework of factors influencing the individual decision to participate in depression trials.

3.3.1. Health state

The decision whether to participate in a depression trial—or in the case of gatekeepers to invite patients to participate—is filtered through consideration around the patient's health state. There were two key facets of this: firstly the impact of depression on the patient and their ability to engage with trials, and secondly the potential impact of the trial on the patient's health state—positive, neutral or negative.

In terms of the impact of depression, the presenting symptoms of the condition, such as lack of concentration and confidence and low motivation were noted to be barriers to participation: "*When I get depressed, everything seems hard on me*" (Carey et al., 2001). The relapsing-remitting nature of the disease, as well as the impact of comorbid conditions could also adversely affect recruitment (Mason et al., 2007; Barnes et al., 2012; Van Der Weele et al., 2012; Tallon et al., 2011). Here patients could easily fall into either

Table 5
Barriers to participating in depression trials.

Source paper	Expression of depression symptoms (*Presentation, endorsement and impact of depression symptoms*)	Risk of trial to mental health (*Fear of symptom exacerbation*)	Stigma (*Perceived, self, double stigma*)	Protecting the vulnerable patient (*Concerns about capacity and welfare of patients*)	Presenting depression trials to patients (*Difficulties introducing research to patients with depression*)	Treatment preferences (*Patient and clinician preferences for particular trial treatments*)	Views of trial processes and procedure (*Inconvenience and burden*)
1. Barnes et. al. (2012)	X	X				X	
2. Bartlam et. al. (2012)		X				X	
3. Carey et. al. (2001)	X		X				X
4. Chew-Graham et. al. (2007)		X				X	X
5. Cramer et. al. (2011)	X					X	
6. Dowrick et. al. (2007)	X	X		X	X		X
7. Fairhurst and Dowrick (1996)				X	X		X
8. Hetherton et. al. (2004)		X		X	X		
9. Hinton et. al. (2006)	X		X				
10. Mason et. al. (2007)	X	X		X	X		
11. Mendel et. al. (2011)							
12. Schroer et. al. (2009)	X	X	X			X	
13. Shellman and Mokel (2010)	X		X	X	X		
14. Tallon et. al. (2011)	X		X			X	X
15. Van Der Weele et. al. (2012)	X	X	X	X	X	X	X

of the "too ill" or "too well" categories; both of which meant enrolment into a trial was less likely. Those who declined trial participation often reported that they did not feel depressed or were happy with their situation (Van Der Weele et al., 2012).

Patients were less likely to consider enrolling in depression trials when they were experiencing remission of symptoms as they felt a need to protect their the wellness or health state (Dowrick et al., 2007; Van Der Weele et al., 2012), and patients voiced concern that participation may lead to deterioration in health status if they were otherwise coping: "*If I felt that I'd reached a stage with my depression that it was no longer a factor in a) my working life, b) my social life, c) my domestic life, then I wouldn't [participate], because you're on the straight and narrow and you don't want anything to demur from that or jeopardise it*" (Dowrick et al., 2007).

Core issues arose in terms of the potential impact of the trial on the patient's health, which were typically viewed in the context of risk versus rewards in the decision about participation. Depression trials were perceived with caution by both patients and professionals, with welfare issues a key consideration. For patients, there was awareness that participating in trials might carry risks, particularly for those that are older and/or in poor health, and how participation may affect the individual's ability to cope and manage their illness: "*Well, being older and having more diseases and entering a trial with a drug, you cannot be sure on the body's reactions*" (Bartlam et al., 2012).

Nine papers addressed issues from the perspective of gatekeepers and other professionals (general practitioners, other physicians, nurses, acupuncturists etc.) (Chew-Graham et al., 2007; Hetherton et al., 2004; Dowrick et al., 2007; Fairhurst and Dowrick, 1996; Hinton et al., 2006; Mason et al., 2007; Mendel et al., 2011; Schroer et al., 2009; Shellman and Mokel, 2010). Patients with depression were typically viewed as vulnerable, often leading to protectiveness on the part of professionals. Here trials were sometimes viewed as an extra demand that would overburden patients and generate more distress. Clinicians particularly were less likely to refer patients who were unwell, for fear of further deterioration in the patient's health: "*sometimes you're so anxious to get this person feeling better you, anything you think might jeopardise that or stall it you're bit disinclined to do*" (Mason et al., 2007). In contrast to this, patients reported being more amenable to participation if their condition was currently impacting negatively on their quality of life; here a key factor was potential alleviation of symptoms: "*I decided it would be helpful if I could improve my health*" (Carey et al., 2001).

