

# **What are effective methods to recruit research participants into mental health trials?**

A thesis submitted to the University of Manchester for  
the degree of Doctor of Philosophy (Ph.D.)  
in the Faculty of Biology, Medicine and Health

**2017**

**Adwoa Hughes-Morley**

**Division of Population Health, Health  
Services Research & Primary Care**

# Contents

---

<b>Contents</b> .....	<b>- 1 -</b>
<b>Figures</b> .....	<b>- 7 -</b>
<b>Tables</b> .....	<b>- 7 -</b>
<b>Images</b> .....	<b>- 8 -</b>
<b>Abbreviations</b> .....	<b>- 9 -</b>
<b>Abstract</b> .....	<b>- 12 -</b>
<b>Lay abstract</b> .....	<b>- 13 -</b>
<b>Declaration</b> .....	<b>- 14 -</b>
<b>Copyright statement</b> .....	<b>- 14 -</b>
<b>Acknowledgements</b> .....	<b>- 15 -</b>
<b>Dedication</b> .....	<b>- 16 -</b>
<b>About the author</b> .....	<b>- 17 -</b>
<b>Chapter 1: Introduction</b> .....	<b>- 18 -</b>
1.1' Rationale for the thesis.....	- 18 -
1.2' Aims and objectives of this thesis .....	- 18 -
1.3' Overview of the studies.....	- 19 -
1.4' Thesis structure .....	- 20 -
1.5' Rationale for submitting thesis in the alternative format .....	- 21 -
<b>Chapter 2: Background literature</b> .....	<b>- 22 -</b>
2.1' Chapter overview .....	- 22 -
2.2' 'No health without mental health': the need for improved treatments for mental illness.....	- 22 -
2.2.1' Introduction .....	- 22 -
2.2.2' The conceptualisation of mental health and mental illness.....	- 23 -
2.2.3' Incidence and prevalence.....	- 26 -
2.2.4' Morbidity, mortality and burden.....	- 28 -
2.2.5' Recognition and treatment .....	- 29 -

2.3	'Testing treatments': evidence-based practice and the randomised controlled trial .....	- 33 -
2.3.1	Introduction .....	- 33 -
2.3.2	Evidence-based practice: what it is .....	- 33 -
2.3.3	The process of evidence based practice .....	- 36 -
2.3.4	The randomised controlled trial .....	- 38 -
2.4	The recruitment problem.....	- 43 -
2.4.1	'Notoriously difficult': Recruiting participants into mental health trials.....	- 45 -
2.5	Impacts and implications of the recruitment problem.....	- 51 -
2.6	Efforts to address the recruitment problem at the policy level.....	- 52 -
2.6.1	Introduction .....	- 52 -
2.6.2	The UK and US policy efforts: divergent solutions .....	- 52 -
2.6.3	'Nothing about me, without me': patient and public involvement in research .....	- 54 -
2.6.4	Moving from the 'art of recruitment' to a 'science of recruitment' .....	- 59 -
<b>Chapter 3: Thesis methodology and methods.....</b>		<b>- 65 -</b>
3.1	Chapter overview.....	- 65 -
3.2	Choosing research methods: by choice or by chance?.....	- 65 -
3.2.1	Through a lens: research paradigms and the generation and interpretation of knowledge .....	- 65 -
3.2.2	Quantitative research .....	- 67 -
3.2.3	Qualitative research.....	- 68 -
3.2.4	The author's disciplinary background – health services research .....	- 70 -
3.2.5	Pragmatism: paradigm war and peace .....	- 71 -
3.2.6	Mixed methods research as an attractive partner to pragmatism .....	- 73 -
3.3	Summary of methodology and methods selected for this thesis.....	- 75 -
3.3.1	The Medical Research Council Complex Interventions Framework.....	- 76 -
3.4	Thesis methodology .....	- 78 -
3.4.1	Introduction.....	- 78 -

3.4.2	Developing and evaluating a recruitment intervention for mental health trials using the MRC framework.....	- 79 -
3.5	Methods – Study One: Factors affecting recruitment into depression trials: systematic review, meta-synthesis and conceptual framework.....	- 81 -
3.5.1	Rationale.....	- 81 -
3.5.2	Objectives .....	- 82 -
3.5.3	The systematic review.....	- 82 -
3.5.4	Systematic literature search.....	- 83 -
3.5.5	Appraising the quality of qualitative research .....	- 84 -
3.5.6	Synthesising results: meta-synthesis .....	- 85 -
3.5.7	Conceptual framework.....	- 87 -
3.5.8	Strengths and limitations.....	- 87 -
3.6	Methods – Study Two: What can we learn from trial decliners about improving recruitment? Qualitative study.....	- 89 -
3.6.1	Rationale.....	- 89 -
3.6.2	Objectives .....	- 90 -
3.6.3	The REFRAMED Trial.....	- 90 -
3.6.4	Linked qualitative study.....	- 90 -
3.6.5	Methods: qualitative study.....	- 92 -
3.6.6	Patient and public involvement.....	- 96 -
3.6.7	Strengths and limitations.....	- 96 -
3.7	Methods – Study Three: Evaluating the impact of advertising patient and public involvement on trial recruitment: an embedded cluster randomised recruitment trial .....	- 98 -
3.7.1	Rationale.....	- 98 -
3.7.2	Objectives .....	- 98 -
3.7.3	The randomised controlled trial (revisited) .....	- 99 -
3.7.4	The START model .....	- 103 -
3.7.5	Design: The EQUIP host trial.....	- 105 -
3.7.6	Design: Developing the recruitment intervention.....	- 107 -

3.7.7	The control arm: the standard EQUIP trial invitation .....	- 113 -
3.7.8	Method: the embedded recruitment trial design .....	- 114 -
3.8	Chapter Summary.....	- 122 -
<b>Results.....</b>		<b>- 123 -</b>
<b>Chapter 4: Factors affecting recruitment into depression trials: Systematic review, meta-synthesis and conceptual framework .....</b>		<b>- 124 -</b>
<b>Chapter 5: What can we learn from trial decliners about improving recruitment? Qualitative study .....</b>		<b>- 127 -</b>
<b>Chapter 6: The impact of advertising patient and public involvement on trial recruitment: embedded cluster randomised recruitment trial .....</b>		<b>- 130 -</b>
<b>Chapter 7: Overall discussion and conclusions.....</b>		<b>- 133 -</b>
7.1	Overview .....	- 133 -
7.2	Revisiting thesis aims and objectives.....	- 133 -
7.3	Overview of studies and principal findings.....	- 134 -
7.3.1	Summary of main findings: Study One .....	- 134 -
7.3.2	Summary of main findings: Study Two.....	- 134 -
7.3.3	Summary of main findings: Study Three.....	- 135 -
7.3.4	What does this research add?.....	- 135 -
7.4	Interpreting findings in the context of the wider literature .....	- 137 -
7.5	Key methodological strengths and limitations .....	- 140 -
7.5.1	Rigour .....	- 140 -
7.5.2	Reflexivity and triangulation .....	- 141 -
7.5.3	Adopting a mixed-methods approach .....	- 142 -
7.5.4	Patient, public and stakeholder involvement .....	- 143 -
7.5.5	Part of a wider endeavour to develop an evidence base for recruitment .....	- 145 -
7.5.6	Failure to recruit a host depression trial to evaluate the intervention....	- 146 -
7.5.7	The role of the qualitative study .....	- 149 -
7.5.8	Optimisation of the PPIR leaflet .....	- 150 -
7.5.9	Cluster randomisation .....	- 150 -
7.5.10	Absence of a formal process evaluation .....	- 150 -

7.6	The lack of effectiveness observed in the recruitment intervention .....	- 151 -
7.6.1	Implementation .....	- 151 -
7.6.2	Mechanism.....	- 152 -
7.6.3	Context.....	- 154 -
7.7	Challenges .....	- 156 -
7.8	Dissemination of findings: impact .....	- 158 -
7.9	Ongoing research linked to this thesis.....	- 163 -
7.9.1	Assessing effectiveness of the recruitment intervention in the Culturally-adapted Family Intervention for African Caribbean people Diagnosed with Schizophrenia study .....	- 164 -
7.9.2	Assessing effectiveness of the PPIR intervention in the Software Architecture for Mental health Self-management study.....	- 164 -
7.9.3	Meta-analysis to evaluate the effectiveness of the PPIR leaflet on recruitment and retention .....	- 165 -
7.9.4	Development of a PPIR intervention for surgical trials .....	- 165 -
7.10	Recommendations for recruitment practice, policy and research.....	- 166 -
7.10.1	Recommendation 1: An urgent need to investigate patient centred-trial designs to aid recruitment .....	- 166 -
7.10.2	Recommendation 2: A focus on eligibility is required.....	- 167 -
7.10.3	Recommendation 3: Further rigorous evaluations of impacts of PPIR is required.....	- 168 -
7.10.4	Recommendation 4: Embedding trials of recruitment interventions routinely within ongoing mental health trials .....	- 168 -
7.10.5	Recommendation 5: Dissemination of effective and ineffectiveness recruitment interventions.....	- 169 -
7.10.6	Recommendation 6: Retention needs attention .....	- 170 -
<b>8.</b>	<b>Conclusions .....</b>	<b>- 171 -</b>
<b>9.</b>	<b>References .....</b>	<b>- 173 -</b>
<b>10.</b>	<b>Appendices.....</b>	<b>- 215 -</b>
	Appendix A: REFRAMED trial ethical approval letter .....	- 216 -

Appendix B: Reply form for patients declining participation in the REFRAMED trial.....  
..... - 221 -

Appendix C: REFRAMED RISK assessment procedures..... - 224 -

Appendix D: START ethics amendment letter ..... - 233 -

Appendix E: EQUIP ethics amendment letter ..... - 236 -

Appendix F: EQUIP trial invitation cover letter ..... - 239 -

Appendix G: EQUIP Participant information sheet ..... - 239 -

Appendix H: EQUIP trial ‘Consent to Contact’ form ..... - 243 -

Appendix I: statistical analysis (Study Three)..... - 243 -

# Figures

---

Figure 1: Overview of studies included in thesis .....	- 19 -
Figure 2: The Trial enrolment process .....	- 43 -
Figure 3: Levels of involvement .....	- 55 -
Figure 4: MRC framework for developing complex interventions.....	- 77 -
Figure 5: Framework for developing and evaluating a recruitment intervention for mental health trials.....	- 80 -
Figure 6: Scope of the search in the systematic review .....	- 84 -
Figure 8: EQUIP trial recruitment flowchart .....	- 106 -

# Tables

---

Table 1: Comparison of guidelines for diagnosing mental illness .....	- 25 -
Table 2: Hierarchy of evidence of the efficacy of an intervention .....	- 37 -
Table 3: Barriers to participation .....	- 47 -
Table 4: : Barriers to mental health trial participation.....	- 48 -
Table 5: Recruitment interventions identified in systematic reviews as having evidence of effectiveness.....	- 60 -
Table 6: Theories and models pertaining to recruitment .....	- 63 -
Table 7: The ontology, epistemology and methodology of alternative paradigms.....	- 67 -
Table 8: General characteristics of pragmatism.....	- 72 -
Table 9: Core Characteristics of Mixed Methods Research .....	- 74 -
Table 10: Some strengths and weaknesses of mixed methods research .....	- 75 -
Table 11: What makes an intervention complex? .....	- 76 -
Table 12: The key characteristics of a systematic review .....	- 82 -
Table 13: Distinction between the qualitative study and REFRAMED.....	- 91 -
Table 14: Key features of a randomised controlled trial .....	- 99 -
Table 15: Comparison between START and the work in this thesis .....	- 105 -
Table 16: Core principles of the recruitment intervention advertising PPIR .....	- 111 -
Table 17: Content of the finalised leaflet advertising PPIR.....	- 113 -
Table 18: 2x2 cross-factorial design of the PPIR recruitment trial embedded within the EQUIP host trial.....	- 116 -



**Table 19: Suggestions by PPIR groups for the research and action taken..... - 144 -**

**Table 20: A comparison of depression and SMI..... - 147 -**

**Table 21: Peer-reviewed publications and contributions arising from the thesis.....  
..... - 160 -**

**Table 22: Presentations arising from the thesis ..... - 161 -**

## **Images**

---

**Image 1: Workshop breakout group discussing ‘core principles of the recruitment  
intervention’ ..... - 110 -**

**Image 2: Feeding back the breakout discussion to the wider group ..... - 110 -**

**Images 3 and 4: creating the ‘mock ups’ ..... - 111 -**

# Abbreviations

---

BME	Black and Minority Ethnic
CaFI	Culturally-Adapted Family Intervention for African Caribbeans diagnosed with schizophrenia and their families: A feasibility study of implementation and acceptability
CMHT	Community Mental Health Team
CONSORT	Consolidated Standards of Reporting Trials
CBT	Cognitive Behavioural Therapy
CENTRAL	Cochrane Central Register of Controlled Trials
CRHHT	Crisis Resolution and Home Treatment Team
CRN	Clinical Research Network
CRO	Contract Research Organisation
CSO	Clinical Studies Officer
CTTI	Clinical Trials Transformation Initiative
CTU	Clinical Trials Unit
DSM	Diagnostic and Statistical Manual for Mental Disorder
DALY	Disability Adjusted Life Year
EIPS	Early Intervention in Psychosis Services
EQUIP	Enhancing the Quality of User Involved Care Planning in Mental Health Services trial
FDA	Federal Drug Administration
GEE	Generalised Estimating Equation
GLMM	Generalised Linear Mixed Models
GPs	General Practitioners
HIV	Human Immunodeficiency Virus

HRA	Health Research Authority
HTA	Health Technology Assessment
ICC	Intra-cluster Correlation Coefficient
ICD	International Classification of Diseases
ICJME	International Committee of Medical Journal Editors
IMD	Index of Multiple Deprivation
ISRCTN	International Standard Randomised Controlled Trial Number
MRC	Medical Research Council
NHS	National Health Service
NIH	National Institutes of Health (US)
NIHR	National Institute for Health Research (UK)
NICE	National Institute for Health and Care Excellence
NRES	National Research Ethics Service
OR	Odds Ratio
PPIR	Patient and Public Involvement in Research
PRIMER	Primary Care Research in Manchester Engagement Resource
QALY	Quality-Adjusted Life Years
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REFRAMED	Refractory depression - Mechanisms and Efficacy of Radically Open Dialectical Behaviour Therapy trial
RO-DBT	Radically-Open Dialectical Behavioural Therapy
SAMS	Software Architecture for Self-Management of Mental Health and Dementia
SMI	Serious Mental Illness

START	Systematic Techniques for assisting Recruitment to Trials
SURP	Service User Research Panel
SWAT	Study Within A Trial
TMG	Trial Management Group
TPB	Theory of Planned Behaviour
UK	United Kingdom
UKCRC	UK Clinical Research Collaboration
US	United States
WHO	World Health Organisation
YLD	Years Lived with Disability

# Abstract

---

The University of Manchester, Adwoa Hughes-Morley, Doctor of Philosophy,  
'What are Effective Methods to Recruit Research Participants into Mental Health Trials?'  
2016

**Background:** There is a great need for effective treatments for mental health problems. Randomised controlled trials are the gold standard for evaluating treatments, however recruitment into trials is challenging, highlighting a clear need for evidence-based recruitment strategies. This thesis aimed to systematically develop a recruitment intervention and evaluate its effectiveness for improving the recruitment of participants into mental health trials.

**Methods:** A mixed-methods approach, adopting the Medical Research Council's complex interventions framework: 1) a systematic review to identify the evidence base and describe the factors affecting recruitment into depression trials; 2) a qualitative study to understand patients' decision-making process in declining to enrol in a depression trial; 3) development of a recruitment intervention, using Participatory Design methods; and 4) evaluation of the recruitment intervention, using a randomised controlled trial, embedded in an ongoing mental health trial (the EQUIP trial). The primary outcome was the proportion of participants enrolled in EQUIP.

**Results:** From the systematic review, a conceptual framework of factors influencing the decision to participate was developed, which highlighted that the decision to enrol involves a judgement between risk and reward. Findings suggested that patient and public involvement in research (PPIR) might be advertised to potential participants to reduce such perceived risk. The qualitative study found positive views of trials. Interviewees' decision making resembled a four-stage process; in each stage they either decided to decline or progressed to the next stage. In Stage 1, those with an established position of declining trials opted out – they are termed 'prior decliners'. In Stage 2, those who opted out after judging themselves ineligible are termed 'self-excluders'. In Stage 3, those who decided they did not need the trial therapy and opted out are termed 'treatment decliners'. In Stage 4, those who opted out after judging that disadvantages outweighed advantages are termed 'trial decliners'. While 'prior decliners' are unlikely to respond to trial recruitment initiatives, the factors leading others to decline are amenable to amelioration as they do not arise from a rejection of trials. We recruited a host mental health trial (EQUIP), and worked with key stakeholders, including mental health service users and carers, to develop an intervention using a leaflet to advertise the nature and function of the PPIR in EQUIP to potential trial participants. 34 community mental health teams were randomised and 8182 patients invited. For the primary outcome, 4% of patients in the PPIR group were enrolled versus 5.3% of the control group. The intervention was not effective for improving recruitment rates (adjusted OR= 0.75, 95% CI= 0.53 to 1.07, p=0.113).

**Conclusions:** This thesis reports the largest ever trial to evaluate the impact of a recruitment intervention. It also reports the largest trial of a PPIR intervention and makes a contribution to the evidence base on trial recruitment as well as to that assessing the impact of PPIR. Two further embedded trials are underway to evaluate the effectiveness of different versions of the recruitment intervention in different trial contexts and patient populations. This will also allow the results to be pooled to generate a more precise estimate of effect; to evaluate the impact of the intervention on trial retention; and to explore patient experiences of receiving the intervention.

# Lay abstract

---

## Why was the research in this thesis done?

There is a need for better treatments to help people with mental health problems, but recruiting patients into randomised controlled trials to test new mental health treatments is very difficult. More effective recruitment strategies are urgently needed. This thesis aimed to develop and test a strategy for recruiting patients into mental health trials.

## What was done?

The Medical Research Council's 'Framework for Developing Complex Interventions' was used to:

1. Review the literature in a systematic way to find out about the factors that affect recruitment into trials recruiting people with depression
2. Speak with people who chose to not take part in a depression trial to understand their reasons as well as how they went about making their decision
3. Develop a new strategy for recruiting patients, by working together with patients, carers and other key people
4. Test this strategy using a real trial which aimed to recruit people with mental health problems. Patients invited into a mental health trial were randomly sent the new strategy or not. Findings compared how many people who did or did not get the new strategy actually took part in the trial

## What did the thesis find?

The results of these studies found patients and doctors make a judgement between 'risk and reward' before deciding whether to take part in a trial. Most people who chose to not take part in a trial were positive about trials, but did not enrol because they felt they did not need the trial treatment. People who declined fell into different 'types'; however most were likely to consider taking part in future trials. We developed and tested a strategy for recruiting patients, which was to directly tell people being asked to take part in a trial about the patient and public involvement that had already taken place in that trial, using a leaflet. We hoped that people learning about the patient and public involvement might see the trial as less 'risky'. Findings showed that sending a leaflet about patient and public involvement was not effective as it did not increase the numbers of people actually taking part in the trial.

## What difference does this thesis make?

This thesis adds to our understanding of how people make the decision to decline trials; to our understanding of what does and does not work for improving recruitment; and to understanding the impact of patient and public involvement. Further research building on this work is now underway.

## Declaration

---

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning

## Copyright statement

---

**i.** The author of this thesis (including any appendices and/or schedules to this thesis) owns certain copyright or related rights in it (the “Copyright”) and s/he has given The University of Manchester certain rights to use such Copyright, including for administrative purposes.

**ii.** Copies of this thesis, either in full or in extracts and whether in hard or electronic copy, may be made **only** in accordance with the Copyright, Designs and Patents Act 1988 (as amended) and regulations issued under it or, where appropriate, in accordance with licensing agreements which the University has from time to time. This page must form part of any such copies made.

**iii.** The ownership of certain Copyright, patents, designs, trade marks and other intellectual property (the “Intellectual Property”) and any reproductions of copyright works in the thesis, for example graphs and tables (“Reproductions”), which may be described in this thesis, may not be owned by the author and may be owned by third parties. Such Intellectual Property and Reproductions cannot and must not be made available for use without the prior written permission of the owner(s) of the relevant Intellectual Property and/or Reproductions.

**iv.** Further information on the conditions under which disclosure, publication and commercialisation of this thesis, the Copyright and any Intellectual Property and/or Reproductions described in it may take place is available in the University IP Policy (see <http://documents.manchester.ac.uk/DocuInfo.aspx?DocID=24420>), in any relevant Thesis restriction declarations deposited in the University Library, The University Library’s regulations (see <http://www.library.manchester.ac.uk/about/regulations>) and in The University’s policy on Presentation of Theses

## Acknowledgements

---

Firstly, I would like to thank my supervisory team, Prof. Peter Bower, Prof. Bridget Young, Dr. Mark Hann and Dr. Waquas Waheed. Your expertise, pursuit of excellent, clarity of guidance and support throughout this process has been inspirational. I would also like to thank my advisor, Dr. Sarah Knowles for her support.

I am incredibly grateful to my wonderful family and friends for their ongoing love and support. While I am unable name all of you for want of space, I could not have done this without you.

I would like to thank the NIHR Clinical Research Network Mental Health's Service User Research Panel (SURP), particularly Mr. Tim Rawcliffe for his support, and Primary Care Research in Manchester Engagement Resource (PRIMER). I would also like to thank the African Caribbean Mental Health Service and the Salford Citizen Scientists for their support with reaching members of the community.

Thank you to all participants who took part in the studies and the experts who participated in the stakeholder workshops. I would also like to thank the following collaborators: The MRC START team - in particular Prof. Sandra Eldridge, Drs. Peter Knapp, Jo Rick, Nicola Small and Mrs. Vichithranie Madurasinghe; The REFRAMED trial team - especially Dr. Roelie Hempel, Profs. Thomas Lynch and Ian Russell; The EQUIP trial team - particularly Mrs. Claire Fraser, Profs. Karina Lovell, Chris Roberts, Drs. Oonagh Meade, Neil O'leary, and Ms. Lauren Walker. I would specifically like to thank Mrs. Lindsey Cree and Ms. Donna More, whose input and experiences richly informed the recruitment intervention; The CaFI team - namely Miss. Amy Degnan, Dr. Dawn Edge and members of the CaFI RAG – Ms. Michelle Ayavoro, Mrs Daisy Barratt, Rev'd. Paul Grey, Mrs. Sonia Lindsay, Mrs. Mary Maynard, Ms. Natasha Peniston, Mr. Anthony Stephens and Mrs. Yvonne Thomas; The SAMS team and PPIR partners- specifically Dr. Iracema Leroi, Ms. Gemma Stringer, Dr. Samuel Couth, Profs. Alistair Sutcliffe and Peter Sawyer.

Finally, I would like to thank the National Institute for Health Research (NIHR), who funded this Doctoral Research Fellowship (NIHR DRF 2012-05-1128) and staff at the Trainees Coordinating Centre for their ongoing support throughout this fellowship. This thesis presents independent research funded by the NIHR. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.



## Dedication

---

I dedicate this thesis to my mother Mrs. Philomena Patience Morley, my father Mr. Keith Morley and my fiancé Dr. Jonathan Richard Parker. Your unwavering love, patience and support ensured that I survived beyond expectation and thrived beyond expectation. Through each of you I have become a better person; and I hope to become a better person yet for each of you.

## About the author

---

Adwoa is currently a Research Fellow at York Trials Unit (YTU), The University of York, where she contributes to the unit's programme of cutting edge trials. She has a background in health services research, often involving large complex collaborative projects adopting mixed methods approaches. Current studies include 'Connect', a multi-agency collaboration with North Yorkshire Police to develop and evaluate new approaches to assist the police with dealing with people experiencing mental health problems. Adwoa also coordinates YTU's methodological programme of trials embedded within ongoing trials to evaluate the effectiveness of interventions for improving trials. This includes trials of recruitment interventions.

In 2012 Adwoa was awarded a National Institute for Health Research (NIHR) Doctoral Research Fellowship, a personal award aimed at individuals of outstanding potential to undertake a customised research training programme. This thesis forms the research undertaken as part of the Fellowship, which aims to lead to the award of a doctorate. Adwoa is a member of the MRC Hubs for Trial Methodology Research's Recruitment Working Group as well as the Patients' Perspective theme.

From 2009-2011 Adwoa managed the £2.3m Medical Research Council funded collaborative care for depression trial (CADET). One of the largest collaborative care trials in the world, CADET recruited its sample size ahead of schedule and was recognized as a good practice exemplar by the NIHR. Between 2007 and 2009 Adwoa supported the recruitment of trial participants into studies adopted by the Welsh Mental Health, Learning Disabilities and Dementia and Neurodegenerative Diseases research networks. Prior to this, she worked in the National Health Service: initially as part of a clinical network exploring effective ways of working with people with personality disorders in the community; and later within a Primary Care Mental Health Team delivering psychosocial interventions to patients with common mental health problems such as depression.

Adwoa therefore has a keen interest in evidence-based interventions for mental health problems; in mental health trials; and in trials methodology, particularly recruitment. She is delighted to have had an opportunity to make a contribution to the evidence base on trial recruitment. Adwoa has a BSc in Health Sciences and a Postgraduate certificate in Mental Health, both from The University of York.

# Chapter 1: Introduction

---

## 1.1 Rationale for the thesis

Mental health disorders are the leading cause of disability worldwide, and randomised controlled trials are the gold standard for evaluating treatments. Yet the recruitment of participants is the most challenging aspect of undertaking trials, which is more so for trials recruiting patients with diagnoses of mental health problems. Consequences of poor recruitment include increased costs and effort, sampling bias, reduction in statistical power, delays in the generation of evidence and the subsequent adoption of effective interventions, as well as in some cases the continued use of interventions that are ineffective and/or harmful to patients. Trialists use many strategies in attempting to improve recruitment; however few recruitment interventions have been rigorously evaluated in real-life trials, leading to increasing calls in the UK and internationally for a better evidence base. The need to robustly develop and evaluate trial recruitment interventions has been highlighted as the number one methodological priority by trialists. One way of increasing the evidence base is to develop recruitment interventions and then rigorously evaluate them for effectiveness using randomised controlled trials embedded in ongoing, 'host' trials.