3.3.2. Attitudes towards research and trial interventions

Attitudes towards research and trial interventions were a theme represented in all but two papers. A key facilitating factor in patients enrolling in depression trials was trials offering potential access to services to meet mental health needs. Both patients and professionals considered trial interventions as a potential resource to be accessed in order to address patients' depression treatment needs. This was particularly the case where there was a lack of local resources. For clinicians, referral into a depression trial could be an acknowledgement that "all else has failed" in terms of the treatment they could provide to their patients: "*When I refer patients…it is when I have completely exhausted my own resources*" (Fairhurst and Dowrick, 1996). Depression trials could also provide improved services that were

Table 6
Factors serving as facilitators in depression trials.

Source paper	Access to services to meet mental health needs (*viewing the trial as a resource*)	Altruism	Marketing (*to both patients and gatekeepers*)	Trust (*in researchers, referrers*)
1. Barnes et. al. (2012)				
2. Bartlam et. al. (2012)	X		X	X
3. Carey et. al. (2001)	X	X		
4. Chew-Graham et. al. (2007)	X		X	
5. Cramer et. al. (2011)	X	X		
6. Dowrick et. al. (2007)	X	X		X
7. Fairhurst and Dowrick (1996)				
8. Hetherton et. al. (2004)	X			
9. Hinton et. al. (2006)				
10. Mason et. al. (2007)				
11. Mendel et. al. (2011)	X		X	
12. Schroer et. al. (2009)	X			
13. Shellman and Mokel (2010)	X			X
14. Tallon et. al. (2011)	X	X		
15. Van Der Weele et. al. (2012)	X			X

local and relevant in the day-to-day management of patients: "*Well there's nowhere else to send these patients, so they get something out of it, as do us GPs who are doing the extra work*" (Chew-Graham et al., 2007).

For patients, participating in depression trials could enable access to otherwise unavailable treatment options. Another motivating factor was a general preference for interventions that did not involve antidepressant medication, because of perceived disadvantages such a dependence, toxicity, contraindication with other medication and side effects (Cramer et al., 2011; Schroer et al., 2009; Bartlam et al., 2012; Tallon et al., 2011). Patients who previously had experience of the active trial interventions were also more likely to decline participation, particularly when they had found it to be a negative experience (Barnes et al., 2012). Conversely, options for innovative treatments (such as acupuncture) could be appealing (Schroer et al., 2009).

Randomisation was potentially a significant barrier to the recruitment of depressed patients (Hetherton et al., 2004; Chew-Graham et al., 2007; Fairhurst and Dowrick, 1996; Carey et al., 2001). For GPs, randomisation was often a difficult procedure in practice, even though they acknowledged its value. The traditional responsibility of GPs is the well-being of individual patients, which is promoted by directing them to the best possible treatment for their presenting problems. Randomisation presented GPs with a competing responsibility, specifically, to prioritise scientific advancement from which future patients would benefit. Faced with an ethical dilemma between care of their patients and research interests, GPs often opted to adhere to their traditional role and did not risk their patient being randomised to the non-desired arm of the study. Clinician referral to a trial was also often perceived as a recommendation for the active trial interventions (Schroer et al., 2009), and some GPs viewed treatment as usual by GPs as inferior and believed that patients would be disappointed or "could not cope" if they were randomised to a "usual GP care" control group (Hetherton et al., 2004; Schroer and Macpherson, 2009). Support for this came from the patient perspective, who considered randomisation to the "wrong" allocation a potential risk; patients not randomised to the intervention arm often voiced disappointment: "*I wasn't in a group. I wanted to be*" (Carey et al., 2001). Equipoise was highlighted as a fundamental requirement of successful RCTs: all treatment arms being perceived as equally effective or ineffective by both the health professional and the prospective participant (Fairhurst and Dowrick, 1996). However this was often difficult to achieve in practice for GPs in the context of psychological therapy trials as this went against the predominant professional attitude of benign paternalism: "*Faced with a patient, in your own mind you've made a therapeutic decision one way or another: either they need* [*trial intervention*] *or they don't*" (Fairhurst and Dowrick, 1996).

Altruism, the desire to help others and contribute to further knowledge and treatment, was discussed in four studies (Cramer et al., 2011; Carey et al., 2001; Dowrick et al., 2007; Tallon et al., 2011). Altruism was an important consideration in patients enrolling into depression trials; however it did not appear to be the sole consideration for many potential participants. Whilst patients wanted to help, this willingness to participate appeared to be enhanced when there was a sense that they were also helping themselves: "*I felt that I was being helped yet helping others at the same time*" (Tallon et al., 2011). If helping others involved making no personal gains, or indeed, risking the stability of one's mental health, then patients with depression were less likely to participate.

3.3.3. Engaging the patient

"Engaging the patient" focuses on communication and the relationships between the patient, gatekeepers and trial team, and includes themes of stigma, the presentation of depression trials to patients, marketing and trust. Stigma was a theme reported in six studies (Carey et al., 2001; Hinton et al., 2006; Schroer et al., 2009; Shellman and Mokel, 2010; Tallon et al., 2011; Van Der Weele et al., 2012). Depression was reported to be viewed as a highly stigmatised condition by patients, associated with severe mental illness or "craziness". Patients often viewed depression as a much more severe mental state than the condition which they were experiencing themselves, or associated with mental or moral "weakness". This resulted in "double stigma", which was a barrier both in terms of patients accessing care in general, and into depression trials in particular. The diagnostic label "depression" was a term that patients could be fearful of, and which they sought to avoid; clinicians might in turn de-emphasised the diagnostic label, and avoided the potential stigma associated with enrolling in a depression trial. While this was an issue across genders and age groups, older men, and men of lower socio-economic status were reported to be particularly reluctant to be diagnosed as depressed.

Five papers discussed challenges in presenting depression trials to patients (Cramer et al., 2011; Chew-Graham et al., 2007; Hetherton et al., 2004; Dowrick et al., 2007; Mason et al., 2007). In general, clinicians often found it difficult to introduce the trial in a depression consultation, where patients presented as emotionally vulnerable and distressed. This is linked with the "health state" theme, and underscores communication as particularly problematic in this context: i.e. it was difficult to raise research in a clinical consultation, and where raising the unrelated issue of research may lead to negative clinical effects, those issues were exacerbated. Raising the issue of trials was described as a "sales pitch" by GPs (Mason et al., 2007). To introduce the trial detracted from focusing on presenting problems and was felt to be detrimental to patients, and this appears to undermine GPs' ability and willingness to introduce the research at

Table 7
Examples of first- and second-order constructs and synthesised themes.

First order construct	Second order constructs	Sub-theme	Third order construct: Synthesis of main findings into an explanatory framework
"*There's more shame associated with admitting to symptoms of depression, admitting to failure.*" (Hinton et. al., 2006)	Because older men tend not to endorse depressed mood or sadness, they were often viewed as more reluctant to accept the diagnosis of depression and the treatment recommendations (Hinton, 2006).	***Expression of depression symptoms***	**Health state** Consideration around the patient's health state is a key factor for both patients and referring clinicians.
"*Is this going to do my patient any good, or am I just doing it for the study's sake?*" (Mason et. al., 2007)	GPs described the presenting symptoms of depression, such as lack of concentration and confidence and low motivation, as barriers to patients agreeing to take part in research. Some patients were characterised as too ill, distressed, distracted, inward focused and indecisive to be involved in research and this sometimes constrained GPs' willingness to introduce the study to them (Mason, 2007).	***Risk of trial to mental health***	The diagnosis of depression often lends to patients being characterised as vulnerable, often leading to protectiveness on the part of the treating clinician
"*I mean, the issue is if a person is really truly depressed, to what extent is he truly autonomous? To what extent is he or she in a position to make a decision, you know, in terms of giving their consent to a trial with all the informed information that goes with it?*" (Dowrick et. al., 2007)	The capacity of patients with depression, particularly severe or longstanding depression, to provide valid informed consent was a cause for concern (Dowrick, 2007).	***Protecting the vulnerable patient***	
"*Well, I thought it's bothersome that it's so far away. That was a reason not to do it… the travelling is still a big nuisance… If I had to pay the taxi myself it would be a bit too much for me. Taxis are quite expensive…that would be reimbursed*" (Van Der Weele et. al., 2012)	Several GPs saw research as an extra demand that would overburden patients and generate more distress (Van Der Weele et. al., 2012).	***Burden***	
"*Well there's nowhere else to send these patients, so they get something out of it, as do us GPs who are doing the extra work*". GP (Chew-Graham et. al., 2007)	The trial was perceived to be local, relevant and offered an additional service to them in the day-to-day management of a particularly underserved patient group (Chew-Graham, 2007)	***Access to services to meet mental health needs***	**Attitude towards trial interventions** Here tension is played out between equipoise and access. Both patients and clinicians see depression trials as a potential platform to access valued services. Strictly the trial interventions are in equipoise, but in the context of people *seeking* services and wanting access, that is not the case. So the trial is presented as a neutral test, but is not *received* as such, because people want support
"*I wasn't in a group. I wanted to be just (for) experience, like to know what other people go through and maybe I could learn something from them.*" (Carey et. al., 2001)	Even those participants who were not randomized to a group intervention commented on their desire to be part of one (Carey, 2001).	***Treatment preferences***	
"*I guess I wanted to be part of something, to help out society … I just thought it might help somewhere down the line.*" (Carey et. al., 2001)	Patients also noted that participating in the research allowed them to make a contribution to the care of other patients, and to contribute to science through their participation (Carey, 2001).	***Altruism***	
"[*The randomization process*] *is the reason why they didn't get into the study in the first place. It stopped it*". (Fairhurst and Dowrick, 1996)	Although the GPs recognised the value of randomisation and agreed to participate in the process, the majority of them found the procedure difficult in practice. The traditional responsibility of GPs is the well-being of individual patients which is promoted by directing them to the best possible treatment for their presenting problems. The randomisation and recruitment procedures presented GPs with a competing responsibility, specifically, to prioritise scientific advancement from which future patients would benefit (Fairhurst and Dowrick, 1996)	***Randomisation***	
"*Sometimes I think they're not as forthcoming because of the stigma. They will not say, 'I feel sad' or 'I feel depressed.' They'll say 'I have a stomach ache.'*" (Hinton et. al., 2006)	Depression's stigma may result not only from its association with "vulnerability" or "weakness," but also from its association with severe mental illness or "craziness." These are theoretically separable sources of stigma, and as a result, patients may be vulnerable to "double stigma" and amplification of their suffering (Hinton, 2006)	***Stigma***	**Engaging the patient** Introducing depression trials to patients can be particularly difficult in the context of patients presenting as emotionally vulnerable and distressed, as well as avoiding the stigmatising label of a mental illness diagnosis
"*To raise the research seemed alien to the atmosphere of the consultation.*" (Hetherton et. al., 2004)	As the trial was concerned with patients who presented with depression or anxiety, recruitment involved raising the issue of the research with patients who possibly presented as emotionally vulnerable or distressed. It seems that this context undermined GPs' ability to introduce the issue of research at all (Hetherton, 2008)	***Presenting depression trials to patients***	Effective marketing of trials to patients and clinicians, as well as trust in the integrity of the trial and trialists promotes willingness to participate. Trial communication might aim to enable people to consider whether they are in a "win:win" situation in which both they and others might benefit. Stigma negatively affects recruitment, Depression trials need to "normalise" depression, and use "neutral", non-stigmatising language in participant communication
"*It must be said by a physician I visit regularly … Then I would like to agree, because my physician tells me this*" (Bartlam et. al. 2012)	First amongst those processes that could mitigate risks to participation was the reliability of the person suggesting inclusion, almost invariably seen ideally as a physician (Bartlam et. al. 2012)	***Trust***	
"*In my opinion, the issue is that older persons are not aware of clinical studies and researchers*		**Marketing**	