## 1.2 Aims and objectives of this thesis

The central aim of this thesis is to contribute to existing literature on evidence based trial recruitment, by adopting a systematic approach using the MRC complex interventions framework to develop and test the effectiveness of an intervention for recruiting participants into mental health trials. The research is guided by four main objectives, which are to:

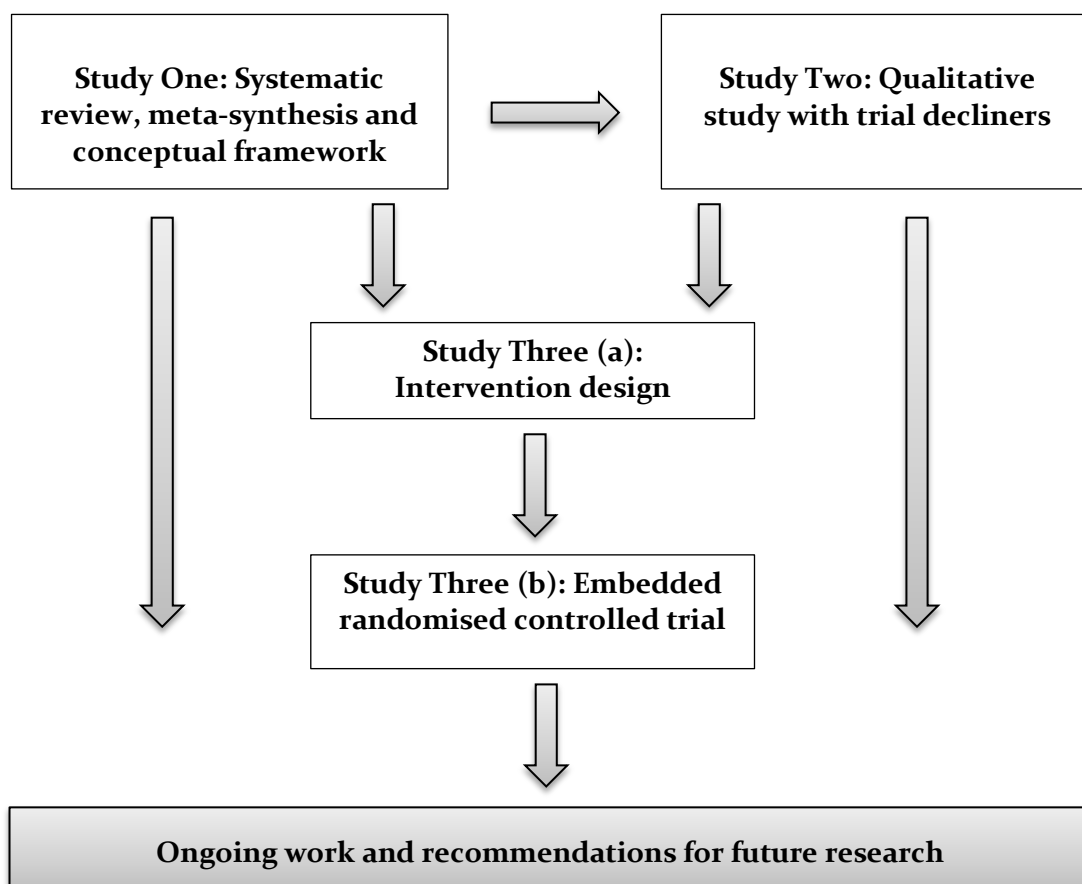
1. Identify and describe the factors affecting recruitment into depression trials. This is achieved through a systematic review, meta-synthesis and development of a conceptual framework (Study One)
2. Identify potential components of a possible recruitment intervention. This is undertaken using qualitative interviews with patients who declined to participate in a depression trial (Study Two)
3. Develop an intervention for recruiting participants into mental health trials. This uses Participatory Design methods with key stakeholders (Study Three)

- Determine the effectiveness of the intervention for improving recruitment. This adopts a randomised controlled trial design, embedded in an ongoing trial recruiting patients with mental health problems (Study Three)

### 1.3 Overview of the studies

This thesis adopts a mixed methods approach and combines qualitative and quantitative methods to allow the strengths of each to complement the other [1]. The thesis comprises of three separate studies which are designed to build on each other. An outline of the three studies and how they fit together is provided in Figure 1. Study One is a systematic review and meta-synthesis of qualitative studies. Findings lead to Study Two, which is a qualitative study. Study Three is informed by studies one and two and adopts Participatory Design methods to design a recruitment intervention, which is then evaluated using a randomised controlled trial, embedded in an ongoing mental health trial.

Figure 1: Overview of studies included in thesis



## 1.4 Thesis structure

This thesis is presented in the 'alternative format' and is composed of three separate studies that are presented as the three 'results' chapters. Consequently, the chapters reporting the results of the three studies have either already been published in open access peer-reviewed journals, or have been drafted and submitted to a target journal.

This thesis is structured in seven chapters. Chapter 1 introduces the rationale for and structure of the thesis. Chapter 2 provides a review of the background literature, including: mental health and the need for more effective treatments; evidence based practice and the randomised controlled trial; the recruitment problem; efforts to address the recruitment problem, including patient and public involvement; and the need for robust evaluations of recruitment interventions. In Chapter 3 an overview of the thesis methodology and the specific methods used in each of the three studies is provided. Chapters 4 to 6 report the results of the studies undertaken and are presented as the following journal articles:

### Study One (Chapter 4)

Hughes-Morley, A., Young, B., Waheed, W., Small, N., & Bower, P. (2015). Factors affecting recruitment into depression trials: systematic review, meta-synthesis and conceptual framework. *Journal of Affective Disorders*, 172, 274-290.

### Study Two (Chapter 5)

Hughes-Morley, A., Young, B., Hempel, R.J., Russell, I.T., Waheed, W., & Bower, P. (2016). What can we learn from trial decliners about improving recruitment? Qualitative study. *Trials*, 17:494

### Study Three (Chapter 6)

Hughes-Morley, A., Hann, M., Fraser, C., Meade, M., Lovell, K., Young, B., Roberts, C., Cree, L., More, D., O'Leary, N., Callaghan, P., Waheed, W., & Bower, P. (2016). The impact of advertising patient and public involvement on trial recruitment: embedded cluster randomised recruitment trial. *Trials*, 17:586

Study One has undergone peer review and is published in the *Journal of Affective Disorders*, which has an impact factor of 3.570. Impact factor is a proxy measure for quality, which reflects the average annual number of citations in a journal. Studies Two

and Three have been peer reviewed and published in *Trials*. *Trials* has an impact factor of 1.859. The published studies are presented in their journal format.

The author (AH-M) is first author for all included journal articles and conceived as well as led on the conduct and reporting of the studies. Thus she performed the inception, planning, data cleaning, data analysis, manuscript writing, manuscript submission and revisions. The collaborating authors of the journal articles contributed by assisting with data extraction, access to the study populations, patient and public involvement, participant recruitment, randomisation, statistical support and supervisory oversight. At the beginning of each chapter containing a journal article, a 'contributions' statement provides further details of collaborating authors' contributions to each article. AH-M conceptualised and wrote all other sections of the thesis.

Chapter 7 concludes the thesis by summarising the results and discussing the strengths and limitations of the thesis overall. This chapter also makes recommendations for future research and recruitment practice and provides an overview of the ongoing work emerging from this thesis.

## **1.5 Rationale for submitting thesis in the alternative format**

The motivation for submitting this thesis in the alternative format is to ensure timely publication of research findings. The purpose of this thesis is to add to the evidence base for clinical trial methodology, by developing and evaluating an intervention for recruiting research participants into mental health trials. In order to avoid duplication of effort; to advance shared knowledge; and to reduce harm to patients, there is a need for researchers to publish their findings. Currently, a large proportion of research undertaken remains unpublished, sometimes years following study completion [2]. This creates ethical problems, as harms that might otherwise be preventable continue to occur because the results of existing research remain inaccessible. Failure to publish research findings also constitutes research waste, both of time and resources, which arguably, is no longer justifiable [3][4]. Recently, initiatives by institutions such as the World Health Organisation (WHO) [5] and AllTrials [6] have highlighted the need for the mandatory reporting of trials. Thus the timely reporting of research findings is an ethical and a moral imperative, as well as being vital to developing an evidence base. In submitting the thesis in the alternative format, the aim is to assist with this timely reporting of its findings.

# Chapter 2: Background literature

---

## 2.1 Chapter overview

This background chapter aims to highlight the need to develop recruitment interventions and evaluate their effectiveness for improving participant recruitment into mental health trials. In so doing, the chapter will address the following:

1. Mental ill health, the impact on the person and the complexities around the diagnosis, treatment and outcomes
2. Evidence based practice and the randomised controlled trial
3. The recruitment problem, how this relates to mental health trials and its impact
4. Efforts to address the recruitment problem, including patient and public involvement, and the need for a 'science of recruitment'
5. The specific factors influencing recruitment into mental health trials
6. Proposed solutions to enhance recruitment into mental health studies
7. Theories to inform the development of recruitment interventions

In this chapter we provide an outline of relevant and methodologically robust literature, rather than present an exhaustive systematic review.

## 2.2 'No health without mental health': the need for improved treatments for mental illness

### 2.2.1 Introduction

In this section we<sup>1</sup> aim to highlight the need to develop and evaluate effective treatments for mental illness, and the complexities associated with managing the following: the conceptualisation of mental illness; its prevalence and incidence; its identification and

---

<sup>1</sup>In this thesis we use the active voice wherever possible. In particular, the first person plural pronoun 'we', rather than 'I', is used throughout the thesis, in both the published and the non-published chapters. In the non-published chapters solely written by AHM, 'we' is used to maintain consistency between the published and non-published chapters; to include the reader where relevant; and in acknowledgement of the collaborative nature of the work. AHM is responsible for the decisions and choices made in this thesis, and as already highlighted in the previous chapter, led on all the work in this thesis and wrote all sections of the non-published chapters.

treatment; and current treatment, which highlights a need for well-developed and trialled interventions to improve outcomes for patients.

## 2.2.2 The conceptualisation of mental health and mental illness

Mental health can be defined as:

*'A state of well-being enabling individuals to realise their abilities, cope with the normal stresses of life, work productively and fruitfully, and make a contribution to their communities' [7] - p4.*

Indeed, such is the fundamental nature of mental health to overall health that there can be 'no health without mental health' [8], [9]. However, mental health is not a universal health state, with mental illness being prevalent across all societies globally and accounting for significant disability and disease burden.

Mental illness is a broad term generally characterised by dysregulation of mood, thought, and/or behaviour [10]; however, definitions of mental illness vary depending on its conceptualisation [11]. It is important to note that there is no internationally agreed operational definition of mental illness [12][13]; this has far-reaching implications for developing a science of mental illness and can create difficulties for professionals when it comes to understanding, responding and developing appropriate treatments which can be robustly evaluated for effectiveness [14][15][16].

In the United Kingdom (UK) National Health Service (NHS), ongoing difficulties with treating mental illness has been rooted in a history of uncertainty regarding the optimal provision of care for patients, and indeed, whether care should be provided at all. Increasing complexity coupled with very high rates of comorbidity also result in difficulties with classification, which has an adverse impact on delivery of care [17]. It has been suggested that such uncertainties partly arise from the differing explanatory models used to frame the conceptualisation of mental illness [18][19]. For instance, while the biomedical model of mental illness posits that mental disorders are brain diseases and emphasises pharmacological treatment to target presumed biological abnormalities [20], the sociological model conceptualises mental illness as a consequence of the person failing to respond adaptively in the face of overwhelming environmental stress [21]. Kendler (2008) argues that such models are based on the incorrect assumption that psychiatric illnesses can be understood from a single perspective, and suggests that a more appropriate scientific model for mental illness should emphasise the understanding of



mechanisms, an approach that fits with a multi-causal framework and provides a potentially realistic paradigm for scientific progress [22].

In this thesis we define ‘mental illness’ broadly and include common mental health problems such as anxiety and unipolar depression as well serious mental illness such as psychosis and schizophrenia. This definition adheres to standardised definitions of mental illness, which involves dysregulation of mood, thought, and/or behaviour [12], [13]. Our definition does not include neuropsychiatric conditions such as dementia and neurodegenerative diseases; intellectual disabilities; or personality disorders. There is a consensus that the latter diagnoses are not mental illnesses [23]; while neuropsychiatric conditions and intellectual disabilities arguably have different underlying processes and issues [24].

In the UK, management of mental illness begins with a diagnosis based on criteria specified in the Diagnostic and Statistical Manual of Mental Disorders (DSM)[12] and International Classification of Diseases (ICD) diagnostic manuals [13]. Table 1 compares the two guidelines [12][13].

**Table 1: Comparison of guidelines for diagnosing mental illness, adapted from American Psychological Association website [25]**

	<b>DSM</b>	<b>ICD</b>
<b>Origin</b>	Developed in the US	Developed in Europe
<b>Produced by</b>	A National Professional Association: The American Psychiatric Association	A global health agency: the World Health Organisation
<b>Intended reach</b>	US psychiatrists: however used globally	Global: multidisciplinary and multilingual
<b>Approved</b>	By Assembly of The American Psychiatric Association	By the World Health Assembly comprised of health ministers of member countries
<b>Distributed</b>	At a cost; revenue generated from sale of book and related products	Widely and at a reduced cost to low-income countries; available online
<b>Current version</b>	Current version: 5	Current version: 10

Whilst the ICD can be used to classify most medical disorders, the DSM focuses on mental and behavioural disorders. However, both classify mental illnesses based on clinical consensus. Since version III of the DSM, there has been a division between professionals who adhere to DSM due to what they perceive to be better research classification, and those who adhere to ICD because they perceive it to allow more clinical discretion in making diagnoses [26]. As a consequence of poor definitions of mental illnesses from these diagnostic manuals, which also demonstrated poor test-retest reliability and temporal instability, some argued that the beliefs of the psychiatrist seemed to take precedence over the patient characteristics during the diagnostic process [26]. Another dilemma central to this psychiatric classification debate is the relationship between psychotic and affective symptoms and whether they should be considered separate disease entities or as part of a rich psychopathology, distributed across multidimensional spectra [27]. Other limitations of these diagnostic categories often include failing to align with findings from clinical neuroscience and genetics; not being predictive of treatment response; and not capturing

fundamental but underlying mechanisms of dysfunction [28]. The impact of this has been to impede research on aetiology and pathophysiology as well as the development of new treatments [28][29].

To summarise, the conceptualisation of mental illness is a complex but important issue that requires consideration in the management of patients and the development and evaluation of new treatments. It is important to consider the limitations of current diagnostic approaches, which can have potentially negative impacts on research as well as treatment. We focus on incidence and prevalence in the next section.

### **2.2.3 Incidence and prevalence**

In this thesis we focus on depression, schizophrenia and other psychotic disorders, which are the mental health problems that have been demonstrated to cause the most burden [30]. Depression, also known as unipolar depression or major depressive disorder, is a broad and heterogeneous condition characterised by depressed mood and/or loss of pleasure in most activities and a range of emotional, cognitive, physical and behavioural symptoms [31]. The term 'severe and persistent mental illness' (SMI) can be used to refer to the group of psychotic disorders that includes schizophrenia, schizoaffective disorder, schizophreniform disorder and delusional disorder which has a duration of service contact of two years or more [32][33]. SMI is characterised as a major psychiatric disorder, or cluster of disorders, in which a person's perception, thoughts, mood and behaviour are significantly altered. Symptoms of SMI can be divided into 'positive symptoms', such as hallucinations (perception in the absence of any stimulus) and delusions (fixed or falsely held beliefs), and 'negative symptoms', such as emotional apathy, lack of drive, poverty of speech, social withdrawal and self-neglect [34].

The difficulties in defining mental illness make it difficult to report robust estimates of prevalence and incidence. Additional difficulties arise due to people with mental illness being less likely to participate in mental health surveys and more likely to offer false negative responses if asked about psychotic symptoms as part of survey interviews [35].

The most prevalent mental illness worldwide is depression, which affects approximately 350 million people [36]. The most up to date and comprehensive systematic review, which involved 120 prevalence and incidence studies of major depressive disorder identified the global point prevalence for depression at 4.7%. Consistent with existing literature, prevalence in women was higher than in males. For women, the point prevalence was

5.9%, while men had a point prevalence of 3.8%. The 12 month prevalence for women was 7.2%, while for men this was 3.9% [37]. The annual pooled incidence was 3%, with women having a higher incidence (3.4%), than men (2.7%). The authors detected a time effect which suggested that the prevalence of depression had increased over time. This study identified significant heterogeneity between the studies and estimates, and found that prevalence period, sex, year of study, depression subtype, survey instrument, age and region were significant determinants of prevalence, explaining 57.7% of the variability between studies [37]. In the UK, a descriptive epidemiological study within UK Biobank involving 172,751 adults aged 40-69 found prevalence rates for probable single lifetime episode of major depression to be 6.4%; probable recurrent major depression (moderate) to be 12.2%; and probable recurrent major depression (severe) to be 7.2% [38].

According to the Global Burden of Disease Study 2010, the largest ever systematic description of the global distribution and causes of major diseases and injuries, the global prevalence cases for schizophrenia in 2010 was 21,500,000 [39]. Combined prevalence estimates from another high-quality systematic review has found median values per 1,000 persons (10%-90% quantiles) for the distributions for point, period, lifetime, and lifetime morbid risk to be 4.6, 3.3, 4.0, and 7.2 respectively. This study found no significant difference between men and women and between urban, rural, and mixed sites [40]. The prevalence of schizophrenia in migrants was higher compared with native-born individuals: the migrant-to-native-born ratio median (10%-90% quantile) was 1.8 [40].

In England, the largest systematic review of incidence rates for schizophrenia and other psychoses identified 83 studies between 1950 and 2009. The pooled incidence of all psychoses was 31.7 per 100,000 person-years; 23.2 for non-affective psychoses; 15.2 for schizophrenia; and 12.4 for affective psychoses. For men aged 45 years and under, the incidence rate of schizophrenia was twice that of women; however over the age of 45 years there were no significant differences between women and men. The opposite was found for affective psychoses with no significant difference found between men and women aged 45 years and under, but an increased incidence in women aged over 45 years old. Rates of disorders were elevated in ethnic minority groups compared with the white British population in England for schizophrenia: African Caribbean (pooled rate ratio [RR]: 5.6; 95%CI: 3.4-9.2), black African (pooled RR: 4.7; 95% CI: 3.3-6.8) and South Asian groups (pooled RR: 2.4; 95%CI: 1.3-4.5) [41].

Thus the data available suggests that depression is the most common mental illness, whilst SMI is not uncommon. In the next section we discuss the impact of depression and SMI on the person and on society.

#### 2.2.4 Morbidity, mortality and burden

According to the Global Burden of Disease study, depression is a leading cause of disease burden [42][43]. It is the biggest cause of sickness absence in the UK, accounting for 70 million sick days in 2013 [44]. In 2010 depression accounted for 8.2% of global Years Lived with Disability (YLDs). Although no mortality was attributed to it as an underlying cause, depression was a leading cause of Disability Adjusted Life Years (DALYs), accounting for 2.5% (1.9%-3.2%) of global DALYs. The DALY measures overall disease burden, expressed as the number of years lost due to ill-health, disability or early death [43]. Higher estimates were found in females and adults of working age. Depression accounted for 16 million suicide DALYs and almost 4 million ischemic heart disease DALYs. This attributable burden increased the overall burden of depressive disorders from 3.0% to 3.8% of global DALYs [42].

Thus depression is a leading cause of disease burden and a major contributor to the burden for suicide and ischaemic heart disease. Alongside others, the authors of the Global Burden of Disease studies have highlighted the importance of including depressive disorders as a public-health priority and implementing cost-effective interventions to reduce its burden [42] [43] [45].

SMI is among the most burdensome and costly illnesses worldwide [46]. Life expectancy for people with SMI is reduced by approximately 10 years, predominantly due to suicide. In the UK, a prospective study of the mortality rates of a community cohort of people with schizophrenia identified a mortality risk of between two and three times that of the general population [47]. This study also found cardiovascular mortality to be increased relative to the general population [47].

Data from the Global Burden of Diseases study shows schizophrenia causes a high degree of disability and accounted for 0.5% of total, all cause DALYs in 2010 [39]. Aside from the individual suffering from the condition, SMI places considerable burden on families and carers [39]. The indirect costs of SMI are multifaceted and include loss of productivity through impairments, disability and premature death, burden on families and caregivers, as well as some legal problems, which can include violence [46].

People with depression and SMI are among the most excluded in society. There is no single accepted definition of the concept of social exclusion and existing empirical research is generally limited to focusing on the experiences of being excluded within an

institutional or semi-institutional setting [48]. However, the Social Exclusion Unit has defined social exclusion as:

*“...what can happen when people or areas suffer from a combination of linked problems such as unemployment, poor skills, low incomes, poor housing, high crime, poor health and family breakdown’ [49] - p3.*

Despite many people with depression and SMI wanting to work, employment rates are the lowest of any group with long term conditions [50]. This often leads to social isolation, which is an important risk factor for deteriorating mental health and suicide [51]. Coupled with unemployment, hospital admissions and difficulties paying accommodation costs are factors which contribute to the disproportionately high rates of people with SMI being homeless, on the streets or living in insecure housing [52]. Additionally, issues around stigma and discrimination are pervasive throughout society [53], with employers often being reluctant to employ someone with mental illness [54]. Many people fear disclosing their condition, even to family and friends, which can lead to further social isolation.

Depression and SMI are also costly, being respectively the most expensive and third most expensive mental health conditions to manage in the UK, despite SMI having relatively low prevalence [45]. A mental health expenditure review by the King’s Fund estimated the total costs to the UK, including direct health and social care, informal care, criminal justice services and lost employment in 2007 was £7.5 billion for depression and £4.01 billion for SMI; by 2026 this is estimated to be £12.15 billion for depression and £6.5 billion for SMI [45].

In summary, depression and SMI bear an enormous burden in terms of mortality, morbidity, disability, social exclusion and high costs to the individual suffering from the disorders, on healthcare systems, on society, as well as on families. In the following section we will discuss the need for improved treatments.

### **2.2.5 Recognition and treatment**

Treatment for depression and SMI begins with recognition; however mental illness is often poorly recognised by professionals, meaning most people are not correctly diagnosed or adequately treated when they present to health services. This has led to a UK Department of Health mental health strategy highlighting the need for improved recognition and treatment [9]. Poor recognition in turn leads to a large treatment gap, which the WHO estimates at between 35% and 50% for high income countries such as the UK [55].

In the UK there are clinical guidelines developed by the National Institute for Health and Care Excellence (NICE), whose role is to provide clear published guidance on treatment options within the NHS. NICE base their guidelines on systematic reviews and meta-analyses, combined with an economic review of intervention costs. These guidelines form the treatments used as standard care. Guidelines have been published for the management of depression in adults [31] and for psychosis and schizophrenia in adults [34]. For depression, a stepped-care model is recommended, which aims to provide a framework in which to organise the provision of services, and supports practitioners in identifying and accessing the most effective interventions. In stepped care the least intrusive, most effective intervention – whether psychological, pharmacological, disease management or combined - is provided first; if the patient does not benefit from the intervention initially offered, they are then offered an appropriate intervention from the next step [31]. For SMI, NICE recommends that care across all phases of the disorder should be attentive to the service user experience; physical health; support for carers and peer support and self-management. For preventing psychosis, NICE recommends cognitive behavioural therapy (CBT). For first and subsequent episodes of psychosis, a range of antipsychotic, psychological (CBT or arts therapies), social, occupational, educational and disease management interventions are recommended. Recommended service led interventions include Early Intervention in Psychosis Services (EIPS) and Crisis Resolution and Home Treatment Teams (CRHTTs) [34].

NICE and the formation of the guidelines have received criticism for being subjective and ostensibly illustrating Foucault's notion that the authority of medicine acts to promote a technological view of the nature of human problems, which in turn strengthens medical hegemony [56]. For instance, there are reports that in developing the depression guideline, the NICE Panel briefly considered the complexity and heterogeneity of depression, and numerous methodological problems with evaluating treatments, including antidepressants. However, the guideline recommendations make no reference to these issues and ignored evidence that questioned the analysis of antidepressant trials [57]. Arguably, the guidelines demonstrate how contradictory data are managed so as not to jeopardise the currently predominant view that depression and SMI are valid and uncontested medical conditions that should be treated with medication [57]. The guidelines have also been construed as misleading by implying, through their recommendation of certain treatments, that such treatments are clinically effective and curative. For example, concerns have been raised about the perceived dominance of CBT as a preferred psychological treatment option for both depression and SMI, when high-

quality systematic reviews have shown CBT to lack superiority over lower cost treatment options [58][59].

Even with the use of treatments as recommended by NICE, recovery rates from symptomatic exacerbation or relapse are low and side effects of pharmacological treatments are high. These include weight gain; extrapyramidal side-effects such as tardive dyskinesia and Parkinsonism; prolactin increase; life threatening arrhythmia; and sedation. Such side effects often lead to discontinuation of treatment by patients, leading to exacerbation of their mental health condition [60]. Systematic reviews show that recurrent rates are high for depression, with as many as 80% of those requiring multiple treatments relapsing within a year of achieving remission [61]; for SMI recovery rates are even lower, with the median proportion of patients with schizophrenia who meet the recovery from their symptoms for at least two years being only 13.5% [62].

The range of evidence based interventions for managing depression and SMI are limited, as is the evidence on their effectiveness. For example, a systematic review to identify early interventions to prevent psychosis found no conclusive evidence of benefit for any specific intervention [63]. NICE itself has recognised that existing treatments are not optimal, and has made 10 high-priority recommendations for research for depression [31], and five such recommendations for psychosis and schizophrenia [34], in order to improve NICE guidance and future patient care. These are areas where clear gaps exist where NICE have not been able to make treatment recommendations.

In the face of unsatisfactory treatments, systematic reviews, patient groups and other stakeholders have increasingly called for the need to develop effective interventions that have been robustly evaluated in randomised controlled trials for treating and managing people with depression and SMI [63][64][61][39]. Evidence of longer term outcomes of treatment is also needed, in addition to including patients who are not currently well presented in trials [65]. As well as developing and evaluating novel antidepressants and antipsychotics, a range of other promising strategies have been identified that can be evaluated in trials, including cognitive adaptive therapy, service-user involvement in care planning, first-episode psychosis intervention, healthy lifestyle interventions, integrated treatment for co-occurring disorders, interventions targeting older individuals, peer support services, physical disease management, prodromal stage intervention, social cognition training, supported education and supported housing [66].

To summarise, effective treatment for people with depression and SMI is thwarted by poor recognition by clinicians and unsatisfactory treatments. While treatment guidelines are



available, these are limited in that they do not acknowledge the complexities and heterogeneity of the conditions. High relapse rates coupled with clear gaps in the evidence base means that the need to develop and test treatments for depression and SMI is a national priority. In the next section we turn our attention to the testing of these treatments.

## **2.3 ‘Testing treatments’: evidence-based practice and the randomised controlled trial**

### **2.3.1 Introduction**

In this section we will review the following:

1. Evidence based practice, the challenges and the randomised controlled trial
2. The nature of trials and the extent of the recruitment problem
3. Attempts to address recruitment problems to date
4. The specific factors influencing recruitment into mental health trials
5. Proposed solutions to enhance recruitment into mental health studies
6. Theories and models that might inform the development of recruitment interventions

### **2.3.2 Evidence-based practice: what it is**

To improve health, clinical and health services and to minimise iatrogenic effects of treatments, research:

*‘Is a necessary and plausible tool for judging the value of what we do for and to patients’ [67]-p315.*

By acknowledging that treatments can sometimes do more harm than good, research attempts to minimise unintended harm to patients by firstly admitting uncertainties about treatment effects, and secondly introducing tests of treatments to adequately reduce these uncertainties [68]–[70]. Such tests of treatments is crucial and underpins evidence based practice, long advocated by clinical scientists including Cochrane, Chalmers and Sackett [71]–[73]. The terminology ‘evidence based medicine’ was originally coined by Guyatt [74] and has subsequently been defined as requiring:

*‘The integration of best research evidence with clinical expertise and patient values’ [75] - pl.*

In evidence based medicine, optimal care is provided to patients through the practitioner informing their clinical expertise with the best available external clinical evidence from systematic research, combined with the needs and preferences of their patient [75]–[77]. The alternative system to evidence based medicine is empirical diagnosis and treatment, which is subject to individual, cultural and training bias [78], [79] and has become less popular as practitioners have gained increased access to emerging evidence in our information age [78]. Evidence based medicine represented a paradigm shift whereby

intuition, unsystematic clinical experience and pathophysiological rationale were to be consigned as potentially detrimental to patients [80]. Whilst policy makers, purchasers and clinicians in other branches of medicine greeted evidence based medicine with some enthusiasm, some viewed this movement with caution, particularly in psychiatry, a speciality described as being characterised by ideology and controversy [81]. Psychiatrists argued that: there is little evidence that the model can be adapted to their field [82]; the psychiatric diagnostic system, being based on expert consensus rather than experimental evidence was incompatible with evidence based medicine [83]; evidence based medicine was of limited relevance to complex mental health problems [82], [83]; the model offered little tangible benefit to practitioners and their patients [82], [84]; the diagnostic system, the manner in which data were gathered, and financial factors result in a model that is misleading and even dangerous [82]. Despite its detractors, evidence based medicine is now firmly established in all fields of medicine including psychiatry, which now displays an explicit enthusiasm for experimental design and trials [81], [85].

In the UK, the consequent establishment of the Cochrane Collaboration and NICE promoted evidence based medicine as an orthodoxy of contemporary healthcare practice [86], [87]. Here, the goal was to support practitioners to adopt treatments demonstrated through research to be clinically and cost-effective, while discouraging practices that do not qualify as such. This has become the gold standard for the commissioning and provision of health services, in the UK and internationally [87], [88] and has evolved beyond clinical treatments to practitioner and patient behaviour and health services research, all aspects of health and social care and the generation of evidence for randomised controlled trials [89], [90]. The concept of evidence based medicine has been broadened to 'evidence-based practice' [91]-[93] to reflect the wider use of the evidence based approach and the benefits of entire health and social care teams and organisations adopting a shared evidence-based approach [93]. This evolution in scope also sees an evolved definition, which now:

*'Requires that decisions about health care are based on the best available, current, valid and relevant evidence. These decisions should be made by those receiving care, informed by the tacit and explicit knowledge of those providing care, within the context of available resources'* [93] - p4.

Evidence based practice has been attributed as the key to the success of modern healthcare, which has witnessed extraordinary improvements in life expectancy and quality of life in the last century [89]. Well-researched and targeted treatment and prevention programmes in mental health can reduce deaths, years lived with disability, stigma, poverty, and can promote social capital as well as individual and national

development [94]. The grounding of clinical practice in science and empiricism also led globally to safer, more consistent and more cost effective clinical care [95]. Evidence based practice has also generated significant advances in methodology that has enabled practitioners to distinguish between helpful and harmful treatments, identify major problems with publication bias, and identify and commence the address of industry conflicts of interest [96].

However, proponents of evidence based practice have argued that the movement is in crisis [97]–[100], arising from the challenges in implementation of evidence based practice [101]. Greenhalgh *et. al.* (2014; 2016) argue that there has been unintended consequences of evidence based practice [97], [102]. First, that there is a distortion of the evidence based ‘quality brand’, which has been misappropriated by the vested interests of the commercial pharmaceutical and medical industries, who increasingly set the research agenda. Second, that although a measure of its success, the large volume of evidence, especially that generated by clinical guidelines makes it unmanageable and unfathomable for practitioners treating patients. Third, that since the large gains in health improvement and scientific advance have already been made, evidence based practice is now increasingly focused on marginal gains, meaning that statistically significant benefits may be marginal when applied to patients in practice. Fourth, an overemphasis on inflexible algorithmic rules and technological prompts may produce care that is management driven rather than patient centred. Finally, that while the population ages and chronic and multi-morbid diseases become increasingly prevalent, evidence based guidelines often fit poorly with the complex multi-morbidities seen in practice [97], [102].

To herald the renaissance of the evidence based practice movement, Greenhalgh *et. al.* [97] argue for a return to ‘real’ evidence based practice which places the ethical care of the patient as the top priority; demands individualised evidence in a format understandable to both patients and practitioners; is characterised by expert judgement rather than mechanical rule following; places shared decision making with patients at its core and is patient centred. Thus they offer a preliminary agenda by refocusing on providing useable evidence that can be combined with context and professional expertise so that individual patients obtain optimal care [97]. Despite its limitations, evidence based practice continues to be considered the most complete paradigm for delivering safe and effective healthcare for patients [103].

To summarise, evidence based practice is a movement that has been critical to improving life expectancy and quality of life for people throughout the world. However, it is beset with challenges, mainly to do with implementation. In the next section we discuss the

process of evidence based medicine, the levels of evidence and the randomised controlled trial.

### **2.3.3 The process of evidence based practice**

The process of evidence based practice, originally proposed by Cook *et. al.* (1990) [104], involves the informed and effective use of all types of research evidence and starts with the practitioner identifying a clinical uncertainty to ask an answerable question; searching for the best evidence; critically appraising the evidence for its validity and relevance; integrating the evidence with clinical expertise and the patient's values; and evaluating performance [104]. These phases have been evaluated for effectiveness in randomised controlled trials [105]–[109], and remain the basis of evidence based practice and teaching to date [93].

The cornerstone of evidence based practice is critical appraisal, the process of assessing and interpreting evidence by systematically considering its validity, results and relevance [110]–[112]. A range of methods are available to appraise the evidence; however, the most prevalent tool is the research hierarchy [113], [114], which ranks the body of evidence according to the level of bias associated with the different study designs that have contribute to the evidence base. This hierarchy, also known as the levels of evidence, has helped to raise awareness of what constitutes 'good' evidence, and that some types of evidence are more trustworthy than others [110], [115]. However, it has also been criticised for leading to misconceptions and abuses, particularly the use of criteria designed to guide inferences about the main effects of treatment being uncritically applied to questions about aetiology, diagnosis, prognosis, or adverse effects [115]. Nevertheless, the hierarchical system remains the mainstay of classification in evidence based practice [110] with a number of different ranking systems having been proposed [111], [116]–[119][120][121]. In the UK, the most prevalent system was proposed by the Scottish Intercollegiate Guidelines Network and adapted by NICE [122], [123]. Table 2 outlines the hierarchy of evidence.

**Table 2: Hierarchy of evidence of the efficacy of an intervention, adapted from Weightman et. al. 2005 [123]**

Level of evidence	Type of evidence
I++	High-quality meta-analyses of RCTs, systematic reviews of RCTs or RCTs with a very low risk of bias
I+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

*\*Studies with a level of evidence (-) should not be used as a basis for making recommendations.*

The hierarchy of evidence classifies studies based on their potential for bias, with trials and systematic reviews accorded the highest level due to them being designed to be unbiased and being less associated with systematic errors. Some have criticised this dominant hierarchical levels of evidence for failing to incorporate all types of research evidence, however [124][125]. In particular, it has been argued that qualitative research is more likely to be classified as lower quality evidence – or indeed excluded altogether – although such research may provide high quality evidence depending on the problem being addressed [125]. Here, alternative models such as the Research Pyramid have been proposed to take into account qualitative research [124][125].

Regardless of the model assessing the evidence base however, all hierarchies and models assign the randomised controlled trial and systematic reviews the highest grades, whilst expert opinions and non-analytical studies are at the lowest levels. Trials minimise bias and confounding through random allocation of participants to different trial arms and in some cases, the use of blinding. Non-analytical studies or expert opinions on the other hand are at high risk of biased from the author’s opinion or experience, with confounding factors not controlled for [110]. Thus the ideal of evidence based practice is to combine

'best evidence' from high quality randomised controlled trials with clinical expertise and the needs and wishes of patients to provide optimal care [97].

In summary, the process of evidence based practice involves several phases, a core part of which is critical appraisal of the evidence. Despite being open to misconceptions and abuses, the research hierarchy is the mainstay of evidence classification, which prioritises the randomised controlled trials due to trials minimising bias and confounding. We discuss the randomised controlled trial in detail in the following section.

### 2.3.4 The randomised controlled trial

According to Bulpitt, a randomised controlled trial (to which we refer hereonin as a 'trial') is:

*'A carefully and ethically designed experiment which includes the provision of adequate and appropriate controls by a process of randomisation, so that precisely framed questions can be asked'. [126] - pvii*

The basic principles of the trial are the comparison, under controlled conditions, of two or more interventions and the statistical analysis of the possibility of error [127]. The three features of a trial are: use of a control group; random allocation; and blinding. In health research, the term 'intervention' can refer to therapeutic treatment such as pharmacotherapy or psychological therapy, surgical procedures, medical devices, behavioural treatments, process-of-care changes and preventive care. Beyond clinical care, such as in health services research, 'intervention' may refer to any strategy or model being evaluated such as a training to enhance practitioner behaviour or initiatives to improve the recruitment of participants into trials. A 'control group' acts as the comparator to the intervention being evaluated and can include a traditional treatment, a placebo, or the exclusion of active treatment. Randomisation aims to introduce balance and reduce selection bias by distributing confounding variables equally amongst study arms [128], [129]. Blinding keeps trial participants, practitioners and outcome assessors unaware of the assigned intervention, so that they are not influenced by that knowledge and become biased. Trials can adopt single, double or triple blinding procedures [130].

While other research designs can detect associations between an intervention and outcome, they cannot exclude the possibility that the association was caused by an extraneous variable linked with both intervention and outcome [131]. Since trials, and in

particular meta-analyses of large trials are significantly more likely to be informative and less likely to misinform, they are the gold standard for evaluating the effectiveness of interventions [132]. Thus trials are necessary to improve health, healthcare efficiency and to minimise iatrogenic effects of treatments and are considered by the healthcare and scientific communities, including the Medical Research Council (MRC) as the most scientifically rigorous, unbiased way of comparing alternative interventions [133]–[135]. The elevation of the trial above other methods for generating evidence is on the basis that it stands:

*'Second to no other method in protecting the scientist and the reader against bias, confounding, and other generators of false conclusion' [67] - p315.*

This was also Archie Cochrane's view, who in 1972 asserted that the importance of the trial could not be exaggerated [71].

The importance attributed to trials has seen governments in the UK and other developed countries place them at the forefront of national health strategies. Internationally, different models emerged to deliver trials and other high quality research. In the USA the National Institutes of Health was established to drive forward the research agenda and currently spends approximately 10% of its budget on trials [136]. The Canadian Institutes of Health Research was established with one of its original strategic priority areas being trials [137]. Internationally, the WHO also places trials as a core of its research strategy, with a particular focus on the identification of trials using registry platforms to enhance access to trials and trial information for patients and families [138].

According to the UK Clinical Research Collaboration (UKCRC), a partnership of the main stakeholders that influence clinical research across the business, public and charitable sectors in the UK, spending on evaluating interventions to prevent disease and treat health conditions account for a minimum of 15% of total research expenditure [139]. In the UK, the strategy document 'Best research for best health' promoted research as the '*core business of the NHS*' on the basis that NHS care depended on evidence based research, and established research infrastructure and funding streams to support the delivery and quality of trials, including Clinical Research Networks (CRNs), Clinical Trials Units (CTUs), Health Technology Assessment (HTA) and a programme of Pragmatic Clinical Trials to address questions of direct relevance to the NHS [140]. In Scotland, a new health science program placing trials at its core complements that in the rest of the UK and aims to create a powerful internationally competitive programme [141].



Alongside publicly funded research, there has been a significant growth in industry sponsored trials for pharmacological interventions identified as potentially commercially profitable. In the USA, medical research funding from industry accounted for 58% of total research expenditure in 2012 [142]. In Europe, approximately 70% of medical research is industry funded, while globally industry sponsored research accounts for 61% of research funding [142]. Thus the majority of pharmacological intervention and medical device trials are sponsored by the commercial sector. Although commercial sponsorship of pharmacological trials raises issues of potential bias relating to financial conflicts of interest since favourable trial results present strong financial incentives for commercial companies [143], [144], there continues to be a growth in this sector, in particular a shift in companies outsourcing trial activities to increase their profit margins and better position themselves in the rapidly-changing healthcare environment [145]. This has given rise to Contract Research Organisations (CROs), service organisations that provide research and support services to pharmaceutical, biotechnological, and health companies [145]. In the UK and elsewhere, governments have welcomed and supported industry funded research as part of wider national research strategies to foster internationally competitive research environments [146][136], [140]. Such organisations have now become an integral part of the development of pharmacological interventions in the UK and internationally [145], [147].

However, despite their importance and the drive to undertake more trials, a cautionary note must be struck as trials are not a panacea, with their design, conduct, interpretation and reporting being open to a range of potential biases which can impact on their quality and validity. An influential early methodological study involving 33 meta-analyses from the Cochrane Pregnancy and Childbirth database identified inadequate trial methodology, particularly poor allocation concealment, which was associated with bias. The authors found odds ratios were exaggerated by 41% for inadequately concealed trials and by 30% for unclearly concealed trials [148]. Trials that were not double-blind also yielded larger estimates of effect, with odds ratios being exaggerated by 17% [148]. The authors called for readers to be wary of the pitfalls of poor allocation concealment and inadequate blinding, and for investigators to improve their design, execution, and reporting of trials [148].

Concerns about the quality of trials has led to the development of a number of component, scale and checklist quality assessment tools for reporting trials, which are used as proxy measures for methodologic quality [149][150][151]. In recent years, methodological work has led, for example, to reporting guidelines such as the Consolidated Standards of Reporting Trials (CONSORT) and its revisions [152]–[154] and extensions, such as for

cluster [155], [156] and pragmatic trials [157]. A Cochrane systematic review to determine whether the CONSORT statement improved the quality of reports of trials found consistent improvements, and indicated that adoption of CONSORT by journals may benefit the completeness of reporting of trials they publish [158]. This review also identified that despite relative improvements when CONSORT is endorsed by journals, the completeness of reporting of trials remains sub-optimal [158]. Others further suggest that focusing on reporting quality, a proxy for methodologic quality, may hide the real methodologic quality of trials, as some well-conducted trials may simply be reported badly [151][159]. Thus it has been suggested that a clear distinction should be made between methodologic quality and reporting quality of trials [151][159].

Depression and SMI trials face additional issues. Psychological treatments are difficult to standardise and disability is a difficult endpoint to measure [160]. Some have viewed the conventional trial with caution for being reductionist or unrepresentative of complex clinical practice [161], [162]. They argue that while trials are able to generate good evidence for pharmacotherapy (which tends to be a standardised and well-defined intervention), trials cannot generate good evidence for psychological, social, organisational or service level interventions, which tend to be complex in nature [161], [163]. Complex interventions “built up from a number of components, which may act both independently and interdependently”[164] - p2, and require an interactive development life-cycle [164]. The active ingredient in a complex intervention is not easily evident; many mental health interventions are multi-faceted or involve organisational restructuring as well as individual intervention [163], [165]. Furthermore, in a pragmatic trial of a psychological intervention for instance, there are usually a number of effects that can make the definition of the intervention difficult: treatment effects from the actual intervention protocol, therapist-specific effects, effects of the environment within which the treatment is delivered or other ancillary effects on the treatment [164]. Since the publication of the MRC Complex Intervention Framework an emphasis has been placed on trials in mental health as they can be adapted to evaluate complex health interventions and technologies, as well as to undertake process evaluations of treatments and outcome [165]. In fact, because complex interventions have known and unknown factors impacting on outcome, trials should be the primary point of call in mental health research:

*‘Only an adequately powered randomised design technique allows these variables to be properly controlled: those that are known and those that are not known.’*  
[165] - p270

Whilst some have contested this view for potentially neglecting the contribution that other well-established methodologies can make to mental health [161], it remains the dominant view.

Sample sizes in mental health trials are often small, making them susceptible to bias. One study has used two Cochrane databases to assess the changes in characteristics of 135 trials of psychotherapies for treating depression, the temporal changes in trial quality, and the quality differences among different therapeutic approaches [112]. In this study, positive changes in quantity and improvements in methodological quality at study-level over the past 50 years were reported. Despite these apparent improvements, the trials were still at high risk of bias as assessed by the Cochrane Risk of Bias tool [112]. Sample sizes were small, with the average number of participants randomized to each treatment arm: 13.9 for behavioural therapy, 26.6 for cognitive behavioural therapy, 20 for third wave cognitive behavioural therapy, 20.3 for humanistic therapy, 38.9 for integrative therapy, and 27.0 for psychodynamic therapy respectively. The risk of bias for researcher allegiance also increased in the last decade. Additionally, a limitation of this study was that the authors did not determine whether the observed changes in quality resulted from actual improvement in trial quality and/or from improved reporting [166]. Another study which focused on the content and quality of 2000 trials on the Cochrane Schizophrenia Group's Register over 50 years found that in general the trials were short (54% <6 weeks), small (mean number of patients 65), and poorly reported (64% had a quality score of  $\leq 2$ , with a maximum score of 5) [167]. The authors' were critical in their conclusion:

*'Half a century of studies of limited quality, duration, and clinical utility leave much scope for well planned, conducted, and reported trials.'* [167] - p1

An update on this study, which assessed the content and quality of 10,000 trials on the Cochrane Schizophrenia Group's Register over 60 years [168] found some improvements, in particular a large increase in the number of trials and an improvement in the accessibility of reports. However, trials remained small (median 60 people) and often employed new non-validated outcomes scales, with 2194 different scales employed, and every fifth trial introducing a new rating instrument [168]. It is clear therefore that the methodologic, conduct and reporting of trials have scope for improvement. There is also a need for larger trials, particularly those that are more patient-centred, with greater clinical utility and of direct value patients and their families.

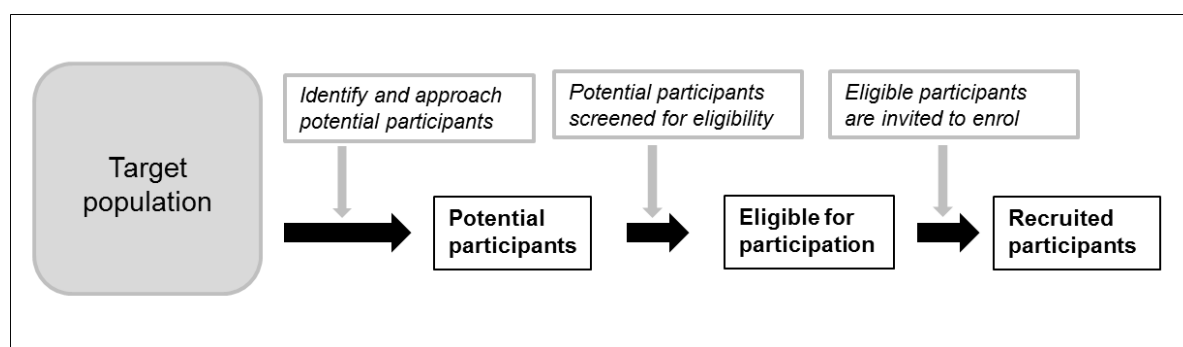
In summary, trials are currently the best available method for robustly evaluating clinical and methodological interventions, which has led to both policy and commercial motivations to conduct more trials. However, trials are only good as their methodological

conduct, with a range of limitations identified in the literature. There are additional complexities inherent in undertaking mental health trials. Moreover, the quality of current trials for depression and SMI is low, highlighting a need for better quality trials. In the next section we discuss the issue that slows the progress of most trials: recruitment.

## 2.4 The recruitment problem

In the promotion of trials as critical to health improvement, their numbers worldwide increased from 5633 in 2000 to 218315 in 2016 [169]. The International Standard Randomised Controlled Trial Number registry (ISRCTN), a primary clinical trial registry recognised by WHO and International Committee of Medical Journal Editors (ICMJE) currently has 14701 [170], while the Cochrane Central Register of Controlled Trials (CENTRAL) currently holds 403898 trials [171]. This high level of trial activity requires large numbers of patients and practitioners to participate, since for a trial to answer the research question it addresses, the sample size must be sufficiently large to contribute to its power, that is, to be able to detect the effect of an intervention if one exists [172]–[176]. This necessitates enrolling and retaining sufficient participants into each trial arm. This trial recruitment process can be described using both qualitative and quantitative data [177] and is outlined in Figure 2.

**Figure 2: The Trial enrolment process, adapted from Gross (2002) [177]**



During the trial design phase, trialists define the target population to be enrolled, based on the condition under study. For instance, in recruiting patients into a treatment trial for schizophrenia, trialists could target community mental health teams, psychiatric wards or specialist services such as early intervention in psychosis services. The trial team then identifies and approaches a subgroup of the target population, that is, the potential participants. Following identification, potential participants are screened for eligibility based on the trial's inclusion and exclusion criteria. Those that are eligible to participate

are then asked to provide their informed consent and enrolled into the trial, should they provide consent. In this process which involves a number of phases, any factor that impacts on any stage can potentially lead to poor recruitment.

The recruitment and retention of participants is often the most challenging and expensive aspect of a trial. Trialists often under-estimate the extent of the recruitment challenges when planning a trial, leading to what has been described as the cognitive bias of 'Lasagna's Law'[178] or 'Muench's Third Law' [179], which states that:

*'In order to be realistic, the number of cases promised in any clinical trial must be divided by a factor of at least ten.'* [179]- p1

An extension to these laws states that the percent yield of those screened or initially contacted is related to the restrictiveness of the trial protocol's eligibility criteria and patients' motivation to enrol [180].

Recruitment represents approximately 32% of total trial costs [181]; in the commercial sector globally, the cost of a trial per patient is approximately \$23600 (approximately £17246, calculated on 25<sup>th</sup> June 2016) [182]. For publicly funded trials, data suggests that in 2012 the mean cost of a trial per patient in the UK was approximately £7928, higher than in Spain (£5939), Germany (£5876), Italy (£5810), and Poland (£4614)[183]. Thus the UK performs particularly poorly in participant recruitment.

In a UK review of 114 trials funded by the Medical Research Council and the NIHR HTA in 2006, only 31% of all trials recruited successfully, 45% of trials recruited less than 80% of their target, and 53% were awarded an extension [184]. An update on this review found that while recruitment appears to have improved in recent years, publicly funded trials in the UK continue to struggle to recruit, and both time and financial extensions were requested in 45% of trials [185]. This review found no evidence of recruitment improving over the assessment period of 2002 to 2008. Internationally, a retrospective cohort of 1017 trials in Switzerland, Germany, and Canada found that the most frequent reason for trial discontinuation was poor recruitment; and that discontinuation was common for trials involving patients (28%), and less common for trials involving healthy volunteers (3%) [186]. This study also found that investigator-led trials (as opposed to industry sponsored trials) and those with smaller planned sample sizes were at higher risk of discontinuation due to poor recruitment [186]. In the commercial sector recruitment difficulties are also acute, with more than 80% of these trials failing to meet recruitment targets [187]. Thus achieving the appropriate levels of patient enrolment has been a significant obstacle to

evidence-based practice [188]. Such is the extent of the recruitment problem that it is the cause of policy, scientific and commercial concern [184], [189]–[192].

In sum, there is an increasing need for trial participants; however recruitment is the most resource intensive and consistently the most difficult aspect of a trial, and often leads to trial failure. We review issues specific to mental health trials in the next section.

#### **2.4.1 ‘Notoriously difficult’: Recruiting participants into mental health trials**

The exact magnitude of difficulties with recruiting patients into mental health trials is unknown as there is an absence of robust evidence in the literature. For example, limitations within the evidence base do not permit a clear interpretation of the barriers, moderators, and benefits involved in participation [193]. Despite this, there is a consensus that mental health trials experience particular challenges in recruiting participants; so much so that they have attained a level of notoriety [194]–[204]. Mental health trials often fail to recruit to target or fail altogether. Indeed, within the trials community there is a unique but substantial body of literature illustrating failure to recruit participants into mental health trials [195], [198], [200], [204]–[214][215]; this has not occurred in other health conditions. Even if mental health trials do not fail, recruitment has been described as ‘excruciatingly slow’ [216] and there appears to be an endemic problem of low statistical power caused by inadequate, small sample sizes; usually a result of failure to recruit and retain a sufficient number of participants [166]–[168], [217]. It is difficult to obtain an accurate picture of the causes of poor recruitment into these trials from existing literature, since inherent limitations means the body of literature mainly consists of:

1. Individual case studies of the recruitment experiences of trial teams, which offer post-hoc outlines of issues without them being subjected to formal, prospective evaluation
2. Retrospective descriptive studies without comparison groups
3. Studies which assess hypothetical participation or willingness to participate in trials
4. Qualitative studies which simply ask respondents to state their reasons for participation or non-participation, rather than in-depth exploration of the issues

It is important to highlight here that high-quality qualitative studies conducted alongside ongoing trials show that patients diagnosed with mental health problems can actually be

eager to participate in trials; and that when they do participate, they tend to evaluate their experiences of participation positively [218][219]–[222]. Furthermore, patients also endorse the feeling of hope associated with research participation [223][222]. Thus on the whole, patients appear to want to enrol in mental health trials.

However, barriers to the recruitment of participants into trials have been widely reported for mental health trials, as well as for the conduct of trials more generally. This forms the largest body of the recruitment literature, with 11 systematic reviews focusing just on this issue to date [203], [224]–[228]. The earliest recruitment systematic review on the topic identified a range of barriers related to both patients and clinicians [224]. One key limitation of this review is that it did not undertake quality assessment of the included studies. Another systematic review addressed the topic of improving the recruitment activity of clinicians in trials [229]. In Table 3 we outline some of the barriers that have been identified from two systematic reviews that are thought to affect all trials [224] [229].

**Table 3: Barriers to participation, adapted from Ross et.al. (1999) [224] and Fletcher et.al. (2012) [229]**

<b>Barriers to clinician participation</b>	<b>Barriers to Patient Participation</b>	<b>Clinician as barrier to patient participation</b>
Time constraints	Additional procedures and appointments	Protocol causing problem with recruitment
Lack of staff and training	Travel problems and costs	Clinician concerns about information provision to patients
Worry about the impact on doctor-patient relationship	Patient preferences for a particular treatment (or no treatment)	Clinician influencing patient decision not to join
Concern for patients	Worry about uncertainty of treatment or trials	Difficulty communicating trial methods
Loss of professional autonomy	Patient concerns about information and consent	Ease of understanding and carrying out RCT methods
Difficulty with the consent procedure	Protocol causing problem with recruitment	clinical workload associated with trial participation
Lack of rewards and recognition; financial and otherwise	Clinician concerns about information provision to patients	Patient-clinician relationship
Insufficiently interesting question	Clinician influencing patient decision not to join	Effect on patients
Effect on clinical practice	Mistrust	
	Competing demands	
	Unintended outcomes	
	Lack of access to information	
	Stigma	
	Inadequate health insurance coverage	
Immigration status		

From these systematic reviews, there appear to be three key recruitment barrier domains in trials across all disease areas, relating to:

- 1) Clinician participation
- 2) Patient participation
- 3) Clinician as barrier to patient participation.