Table 7 (*continued*)

First order construct	Second order constructs	Sub-theme	Third order construct: Synthesis of main findings into an explanatory framework
should make an effort to inform older persons. If older persons become more aware of the problem, they will get involved more easily." (Bartlam et. al., 2012)	Making the general public more aware of the importance of trials was seen as a way of increasing participation (Bartlam et. al., 2012).		
"*The (referral) form was so simple, it was no hassle to refer on.*" (Chew-Graham et. al., 2007)	It appeared that the simplicity of the intervention concept (attending a group with other stressed women and being taught skills to cope better) helped participants and recruiters to understand and promote the groups (Cramer, 2011).	***Trial processes***	

all: "*To raise the research seemed alien to the atmosphere of the consultation*" (Hetherton et al., 2004). Not only was this alien to the atmosphere of the consultation, it was also alien to the caring of the depressed patient as to listen empathically to the patient's problems and then introducing the research was found to be awkward. The confidence of GPs to introduce depression trials to patients related to their knowledge of the trial and remembering the trial criteria, familiarity with the paperwork, the patient's acceptance of the depression diagnostic label, belief in the purpose and clinical relevance of the trial, and the acceptability of the interventions (Mason et al., 2007; Hetherton et al., 2004). More practical and pragmatically, heavy workloads within GP practices could also result in delays in sending invitation letters to relevant patients after clinical note searches, or clinical teams refusing to participate in trials altogether, both of which negatively impact on recruitment (Cramer et al., 2011; Chew-Graham et al., 2007; Mason et al., 2007).