For concerns around clinicians, there appears to be difficulties around resource, capacity, skills and lack of incentives, alongside professional unease such as concern for the patient and the impact of the trial on the relationship with their patients. For patients, the concerns seem to be around: inconvenience and access; preferences and concerns around treatments and outcomes; clinician influence; protocol-related issues; and issues around trust and stigma.



Currently, no reviews have looked specifically at the issues of recruiting participants into depression and/or SMI trials. In addition to the barriers in Table 4 however, two systematic reviews focusing on recruiting participants into mental health *research* more generally have identified additional barriers to enrolling people with a diagnosis of mental illness. A review by Woodall *et. al.* (2011) looked at participation in mental health research and specific gender, ethnicity and age barriers [230]; whilst Brown *et. al.* (2014) reviewed barriers to recruiting ethnic minorities to mental health research [231]. As these reviews do not specifically focus on trials, where issues around randomisation might play a prominent role, it is unclear to what extent these issues are accurately reflective of mental health trials. The reviews also have a number of limitations. For example, Woodall’s review [232] had a limited search strategy focusing exclusively on three electronic databases (Medline, PsychInfo and EMBASE), with no searches of other sources. This means that there was a high probability that some relevant studies may have been omitted. Studies were also not evaluated for methodological quality in this review. However, these reviews are the only ones in the body of literature that address participation issues in mental health research. Thus we must be cautious about translating the data from these reviews to mental health trials. In Table 4, we highlight the specific barriers identified around participation in mental health research (as opposed to issues identified as barriers relating to ethnicity, such as immigration status; or general issues that relate to all trials, such as travel problems and costs).

**Table 4: Barriers to mental health trial participation, adapted from Woodall 2010 [233] and Brown 2014 [231]**

<b>Barriers</b>
Stigma of mental illness
Acceptance of illness
Help-seeking/negative attitude to psychotherapy
Underutilization of mental health services
Severity of illness
Fear of relapse or exacerbating illness
Psychopathology/substance misuse
Trust, Distrust and/or fear of research

From Table 5, barriers to participation in mental health research are around stigma; acceptance of illness; trust; help seeking and attitudes to therapy; fear of relapse or exacerbation of illness; psychopathology. We discuss these in turn. Some of the barriers are related, in which case they are grouped and discussed together.

#### ***2.4.1.1 Stigma***

Stigmatization and discrimination of individuals with mental illness is a worldwide and pervasive problem that can occur inside and outside psychiatric institutions with significant negative consequences [234], [235][236][53], [237]. Individuals experiencing mental illness may fear the repercussions of revealing their condition to their GP, family, friends and employers. The negative effects of psychiatric labelling can also deter people from accessing treatment and/or services and to fully participate once they have access [236], [238]. Clinicians can also sometimes resist formally diagnosing patients in an effort to minimise the negative impact of stigma [239], which can impact on research.

#### ***2.4.1.2 Acceptance of illness, help seeking/poor negative attitudes to psychotherapy, and under-utilisation of mental health services***

Patients (and their families) are sometimes unable or unwilling to accept the mental illness diagnosis [240]. For instance, patients are often reluctant to accept the diagnosis of psychosis [240]–[243]. Furthermore, poor public understanding of psychiatric treatment means that psychiatric treatment can unduly be perceived as harmful, limiting willingness to access such interventions [244]. As discussed earlier, the incidence and prevalence of mental disorders differ by age, gender and ethnicity. In primary care, clinicians are less likely to detect mental health problems in younger patients, in men, and in BME patients; possibly because they are less likely to seek help for mental health problems [245], [246]. Differences in pathways into mental health care means, for example, that BME groups are more likely to have contact with mental health services via the criminal justice system and to be compulsorily admitted to psychiatric hospitals [247]–[249]. When people do present to services, mental illness can also often go unrecognised by healthcare professionals, meaning that effective diagnosis can become a challenge [250]–[253]. All of this can significantly affect trial recruitment, with women and BME patients being particularly under-represented [254].

### ***2.4.1.3 Severity of illness/fear of relapse or exacerbating illness***

Mental illness can adversely impact on the person's capacity, ability and motivation to participate in research [255], [256]. Severe mental illness may inhibit an individual's understanding and appreciation of the risks involved in research or from assessing potential risks against potential benefits [242]. While the presence of a psychotic disorder does not necessarily indicate impaired capacity, people with psychotic disorders may experience delusions, apathy, lack of insight, and impaired memory and mental flexibility; all of which can contribute to impaired decision-making capacity [257], [258][259], [260]. Likewise, severe presentation of depression, even without psychotic symptoms, can impair concentration and abstract reasoning capability, and can also be associated with nihilism and a decrease in concern for personal well-being [261]–[264]. Recruitment rates may be lower in trials involving some mental health disorders (such as acute mania, first-episode psychosis) than in trials involving other conditions (such as anxiety) [232].

### ***2.4.1.4 Psychopathology/substance misuse***

Patients with mental illness experience a considerable degree of comorbidity [265]–[268]. Mental illness and comorbid substance misuse, otherwise known as 'dual diagnosis' is common [269]. The consequences of dual diagnosis include poor medication compliance, physical comorbidities and poor health, poor self-care, increased suicide risk or aggression, increased sexually risky behaviour, and possible imprisonment [270]. They are therefore less likely to engage with services and more likely to be excluded from trials, limiting the generalisability of many clinical trials in mental health [271]. High exclusion rates also means that trialists screen large numbers of patients to achieve recruitment goals, increasing recruitment effort and reducing generalisability [272].

### ***2.4.1.5 Trust, Distrust and/or fear of research***

Studies have found that often, declining to participate in research was based on a fear of not knowing what was involved in the research, concerns about confidentiality of information and concerns by patients that their personal information may be misused [273]. For African Americans, mistrust as a barrier often stems from mistrust of research more generally, which can be linked to the legacy of unethical research conducted by researchers, particularly the Tuskegee syphilis study [274], [275]. An additional barrier is related to suspicion about mental health services and legal documents, with a perception

that encounters with psychiatrists will often be followed by involuntary hospitalisation [275][275].

In summary, for mental health trials recruitment difficulties are more severe than for trials in general. There are a range of additional barriers acting to impede recruitment into mental health research. Translating findings of systematic reviews focusing on research studies for trials must be made with caution, in the absence of specific evidence for depression and SMI trials. In the next section we discuss the impact of the recruitment problem.

## **2.5 Impacts and implications of the recruitment problem**

Failure to recruit and retain participants can significantly affect trials in a number of ways. It can lead to reduced sample size, which reduces the power of a trial. Inadequately powered trials are at increased risk of type II error - that is, reporting clinically relevant effects to be statistically non-significant [276]. This may inhibit the development of reliable evidence and lead to delays in the adoption of effective interventions [184]. Delayed recruitment prolongs uncertainty about the effectiveness of treatment and extends exposure to ineffective or dangerous treatment [277]. It also raises ethical concerns when participants are exposed to an intervention which at the completion of the trial is still uncertain whether more harm than good has been caused [278].

Recruitment difficulties can disrupt a trial's project timeline and increase research costs as well as workload [279]-[281]. A common approach is to extend the length of the trial [184], [185], which has significant cost implications and is something that funders - both public and commercial - are increasingly unwilling to bear [190], [191], [282], [283]. More resources being diverted to extend recruitment within existing trials may mean less money being invested in new trials, resulting in fewer trials being undertaken [184].

Poor recruitment into a trial may mean that findings may not be representative of the relevant clinical population, meaning the study lacks external validity. The external validity of trials hinges on the assumption that research participants represent populations from which they are drawn; that findings are generalisable [284], [285]. Poor recruitment may also mean that trials are often unable to access sufficient numbers of certain population groups; particularly women, children, the elderly, those with multi-

morbidities, ethnic minorities, meaning again that they have limited external validity [286]–[290].

Thus poor recruitment has a number of important impacts and implications including scientific, ethical and economic. We next consider efforts undertaken to date to address the recruitment problem.

## **2.6 Efforts to address the recruitment problem at the policy level**

### **2.6.1 Introduction**

In this section we provide an overview of:

- Policy efforts to improve the recruitment problem
- Patient and public involvement in research (PPIR), in particular critically assessing the following:
  - The complexities around its conceptualisation and definition
  - Its potential benefits as well as its limitations
  - The need for robust evaluations of the impact of PPIR

### **2.6.2 The UK and US policy efforts: divergent solutions**

In the UK and elsewhere, policy concerns that trials are not meeting their planned recruitment targets has led to a drive to increase the number of people who enrol in trials [140], [141], [291]. In the UK and the US, the two countries with the highest levels of recruitment activity, different paths were pursued to address the recruitment problem. The US National Institutes of Health (NIH) in the 1993 Revitalisation Act mandated the inclusion of racial and ethnic minorities and other underserved groups, in particular African Americans, Latinos, Native American and women as participants in their funded trials [292], [293] [294]. This pressure to enrol underserved groups in trials gave rise to what Epstein coined ‘recruitmentology’, to refer to:

*‘An empirical body of studies scientifically evaluating the efficacy of various social, cultural, psychological, technological, and economic means of convincing people (especially members of ‘hard-to-recruit populations’) that they want to become, and remain, human subjects.’ [295] - p801.*

Under the pressure of the NIH mandate, Epstein argues that the task of recruitment transformed into an applied science which presupposes and generates knowledge about

the characteristics of medically underserved communities [295]. Thus the US focus on addressing the recruitment problem via the NIH mandate attempted to recruit racially diverse participants, conceptualise race while simultaneously grappling with problems of trust, collective memory and participation [295]. This emerged from a long history of women and minorities being ignored or abused by medical research in the USA [296]. Among such abuses was the US Public Health Service Tuskegee Study, in which more than 400 African American men with syphilis were enrolled into a study investigating syphilis but were not informed of the purpose of the study; that they had the disease; nor provided with treatment, even when treatment became available, a consequence of which was more than 100 of the men dying from syphilis or its complications [297]. This surge in recruitment research following the NIH mandate highlighted issues around inequality, representation and health care access; however it has largely contextualised barriers to participation for underserved populations through frameworks of cultural and therapeutic misconceptions, poor health literacy, mistrust in the health care system, or fears related to experimentation [298]. This is evidenced in systematic reviews of the trial recruitment literature led from the USA which exclusively focus on vulnerable and under-represented populations [225], [299]–[302].

In the UK, a parallel but contrasting movement occurred where the ambition of the NIHR was broader and aimed to see '*more patients and health professionals participating in health research*' [140]- p6. The new infrastructure of CRNs and CTUs and support staff such as Clinical Studies Officers and Research Nurses aimed to support the delivery of trials and to identify efficiently and comprehensively patients eligible, in order to facilitate recruitment into trials [140]. This also established the principle of engaging professionals and patients with research, particularly the concept that patients using the NHS would routinely be offered opportunities to take part in research [140][303]. Currently the NIHR invests £645 million, approximately 62% of its total annual budget on infrastructure [304]. This investment has seen the NIHR recruit three million NHS patients in England into research in the past six years through its CRNs [304].

This infrastructure support means that trialists can recruit from a wider range of sites and can therefore increase the numbers of *absolute* patients recruited. However, the *proportion* of patients enrolling into trials remains low [305]. While the literature around recruitment rates is sparse, a rapid review of prevention and intervention trials focusing on metformin and exercise found that randomisation rate as a percentage of those approached was 2.6% for metformin prevention trials and 36.4% for metformin treatment trials. For exercise prevention trials the randomisation rate was 1.9% while the randomisation rate for

exercise treatment trials was 16.4% [305]. Low uptake in recruitment limits the representativeness of the sample and reduces the external validity of a trial [285]; is inefficient thus requires more resources [306]; and may introduce volunteer bias [307]. Thus there is a need to develop recruitment strategies with the capacity to increase both the *absolute* numbers of patients entering mental health trials, as well as the *proportion* of potentially eligible individuals participating [307].

To recapitulate, governments of the two countries with the highest recruitment activities took different approaches to address the recruitment problem: in the US there was the mandating of the inclusion of under-represented people in trials; whilst in the UK policy focused on building the research infrastructure and capacity. Whilst some advances have been made in terms of absolute numbers, the proportion of people recruited into trials remains low. The next section focuses on another policy that can impact on recruitment and is common to the UK, US and other developed nations; that of PPIR.

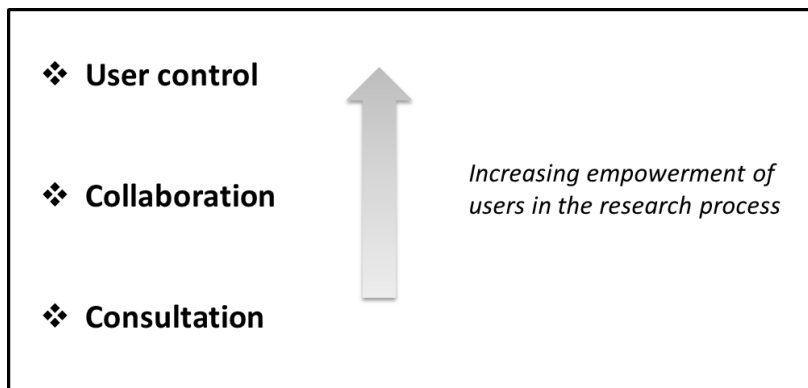
### **2.6.3 ‘Nothing about me, without me’: patient and public involvement in research**

PPIR is about empowering individuals and communities to play a greater role in shaping health and research to maximise benefits to both patients and society [308]. Also referred to as ‘user involvement’, ‘lay involvement’, ‘consumer involvement’, or ‘stakeholder participation’, PPIR has been defined by INVOLVE, the PPIR arm of the NIHR as:

*‘Research being carried out ‘with’ or ‘by’ members of the public rather than ‘to’, ‘about’ or ‘for’ them’. (Emphasis in original) [309] - p1*

This is the definition we will use in this thesis and is the definition used in the NHS, and that which researchers undertaking publicly funded trials in the UK most frequently use. This definition of PPIR is broad, and involves individual patients, all groups who represent patients, as well as national and international consumer organisations taking roles in the development, conduct and governance of research [310]–[312]. In mental health research, PPIR can refer to consultation or collaboration with patients on activities such as selecting which outcomes to measure, designing recruitment materials and presenting findings; or it can refer to user control, where patients lead the research themselves, for example, to understand the needs of patients [313] or to explore perceptions of user involvement [314]. Figure 3 outlines these ‘levels of involvement’, which is adapted from the works of Arnstein (1969) and Feingold (1977) [310], [315].

**Figure 3: Levels of involvement, adapted from Arnstein (1969) [310] and Feingold (1977)[315]**



It is necessary for us to distinguish the term ‘involvement’ from ‘engagement’, which is the sharing of information and knowledge about research by professionals, such as through newspapers or other media; and ‘involvement’ from ‘participation’, which is the recruitment of patients or others to enrol in trials or other research [309]. PPIR is well-established as public policy in the UK and other developed countries and is increasingly mandated for publicly-funded trials [316]–[319]. For example, in applying for funding with the NIHR, researchers are expected to ‘*actively involve the public in their research*’ [320] - pl and are requested to outline their PPIR plans at both the outline and full application stages. Where researchers plan no PPIR, they are required to provide a justification. The Chief Medical Officer for England, Professor Davies, has underlined the policy rationale for mandating PPIR:

*‘No matter how complicated the research, or how brilliant the researcher, patients and the public always offer unique, invaluable insights. Their advice when designing, implementing and evaluating research invariably makes studies more effective, more credible and often more cost effective.’* [321] - Foreword

Some have argued that the policy in the UK to embed PPIR has its basis in prevailing notions of accountability rather than evidence-based practice [312]. However, the argument by Professor Davies appears to combine the policy argument for researchers to undertake PPIR with the epistemological and the methodological arguments. The policy argument mandates the inclusion PPIR for researchers to obtain funding; the epistemological argument proffers that patients have better knowledge of their own health conditions than researchers who do not have first-hand experience; and the methodological argument posits that PPIR produces ‘better’ patient-focused research by offering valuable insights into its prioritisation, design, implementation and evaluation,



making trials more effective and credible [322], [323]. Thus it is argued that PPIR positively impacts on the research itself but also has positive impacts on researchers undertaking PPIR, research participants as well as the wider community [323]. There is a further, moral argument for PPIR, which suggests that involvement is the right of citizens, thus they should have a voice in publicly funded research; here the phrase '*nothing about me, without me*' is frequently cited [324][325]. According to the moral argument, the individual has a right to be fully involved about any health care or research intervention being done 'to' them as a person. A key feature of this moral argument is that PPIR is justified regardless of any practical benefits it might incur. This argument also sees PPIR as the right of the individual citizen, who it is thought, should have a voice in the public services that they pay their taxes to fund [326].

It is widely acknowledged that the potential benefits of PPIR are considerable [322], [323], although the evidence base is complex. A systematic review of the conceptualisation, measurement, impact and outcomes of PPIR identified a range of benefits for service users, researchers and communities, which improved the quality and appropriateness of research [327]. Impacts occurred at all stages of research, including:

- The development of user-focused research objectives
- Development of user-relevant research questions
- Development of user-friendly information
- Questionnaires and interview schedules
- User-focused interpretation of data
- Enhanced implementation and dissemination of study results [327].

Service users also felt empowered and valued, as well as gaining in confidence and life skills. Researchers gained increased understanding and insight into their research area, along with respect and a good rapport with the community. The community involved in research moreover became more aware and knowledgeable about their condition [328].

There is evidence from systematic reviews that PPIR can help to build important links with the community and assist with accessing participants; with improving response and recruitment rates; with development of greater empathy with research participants; and better informed consent based on more informed participants [327][329], [330] [331]. There is moderate quality evidence that involving consumers in the development of patient information material results in material that is more relevant, readable and understandable to patients, without affecting their anxiety. This PPIR informed material also improved patients' knowledge [331]. For mental health trials, an observational study

involving 374 trials on the UK Mental Health Research Network database found that trials with more PPIR were associated with an increased likelihood of achieving their recruitment targets [332]. A poll of 1295 British adults commissioned by the Health Research Authority (HRA) found that 44% of respondents thought that trials using PPIR would increase their confidence and trust in a trial [333], [334]. An additional 49% of respondents stated they were not sure either way, although very few thought PPIR would reduce their confidence. The authors issued a press release widely advertising that:

*'If health researchers communicate the fact that patients and the public have been involved in the design of their research when approaching potential study participants, it might help to boost recruitment'* [333], [334].

To achieve these effects, it would be necessary for trialists to directly advertise that PPIR to patients; however, current recruitment practice does not routinely advertise PPIR to potential participants at the point of enrolment [308], [335]. In the era of evidence based practice, a clear effectiveness case can be made for robustly evaluating this recommendation to determine whether directly advertising PPIR to potential participants positively impacts on recruitment, for which participants, and in what contexts. The HRA recommendation is based on a survey of members of the public, who were asked to make a hypothetical decision. An ethical case can also be made about determining whether advertising PPIR to potential participants may be harmful, since a systematic review has identified some negative impacts of PPIR across all stages of the research process [308]. Further, an economic case can be made to evaluate whether advertising PPIR serves as a good use of resources [308].

There are questions about whether PPIR should be about more accountability or about better research however, alongside uncertainty about why and how to do involvement well and evaluate its impact [336]. This includes how to identify, involve and support a diverse range of individuals, in ways that allow them to work in partnership to genuinely influence decision-making [336]. There are also the challenges of implementing PPIR, which is complex: studies of its implementation tend to yield suboptimal evidence of impact [337][329][336]. Moreover, PPIR has not been universally welcomed, with some professionals feeling threatened by the active involvement of patients and other stakeholders [322][336]. Systematic reviews [328][327][329] [330] have identified specific challenges to implementing PPIR, alongside some negative impacts. These can include some service users feeling under-prepared and therefore unable to contribute to the research, whilst others have felt overburdened with the work involved, not listened to, frustrated and marginalised. Researchers doing PPIR have also reported difficulties

undertaking PPIR in meaningful ways due to resource constraints. Practical aspects of planning, collaborating with users and managing the PPIR could be both time consuming and costly. Incorporating user views into the research agenda may lead to divergence from scientific methods and cause ethical dilemmas during the protocol design stage. Recruiting hard-to-reach groups such as Black and Minority Ethnic (BME) groups, older people, people with disabilities can also prove difficult [338]. This, it has been argued, leads to disappointing outcomes which results criticisms of PPIR for being exclusive and tokenistic [339][329] [330].

The principles underlying PPIR is also mired in confusion and contradiction, including lack of clarity about scope and purpose and limited conceptual and empirical work to underpin policy and practice [340]. The underlying rationale for doing PPIR is rarely made explicit [322]. PPIR is also poorly defined, theorised and conceptualised [341], [342], with a range of terms and definitions used to describe very similar things. The definition used by INVOLVE itself is contentious, with some arguing that the term 'public' is confusing; while others argue that the term 'patient' fails to capture the 'expert' nature of the experiential knowledge brought specifically by patients [343]. Conversely, the term 'patient', with its passive connotation has also been criticised [344]. PPIR has been often been conceptualised as a 'complex intervention' where context and process are important underpinning factors forming the PPIR 'architecture' [308][164][345], [346]. Recently however, others have argued that the conceptualisation of PPIR as a complex intervention has derailed the development of an evidence base [347], yet alternative conceptualisations remain to be tested.

This confusion and contradiction constrain the generation and reporting of evidence for PPIR, which has been described as weak [308], [329], [330][348][327]. Efforts to develop a solid evidence base on PPIR are limited by the non-standard and non-empirical nature of much of the literature [349]. Questions have been raised regarding whether PPIR should even be assessed for impact, given moral arguments about its intrinsic value [345]. An absence of robust instruments capable of capturing or measuring PPIR impact, has led to a dearth of formal evaluation of impact [308]. Although some high quality qualitative studies of the impact of PPIR exist, most of the evidence on PPIR consist of case study reflections of PPIR, cross-sectional studies reporting individual or organisational views with relatively little critical evaluation [308], [329], [330][350]. Thus quantitative evidence around its impact is sparse, and that which exists is of poor quality and lacking in rigour [351] [327]. For instance, outcomes of PPIR are typically reported using narrative description, which is usually too brief to provide a full understanding of impact [308].

There is therefore a need to assess the effectiveness, cost effectiveness and ethical impacts of PPIR using high-quality methodological research [328], [337], [340], [351]–[354] [355].

To summarise, different efforts by governments has led to divergent attempts to address the problem of participant recruitment. However, a common approach is the use of PPIR, which is deeply embedded within publicly funded trials in the UK and elsewhere with a top-level mandate. Despite its prevalence, there is little rigorous evaluation of the impact of PPIR, predominantly due to complexities around its conceptualisation and implementation. Thus much about the impact and harms of PPIR remains unknown. There is a need for rigorous evaluation of the impact of PPIR; one clear way to add to the evidence base would be to evaluate the recommendation by the HRA for trialists to advertise PPIR to potential participants.

#### **2.6.4 Moving from the ‘art of recruitment’ to a ‘science of recruitment’**

*‘There is a peculiar paradox that exists in trial execution - we perform clinical trials to generate evidence to improve patient outcomes; however, we conduct clinical trials like anecdotal medicine: (1) we do what we think works; (2) we rely on experience and judgement and (3) limited data to support best practices.’* Monica Shah, quoted in - , [356]

Despite trials being critical to evidence based practice, the methods and infrastructure for undertaking them are largely evidence free [4], [357]. Inefficient conduct of research is wasteful, especially if it results in poor recruitment and retention of participants in well-designed studies addressing important questions [4].

It is not clear why some trials recruit well while other trials do not [358][185]. Within individual trials investigators adopt many strategies in a bid to improve recruitment [359]. However, it is difficult to determine the effects of these interventions without them being subjected to robust methodological assessment. Indeed, such idiosyncratic and methodologically un-tested recruitment methods have led to some observing that that recruitment success often seems to be a result of luck rather than anything else [360].

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 [197], [361], [362]. The importance of recruitment and retention to trials, clinical practice and policy received relatively little attention [363]. The use of a myriad of recruitment methods without systematic evaluation results in replication of effort and an absence of shared learning. As a consequence, very few of the proposed

strategies for improving recruitment have evidence of effectiveness, leading to the conclusion that:

*'Recruiting for science has not been underpinned by a science of recruitment'* [364]  
- p393.

Bower *et. al.* (2009) [365] proposed that three key areas of improving recruitment should form the focus of future work: developing a repository of evidence-based techniques and methods which can be introduced by trial teams; developing the infrastructure to support recruitment; and increasing public engagement with research, to improve participation by both clinicians and patients [365]. In other recommendations for reducing waste in research, the need for trialists to increase the efficiency of recruitment and retention were highlighted as being key priorities [4].

A large number of proposed solutions to address recruitment difficulties have been reported in the literature [190], [366]–[370]. A Cochrane systematic review identified 46 recruitment interventions that had been tested in real-world randomised or quasi randomised controlled trials. However, only three of these interventions had evidence of effectiveness in real trials: telephone reminders to non-respondents; use of opt-out rather than opt-in procedures for contacting potential participants; and open designs where participants knew which treatment they were receiving in the trial [370]. The effect sizes are presented in Table 5.

**Table 5: Recruitment interventions identified in systematic reviews as having evidence of effectiveness**

Intervention	Effect size	Original Paper (s)
Telephone reminders to non-respondents following a written invitation to take part in a trial	RR 1.66, 95% CI 1.03 to 2.46	Nystuen & Hagen (2004) [371]
Use of opt-out, rather than opt-in, procedures for contacting potential trial participants	RR 1.39 95% CI 1.06 to 1.84	Trevena <i>et. al.</i> (2006) [372]
Open designs where participants know which treatment they are receiving in the trial	RR 1.25 95% CI 1.09 to 1.36	Avenell <i>et. al.</i> (2004) [373]

Only one of these interventions involved some patients with depression [371]: this study by Nystuen *et al.* (2004) was a trial of a structured telephone follow-up versus no telephone follow-up to a recruitment letter into a community-based trial. 703 employees who were sick-listed for more than 7 weeks due to psychological problems or musculoskeletal pain were eligible. The employees received a written invitation to participate in a study comparing standard treatments with a solution-focused follow-up, and were randomly allocated to an intervention or control group. Those who did not respond within 2 weeks received either 'no telephone reminder' (n = 242) or 'attempted telephone reminder' (n = 256). The outcome was enrolment to the trial. Whilst an *intention to recruit* analysis revealed no significant differences between the groups, an *intention to phone* analysis among non-responders revealed significant differences between 'no reminder' (recruited 4.5%) and 'attempted telephone reminder' (recruited 12.1%) ( $P = .003$ , odds ratio 2.89, 95% confidence interval 1.42–5.90). An analysis of *numbers needed to phone* showed that to recruit one more person in this group of non-responders, 13 persons needed to be phoned (95% CI = 8–33).