Issues around trust were reported in four trials (Bartlam et al., 2012; Dowrick et al., 2007; Shellman and Mokel, 2010; Van Der Weele et al., 2012). Trust in the people conducting trials was reported to be an important factor (Dowrick et al., 2007; Shellman and Mokel, 2010), as was the opinion and endorsement of valued individuals and organisations such as ethical review boards, family and clinicians (Bartlam et al., 2012; Dowrick et al., 2007; Shellman and Mokel, 2010; Van Der Weele et al., 2012). Having high levels of trust, particularly in one's doctor, was seen as very important in influencing patients' decision as to whether or not to enrol in depression trials (Bartlam et al., 2012; Van Der Weele et al., 2012). This was especially crucial if the doctor was the one making the initial approach about trial participation: "*If it was my doctor suggested it: 'will you try this?' I'd say yes, but if anybody else asked me, I would probably say no*" (Bartlam et al., 2012). However the involvement of doctors does not always motivate trial enrolment: "*I was visiting my GP and he said 'You're not suitable for that… you don't need it'… He just didn't see the need in my case*" (Van Der Weele et al., 2012). Mistrust on the other hand was an important factor in refusal to participate, particularly for older African-Americans (Shellman and Mokel, 2010). This mistrust expressed itself as concern about researchers' motives and research conduct, extensive questioning by gatekeepers and professionals during initial meetings, and refusal to participate.

4. Application of the synthesis to develop a conceptual framework of key factors involved in patients' decision to participate in depression trials

The line-of-argument synthesis entails the construction of an interpretation (Noblit and Hare, 1988). While the secondary data suggested that the authors of the included studies were aware of the tension between concerns about the patient's welfare and the potential benefits of trial participation, the line-of-argument approach enabled us to explicitly conceptualise these contradictions to combine findings across the studies. This allowed us to develop new insights in the form of a conceptual framework of the key factors involved in the patient's decision to participate (Fig. 2).

This conceptual framework focuses on the patient and the gatekeeper and their weighing up of the participation decision. In reaching the participation decision, the patient and gatekeeper rely on the third-order constructs of *health state*, *attitudes towards trial and research interventions* and *engaging the patient* to weigh up the risks and rewards of the participation decision. According to our framework, there are two key points at which decisions are made as to whether or not to participate in a depression trial. Firstly, the gatekeeper needs to make a decision as to *whether or not to inform the patient* about the opportunity to participate in the trial (i.e. the patient needs to be exposed to the recruitment method). Secondly, once the patient is exposed to the recruitment method, they are able to make the *decision to accept or decline* trial participation. In both cases, the gatekeeper and patient are faced with a difficult decision involving risk.

For the gatekeeper, the assessment of risk is centred on negotiating the tension between the difficulties introducing depression trials and the need to protect the vulnerable patient from involvement in such trials, against accessing new avenues of care to address their patient's needs; an assessment moderated by their trust in the research team conducting the depression trial. For the patient, risk assessment involves balancing rewards (both the personal need to access treatment and support and feelings of altruism), against the risks of stigma, of "losing out" by being randomised to the "wrong" intervention arm, or of encountering adverse effects of trial involvement. Here, our line-of-argument synthesis allows us to focus the weighing up decision on the sub-themes that present with the most contradictions.

5. Discussion

5.1. Summary of key findings

Our review highlights that the decision to enter a depression trial depends on the patient's health state at the time of the approach; on their attitude towards the interventions being evaluated within the trial; and on the extent to which patients become engaged with the trial. Our conceptual framework emphasises that the decision to participate by both the gatekeeper and the patient involves a judgement between risk and reward.

5.2. Comparison with existing literature

As in our review, the previous meta-synthesis of Mccann et al. (2013) identified that people's health state and health care situation at the time of being invited to participate in a trial were salient to participation decisions, and that being able to perceive some personal benefit from trial participation was clearly associated with

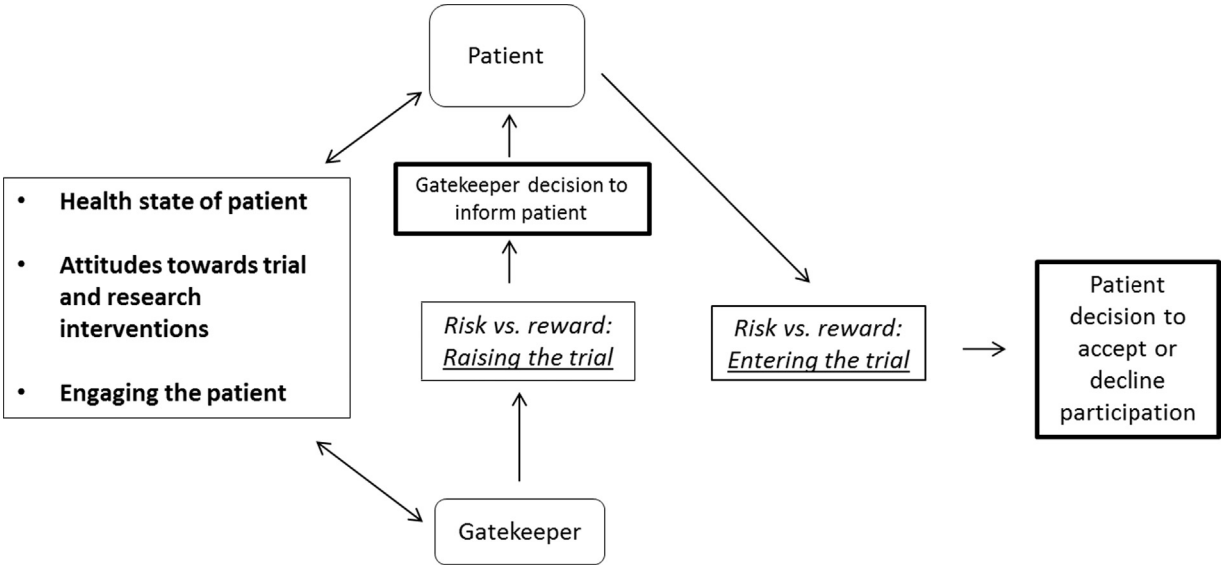

Fig. 2. Conceptual framework of factors influencing the decision to participate.

willingness to take part. Personal benefit has also been found in another meta-synthesis to be a primary driver influencing the participation of Chinese individuals in trials, particularly for those who were already unwell and did not have access to any other effective treatment (Limkakeng et al., 2013).

In contrast to previous meta-syntheses (Mccann et al., 2013; Limkakeng et al., 2013), our framework more clearly outlines the tension between risks and reward. Our synthesis also emphasises the role that gatekeepers play in the recruitment of patients into depression trials, and that there is often a protective bias in their predictions of the vulnerabilities of patients with depression (Roberts and Kim, 2014; Jenkinson et al., 2014).

Our synthesis relates to two published concepts: the *therapeutic misconception* (Appelbaum et al., 1982) and *injurious misconception* (Snowdon et al., 2007). Therapeutic misconception involves an over-stated sense of benefit, and occurs when participants demonstrate difficulties in appreciating the distinction between clinical treatment and research, therefore incorrectly attributing therapeutic intent to research procedures. Injurious misconception was proposed as a counterpart to therapeutic misconception, and is a product of a particularly keen and discomforting sense of distinctions between care and research and a correspondingly over-stated sense of risk and threat associated with research. It has been argued that equipoise can be extremely difficult for mental health trials, particularly for trials of psychological therapy. This may be due to widespread assumption that psychological therapy is always helpful to patients—or at least not harmful—despite evidence that there can be iatrogenic effects (Barlow, 2010; Lilienfeld, 2007; Nutt and Sharpe, 2008). Such trials also cannot be double blind, use a "credible" placebo, and typically have strong practitioner effects and patient preference (Parry and Barkham, 2009).

Given the literature suggesting that people take part in clinical trials mostly for altruistic reasons, and that deriving personal benefit is a secondary consideration, the strong theme that patients predominantly enrol in depression trials to access to services to meet mental health needs is noteworthy (Jenkins and Fallowfield, 2000; Andresen et al., 2010; Hussain-Gambles, 2004; Cox, 2000; Dixon-Woods and Tarrant, 2009; Sharp et al., 2006; Ross et al., 1994; Criscione et al., 2003; Bevan et al., 2012; Cassileth et al., 1982; Emanuel and Patterson, 1998; Ross et al., 1999; Loraas, 2009). Whilst altruism is certainly identified as a distinct theme in this review, it is overshadowed by the idea of personal benefit, which in this context is the need of patients to address mental health needs. The term "conditional altruism" has been coined to describe the general willingness to help others that may initially incline people to participate in a trial, but that is unlikely to lead to trial enrolment in practice unless people also recognise that participation will benefit them personally, or that they will not be disadvantaged from doing so (Mccann et al., 2010). Strong patient preferences around trial interventions are common in mental health research (Howard and Thornicroft, 2006), and such preferences around trial interventions have been found to affect recruitment (King et al., 2005).

5.3. Research implications

Systematic reviews have consistently highlighted the knowledge gap around effective strategies aimed at those recruiting into trials (Treweek et al., 2013) and this review is intended to guide the development and evaluation of interventions to improve recruitment into depression trials. Our key finding that patients and gatekeepers weigh up the risks and rewards of the participation decision by taking into account *health state*, *attitudes towards trial and research interventions* and *engaging the patient* has methodological implications for innovations in trial design and delivery. This in turn has the potential to positively impact on the recruitment of participants.