The two systematic reviews focusing on barriers to participation in mental health research identified some potential solutions to the recruitment barriers [231], [232], [374]. However, the reviews found no studies that systematically tested the effectiveness of the proposed solutions:

*'Making it difficult to attribute successful recruitment to a particular method'*  
[232] -p7.

Many other systematic reviews of recruitment interventions include studies that randomise patients to hypothetical trials; to trials of recruitment to non-randomised studies (e.g., case control studies); or to studies with no control groups [229], [232], [375]–[377]. Very often the methodological rigour of the studies is poor, with little or no statistical reporting, making it very difficult to determine the effectiveness of such interventions. All systematic reviews on the topic have called for an urgent need for systematically evaluated recruitment strategies, particularly those tested in trials [190], [229], [232], [291], [358], [366]–[370], [375], [378], [379].

#### ***2.6.4.1 The need to develop and evaluate a theory-informed recruitment intervention for mental health trials***

Recruitment is now highlighted as the methodological research priority for trialists in the UK [380]. More evidence for recruitment strategies is urgently required. One way of

improving recruitment is to develop a repository of evidence-based techniques and methods, which can be introduced by research teams [188], [381]. In a recent Cochrane review, the authors concluded:

*'Trialists should include evaluations of their recruitment strategies in their trials, and funders should support this because the number of interventions that have been rigorously evaluated in the context of a real trial is low.'* [370] p-13

Evaluating recruitment strategies by embedding them within a real, 'host' trial is considered the most rigorous method of evaluating recruitment strategies [367], [370], [382]. Embedding across ongoing host trials increases the generalisability of findings. The concept of embedded trials is viewed positively by stakeholder groups such as principal investigators, research managers, ethical committee chairs and funder representatives [383]. However, some potential challenges to embedded trials have been highlighted, such as: increased management burden for host studies; compatibility between the host and the embedded trial; and the impact of the embedded trial on host trial design and relationships with collaborators [383]. For embedded recruitment trials, there were concerns that host investigators might have strong preferences, limiting the embedded trial investigators' control over their research. The Systematic Techniques for Assisting Recruitment to Trials (START) project seeks to develop and test recruitment interventions by embedding trials across actively recruiting host trials and evaluating their impact on recruitment [384].

In developing recruitment interventions, it is important to consider the underlying theoretical models that might help to explain any mechanism of effect. Much of the current research on trial recruitment is not grounded in robust theory to guide intervention development, leading to trial recruitment research being described as atheoretical [188], [385], [386]. However, there are a range of theories that can be drawn on to inform the development and evaluation of future recruitment interventions, although the literature is sparse where this relates to trial recruitment. In Table 6 we provide an overview of potential theories and models that can be adopted for trial recruitment research. We have categorised these into economic, behavioural-based and community-based theories and models.

**Table 6: Theories and models pertaining to recruitment**

<b>Economic</b>	<b>Behavioural-based</b>	<b>Community-based</b>
Social validation [387], [388]	Theory of planned behaviour [389], [390]	Social marketing [391]
The business model [392]	Protection motivation theory [393]	The matching model [394]
Marketing model [395]	Behavioural change theory [396]	Community-driven model [397]
Commodity theory [398], [399]	Transtheoretical model [400]	Peplau's theory of interpersonal relations [401], [402]
Economic model [403]		

The most well-known models recently used in UK trials are the Business Model [392], the theory of planned behaviour [389], [390] and social validation [387], [388].

The business model uses insights from marketing theory and suggests that trials can be regarded as businesses, with similar dimensions, including 'marketing', 'sales' and 'ongoing client management' [184][392]. The model aims to inform and structure the entire management of a trial, and is fundamentally an ongoing assessment of the sales and marketing capability of a trial. By improving trial processes, it is argued that participant recruitment can be improved. The model can be applied in various ways to assist the conduct of trials, including: to guide recruitment planning; as a diagnostic tool if trials experience difficulties, and; to audit the progress of trials. The model has four domains: (1) Building Brand Values (2) Product and Market Planning (3) Making the Sale and (4) Maintaining Engagement. Each of the four domains has three components. The twelve components are considered as links in a chain; if one link is underdeveloped then the entire chain is compromised. This model is being actively developed, and to date has been applied in a number of successful trials as case studies, demonstrating promising results [291], [392], [404], [405].

Another potentially useful theory is the Theory of Planned Behaviour (TPB), which is an extension of the Theory of Reasoned Action [406], [407]. The TPA provides a relatively simple basis for identifying where and how to target individual's *behavioural* change attempts. The TPB is a predictive and motivational model, and combines 'attitude' (that is, whether the person is in favour of doing it); 'subjective norm' (how much the person feels social pressure to do it); and 'perceived behavioural control' (whether the person feels in control of the action) to form intentions that predict behavioural outcomes. A widely



utilised model in psychology, the TPB has been used to examine cancer trial participation [408]. A meta-analysis found evidence of the predictive utility of the model [409].

A corollary of social comparison theory [387], 'social validation' posits that people frequently use the beliefs, attitudes, and actions of similar others as standards of comparison for their own beliefs, attitudes, and actions. This therefore suggests that people may be more willing to comply with a request to enrol in a trial if they believe that others are already engaged in a trial [387], [388], [399]. This has been used alongside other marketing strategies in the UK [410], as well as to encourage survey participation [388]. This theory may be particularly relevant to the inferred impact of PPIR boosting recruitment suggested by the HRA, where the involvement of patients in research was found to increase respondents' reported confidence in research.

## **Summary**

Mental illness is common worldwide, with significant consequences for the individual and for society. There is a need to develop new, well-evaluated and effective interventions to alleviate mental health problems. However, the evaluation of such interventions in rigorous trials is often stymied by inadequate recruitment of research participants, leading to both policy and scientific concerns. There are many barriers to successful recruitment of participants into mental health trials. Strategies to improve recruitment are rarely evidence based, so it is unclear what effects these strategies have on participant recruitment. There is therefore a need for evidence-based recruitment strategies to enable mental health trials to recruit adequate samples on time and within budget. The HRA has made a recommendation for trialists to advertise the PPIR used in their trials to potential participants, which they argue might help boost recruitment. An effectiveness, ethical and economic case can be made for a robust evaluation of this recommendation.

In the next chapter we describe the thesis methodology and methods.

## **Chapter 3: Thesis methodology and methods**

---

### **3.1 Chapter overview**

In Chapters 1 and 2 we provided an overview of the thesis and demonstrated that there is a need to develop and robustly evaluate interventions aimed at improving recruitment into mental health trials. This chapter presents an overview of the general methodology employed in this thesis, along with a justification of the methods used. In this chapter we will discuss the following:

1. Research paradigms and their methodology
2. The rationale for using mixed methods in this thesis
3. The MRC framework for developing and evaluating complex interventions and how this informed the objectives of the thesis
4. The methods used in the three component studies, including rationale, participants and sampling, data analysis, and strengths and limitations

### **3.2 Choosing research methods: by choice or by chance?**

The choice of research methods, and the way in which they are implemented is largely determined by the research question, as different research methods are appropriate for addressing different research questions [411], [412]. There are other reasons however why researchers adopt certain methods; this includes funding, politics, resources, the underlying philosophies of science and the disciplinary background as well as worldview of the researcher [412], [413]. Indeed, some contend that there is an interplay of social, political and scientific forces which influence what type of evidence is generated and what is taken notice of and used [414].

#### **3.2.1 Through a lens: research paradigms and the generation and interpretation of knowledge**

There are three elemental aspects of research: epistemology, methodology, and method [415]. Research methodologies and how they produce knowledge are embedded in particular political and ideological positions. These positions are known as ‘paradigms’, a term first coined by Kuhn [416]. From a research perspective, a paradigm can be defined as:

*'A worldview that defines, for its holder, the nature of the world, the individual's place in it, and the range of possible relationships to that world and its parts'. [417]*  
- p107

Paradigms represent our basic beliefs and the lens through which we view the world as researchers. A paradigm is defined according to three fundamental beliefs:

1. *Ontology*: the nature of the phenomena being investigated and what is there that can be known
2. *Epistemology*: knowledge and the nature of the relationship between the knower and what can be known
3. *Methodology*: how we go about obtaining knowledge [416]

In Table 7, we provide an overview of the most prominent paradigms in health services research, along with their ontological, epistemological and methodological assumptions. These paradigms are critical realism, constructionism, positivism, post-positivism, and pragmatism.

**Table 7: The ontology, epistemology and methodology of alternative paradigms.**  
**Adapted from Guba and Lincoln (1994) [417], with additional content from Hussain (2013)[418].**

Paradigm	Ontology	Epistemology	Methodology
Critical realism	Values shape our inquiry into reality which are transformed into a political act which determines who are the empowered and disempowered ( <i>Critical realist</i> )	All scientific inquiry is related to the values of the observer including choice of research question, paradigm selection, methods, analysis and interpretation ( <i>Subjectivist</i> )	Participatory and emancipatory approaches
Constructivism	Multiple realities, intangible mental constructions, socially and experiential based, local and specific in nature, and dependent on the individual holding the construction ( <i>Relativist</i> )	The investigator and the object of the investigation are assumed to be interactively linked so that the findings are created as the investigation proceeds ( <i>Transactional/subjectivist</i> )	Hermeneutic and dialectical; interaction and synthesis; ethno methodology; case studies
Interpretivism	Reality is created by individuals and groups ( <i>Interpretivist</i> )	All scientific inquiry is related to the values of the observer including choice of research question, paradigm selection, methods, analysis and interpretation ( <i>Subjectivist</i> )	Qualitative approaches
Positivism	Reality is 'knowable' and driven by natural laws ( <i>Realist</i> )	The biases and values of the researcher must not influence outcomes. ( <i>Objectivist</i> )	Experimental; quantitative approaches
Post-positivism	Reality is driven by natural laws but is not always 'knowable' ( <i>Critical realist</i> )	Objectivity is aimed for but places emphasis on external verification of results and limiting bias as far as possible ( <i>Modified objectivist</i> )	Modified experimental; quantitative approaches
Pragmatism	Reality is the practical effect of ideas (not committed to any one system of reality or philosophical system) ( <i>Pragmatist</i> )	Individual researchers have the freedom of choice to select procedures that best meet their needs	Mixed methods approaches; action research

### 3.2.2 Quantitative research

Quantitative research is based on a positivist paradigm, which assumes that there are objective 'facts' about the world, separate from the beliefs of the individual. Ontologically, the quantitative paradigm assumes that there is only one truth, an objective reality that exists independent of the researcher's perception. Epistemologically, the researcher and the subject of research are independent entities, where the phenomenon is studied objectively without being influenced by the researcher, or the researcher being influenced

by the phenomenon; here research is value-free. Quantitative research requires the reduction of phenomena to numerical values to allow for statistical analysis. Quantitative methods include trials, which apply techniques such as randomisation, highly structured protocols, and structured questionnaires with a limited range of predetermined responses. Sample sizes are large and aim for representativeness [419].

### **3.2.3 Qualitative research**

In contrast, qualitative research focuses on process and meanings and emerged largely in response to criticisms of positivism. Qualitative research concerns itself with aspects of research such as experience and understanding [420], [421] and is rooted in the interpretive and constructionist paradigms, which hold that reality is socially constructed through individual or collective definitions of the situations. The qualitative ontological position is that there are multiple realities and truths based on the researcher's construction of reality. Here, reality is socially constructed and therefore is constantly evolving. Epistemologically, there is no reality independent of our minds: the researcher and the research subject are interactively linked and findings are subjective and sensitive to social context. Techniques used in qualitative studies include in-depth semi-structured interviews and focus groups, and data can take any form including audio recordings, words, images or videos. Samples sizes are small, and rather than aiming for representativeness aim for purposeful samples of respondents to provide important information.

Qualitative research has a natural home in the field of mental health for its ability to align itself with vulnerable groups [422], [423]. Qualitative research can engage with mental health service users and empower the disenfranchised in the research process by giving them a voice [422], [424]. This is important in trials because it can help to identify trial questions relevant to patients concerns; identify the concerns and priorities of patients; and elicit what participants in a process see as being important and significant [425]. Furthermore, qualitative research can assist with the development and evaluation of theories, tools and interventions, as well as assist with translation and implementation into clinical practice [422]. This can be particularly powerful in informing the design of trials, as well as in the recruitment of participants into such studies [425]. There is an increasing emphasis on the adoption of qualitative methodologies within mental health research, where interventions are often complex in nature [422].

### 3.2.3.1 *Quality in qualitative research*

Whilst qualitative research is often criticised for lacking in scientific rigour, ensuring rigour in data collection and analysis is in fact vital to qualitative research [426]. However, the terminology used to appraise the quality of quantitative research – such as internal validity, external validity and generalisability – do not fully apply to qualitative research [427]. Rather, qualitative research can be assessed for quality and rigour using ‘trustworthiness’, which is the conduct and reporting of the research in a transparent and auditable manner [427]. Here, alternative terminology such as credibility, transferability, dependability, confirmability and authenticity are used [427][417]. To address credibility, the researcher should attempt to demonstrate that a true picture of the phenomenon is being presented. To enable transferability, sufficient detail of the context of the qualitative study should be provided to allow the reader to determine whether the context of the study allows finding to translate to similar contexts. For confirmability, the researcher should demonstrate that the findings are clearly derived from the data. To ensure dependability an audit trail should be maintained of the data, methods and decisions [428]. Authenticity is the extent to which the researcher fairly and faithfully describes participants’ accounts. These aspects of trustworthiness are achieved in qualitative research through triangulation and reflexivity.

Triangulation can exist in a number of forms in qualitative research and includes data source, investigator, theoretical and method triangulation [429]. Triangulation refers to the use of multiple methods or data sources in qualitative research to develop a comprehensive understanding of phenomena. Triangulation can be used to provide verification or completeness to the data, which is important to qualitative research as it enables multiple realities to be recognised [430]. Here, triangulation can be used as a means of confirming existing data and to broaden the landscape of the research to offer a deeper and more comprehensive picture [430].

Since researchers view the world through specific paradigms, we bring our subjective perspectives and experiences to the research process [431]. While objectivity is prized in quantitative research and is sought through the use of strategies such as blinding, subjectivity is fundamental to qualitative research [432]. Qualitative research is therefore reflexive, in that the researcher is part of the research: here the researcher is not just an observer, but ‘*an “instrument” in the research process*’ [433] - p1170. Reflexivity is the self-aware analysis of the interconnectedness between the researcher and the object of the

research [434]. Thus it is important to consider how the researcher's background, perspectives, positioning and behaviour might potentially influence the research [434]. Reflexivity aids transparency of the research and minimises error by ensuring that the researcher does not lose the ability to interpret the findings [435]. Whilst there is a debate as to when reflexivity should occur in the research process, there is some agreement that it is required at different stages [436] and in particular during the data creation process [437]. At this stage, reflexive analysis enables the researcher to assess how the data has been shaped by the relationship between the researcher and the object of research [434]. During the data analysis stage reflexivity is also important in the researcher considering their own beliefs, assumptions and perspectives and how this might influence interpretation of participants' experiences and views [434]. However, the author acknowledges that there are limits to self-awareness; it is not easy to be fully aware of the nuances of all our conscious and subconscious motivations at all times during the research process [438]. Nevertheless, throughout the conduct of the qualitative research presented in this thesis, efforts were made to consider the role of the researcher on the research, using strategies including a 'field' diary [435]. We discuss triangulation and reflexivity in the studies in more detail later in Chapter 7.

Beyond validity and rigour, reflexivity is in itself an essential process in qualitative research and research mixing qualitative and quantitative methods. The reflexive research process is about the continuous self-awareness of the ways in which the researcher's background, assumptions, positioning and behaviour impact on the research process [439]. Thus at every step of the research process the researcher assesses their own effect on the context of knowledge production. This process of reflexivity can also be transformative, since experience and knowledge gained by the researcher from earlier in the research process can feed into subsequent stages of the research. Whilst it is beyond our scope in this thesis to offer a detailed debate of the relationship between researcher theoretical perspectives, evidence production and consumption, it is important to offer some information on the author's discipline as well as her worldview.

#### **3.2.4 The author's disciplinary background – health services research**

For the past ten years, the author has worked as a health services researcher. Health services research has been defined as:

*The multidisciplinary field of scientific investigation that studies how social factors, financing systems, organisational structures and processes, health*

*technologies, and personal behaviours affect access to health care, the quality and cost of health care, and ultimately our health and well-being. Its research domains are individuals, families, organisations, institutions, communities, and populations*’.[440] - p16

At a fundamental level, health services research seeks to improve the infrastructure which supports provision of healthcare to ultimately benefit human health. Health care is complex, thus health services research tends to require comprehensive research methods in order to, for example, understand the impact of the delivery and organisation of health services, with a focus on processes as well as outcomes [441]. This tends to require a range of methods to address research questions, which means most health services researchers adopt mixed methods out of pragmatism rather than principle [441].

### **3.2.5 Pragmatism: paradigm war and peace**

*‘Researchers should be open to an ecumenical blend of epistemologies and procedures, and leave the grand debate to those who care about it.’* [442]

It is neither within the scope nor purpose of this thesis to resolve the grand philosophical debates about various research paradigms. Nevertheless, it is necessary to briefly visit the qualitative versus quantitative debate to demonstrate a critical appreciation of the methodologies, as well as to present a rationale for the mixed-method approach adopted to answer the thesis aims and objectives.

The long-running quantitative versus qualitative debate emerged from the ‘politics of legitimacy’ associated with choice of research methods, where quantitative methodologies are particularly regarded as more scientific and ‘objective’ compared with qualitative methods [443]. Methodological allegiances, the ‘firing of philosophical missiles’ about the relative merits of qualitative and quantitative strategies and their perceived incompatibility became known as the ‘paradigm wars’ [444], [445], which according to Gage reached its climax in 1989 [445]. In the aftermath of the paradigm wars emerged the realisation that the ‘oppositional component of the paradigm’, which stated that quantitative and qualitative perspectives must be mutually exclusive and antagonistic was in fact invalid [445]. Pragmatic resolutions to the paradigm conflicts followed the realisation that nothing about objective-quantitative research precluded the description and analysis of processes with interpretive-qualitative methods [445]. Pragmatism is context driven; therefore of critical importance to pragmatists is what is likely to work best within a given context [445]. Table 8 outlines some of the general characteristics of pragmatism.



**Table 8: General characteristics of pragmatism, adapted from Johnson (2004)[1].**

1. Pragmatism finds a middle ground between philosophical dogmatism and skepticism to find a workable solution (sometimes including outright rejection)
2. Rejects traditional dualisms (e.g., rationalism vs. empiricism, realism vs. antirealism) and prefers philosophical dualisms based on how well they work in solving problems
3. Recognises the importance of the natural or physical world as well as the social and psychological world that includes language, culture, human institutions, and subjective thoughts
4. Places high regard for the reality of and influence of the inner world of human experience in action
5. Knowledge is viewed as being both constructed and based on the reality of the world we experience and live in
6. Endorses fallibilism (current beliefs and research conclusions are rarely viewed as perfect, certain, or absolute)
7. Theories are viewed instrumentally (they become true and they are true to different degrees based on how well they currently work; workability is judged on the criteria of predictability and applicability)
8. Endorses eclecticism and pluralism (e.g., different, even conflicting, theories and perspectives can be useful)
9. Human inquiry is viewed as being analogous to experimental and scientific inquiry. Use of this “scientific” or evolutionary or practical epistemology moves us toward larger Truths.
10. Endorses a strong and practical empiricism as the path to determine what works
11. Current truth, meaning, and knowledge as tentative and are changing over time. What we obtain on a daily basis in research should be viewed as provisional truths
12. Instrumental truths are a matter of degree (i.e., some estimates are more true than others). Instrumental truth is not “stagnant,” and, therefore, James (1995: 1907) states that we must “be ready tomorrow to call it falsehood.”
13. Prefers action to philosophizing
14. Takes an explicitly value-oriented approach to research that is derived from cultural values; specifically endorses shared values such as democracy, freedom, equality, and progress.
15. Endorses practical theory (theory that informs effective practice; praxis).
16. Offers the ‘pragmatic method’ for solving traditional philosophical dualisms as well as for making methodological choices.

Pragmatism challenged the idea that qualitative and quantitative methods are incompatible and embraced mixed methods research: for pragmatists, the integration of research methods from different paradigms builds on the strength of each and reduces the

inherent flaws of each [446]. Pragmatists are not methodological purists and are open to any paradigm that fits best with the research aims [447]. Pragmatic logic of inquiry embraces induction (discovery of patterns), deduction (testing of theories and hypotheses) and abduction (discovering the best of a set of explanations for understanding research results) [1]. Pragmatism concerns itself with ‘what works’ and solutions to existing problems and questions [448]. Rather than prioritising methodological purity, pragmatism prioritises the research problem and utilises all methods to understand and address this, including being open to forming an allegiance to any paradigm or theory that best fits with the research aims [447][449][450].

### **3.2.6 Mixed methods research as an attractive partner to pragmatism**

*‘Research approaches should be mixed in ways that offer the best opportunities for answering important research questions’. [1] - p16*

Mixing methods in research has been defined as the combination of both quantitative and qualitative research techniques, methods, approaches, concepts or language in the context of a single study [1]. Mixed methods research can adopt a number of different research strategies related to a complex range of research questions and a complex research design [451]. Five key design approaches for mixing methods in research have been proposed, which we outline below [452]:

1. *Triangulation design* – aims to converge and corroborate results from different methods
2. *Complementarity design* – aiming for elaboration, enhancement, illustration and clarification of the results from one method with results from the other method
3. *Development design* - using the results from one method to help inform the other method: includes sampling, implementation and measurement decisions
4. *Initiation design* - discovering paradoxes and contradictions that lead to a re-framing of the research question
5. *Expansion design* - seeking to expand the breadth and range of inquiry by using different methods for different inquiry components

Combining methods in this way is often referred to as ‘mixed methods’ or ‘multiple methods’. While these two terms are very similar and are generally used interchangeably, they are distinctive approaches that can be characterised by the stage and level at which the methods are mixed or integrated [453]. In multiple methods research each study is complete in itself, with the results of the completed studies then integrated or triangulated

to form a whole [454]. This contrasts with the mixed methods approach adopted within this, where integration occurs during the analysis stages: in this thesis the studies build on each other, with Study One shaping the focus and analysis of Study Two; whilst the recruitment intervention and its evaluation in Study Three is informed by Studies One and Two [455]. Thus this thesis is an example of a ‘development design’ design approach to mixed methods. Mixed methods research strengthens the ability to understand complex social phenomena by utilising both qualitative and quantitative research to offset the weaknesses of either approach alone [456], [457]. Mixed methods research embraces methodological pluralism and more than one paradigm can underlie it; by this nature therefore, it becomes an attractive philosophical partner to pragmatism [1][458]. In Table 9 we outline the core characteristics of mixed methods research.

**Table 9: Core Characteristics of Mixed Methods Research, adapted from Teddlie (2012) [458]**

<ol style="list-style-type: none"> <li>1. Methodological eclecticism</li> <li>2. Paradigm pluralism</li> <li>3. Iterative, cyclical approach to research</li> <li>4. Set of basic “signature” research designs and analytical processes</li> <li>5. Focus on the research question (or research problem) in determining the methods employed within any given study</li> <li>6. Emphasis on continual rather than a set of dichotomies</li> <li>7. Emphasis on diversity at all levels of the research enterprise</li> <li>8. Tendency toward balance and compromise that is implicit within the “third methodological community”</li> <li>9. Reliance on visual representations (e.g., figures, diagrams) and a common notational system</li> </ol>
--

### ***3.2.6.1 Strengths and weaknesses of mixed methods research***

Mixed methods research has a number of key strengths; however there are also limitations to adopting this approach. In Table II we highlight some of the main strengths and limitations of the mixed methods research.

**Table 10: Some strengths and weaknesses of mixed methods research, adapted from Johnson (2004) [1] and Onwuegbuzie (2006) [459]**

Strengths	limitations
<ul style="list-style-type: none"> <li>• Words can be utilised to add meaning to numbers</li> <li>• Numbers can be utilised to add precision to words</li> <li>• Bolsters the strengths of quantitative and qualitative research</li> <li>• Theory can be generated and tested</li> <li>• Can address a more comprehensive range of research questions than either qualitative or quantitative methods alone</li> <li>• The results of the quantitative phase can inform the design of the qualitative phase of the research, and <i>vice versa</i></li> <li>• The strengths of one method can be used to overcome the weaknesses in another method by using both in a study (the <i>complementarity</i> principle)</li> <li>• Convergence and corroboration of findings can offer stronger evidence (the <i>triangulation</i> principle)</li> <li>• Offers additional insights and understanding than is possible with just a single method</li> <li>• Aids the generalisability of findings</li> <li>• Combining qualitative and quantitative methods produces more complete knowledge necessary to inform theory and practice</li> </ul>	<ul style="list-style-type: none"> <li>• Can burden a single researcher to undertake both qualitative and quantitative research, especially if undertaken concurrently</li> <li>• The researcher is required to have knowledge of multiple methods and approaches</li> <li>• Methodological purists continue to argue the need for methodological segregation</li> <li>• Mixed methods is more resource intensive, both in time and costs</li> <li>• Some of the details of mixed research are yet to be fully delineated by research methodologists: for example, the concept of ‘validity’ still requires significant work</li> </ul>

### 3.3 Summary of methodology and methods selected for this thesis

We approached the health services research contained within this thesis from a pragmatic paradigm. The thesis adopts a mixed methods approach and combines qualitative and quantitative methodologies, aiming for robustness and comprehensiveness, to allow for a wider range of questions to be answered than either quantitative or qualitative methodologies individually can allow. This addresses the deficit of either method alone in developing and evaluating a recruitment intervention for mental health trials. As an example of the ‘development design’ approach to mixed methods research, the thesis uses the results from one method to inform the other method:

1. Qualitative methods (to provide depth of understanding) – to systematically explore factors affecting recruitment into depression trials and develop a conceptual framework and; to explore the decision making process of patients who declined to participate in a trial;

2. Quantitative methods (to provide breadth of understanding) - to develop a recruitment intervention and to test its effectiveness using a randomised controlled trial embedded in an ongoing host trial

In undertaking this design we were guided by the Medical Research Council's 'Framework for developing and evaluating complex interventions' [460][164].