The emerging concept of "patient-centred trials" may be adopted to design trials that potential participants and their clinicians perceive to be less "risky" (Mullins et al., 2014; Woolfall et al., 2014). Patient-centred trials have the potential to address the issue of withholding treatment from patients who are seeking help for their problems, for example, by encouraging the use of adaptive trials. Such trials are designed to adjust in a pre-specified manner to changes in clinical practice and could motivate people and their health care providers to view clinical trials as more applicable to real-world clinical decisions. The concept of patient-centred trials may also be applied to evaluate alternatives to untreated (or "treatment as usual") control groups in depression trials and their effect on recruitment. For example, patient preference arms can be included in randomisation into depression trials: here participants with strong preferences are allocated to the intervention of their choice (Bower et al., 2005). An alternative to patient preference is waiting list control trials, in which all patients eventually receive the trial intervention, but are randomised to receive the intervention immediately, or at a later date (Elliott and Brown, 2002). A further option could be the explicit use of the "uncertainty principle" in depression trials, whereby patients are only

entered into trials if clinicians are uncertain which of the trial treatment would be most appropriate for that particular patient (Peto and Baigent, 1998, p. 1170).

Patient and public involvement in trials might be better communicated to prospective participants with the aim of reducing perceptions of risk; specifically to "normalise" depression and reduce stigma, as well as a form of public endorsement to enhance trust in those undertaking depression trials (Boote et al., 2014). To address altruism, trial recruitment communication might aim to enable people to consider whether they are in a "win:win" situation in which both they and others might benefit from their participation (Mccann et al., 2010).

Our conceptual framework represents an early effort to develop an explanatory model. Further qualitative work is required to understand the process of the decision making and the priority placed on the themes identified within this review, to better understand how these factors may be subjected to influence by well-designed recruitment interventions. Additional avenues for further qualitative research may examine recruitment issues in other populations, for instance in patients with anxiety or with serious mental illness, as well as in children and members of minority ethnic groups (Brown et al., 2014; Young et al., 2011). The studies included in our review were fairly homogeneous in their methods of data collection, which generally involved qualitative interviews or focus groups; future research may apply alternative observational methods, such as audio or video recorded consultations (Salmon et al., 2012).

5.4. Limitations

Our literature searches were systematic and transparent, but searching for qualitative studies is complex and necessitates further investigation (Flemming and Briggs, 2007; Tong et al., 2012). Any systematic review of existing literature will not include factors that have not been reported in the peer-reviewed literature, and the synthesis is dependent on the particular studies included. Relevant publications may have been omitted, particularly as we excluded studies not published in the English language for resource reasons. Publication bias also exists in qualitative research (Petticrew et al., 2008), so our exclusion of grey literature may have resulted in bias. While we undertook quality appraisal of included studies, due to resource constrains it was not possible for quality assessment of all studies to be undertaken independently by two authors; however when there was a question about the quality of a paper, this was reviewed by a second author and discussed with the first author. We aimed for transparency in all aspects of this review and synthesis; however the nature of qualitative research means that another researcher may have obtained different results.

The studies included in this review generally adopted a pragmatic approach and were primarily concerned with increasing the numbers of patients recruited, rather than the quality of the recruitment process, which remains poorly delineated (Gross et al., 2002). There is a debate about the limitations of research—both qualitative and quantitative—in identifying clearly, reliably and consistently barriers and facilitators to trial participation (Fayter et al., 2007; Salmon et al., 2007). It is possible that there is some discordance between the factors underlying the motivation to participate in depression trials and participants' accounts of their decision making. For example, stigma could make participants less willing to reveal motivations.

6. Conclusions

This review highlights a number of barriers and facilitators affecting the recruitment of participants into depression trials, which has implications for the design of interventions to improve recruitment into these trials. Findings from the synthesis will enable us to a) undertake further qualitative work to understand the process and priority of decision making for patients approached to participate in depression trials, and b) develop recruitment interventions that can be evaluated using the MRC Complex Interventions Framework (Craig et al., 2008).

Ethics

We did not apply for ethics approval as we conducted a systematic review and meta-synthesis based on published literature.

Role of funding source

The sponsor had no role in the development, design, data collection, analysis or interpretation.

Conflict of interest

All authors declare that we have no competing interests. We have no relationships with companies that might have an interest in the submitted work in the previous 3 years; their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and have no non-financial interests that may be relevant to the submitted work.

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Table A1
Search strategy – Medline.

Search domains	*Search terms used*	*Results in Medline (Search date 5th April 2013)*
Sample	1. Depression/	1. 69,314
	2. Depressive disorder/	2. 55,773
	3. Dysthymic disorder/	3. 935
	4. Mood disorder/	4. 10,109
	5. or/1–4	5. 13,1621
Phenomenon of **interest:** to increase specificity the "recruitment" text word terms only identify publications that refer to the terms more than twice. This was a strategy used in the most recent Cochrane review (Treweek et al., 2013).	6. Research subject/	6. 4756
	7. Patient participation/	7. 16,563
	8. Patient selection/	8. 45,870
	9. Enrol?*.ab. /freq=2	9. 18,050
	10. recruit*.ab. /freq=2	10. 29,625
	11. Participat*.ab. /freq=2	11. 37,227
	12. Enlist*.ab. /freq=2	12. 200
	13. Informed consent.tw.	13. 19,713
	14. Informed consent/	14. 30,084
	15. or/6–14	15. 17,9749
Design, **evaluation, research**: these three constructs have been combined to identify ANY research design that recruits patients with depression.	16. [*Leave blank*]	16. [–]
	17. 5 and 15	17. 2262
Limits	18. limit 17 to (English language and humans)	**2097**

Appendix A. Search strategy – Medline

See Table A1.

Table B1
The papers excluded from the meta-synthesis and reasons for rejection.

Paper	Reasons for rejection
Allen et al. (2009)	This study examined participants' experiences of mindfulness-based cognitive therapy. There was no focus on recruitment issues.
Breland-Noble et al. (2011)	Although this was a qualitative study of recruitment into depression research, the focus is on the recruitment of teenagers, rather than adults.
Edge (2008)	While this study stated that its focus was around access of women with perinatal depression to services and research, the focus was exclusively on access to services of depression in general, and there was no focus on recruitment into clinical trials.
Gaudiano et al. (2013)	This paper did address treatment expectancies in clinical trials of antidepressants versus psychotherapy for depression. However the data presented was only of a quantitative nature.
Grant et al. (2009)	While this paper addressed issues to do with motivation, randomisation and withdrawal in a depression RCT, the data presented was not qualitative in nature.
Kokanovic et al. (2009)	This paper looked at the engagement of ethnic minority communities in a qualitative study of help seeking for depression. It was excluded as the focus was not on recruitment into a clinical trial.
Locock and Smith (2011)	Included 2 interviewees (out of 42) with depression. Therefore insufficiently focused on depression.
Loue and Sajatovic (2008)	The authors described the challenges encountered in recruiting and retaining a sample of severely mentally ill (including depressed) Mexican and Puerto Rican ethnicity for a study of the context of HIV risk. This study did not present qualitative empirical data.
McFarland et al. (2002)	The focus is on patient consent to post-mortem tissue/organ donation for research, not recruitment to an intervention or prevention study.
Minas et al. (2005)	This paper explored problems in carrying out a mental health research project in the general practice setting. It was excluded as the research project was not a clinical trial.
O'Donnell et al. (2007)	This study used hypothetical vignettes and focus groups to discuss GPs management of patients, including depression. The study discussed recruitment of GPs in this context, however this did not involve recruitment of patients
Rost et al. (2000)	While this article considered issues of recruitment into a trail of major depression, it did not present qualitative empirical data.
Simpson et al. (2000)	Whilst the report of this RCT includes a description of the difficulties recruiting participants during the pilot phase of the trial, as well as the reasons given by GPs for not referring, no qualitative data is presented.
Schroer et al. (2012)	This study focused on discussing the feasibility of the acupuncture intervention rather than recruitment into the trial. (The authors have published a separate paper focusing on recruitment, which has been included as part of this review.)
Sloane et al. (2006)	The authors sought to develop a model of participant enrolment via a representative cohort of adult primary care patients maintained for use in multiple projects. The cohort included some depressed patients; however the study did not involve empirical qualitative data.
Steinman et al. (2012)	The focus of this paper was on treatment programme implementation after the trial had been completed.
Uebelacker et al. (2012)	The authors conducted focus groups with Latinos enroled in a Medicaid health plan in order to ask about the barriers to and facilitators of depression treatment in general as well as barriers to participation in depression telephone care management. There was no emphasis on clinical trial recruitment.

Table B1 (*continued*)

Paper	Reasons for rejection
van Weel et al. (2006)	The authors undertook research methodology workshop to raise awareness and interest in longitudinal research in practice-based research networks (PBRNs) among family physicians (FP) and researchers. The discussions covered recruitment, and some patients had depression. However there was no qualitative empirical data presented.
Wasan et al. (2009)	This study used qualitative methodology to address the self-reported reasons for participation in the clinical research of chronic low back pain and to evaluate those reasons in the context of informed consent and the concept of therapeutic misconception. The study did not focus on depression.
Whiting et al. (2008)	The authors aimed to establish the feasibility of conducting a randomised controlled trial to evaluate the efficacy of acupuncture in the treatment of mild-to-moderate depression. While they undertook some qualitative interviews with participants, there was very little reporting of it, with no discussion of themes and no presentation of quotations. Furthermore, the qualitative reporting was presented in terms of the *numbers* of participants who mentioned certain factors.
Willison et al. (2009)	This paper did not address recruitment, but rather consent for use of personal information for research.

Appendix B. The papers excluded from the meta-synthesis, and reasons for exclusion.

See Table B1.

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