### 3.3.1 The Medical Research Council Complex Interventions Framework

Some researchers view the conventional trial with caution for being reductionist or unrepresentative of complex clinical or research practice [161]. They argue that while conventional trials are able to generate good evidence for pharmacotherapy (which tends to be a standardised and well-defined intervention), it cannot generate good evidence for psychological, social, organisational or service level interventions, which tend to be complex in nature [161], [163]. Complex interventions have been defined as being:

*'Built up from a number of components, which may act both independently and interdependently'* [460] - p2.

The active ingredient in a complex intervention is not easily evident; many interventions in mental health research are multi-faceted or involve organisational restructuring as well as individual intervention [163], [165]. Recruiting participants into trials is a complex process involving a range of interacting components such as trial planning, selection of recruitment strategies and a range of relationships including between researchers, clinicians and patients [461]. This has led to trial recruitment being conceptualised as a complex intervention [461]. Table II below highlights what makes a complex intervention.

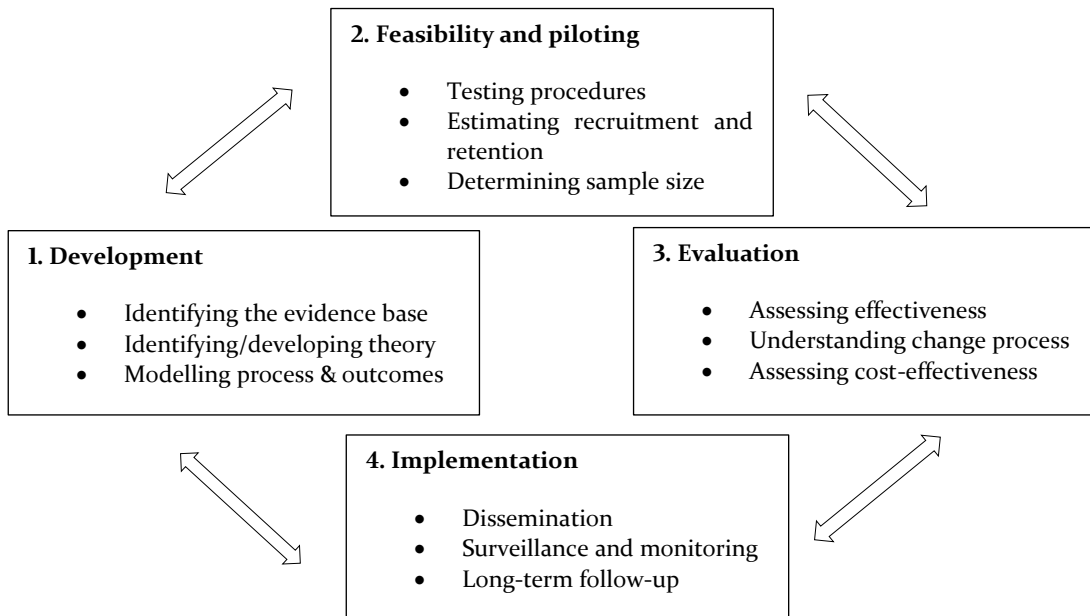
**Table II: What makes an intervention complex? Adapted from Craig (2008) [164]**

- |  |
|--|
| <ul style="list-style-type: none"><li>• Number of interacting components within the experimental and control interventions</li><li>• Number and difficulty of behaviours required by those delivering or receiving the intervention</li><li>• Number of groups or organisational levels targeted by the intervention</li></ul> |
|--|

Whilst there are a range of models, theories and frameworks to describe and evaluate complex interventions [164], [462]-[464], these models are generally interchangeable and

feature only minor differences in their application [461][465]. In this thesis we adopt the most established and widely applied of the frameworks, which was developed by the Medical Research Council in 2000 and updated in 2008 to address identified limitations [164], [460]. Figure 4 outlines the current MRC Framework.

**Figure 4: MRC framework for developing complex interventions, adapted from Craig (2008) [164]**



The 2008 MRC framework consists of four interactive phases: 1) development; 2) feasibility and piloting; 3) evaluation and 4) implementation. Each phase of the framework allows the use of a range of methods, and the authors place emphasis on each phase, in order to evaluate well-developed interventions that are likely to be implemented. The 2008 Framework was a response to the difficulties faced by researchers in attempting to develop and evaluate complex interventions and addresses the limitations of the 2000 framework. The updated framework offers flexible, non-linear movement between the four phases. The 2008 framework also emphasises the importance of the development stage. However, the authors also highlight that each stage must be considered since focusing on one stage may have negative consequences for other stages as it may lead to:

*‘Weaker interventions, that are harder to evaluate, less likely to be implemented and less likely to be worth implementing.’ [164] - p4*

The process from development through to implementation of a complex intervention may also take a wide range of different forms. Within the MRC Framework, the identification of

the evidence base, qualitative research and assessment of effectiveness are important for intervention development and evaluation [164].

The framework highlights that a good theoretical understanding is needed of how the intervention causes change. This is supported by evidence from the published literature evaluating complex interventions, which demonstrate the practical value of theory in determining which aspects of an intervention and its context are likely to be crucial for influencing outcomes [466]. However, few recruitment interventions link with theories or conceptual frameworks, suggesting previous recruitment research have not adopted a systematic approach to intervention development and evaluation. Reviews of recruitment studies also suggest that most published reports of recruitment interventions are either observational or anecdotal in nature and have not undergone the evaluation phase [233]; or those that have undergone the evaluation phase without having undertaken the preliminary phases recommended by the MRC framework [370], [461].

## **3.4 Thesis methodology**

### **3.4.1 Introduction**

The previous section provided an overview of the general methodology used in this thesis, in particular: pragmatism, the theoretical lens underlying this thesis; mixed methods research; and the MRC complex interventions framework. In this section we will describe the specific methods used in the component studies of the thesis. Specifically, this section will describe in detail:

1. How the MRC complex interventions framework informed the development and evaluation of the recruitment intervention in this thesis
2. The systematic review and meta-synthesis methods used to answer our objective of identifying factors affecting recruitment in depression trials and develop a conceptual framework (Study One)
3. The methods used to undertake the qualitative study exploring the decision making of patients invited into a depression trial but who declined
4. How the collaboration with the Systematic Techniques for Assisting Techniques for Assisting Recruitment to Trials (START) project established the feasibility of embedded recruitment trials, which informed the work in this thesis
5. The methods used to develop the recruitment intervention

6. The methods of the embedded trial used to evaluate the effectiveness of the recruitment intervention

### **3.4.2 Developing and evaluating a recruitment intervention for mental health trials using the MRC framework**

This thesis adopts the MRC framework and takes into account all four phases. In the following section, we describe the approach we took in adopting the MRC framework to develop and evaluate a recruitment intervention for mental health trials.

#### ***3.4.2.1 Development***

For the development phase, the MRC framework specifies that:

*'Before undertaking a substantial evaluation, you should first develop the intervention to the point where it can reasonably be expected to have a reasonable effect.'* [164] -p9

The framework further specifies that the research should begin by identifying the relevant evidence, ideally in a systematic review.

1. We initiated the thesis by undertaking a systematic review and meta-synthesis, to develop a conceptual framework of factors affecting recruitment to depression trials (Study One)
2. We then undertook a qualitative study to understand the decision making in declining to participate in a mental health trial (Study Two)
3. We adopted Participatory Design approaches to inform the development of the recruitment intervention to ensure acceptability, compliance and delivery of the recruitment intervention (Study Three)

#### ***3.4.2.2 Feasibility and piloting***

*'The feasibility and piloting stage includes testing procedures for their acceptability, estimating the likely rates of recruitment and retention of subjects, and the calculation of appropriate sample sizes.'* [164] -p10

For this thesis we did not undertake feasibility and piloting. However, the collaboration with the START programme helped to produce the necessary information that a feasibility and piloting phase would have generated. START was a feasibility study developing methodological, logistical and reporting frameworks for undertaking embedded



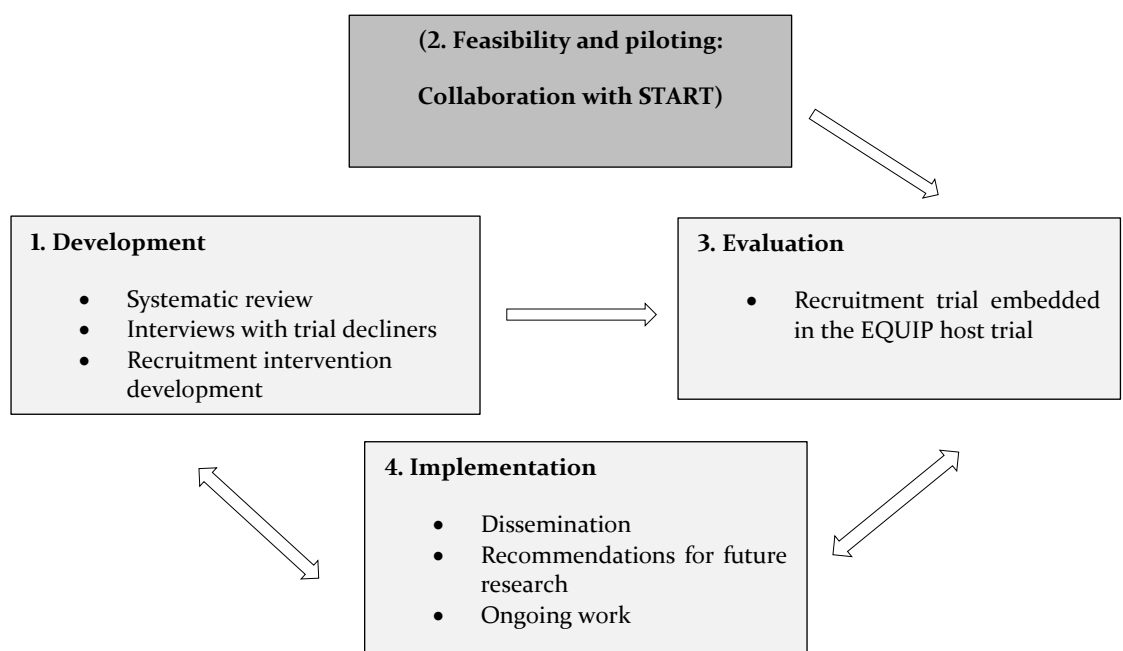
recruitment trials. We actively collaborated with START to test the feasibility of developing and evaluating a recruitment intervention for embedded recruitment trials.

### 3.4.2.3 Evaluation

*'You should always consider randomisation, because it is the most robust method of preventing the selection bias that occurs whenever those who receive the intervention differ systematically from those who do not, in ways likely to affect outcomes.'* [164] -p10

We evaluated the effectiveness of the recruitment intervention in improving recruitment rates, using a randomised controlled trial design, embedded in an ongoing mental health trial (Study Three). Figure 5 outlines the thesis framework for developing and evaluating a recruitment intervention for mental health trials.

**Figure 5: Framework for developing and evaluating a recruitment intervention for mental health trials.**



In the next section we describe the methods selected for each component study and discuss their strengths and limitations.

### **3.5 Methods – Study One: Factors affecting recruitment into depression trials: systematic review, meta-synthesis and conceptual framework**

The corresponding paper is presented in Chapter 4:

**Hughes-Morley A.**, Young B, Waheed W, Small N, & Bower P (2015). Factors affecting recruitment into depression trials: systematic review, meta-synthesis and conceptual framework. *Journal of Affective Disorders*, 172, 274-290

#### **3.5.1 Rationale**

Previous systematic reviews of trial recruitment have mainly focused on recruitment into cancer trials, the recruitment of ethnic minorities, or on barriers to trial recruitment. Few systematic reviews have focused on mental health; even fewer have adopted the meta-synthesis approach; and despite depression being the most common mental health problem, none have addressed recruitment issues from the perspective of patients with depression and the clinicians and gatekeepers tasked with recruiting them into trials. Thus there is a need to systematically explore the literature around recruiting patients into depression trials, from the perspective of patients with depression and gatekeepers. A systematic review was therefore undertaken to support the development and testing of a recruitment intervention. This review identified the factors affecting recruitment into depression trials, to perform a meta-synthesis to identify common themes that describe factors affecting recruitment into depression trials, in order to develop a conceptual framework of factors influencing the decision to participate in depression trials. This review was limited to empirical qualitative studies, to gain insights about the subjective recruitment experiences. This review was limited to qualitative studies so as to obtain an in-depth understanding of the issues and to access phenomena beyond those that researchers might anticipate. Unlike quantitative data derived from trials or observational studies which aggregate data to produce a common effect size, qualitative studies of trial recruitment investigate the subjective experiences of patients and gatekeepers, to gain an understanding of the factors affecting their decision making.

### 3.5.2 Objectives

The three objectives of this systematic review were:

1. To systematically identify relevant qualitative studies describing factors affecting the recruitment of participants into depression trials
2. To perform a meta-synthesis to identify common themes that describe the factors affecting recruitment into depression trials
3. Develop a conceptual framework of factors influencing the decision to participate in depression trials.

### 3.5.3 The systematic review

Decisions for patients in need of healthcare, for policy makers and for researchers should be informed by the best available research evidence [467]. However, large volumes of research evidence can present difficulties for decision makers, who need to access an overview of a research area. Systematic reviews aim to identify, synthesize and appraise relevant empirical evidence that meets pre-specified eligibility criteria to produce reliable findings to inform decision making [112]. Unlike traditional literature reviews which report study results at face value, systematic reviews use transparent and replicable methods for synthesising and critically appraising empirical evidence [467]. We outline the key characteristics of a systematic review in Table 12 below.

**Table 12: The key characteristics of a systematic review, adapted from Higgins & Green (2011)[112]**

- |  |
|--|
| <ol style="list-style-type: none"><li>1. Contains a clearly stated set of objectives, with pre-defined eligibility criteria for studies</li><li>2. Has an explicit, reproducible methodology</li><li>3. Adopts a systematic search that attempts to identify all studies that would meet the eligibility criteria</li><li>4. Includes an assessment of the validity of the findings of the included studies</li><li>5. Presents the findings in a systematic way and synthesises the characteristics and findings of the included studies.</li></ol> |
|--|

The results from multiple studies can be combined to form new interpretations using meta-synthesis for data that is qualitative in nature, or aggregated for quantitative data using meta-analysis [468], [469]. Whilst the majority of systematic reviews are

quantitative in nature and typically aim to determine the effectiveness of interventions or programmes, systematic reviews can be identify qualitative literature and use this to explore the meanings, experiences and values of patients and professionals; processes or interventions; or to investigate methodological issues [370], [470].

The methodology for this review and meta-synthesis was informed by the Centre for Reviews and Dissemination Guidance for Undertaking Reviews in Healthcare [467], the Cochrane Handbook for Systematic Reviews of Interventions [112], Noblit and Hare's guidelines for synthesising qualitative studies [471] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [472]. These are fully described in Chapter 4.

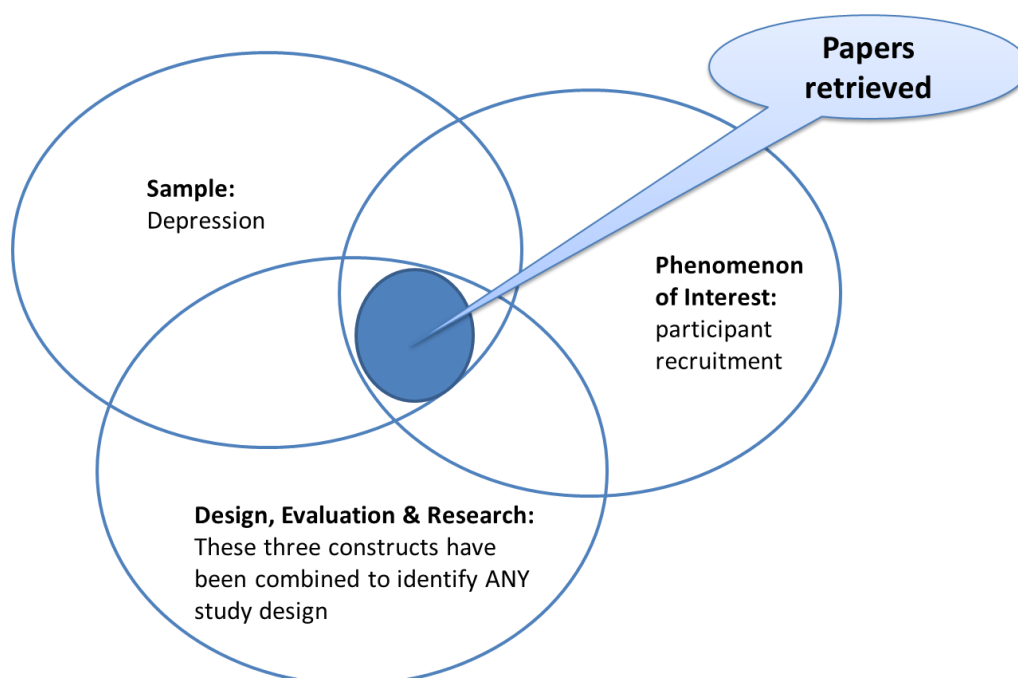
### **3.5.4 Systematic literature search**

The goal in a qualitative meta-synthesis is to retrieve all of the relevant studies in a field, and not just a sample [473]. It is therefore imperative to search multiple electronic databases to retrieve the maximum number of relevant citations [474]. However, there is poor empirical evidence underpinning practice in information retrieval of qualitative research [475], meaning that searching for and identifying appropriate qualitative research has been described as both 'frustrating and difficult'[476]. Development of the search strategy followed the Centre for Reviews and Dissemination's guidance for undertaking systematic reviews [467]. As the aim was to retrieve studies that were qualitative in nature, a modified version of the SPIDER search framework was adopted [477]. The SPIDER framework involves searching by using terms across five domains - Sample, Phenomenon of Interest, Design, Evaluation, Research type. SPIDER is a development on the widely-utilised 'PICO' (Population, Intervention, Comparator, Outcome) [478] and provides a useful framework for specifying criteria for inclusion in systematic reviews of qualitative studies, where there is an absence of 'intervention' and 'comparator', as in our case. Using SPIDER to frame the search, the author tested different search strategies and sought advice from information retrieval experts (a subject librarian and an information service manager with experience of conducting literature searches for systematic reviews).

During the test searches the author identified that a number of studies known to her were not retrieved when the 'qualitative' methodological filters were applied, indicating that the qualitative studies were poorly indexed in the databases [479]. There is also limited evidence to suggest that PICO may be preferred when the primary objective is sensitivity, whereas SPIDER favours specificity [480]. The search strategy therefore did not specify study methodology and was finalised when the author was confident this contained the

best balance of sensitivity and specificity [481]. This strategy utilised the following search terms: 1) Sample = 'depression' search terms; 2) Phenomenon of Interest = 'recruitment' search terms; and 3) Design/Evaluation/Research type= this was left deliberately blank in order to identify ALL possible methodologies. All citations retrieved were reviewed to identify suitable study types. Please see Figure 6.

**Figure 6: Scope of the search in the systematic review**



### 3.5.5 Appraising the quality of qualitative research

There is an ongoing debate about the nature of the knowledge produced by qualitative research, in terms of whether its quality can legitimately be judged, and if so, how [482]. This debate reflects:

*'Diverse disciplinary traditions and allegiances, and many of the limitations of appraisal processes reflect methodological anarchy at a primary research level.'*  
[425] - p1

Despite this ongoing debate however, many now accept the necessity for clear and transparent methods to assess the quality or credibility of qualitative research [467]. This acceptance has led to a large number of quality appraisal tools for qualitative research: in one review, 45 appraisal tools in healthcare alone were identified [483]. Despite this, there

remains a relative absence of empirical work to evaluate such tools [484]–[486], giving rise to uncertainty about the most appropriate tools to adopt in qualitative systematic reviews.

Quality appraisal tools for qualitative research sit along a continuum, with ‘highly structured’ at one end and ‘unstructured’ at the other. Unstructured approaches rely predominantly on individual judgement, such as expert opinion. Examples of structured appraisal tools include the UK Cabinet Office’s Quality Framework (QF) [487] and the Critical Appraisal Skills Programme (CASP) [488]. In one of the few studies evaluating qualitative appraisal tools, Dixon-Woods *et al.* undertook a qualitative and quantitative comparison of three methods for appraising 12 qualitative studies: unprompted judgement, based on expert opinion; the QF; and CASP [486]. The authors concluded that structured approaches did not appear to yield higher agreement than that by unprompted judgement, nor did they produce greater consistency of judgements about whether to include qualitative papers in a systematic review [486]. Structured approaches are widely used to assess studies for inclusion in systematic review, and there is considerable pressure for a structured approach to appraising qualitative research [486]. However, in addition to the problems identified by Dixon-Woods *et al.*, structured assessments have received criticisms for being unwieldy, in the case of the QF, or in the case of CASP, superficiality [486]. Finally, structured approaches have been criticised for being biased towards procedural aspects of research practice [486][489], and for being less insightful and making weaker contributions towards the conceptual development of the field [490].

The author’s approach to quality assessment aimed to assess papers critically, while maintaining a methodologically neutral position. This adopted the ‘Prompts for appraising qualitative research’ developed by Dixon-Woods *et al.* [486]. These criteria take into account methodological rigour, clarity of reporting, as well as the overall contribution made by the study. We categorised papers as ‘Key Paper’ for those that were conceptually rich and methodologically sound, which were appraised as most relevant in terms of their contribution; or ‘Satisfactory Paper’, which were papers that were appraised as making a contribution but less methodologically rigorous. This is discussed in detail in Chapter 4.

### **3.5.6 Synthesising results: meta-synthesis**

A wide range of methods for synthesising qualitative data exists, including critical interpretive synthesis [491] and thematic synthesis [492]. The most well-developed of these methods for synthesising qualitative data, with origin firmly rooted in the interpretive paradigm, is meta-synthesis [493][471]. Whilst the term ‘meta-synthesis’ is

often used, it can also generate confusion as some researchers use it to refer to the actual method of the synthesis, whilst others use it to refer to the whole process of the synthesis, irrespective of the method used [494]. However, there is no fixed nomenclature [494]; thus in this thesis we use the term meta-synthesis to refer to the process of the synthesis, which can be defined as:

*'The theories, grand narratives, generalizations, or interpretive translations produced from the integration or comparison of findings from qualitative studies'* [495] - p366.

Meta-synthesis aims to combine results from different qualitative studies to identify patterns among study results, sources of disagreement or other interesting relationships to gain new insights [471]. Thus its aims are akin to the meta-analysis for quantitative studies; however rather than aggregating results (as in the case of the meta-analysis), the aim of the meta-synthesis is to reconceptualise themes from across a number of qualitative studies to combine phenomena into a transformed whole [471]. The meta-ethnographic approach originally developed by Noblit and Hare [471], it has subsequently been adapted and utilised to support the meta-synthesis of qualitative data in healthcare research, including in depression [496], [497] and trial recruitment [498], [499].

There are a number of reasons why a meta-synthesis was chosen in this context. Firstly, meta-synthesis, as we aimed to operationalise it, is much more than attempt to develop the functional qualitative equivalent of a meta-analysis [500]: far from aggregating the data from individual studies, meta-synthesis aims to increase the interpretive possibilities of the results of individual studies, to enable new insights to emerge [501]. Secondly, meta-synthesis can be incorporated into systematic reviews to inform and develop evidence based practice and research [495] [502][503]. Finally, meta-synthesis can be utilised to enable:

- a) theory building, which generates new theories and concepts;
- b) theory explication, which outlines and explains existing theory
- c) theoretical development [504]

This therefore fits well with our stated objective of developing a conceptual framework of the decision around trial participation, to assist the development of a recruitment intervention that can then be evaluated.

It is important to consider the methodological comparability of studies during the synthesis process [495]. Whilst a debate exists over the appropriateness of synthesising research with different epistemological standpoints, there is increasing agreement that

combining findings from different standpoints can actually enhance the ‘true value’ of the synthesis [495], [505][506]. Furthermore, a pragmatic approach, as outlined earlier underpinned by the concepts of *abduction* (connection of theory to data), *intersubjectivity* (relationship to research process) and *transferability* (inference from the data), can help overcome epistemological differences to allow the inclusion of a variety of research methodologies and theoretical frameworks [507]. This approach provided breadth to the review and enabled the exploration of all published studies to date [507][505].

To achieve the synthesis a lines-of-argument synthesis was utilised, which is a method emerging from meta-ethnography [471]. Lines-of-argument synthesis is fundamentally about inference [471]. Within this approach, statements about the phenomenon of interest are inferred from the selected studies to build up a picture. The lines-of-argument synthesis focuses on the likely response of patients and gatekeepers to recruitment interventions. The synthesis process began with studies quality appraised as ‘Key Papers’, before continuing with ‘Satisfactory Papers’.

### **3.5.7 Conceptual framework**

From the meta-synthesis we developed a conceptual framework, which is defined as a visual or written representation that:

*‘Explains, either graphically or in narrative form, the main things to be studied—the key factors, concepts, or variables—and the presumed relationships among them’ [508] - p18*

This conceptual framework is built by the researcher using existing theory and research, along with their own philosophical paradigm [509]. A conceptual framework represents the researcher’s own interpretation of findings from qualitative analysis and is a tentative theory of the phenomena [509], which may need further development and testing.

This conceptual framework functions to provide justification for research and inform future study design; assess and refine research goals; develop realistic and relevant research questions; select appropriate methods; and identify potential validity threats to conclusions [509].

### **3.5.8 Strengths and limitations**

The strengths of the meta-synthesis of qualitative studies is that it can provide valuable, in-depth insight into experiences, beyond that of individual studies. Furthermore, the



meta-synthesis can also demonstrate where knowledge is lacking, thus it can be effectively used to guide future research. A robust approach was taken to identify and retrieve both qualitative and quantitative studies and then select relevant qualitative studies. Whilst this was a sound approach [494], it was also labour intensive.

There are some limitations to this review. A systematic literature search including only published qualitative literature was undertaken. It did not include factors that have not been identified in the peer-reviewed literature, and the synthesis was dependent on the particular studies included. For resource reasons studies not published in the English language were excluded, meaning that relevant publications may have been omitted. The author aimed for transparency in all aspects of the review and synthesis; however the subjective nature of qualitative research and the process of synthesising the studies means that another researcher may have obtained different results. Additionally, the order in which the meta-synthesis was undertaken, beginning with 'Key Papers' may have affected its outcome. For instance, an alternative approach beginning with older studies may have identified time related differences in findings.

## **3.6 Methods – Study Two: What can we learn from trial decliners about improving recruitment? Qualitative study**

The corresponding paper is presented in Chapter 5:

**Hughes-Morley A**, Young B, Hempel RJ, Waheed W, Russell IT, Bower P (submitted). What can we learn from trial decliners about improving recruitment? Qualitative study. *Trials*

### **3.6.1 Rationale**

Qualitative research concerns itself with meaning, experience and understanding [510]. The knowledge this research generates can be particularly powerful in informing the design of trials, as well as in the recruitment of participants into such studies [425]. Within the MRC framework there is an emphasis on qualitative research being intrinsic to each stage of intervention development and implementation [164].

Although some qualitative studies have identified factors affecting participation in trials by exploring motivations for participation, these have tended to focus on the perspectives of patients who are already enrolled in trials. Few studies have explored issues from the viewpoint of patients who have declined to participate. Understanding the causes of poor recruitment is critical to identifying potential opportunities for a recruitment intervention to address any barriers raised. Our prior systematic review identified only one study which explored the perspectives of patients who had declined trial participation [511]. This study focused on patients' self-reported reasons for their decision but did not explore in detail their accounts of what happened when they received the invitation to join a trial. Understanding how participants respond to the invitation to join a trial and their decision to decline may assist trialists to determine how recruitment practices might be enhanced by well-designed interventions aimed at improving trial recruitment. By exploring this important gap around patients' responses to the invitation to join a trial and how they reach a decision to decline trial enrolment, our goal was to shed light on an area which has been described as a blind spot in the literature [512].

### **3.6.2 Objectives**

The objectives of Study Two were:

- a) To explore patients' accounts of their decision making about taking part in a trial
- b) To understand *how* patients reached the decision to decline the invitation to participate in the trial

### **3.6.3 The REFRAMED Trial**

A qualitative study embedded within the REFRAMED depression trial was undertaken. REFRAMED was an ongoing trial which investigated the effectiveness of Radically Open Dialectical Behavioural Therapy for treatment resistant depression (RO-DBT) [513]. Participants were approached to be recruited into the REFRAMED trial via GP practices, Community Mental Health Teams and Intensive Psychological Therapies services in Dorset, Hampshire and North Wales. Patients were eligible if they were:

- a. Aged over 18 years
- b. Had a current diagnosis of depression
- c. Had not responded to antidepressants

Participants were individually randomised to receive RO-DBT in addition to usual care and antidepressant medication, or to usual care and antidepressant medication.

In REFRAMED, patients declining the invitation to participate could return an 'opt-out' reply form to the trial team. In the reply form, patients could additionally express an interest in being contacted to explore their reasons for declining participation. Patients interested in being contacted provided their contact details and brief demographic information.

### **3.6.4 Linked qualitative study**

To undertake the qualitative study, the author approached the REFRAMED trial team to propose a collaboration to interview this hard-to-reach group to explore how patients made the decision to decline participation in a mental health trial. Thus the linked qualitative study with REFRAMED forms a nested - and distinct - study, using patients approached by, but not included in the REFRAMED study sample. Table 13 is an outline of the distinction between the qualitative study undertaken for this thesis and REFRAMED.

**Table B: Distinction between the qualitative study and REFRAMED**

	<b>REFRAMED Trial</b>	<b>Linked qualitative study</b>
<b>Aims</b>	To evaluate the effectiveness and cost-effectiveness of RO-DBT for patients with treatment-resistant depression.	a) To explore patients' accounts of their decision making about taking part in a trial b) To understand <i>how</i> patients reached the decision to decline the invitation to participate in the trial
<b>Sample</b>	Patients with refractory depression	Patients declining participation in REFRAMED
<b>Study design</b>	Randomised controlled trial	Qualitative study
<b>Interventions</b>	individual and group RO-DBT treatment versus treatment as usual	None
<b>Data collection methods</b>	Face-to-face, telephone, text message	Telephone, email

To undertake this qualitative study, the author independently collected data from the population of patients who had declined participation in REFRAMED, which was data that the REFRAMED team did not have the capacity to collect themselves. Undertaking this work with the REFRAMED team was of mutual benefit to both the author and to the REFRAMED trial team.

In undertaking this collaboration with an ongoing trial that was led from a separate institution, a range of issues had to be discussed, and arrangements put into place, namely:

1. Data arrangements, including transfer and ownership
2. Research ethics, including university arrangements, and obtaining letters of access across multiple primary care trusts
3. Consent arrangements
4. Patient and public involvement in research
5. Publication policy
6. Training, both on REFRAMED, and in preparation for the qualitative interviews

A Research Passport was obtained, along with Letters of Access for all recruiting NHS sites. An honorary contract was also obtained with the University of Southampton (the REFRAMED trial Sponsor), along with remote web-based access to the REFRAMED databases.

### 3.6.5 Methods: qualitative study

This qualitative study, as with the rest of the work in this thesis, was undertaken from the pragmatist perspective. As a paradigm, pragmatism focuses on the usefulness of knowledge and how it can be used to guide behaviour that produces anticipated outcomes [514]. Thus pragmatism is concerned with action and change and the interplay between knowledge and action. Epistemologically, pragmatism aims for a compromise between realism and constructivism to argue that whilst a reality exists outside of human experience, this can only be encountered through human experience [515]. This combines a belief that the world is both real and socially constructed, as well as that all knowledge is social knowledge. Thus the pragmatist belief is that each individual's knowledge is unique because it is based on individual experience, whilst also arguing that much of this knowledge is socially shared because it is derived from socially shared experience [514]. Methodologically, pragmatism focuses on 'what works'; therefore, data collection and analysis methods are selected to reflect the likelihood of gaining insights into the question. Here, the pragmatist approach welcomes methodological pluralism and enables different methods of qualitative sampling, data collection and analysis to be utilised to address research aims [446].

Alternative paradigms such as interpretivism or constructivism have been traditionally associated with qualitative research. However, pragmatism's concern with action and change and the interplay between knowledge and action makes it particularly suitable as a basis for research approaches intervening into the world rather than merely observing the world. Thus in the overall goal of the thesis to apply findings from the qualitative study and meta-synthesis to inform the development and evaluation of a recruitment intervention, the pragmatist approach was particularly appropriate.

Interviews can be structured, semi-structured to unstructured. Structured interviews are generally utilised to gather data for quantitative analysis and adopt a pre-specified list of questions which are covered for each participant in the same order. Unstructured interviews have few pre-determined boundaries. We opted to use semi-structured interviews for this study. Interviews were facilitated by the use of a topic guide to focus on the patient experience of making the decision to decline trial participation, whilst allowing the conversation to follow each participant's own story [516].

In-depth semi-structured interviews were undertaken by telephone and email with those patients who had returned the 'opt-out' reply slip and indicated a willingness to participate in an interview. These participants were all patients who were approached via the GP

route. We opted to undertake telephone and email interviews with this hard-to-reach group from a pragmatic perspective. Personal communication with trialists who have undertaken work with similar patient groups highlighted that many decliners would likely decline face-to face interviews [511]. In consultations with two PPIR groups - the UK Clinical Research Network Mental Health's Service User Research Panel (SURP) and Primary Care Research in Manchester Engagement Resource (PRIMER) - both agreed that in this group of patients, telephone interviews would be the least intrusive and most acceptable option. Telephone and e-mail interview can be used as methods in their own right, or in combination with other methods [422]. Well-planned telephone and email interviews can gather the same material as those held face-to-face, whilst enabling the inclusion of groups that are isolated, geographically dispersed or stigmatised [517], [518].

Recruitment into this qualitative study occurred between August 2013 and January 2015. To minimise recall bias interviews occurred within 3 months of respondents declining to participate in REFRAMED.

#### ***3.6.5.1 Topic guide***

A topic guide was used to ensure consistency across the interviews. Prior to initiating the interviews, a service user from SURP met with AH-M for detailed discussion around the topic guide, and to role play the interview in preparation for conducting the actual interviews. The topic guide was then piloted with two interviewees. This guide consisted of a series of open-ended questions that related to a number of topic areas: patient recollection of being approached about the study; clarity and quality of the information they received; understanding of the trial and the interventions; reasons for declining; and their views on talking therapies, DBT, group therapy and antidepressants. The interviews were recorded using a digital audio recorder. Chapter 5 includes a copy of the topic guide.

#### ***3.6.5.2 Sampling***

Due to the relatively small numbers of patients opting into the qualitative study, there was a chance that random sampling may have led to an unrepresentative sample. Therefore a maximum variation sampling technique was used [448], which is a purposeful sampling method that aims to capture and describe the central themes that cuts across participant variation. Maximum variation sampling looks to identify the uniqueness of each case from a heterogeneous sample, as well as common patterns that emerge from the sample to

capture the core experiences and central, shared aspects of experiences. We used a sampling matrix to identify patients with diverse characteristics based on the demographic criteria of age (under 65 years old - i.e. of 'working age'; or over 65 years old - i.e. of 'retirement age'), gender and participant geographic location/study site (Wales, Hampshire or Dorset). There is an ongoing debate about how many participants are required for a qualitative study, and some have argued that sample size recommendation for qualitative research is moot [519]. However, based on our sampling criteria, we estimated a minimum sample size of 12 participants. Maximum variation sampling is also an emergent approach; findings from initial interviews can inform the subsequent direction of the study [520]. We therefore anticipated that further interviews may be required: later interviews were theoretically sampled to explore and define themes and fill out gaps in knowledge [521], [522]. Interviews were carried out until data saturation was reached; that is, no new themes or information relating to the identified themes emerged. This was operationalised by interviewing the initial maximum variation sample of 12 participants, then continuing to sample an additional eight participants theoretically until no new information was ascertained. Combining maximum variation and theoretical sampling enabled comparison of data from different participant groups constitutes a form of triangulation [523]; the goal in this context was completeness rather than convergence or consensus [524].

### ***3.6.5.3 Data collection, analysis and reporting***

Data were collected and analysed iteratively, starting with the topic guide, but allowing the interviewer to follow participants' responses, gradually focusing on emerging themes and analytical categories. All interviews were transcribed 'intelligent verbatim', that is, excluding hesitations and non-verbal expressions, and the transcripts anonymised. AH-M transcribed six interviews and the remainder were transcribed by professional transcriptionists. All interviews were checked for accuracy against the audio files. Analysis was an ongoing process and interviews were conducted until additional interviews ceased contributing to the analysis. The process of analysis was assisted by qualitative analysis software (NVivo) [525]. The use of this software merely provided a tool to organise and review the data during the analysis process, and did not provide an objective method of analysis [526].

Analysis was interpretive and drew on grounded theory and constant comparison [527]. Grounded theory is particularly useful: 1) when exploring new research areas; 2) when

researchers seek to gain new perspectives in familiar areas; or 3) when studying complex behaviour where salient behaviour has not been identified [528]. Constant comparison is an iterative analysis method whereby each emergent theme or analytic category is searched for across all transcripts and all instances are compared until no new themes or categories can be identified [529]. Transcripts were read and reread, discussed with the supervisory team and compared with emerging understanding from other transcripts. A combination of coding for themes and categories were used for the analysis. The purpose of coding themes was to capture the meaning of the data; whereas categories aimed to sort data into the same place in order to identify and describe the characteristics of the categories to enable definition and comparison [530]. The category coding enabled the generation of the 'stages' of the decision making process, which is presented in Chapter 5. Alongside coding, a holistic consideration of transcripts aimed to retain the context of participants' accounts and enable the identification of 'invisible' aspects of accounts not clearly expressed or not 'fitting' with the rest of the account. Emerging constructs were continually reviewed in the light of new data and were modified to ensure they fitted the data whilst taking into account deviations. Given that the researcher had authored a meta-synthesis, deviant cases whose account did not emerge from existing data were actively sought out. Further analysis involved a two-way process: some unique insights arising directly from inductive analysis, while others drew on the literature [531][532] and might be considered more deductive. Thus refinement of the themes and categories involved an iterative process between the data, literature, and back to the data [522]. Quotations presented in the final write-up were broadly representative of the key themes and reflected a range of views.

#### ***3.6.5.4 Ethical and consent issues considered***

Ethical approval was granted by National Research Ethic Service (NRES) Committee South Central - Southampton A (REC reference 11/SC/0146). This approval was for the whole REFRAMED trial and included permission to undertake a qualitative study to explore the decision making process of patients who declined.

Participants opted into the qualitative study by providing written consent (see Appendix 1). Each participant was informed of the purpose of the study and assured that participation was voluntary, that the data would be anonymised and kept confidential. Participants were asked to reiterate their consent verbally or by email prior to the commencement of each interview. This process of informed consent has been used in a



previous study with trial decliners [511]. This method also recognised that informed consent is an ongoing process, while minimising the burden of participation in the interviews for this hard-to-reach group [533]. This process was also discussed with and approved by two PPIR groups - SURP and PRIMER.

### **3.6.6 Patient and public involvement**

For this qualitative study we sought involvement from two patient and carer involvement groups – SURP and PRIMER. The study plans and topic guide were reviewed by SURP and PRIMER. Feedback from both groups was overwhelmingly positive, and members felt that this was an important and worthwhile study. Three suggestions were made, all of which were implemented. The first was to ‘role play’ the interview with a mental health service user prior to undertaking the study. A member of SURP met with AH-M for detailed discussion around the interview schedule (Chapter 5), as well as to role play the interview in preparation for conducting the actual interviews. The second suggestion was around the timing of the telephone calls, which they suggested should avoid early mornings (to not awaken those who may need to sleep a little later) but include the early evenings to reach those who may work. The third suggestion was to ensure the appropriate management of potential suicide risk in telephoning this group of patients diagnosed with depression. This resulted in the use of a risk protocol, which was the same used by other researchers in the REFRAMED trial (see Appendix C).

### **3.6.7 Strengths and limitations**

To our knowledge this is the first study to focus on the process of decision making when declining a mental health trial. Involving service users in the development of the topic guide ensured that the patient perspective was considered from the very early stages of intervention development. We achieved theoretical saturation.

It has been argued that the absence of visual cues when using email and telephone interviews may result in loss of contextual and non-verbal data and to compromise rapport, probing and interpretation of interview responses [534]. However using these methods enabled us to access a hard-to-reach group with whom we might otherwise not have engaged [535][536]. Whilst we may have lost some ‘quality’ in terms of not being able to access non-verbal cues, we felt this was a necessary price to pay to access this hard-to-reach group.

Due to small numbers of patients declining REFRAMED who opted into this qualitative study, the completion of the study took 16 months, which was longer than anticipated. Whilst ongoing analysis fed into the development of the recruitment intervention, the delay in completion of the qualitative study meant that the qualitative study played less of a prominent role in the development of the recruitment intervention than it could have.

### **3.7 Methods – Study Three: Evaluating the impact of advertising patient and public involvement on trial recruitment: an embedded cluster randomised recruitment trial**

The corresponding paper is presented in Chapter 6:

**Hughes-Morley A.** Hann M, Fraser C, Meade C, Lovell K, Young B, Roberts C, Cree L, More D, O’Leary, Callaghan P, Waheed W, and Bower P (submitted). The impact of advertising patient and public involvement on trial recruitment: embedded cluster randomised recruitment trial. *Trials*

#### **3.7.1 Rationale**

The systematic review and meta-synthesis of factors affecting the recruitment of participants into depression trials undertaken as part of this thesis enabled the development of a conceptual framework, which highlighted that the decision by patients to enrol as participants in trials involves a difficult deliberation involving ‘risk’ [531]. The qualitative study also identified the need for increased patient and public involvement in trials, specifically the presentation and provision of accurate and effective trial information in which patients and the public play a seminal role. Evidence is emerging that PPIR may improve rates of recruitment into trials [537], however the best way to use PPIR to achieve that is unclear. Although many trials use PPIR to improve design and conduct, many do not communicate their use of PPIR clearly to potential participants. Better advertising of PPIR might encourage patient participation, as trials may be seen as more socially valid, relevant and increase patient trust.

The most robust method of evaluating recruitment interventions is to ‘embed’ trials of recruitment interventions in ongoing host trials [370], [383]. However, systematic reviews have identified relatively few of these recruitment trials embedded in ongoing trials [277], [370].

#### **3.7.2 Objectives**

The objectives were to:

1. Work with PPIR stakeholders to develop an intervention directly advertising PPIR in a host trial (the ‘EQUIP’ trial) recruiting people diagnosed with serious mental illness

2. Evaluate its effectiveness on recruitment by undertaking a randomised controlled trial, embedded in the EQUIP trial

### 3.7.3 The randomised controlled trial (revisited)

In Chapter 2 we highlighted that the randomised controlled trial is the most rigorous way of evaluating whether a cause-effect relation exists between an intervention and outcome [131]. We also provided a basic overview of the trial. In this section we describe the features of the trial (Table 14) and how we utilised this method to evaluate the recruitment intervention.

**Table 14: Key features of a randomised controlled trial, adapted from Sibbald (1998)**

[131]

- Outcomes are pre-defined at the outset
- Use of random allocation to experimental intervention or control groups
- Blinding of participants and/or those delivering the experimental intervention (in most cases)
- All groups are treated identically, with the exception of the experimental intervention
- Participants are usually analysed according to the group to which they were allocated (intention to treat analysis)
- The analysis estimates the size of difference in outcomes between the experimental intervention and control groups

Within a trial, random allocation means that each participant has a known chance of being placed in the experimental intervention or control groups, but the group they are to be allocated to cannot be predicted [538]. Random allocation may be at the level of the individual participant or group (cluster) level. The purpose of random allocation is to minimise bias by attempting to distribute confounding variables equally amongst study arms [539]. This guards against potential systematic differences between the experimental intervention and control groups from any influences, known and unknown, that could affect outcome. Blinding ensures that the prior beliefs of participants and those delivering the experimental interventions cannot systematically bias the assessment of outcomes. The use of the intention to treat principle maintains the advantages of random allocation by analysing participants' data in the trial arm to which they were randomised, irrespective of treatment compliance, cross-over into the other arm or retention in the trial. Thus a well-designed and executed trial provides the most robust evidence regarding whether an intervention is effective or not.

### ***3.7.3.1 Pragmatic and explanatory trials***

While trials generate crucial, robust evidence on the effectiveness of interventions, many trials have limited relevance to actual practice [540]. Trials can be explanatory or pragmatic in nature. Explanatory trials assess efficacy: the benefit an intervention produces under ideal circumstances using carefully selected participants. Pragmatic trials measure effectiveness: the benefit the intervention produces under usual circumstances [71], [541]. Pragmatic trials are designed to assess the effectiveness of interventions in routine practice and tend to have outcomes that are attuned with the evidence needs of stakeholders, such as patients, researchers and policy makers. Hence the focus is on the extent to which an intervention works in the real world (as opposed to under optimal conditions) [542]. Since they are designed to test the effectiveness of interventions in real world practice and promote evidence based practice, pragmatic trials are less-perfect experiments than explanatory trials, because they sacrifice some internal validity to attain external validity (that is, generalisability) [540]. Typically, pragmatic trials recruit participants from a range of settings, apply broad eligibility criteria and manage patients in a way that is consistent with usual practice. Thus estimates of intervention effectiveness in pragmatic trials are likely to be similar to those seen in usual practice when knowledge from the trial is translated into practice. For trials embedded within ongoing host trials, findings will relate to the context of the host trial; therefore results are likely to apply to trials recruiting from similar contexts to the host trial.

A distinct strength of the pragmatic trial is that if an intervention is demonstrated to be effective, there can be a level of assurance that the intervention really does work and can be implemented in real practice [543]. However, pragmatic trials have drawn criticisms for having the following limitations:

1. They can sacrifice some internal validity, for example, by not blinding those delivering the intervention, to attain external validity - that is, generalisability
2. If an intervention is shown to be ineffective, it cannot provide information as to whether the intervention is effective under ideal conditions
3. Due to the potential heterogeneity of treatment effect, they often require large sample sizes to detect small intervention effects
4. They present greater design and analytical challenges due to the heterogeneous sample
5. They are less-perfect experiments than efficacy trials

A defence of pragmatic trials is that if in the real-world people do not utilise interventions as directed, the problem must be permitted to occur in a trial, in order to obtain a clear answer as to whether the underlying intervention works in the real world [543]. Furthermore, pragmatic and explanatory trials are not distinct concepts, as trials incorporate differing degrees of pragmatic and explanatory components. This can strengthen internal validity while maintaining external validity. The decisions that trialists make about the designs of their trials therefore make a trial more (or less) pragmatic or explanatory [544]. However, it becomes important to establish the extent to which a trial is pragmatic or explanatory because this is important for the interpretation of findings. For example, a 'positive' explanatory trial does not guarantee that the intervention will work in usual practice; conversely, a 'negative' explanatory trial very strongly suggests that its intervention would not work in usual practice. Similarly, a 'positive' pragmatic trial strongly suggests its intervention would also work in an ideal setting, whereas a 'negative' pragmatic trial does not mean its intervention cannot work in an ideal setting. Tools such as the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) have now been developed to assist trialists in making design decisions that are consistent with their trial's stated purpose [544]-[546].

### ***3.7.3.2 Cluster trials***

The majority of trials adopt individual participant level randomisation, where individuals are assigned to different interventions. Participant level randomisation is not always possible or desirable however, and it can be more appropriate to adopt cluster randomisation. Cluster randomisation can take a variety of forms; the most common is where groups of participants, such as general practices or mental health teams form the unit of randomisation. Cluster randomisation is often used to minimise 'contamination' between the intervention and control groups (e.g. a training intervention aimed at staff within a mental health team) which might occur with individual randomisation and result in dilution bias and as a consequence lead to Type II error (i.e. erroneously concluding there is no effect when the intervention is effective) [547], [548]. To overcome this dilution bias, cluster (mental health team) level randomisation is conducted on the basis that compared with individual staff level randomisation, members of staff in the intervention teams are less likely to contaminate patients in the control arm.

Cluster trials present more challenges in their design, execution, analyses and reporting than individually randomised trials [155], [549]. A design characteristic of cluster trials is

that observations from participants within a cluster are generally more similar than participants in different clusters, meaning that each individual within a cluster adds less new information. This reduces the effective sample size and is called the design effect, the main components of which are the cluster size and the intra-cluster or intra-class correlation coefficient [550]. As a consequence, cluster trials may require significantly larger sample sizes than individually randomised trials. Statistical analysis of cluster trials requires adjustment for intra-cluster dependencies, otherwise the result may lead to erroneous conclusions, resulting in Type I error (i.e. falsely concluding there is an effect when there is no effect). Another potential threat to the validity of cluster trials is where trial recruiters in different trial arms enrol participants differently depending on the cluster allocation: this can result either in bias as a consequence of differential recruitment [547]; or raise ethical issues [551].

The reporting of cluster trials must also allow readers to assess trial quality and understand how the conclusions were reached [552]. Here, the CONSORT extension for cluster trials recognises the need for accurate reporting and provides clear guidelines on the reporting of cluster trials [155].

### **3.7.3.3 *Embedded recruitment trials***

An embedded randomised controlled recruitment trial, also known as a ‘nested’ trial, a ‘trial within a trial’ or a ‘study within a trial’ (SWAT), can be defined as:

*‘A RCT in which an intervention (or several interventions) to enhance recruitment outcomes are tested in the context of another RCT (or several RCTs) known as the host RCT(s)’. [553] - p2*

This test of the effectiveness of the recruitment intervention using a trial conducted in the context of an ongoing host trial forms the most rigorous test developed to date to evaluate the effectiveness of such interventions [383]. In determining the effectiveness of recruitment interventions in real-world settings, embedded recruitment trials can therefore be classified as pragmatic trials.

Systematic reviews have identified a limited number of such embedded trials [367], [370]. A range of scientific, logistical and ethical challenges to embedded trials have been identified [90], [554]:

1. The design and conduct of the embedded trial is often constrained by its host trial

2. The sample size of the embedded trial is limited by the number of participants approached by the host trial. This can sometimes mean that the embedded trial is insufficiently powered to attain statistical significance, although this tends to be more of an issue for retention trials than for recruitment trials as the sample size for recruitment trials is larger, being the number of patients approached, rather than the number enrolled
3. Host trial investigators' resistance to randomising recruitment methods may make implementation difficult
4. Potential ethical concerns around different patient populations being approached differently
5. Potential concern of funders about the impact of embedded trial on host trial progress
6. Additional workload posed by embedded trial on host trial staff
7. The results of single embedded trials may not generalise to other trial contexts

Thus undertaking these trials present real challenges, and trialists often choose to evaluate recruitment interventions using hypothetical, rather than real-life trials [370]. Hypothetical trials present their own difficulties in that potential participants are not making real decisions, therefore it is unclear how generalisable their results are to real-life trials [555]. Furthermore, the small number of embedded trials that have been published tend to be undertaken by the host trial teams themselves in an ad-hoc way, often in response to recruitment problems and/or in the context of clinical trials units [90]. Embedded trials are also often poorly reported [370], [553] not containing sufficient information for replication. In addition, embedded trials have some methodological characteristics that are atypical, such as the eligible population and sample size being restricted to the host trial. These characteristics affect their design, conduct, interpretation and reporting. Guidelines for reporting embedded trials have recently been published [556].

#### **3.7.4 The START model**

To address the thesis objective of systematically developing and evaluating a recruitment initiative in the context of an ongoing host trial, the author collaborated with the Systematic Techniques for Assisting Recruitment to Trials (START) programme. The collaboration with START established the feasibility of recruiting host trials and working with them to develop, evaluate and report the recruitment intervention. We highlight here



that the Chief Investigator for START was also the primary supervisor of the author. This facilitated access to START and ensured START findings would feed into the thesis.

The START program was funded by the Medical Research Council (MRC) Methodology Research Programme to support the routine adoption of embedded trials to evaluate standardised recruitment interventions across multiple ongoing host trials [384]. The program involved three interrelated work packages:

1. Methodology: to develop guidelines for the design, analysis and reporting of embedded recruitment trials
2. Interventions: to develop interventions to enhance recruitment
3. Implementation: to recruit host trials and evaluate interventions through embedded recruitment trials

Through these work-packages, START aimed to rapidly develop a reliable and rigorous evidence base. START aimed to achieve this by evaluating recruitment interventions across a number of host trials simultaneously, in order to maximise sample size and generalisability. Ultimately, this would contribute to the health and wellbeing of patients and carers through better trials. START focused on the recruitment of patients in primary care and community settings and developed and evaluated two recruitment interventions: enhanced patient information sheets (PIS); and multimedia resource (MMI). START aimed to recruit six trials to each of these interventions, conducting a total of 12 embedded recruitment trials.

To meet the aims of this thesis the author collaborated closely with the START team. She shadowed team meetings, the process of methodological development, intervention development and implementation in order to gain valuable insights. She also actively contributed to the START, including to: the START protocol [384]; the development and testing of the PIS and MMI recruitment interventions in ongoing host trials [557], [558]; and the development of guidelines for reporting embedded recruitment trials [553]. Table 15 compares START with the work in this thesis.

**Table 15: Comparison between START and the work in this thesis**

<b>START</b>	<b>Thesis</b>
Develop interventions to enhance recruitment into primary care and community trials	Develop and evaluate an intervention for mental health trials
Collaborate with multiple ongoing host trials (n=12) to test these interventions using trials embedded in the trials	Collaborate with one mental health host trial to test the effectiveness of a recruitment intervention, using the START model. This included adopting the protocol template for working with the host trial
Develop guidelines for the reporting of embedded recruitment trials	Use the START guidelines to report the embedded recruitment trial
Undertake a meta-analysis by combining data form the multiple host trials	No meta-analysis planned
Rapidly develop the evidence base	Make a contribution to the evidence base

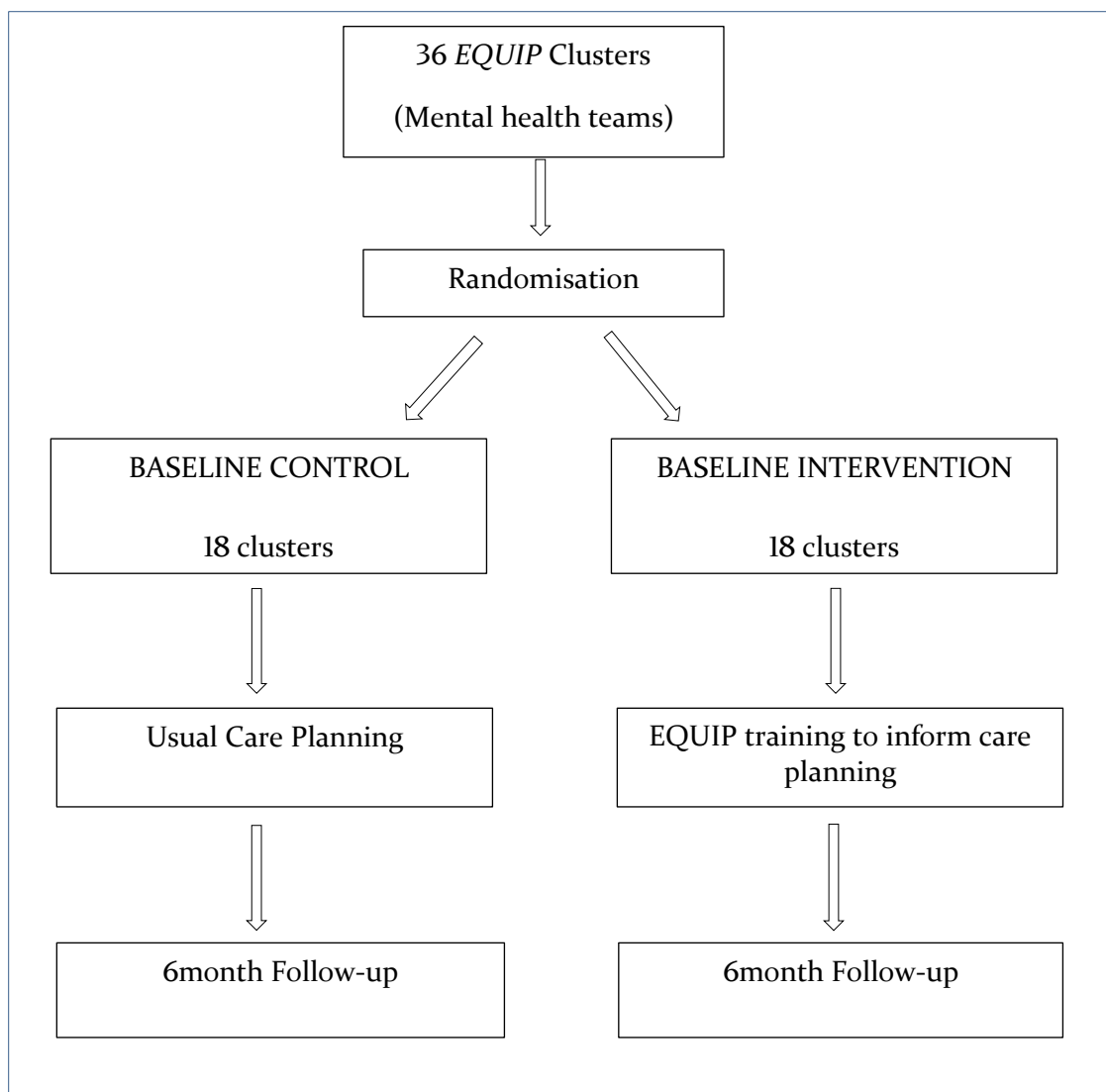
This thesis uses the principles underlying the START programme to develop an independent stream of research, which extends the START methodology to mental health trials and to develop a recruitment intervention specifically for recruiting patients with mental health problems into trials. This thesis represents the first intervention to be systematically developed for mental health trials [370], to recruit an ongoing mental health trial (EQUIP) and to evaluate its effectiveness within the mental health trial. In the following section we describe the EQUIP trial and the development and evaluation of the recruitment intervention.

### **3.7.5 Design: The EQUIP host trial**

We approached the investigators of the EQUIP trial – Enhancing the Quality of User Involved Care Planning in Mental Health Services – and proposed a collaboration to enable the recruitment intervention to be evaluated in the context of a real, ongoing host trial. EQUIP aimed to evaluate the cost-effectiveness of a training intervention for mental health professionals to improve user involvement in care planning for service users with diagnoses of SMI [559]. EQUIP had significant high-quality PPIR and was awarded the 2014 UK CRN Mental Health Prize for ‘Outstanding Carer Involvement’ [560]. The collaboration with EQUIP was initiated as the author’s primary supervisor was a co-investigator on EQUIP; thus the author was aware that its recruitment timeline aligned with that of the work in this thesis.

EQUIP was a multi-centre cluster randomised trial, in which 36 mental health teams and rehabilitation inpatient facilities in England caring for 480 patients were randomly allocated to the training intervention or to usual care. In EQUIP, the mental health team clusters were ‘paired’ at the recruitment stage, based on size and geographic location, and randomly assigned in pairs using minimisation to the training or control arm. Recruitment in each paired clusters operated in parallel (Figure 7).

**Figure 7: EQUIP trial recruitment flowchart [559]**



EQUIP used existing registers maintained by the mental health teams to recruit participants. Recruitment was undertaken by the UK CRN Mental Health CSOs and Research Nurses, who accessed patient details, determined eligibility and mailed trial invitations. Invitations were posted to patients prior to randomisation of clusters. The EQUIP eligibility criteria for patients were:

1. Aged 18 years or older
2. To be under the care of a mental health team
3. To have capacity to provide fully informed consent and to be judged well enough to complete study assessments.

The research team did not have access to patient details until they returned the ‘consent to contact’ form. In clusters where recruitment was deemed to be slow by the trial team, potential participants who did not respond to the initial invitation letter were telephoned by a CSO, Research Nurse or a member of their mental health team to determine whether they received the trial invitation and if they would be interested in taking part. Recruitment and baseline assessment of participants in each cluster pair occurred before the training intervention was delivered to the mental health cluster in the intervention arm, which was within six weeks of the trial invitation being mailed. The host trial team aimed to recruit a minimum of 10 participants per cluster. Details of the EQUIP trial design have been published [559].

### **3.7.6 Design: Developing the recruitment intervention**

#### ***3.7.6.1 Participatory Design***

We adopted Participatory Design approaches [561]–[563] to develop the recruitment intervention.

*‘In Participatory Design the people destined to use the system play a critical role in designing it.’ [564] - pXI*

Originating from Scandinavia in computing and engineering design, Participatory Design has been adopted outside of technology, including interventions for mental health [565]–[568]. Participatory Design offers an evolving set of critical, conceptual and practical tools to support active collaboration with users in the design of interventions, systems, services and products [566]. Participatory Design aims to appreciate the ‘lived experience’ of users and channel those experiences as resources for design [569]. Moving beyond consultation and testing, Participatory Design strives for active contribution of end-users as co-designers throughout the design process [561][566]. In this way, Participatory Design is complementary to other participatory approaches such as PPIR [566]. Involving end-users in the development of interventions closely aligns that intervention with the priorities of potential participants and leads to interventions developed with a better understanding of users’ requirements that may have several advantages: better engagement; relevant and

usable; and minimises anxiety [570]–[573]. This approach is therefore potentially useful for promoting trial recruitment.

In adopting the Participatory Design approach we considered its method, tools and techniques such as workshops [566] and mock-ups [574], as well as the role the end user would play in the design process [561]. Stakeholders can be involved in the following aspects of the design process [566]:

- Developing the design goals and principles that will guide the intervention
- Generating and shaping creative concepts
- Generating, selecting and refining the design direction and look and feel
- Developing content
- Identifying and developing potential distribution and promotion strategies
- Prototyping and refining functionality and implementation strategies

Participatory Design is ideally applied from the inception of a project through to implementation and evaluation; however it can also be introduced gradually and after a project has already commenced the design process [566]. In the next section, we describe the development of the recruitment intervention advertising PPIR in a the EQUIP trial.

### ***3.7.6.2 The intervention: advertising PPIR to potential trial participants***

A recruitment intervention advertising PPIR to potential trial participants was developed, informed by Participatory Design and guided by the MRC framework [164]. We hypothesised that informing potential participants invited to enrol in a trial about active PPIR in the trial would reduce patients' perception of the trial as a 'risk' and therefore increase the likelihood of them enrolling. This hypothesised mechanism was informed by the following:

1. The prior meta-synthesis and conceptual framework, which highlighted that the decision by patients to enrol as subjects in trials involves a difficult deliberation involving 'risk' [575]
2. The qualitative study, which highlighted the need to research the presentation and provision of accurate and effective trial information in which patients and the public play a seminal role [576]
3. 'Social validation', emerging from social comparison theory, which suggests that people may be more willing to comply with a request to enrol in a trial if they

believe that others are already engaged in a trial, as people tend to compare and base their beliefs, attitudes and actions on similar others [387], [388], [577]

4. A survey of public attitudes to research which suggests that PPIR may increase confidence and trust in a trial, if potential participants are reassured that other patients have advised its design [333], [334].

To determine the most appropriate mechanism to deliver the intervention, the latest Cochrane systematic reviews were searched to determine frequently used recruitment and retention interventions [370], [578]. Working closely with the EQUIP team, we reviewed their recruitment strategy and discussed with the EQUIP team to agree a simple, systematic, feasible and acceptable method of delivering the recruitment intervention. Given that the EQUIP recruitment occurred through mental health teams and patients were being approached to enter EQUIP by postal invitations, we selected a leaflet format as the most appropriate delivery mechanism to advertise PPIR to potential participants.

### ***3.7.6.3 Participatory Design workshop***

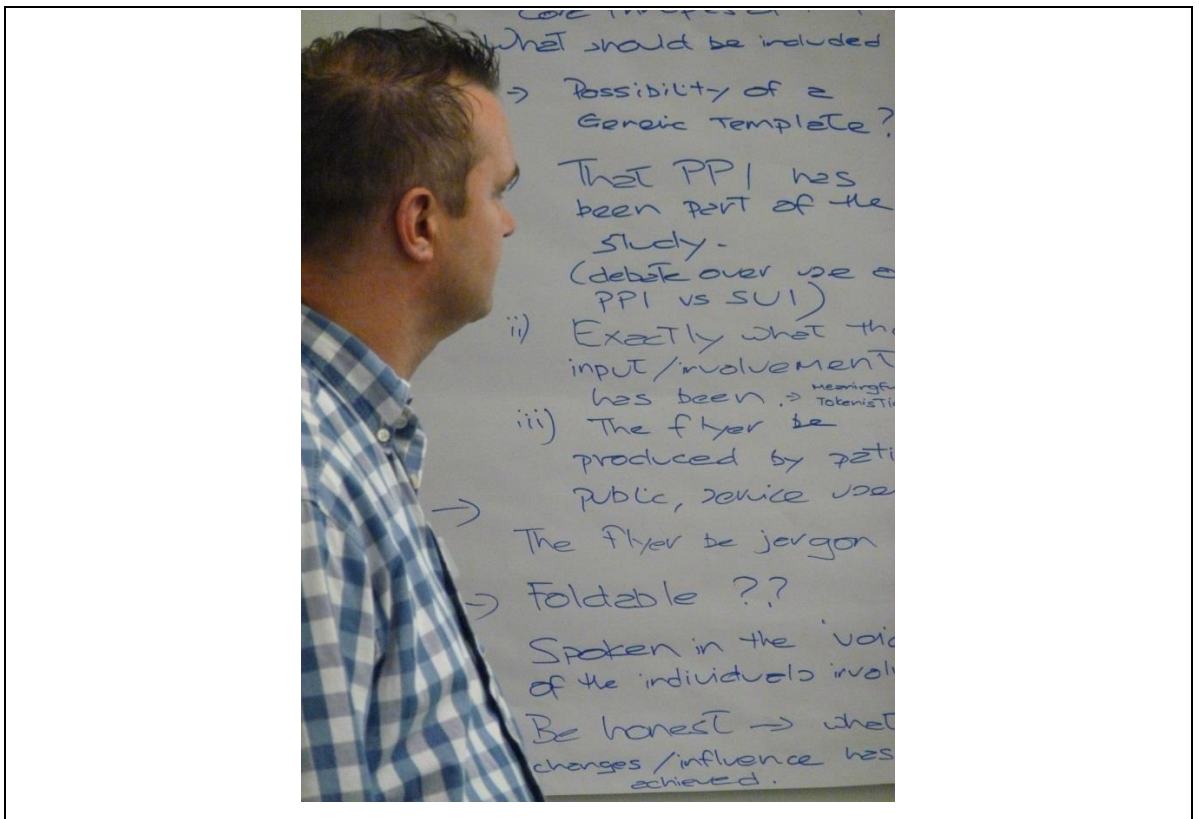
Having agreed the delivery mechanism for the recruitment intervention, the author organised a half-day expert workshop involving key stakeholders. The workshop was advertised widely through a range of sources including the Salford Citizen Scientist Project, PRIMER, SURP, CRN Mental Health, National Research Ethics Service, University of Manchester Research Ethics Committees, and directly to trialists undertaking mental health trials. 27 stakeholders including 15 patients with mental health and physical problems and their carers; principal investigators on trials; trial recruiters; research ethical review board members; and PPIR members of the EQUIP host trial attended.

During the workshop stakeholders were provided with an overview of the project, and presented with the hypothesis of PPIR as a possible recruitment intervention. Stakeholders endorsed the use of the leaflet format for advertising PPIR to improve trial recruitment. In small breakout groups, each comprised of a mix of researchers and PPIR members, and then reconvening, stakeholders discussed and agreed seven 'core principles' for the leaflet advertising PPIR to potential trial participants (see Images 1 and 2, Table 16). All images are used with kind permission of stakeholders.

**Image 1: Workshop breakout group discussing 'core principles of the recruitment intervention'**



**Image 2: Feeding back the breakout discussion to the wider group**



**Table 16: Core principles of the recruitment intervention advertising PPIR**

1. a template leaflet format communicating PPIR should be developed, but this should be tailored for each host trial;
2. the leaflet should be in booklet style;
3. it should be in plain language, with an informal, conversational style;
4. it should include photographs of the PPIR patients and carers, who in their own voice describe *how* they were involved in the trial and what their impact has been;
5. it should include photographs of the research team
6. it should show that PPIR was taken seriously and not tokenistic, should be honest
7. It should be eye catching: bold, bright print, large font, colourful

In line with the principles of Participatory Design, stakeholders were asked to ‘mock up’ their ideal recruitment leaflet advertising PPIR, in accordance with the Core Principles. Stakeholders were assigned to four break-out groups and supplied with paper, scissors, pens and other arts and craft materials (see Images 3 and 4).

**Images 3 and 4: creating the ‘mock ups’**



Each of the four groups presented their prototype leaflets to the wider group, including the key elements of the design. Members then voted for which of the four leaflets they thought was best overall for attracting potential participants. The highest-rated leaflet contained



similar elements to the other leaflets, all of which were aimed at reducing potential perception of the trial as being a ‘risk’ or an unknown quantity to patients. This included:

- a. Making a clear and direct appeal for potential participants to join the trial
- b. Including positive photographs of people with mental health problems which avoided the typical media image of a person holding their heads in their hands, which members discussed as stigmatising [579]
- c. Highlighting benefits to future patients and convenience
- d. Highlighting the person’s right to withdraw from the trial without giving a reason
- e. Emphasising approval by an independent research ethics committee. These were all aimed at reducing potential perception of the trial as being a ‘risk’ or an unknown quantity to patients.

Attending the workshop were two EQUIP PPIR members, Mrs. Lindsey Cree and Ms. Donna More, who volunteered to be photographed and featured in the recruitment intervention advertising the PPIR in EQUIP. Both ladies had active and ongoing involvement in EQUIP. Mrs Cree was a co-applicant and a member of the EQUIP trial management team; and both ladies were members of the training team that delivered the EQUIP user-involvement training intervention to the EQUIP intervention clusters.

#### ***3.7.6.4 Post-workshop intervention design***

The author worked closely with Mrs. Cree and Ms. More to develop a leaflet tailored to the EQUIP host trial, in accordance with the agreed Core Principles. In designing the EQUIP leaflet, we took into account key elements from the four leaflets from the workshop. Mrs. Cree and Ms. More supplied quotations about their involvement in EQUIP and suggested key points to highlight in the leaflet, along with colour templates and layout. Once we had designed and agreed on the initial leaflet, the author emailed a PowerPoint version to the EQUIP trial investigators and Trial Manager and asked for input, specifically to check the accuracy of the content. We also requested a quotation from the EQUIP Trial Chief Investigator (Professor Karina Lovell) for inclusion in the leaflet, which we specified should be about her opinion regarding the impact of PPIR on EQUIP. The trialist input into the leaflet did not alter its content or format.

The author then emailed the initial leaflet to a professional graphic designer at Making Sense, a company with significant expertise in designing patient communication materials ([www.makingsense.co.uk](http://www.makingsense.co.uk)). For the design brief, the author highlighted the agreed ‘core

principles' (Table 16) and focused solely on the visual presentation of the leaflet rather than the content. The graphic designer emailed two initial options for the leaflet, which the author presented to the EQUIP team and PPIR members. The EQUIP team and PPIR members were asked to vote for their preferred design and provide comment. Voting gave priority to PPIR members, so PPIR members' votes were counted twice. These comments related to the colours and visual presentation, and the content did not change. There were three rounds of iterations before the final leaflet was agreed. Table 17 outlines the presentation and content of the final leaflet. The final leaflet is attached in Chapter 6 and was sent in addition to the standard EQUIP trial invitation.

**Table 17: Content of the finalised leaflet advertising PPIR**

Presentational elements	Content
<ul style="list-style-type: none"> <li>• Four-page booklet layout</li> <li>• Photographs of the EQUIP trial team and PPIR members on the front and back pages</li> <li>• Written in plain language; with an informal, conversational style</li> <li>• Included photographs of the PPIR members</li> <li>• Included quotations written by PPIR members</li> <li>• Utilised large font sizes and bright colours</li> </ul>	<ul style="list-style-type: none"> <li>• Front and back pages advertised national award of 'outstanding carer involvement' to EQUIP</li> <li>• Front page highlighted PPIR in EQUIP, and asked patients to consider enrolling in EQUIP</li> <li>• Middle pages of the leaflet contained Photographs of PPIR members</li> <li>• Quotations by PPIR members highlighted why they thought the study was important</li> <li>• A section highlighting issues felt to be important to patients including: helping future patients, convenience, confidentiality, approval by a research ethics committee</li> <li>• Quotation from chief investigator highlighted close working with PPIR members</li> <li>• Highlighted contact details of the EQUIP team</li> </ul>

### **3.7.7 The control arm: the standard EQUIP trial invitation**

The control intervention used in our embedded recruitment trial was the standard EQUIP trial recruitment invitation material. This comprised of the following:

1. A standardised 1 page cover letter, A4 sized in 13 point font, addressed to 'Dear Service User' and signed by the EQUIP Chief Investigator, Prof Karina Lovell (Appendix F)
2. A 4 page Participant Information Sheet, in 12 point font (Appendix G)
3. A 1 page 'consent to contact' form, for participants to complete and return to the study team (Appendix H)
4. A pre-paid, addressed envelope to enable participants to return the 'consent to contact' form back to the EQUIP team

Potential participants were sent these materials in an A4 sized white envelope.

### **3.7.8 Method: the embedded recruitment trial design**

#### ***3.7.8.1 Challenges and solutions***

As highlighted earlier, designing and implementing recruitment trials embedded in ongoing host trials raises significant scientific, logistical and ethical challenges [554]. EQUIP was a cluster randomised trial, where community mental health team clusters were randomly allocated to receive the user-led training in care planning or to continue with usual practice [559]. As previously noted, the EQUIP design meant that it had a limited window of six weeks in which to approach patients within each paired mental health team, organise and undertake all baseline assessments and recruit all participants. Undertaking the embedded recruitment trial in this context raised significant methodological and logistical challenges, which had to be resolved prior to implementing the embedded trial.

The first challenge was around the embedded trial design and the recruitment of patients in clusters, which reduced the power, raised imbalance issues and presented a threat to the host trial in terms of differential recruitment. Individual patient level randomisation would have been the most efficient method for ensuring adequate power for testing the recruitment intervention in the embedded trial, and the author had originally aimed to adopt this approach. It was not possible to undertake patient level randomisation for the embedded trial however, as this was logistically burdensome and not acceptable to the EQUIP Trial Management Group (TMG). Patient level randomisation would have required the CSOs and Research Nurses undertaking the postal mailing of the EQUIP recruitment invitation letters to randomise each patient to the embedded trial (that is, randomise each patient to receive the addition of the PPIR leaflet or not); to record this systematically; and to track the response from each patient to determine outcomes. The EQUIP trial team were reliant on the CSOs to identify participants by obtaining a list of all patients within each mental health team cluster, to ask clinical teams to review the lists of all patients, and

then to invite all potentially eligible participants. At the time of recruitment commencement, the CRN Mental Health had undergone a major organisational restructure, with associated staffing cuts. This meant that the remaining CSOs and Research Nurses already had large workloads, and the EQUIP TMG were careful not to place additional burden on the CSOs and Research Nurses by asking them to do more by undertaking patient level randomisation. Reducing the burden of hosting a recruitment trial was highlighted as a potentially key factor in the success of implementing a recruitment trial [554].

We therefore opted to undertake cluster randomisation, at the level of the mental health teams, using the same cluster pairs as in the EQUIP host trial. This enabled random assignment in the embedded recruitment trial, yet reduced the burden on the CSOs and Research Nurses by removing the need for them to randomise, record allocations or to track patient responses. Rather, mental health teams would be randomised to either the intervention arm, where all patients would be sent the trial invitation with the addition of the PPIR leaflet, or to the control group, where only the standard host trial invitation would be sent. Randomisation was undertaken independently by the host trial statisticians, and the recruitment invitation packs were prepared according to their allocation status by the EQUIP trial office, with additional support from AH-M. The CSOs and Research Nurses received the prepared, sealed, stamped recruitment packs, which they mailed out to patients eligible to be invited in each team. The EQUIP trial office recorded the patient responses, logged recruitment and forward this to AH-M. This cluster randomisation solution ensured robust randomisation and reporting, removed burden from the CSOs and Research Nurses, blinded them to allocation and was acceptable to the EQUIP TMG.

Whilst cluster randomisation was the most appropriate option in this instance, it created additional challenges. As previously mentioned, the EQUIP host trial was a cluster randomised trial. The numbers of clusters available were small – 36 in total. This meant there was a possibility of imbalance in the embedded recruitment trial arms. This posed a risk in that there was a possibility of one arm of trial having a higher recruitment rate than the other (not as a result of the recruitment intervention). The bigger risk to the validity of the findings however was that there would be between-arm differences in patient characteristics, which would impact on the host trial. For example, more women may have been enrolled in EQUIP than men.

To determine the most robust way of ensuring balance between the intervention and control arms for the embedded trial, and to ensure that the embedded recruitment trial

would not adversely impact on the host trial, we sought expert statistical advice from the EQUIP trial statistical team about the best method of allocation for the embedded trial, taking into account the host trial design. The agreed solution was to adopt a cross-factorial embedded randomised controlled trial design with the EQUIP host trial intervention allocation, using pairwise allocation. The embedded trial utilised the same cluster pairs as in the EQUIP host trial and randomised them concurrently: however whilst in EQUIP *one* cluster was assigned to the intervention arm and the *other* to the control arm; the embedded trial randomised *both* clusters to either receive the recruitment intervention, or *both* to the control arm.

Cluster pairs were randomised rather than cluster units to ensure the integrity of the host trial. Pairwise allocation guaranteed that cell wise balance was achieved, that is, having approximately the same numbers of intervention and control clusters for both the EQUIP host trial and the embedded recruitment trial (Table 18).

**Table 18: 2x2 cross-factorial design of the PPIR recruitment trial embedded within the EQUIP host trial**

		<i>EQUIP host trial</i>	
		User-led training intervention	Host trial control (no training)
<i>Embedded Recruitment trial</i>	Intervention arm (sent recruitment leaflet)	User-led training + recruitment intervention = <b>9 clusters, 3164 patients</b>	Recruitment intervention ONLY (no user-led training) = <b>9 clusters, 2218 patients</b>
	Control arm (No recruitment leaflet)	User-led training ONLY (on recruitment intervention) = <b>8 clusters, 1492 patients</b>	NO User-led training + NO recruitment intervention = <b>8 clusters, 1308 patients</b>

This allocation method also ensured the validity of both the host and embedded recruitment trial interventions. Clusters were randomly allocated for their patients to be sent one of two interventions: the standard invitation (control group); or the recruitment intervention in addition to the standard invitation (intervention group). As can be seen from Table 18, the randomisation outcome was a relatively balanced distribution of clusters in the intervention and control arms of both the EQUIP trial and the embedded recruitment trial. However, the randomisation saw larger clusters (that is, clusters with larger patient sizes) being assigned to the recruitment intervention arm of the embedded

trial. We discuss how this imbalance was managed later in the 'statistical methods' section and in Chapter 6.

The recruitment intervention was sent in the same envelope as the EQUIP trial invitation, which also contained a cover letter, a participant information sheet and a 'consent to contact' response form and stamped addressed envelope. The embedded recruitment trial thus measured the incremental benefit of being sent the PPIR intervention.

There was an additional challenge to do with obtaining ethical permissions within tight deadlines. The logistically complex issues to be resolved in the planning and execution of the randomisation procedure for the embedded recruitment trial led to delays in gaining NHS ethics permission to initiate the embedded trial. This meant that the mailing of invitations to the first two clusters in the EQUIP trial occurred before we received NHS ethics approval to undertake the embedded trial. Thus the first two EQUIP clusters could not be included in the embedded trial.

Finally, the EQUIP team found recruiting adequate numbers of patients in the limited recruitment window prior to the delivery of their training intervention to be challenging. Fewer numbers of recruited patients than anticipated within each of the mental health team clusters also led to slower than anticipated recruitment. This meant that the EQUIP team found it necessary to extend recruitment from an originally planned 24 mental health team clusters to 36 clusters. This created additional logistical challenges for the embedded trial. Additional clusters recruited were required to be randomised to the embedded trial within tight timelines; there was a need to organise the supply of additional recruitment leaflets to the trial team and to assist with the packing of the trial invitation packs; and additional Research Letters of Access had to be organised for AH-M for each additional site, to enable her to access the data.

### ***3.7.8.2 Outcome measures***

In EQUIP, CSOs, Research Nurses or mental health teams telephoned patients who did not respond to the postal invitation in clusters where recruitment was poor. The latest Cochrane systematic review of recruitment intervention reported evidence that telephone follow-up prompting of patients who do not respond to invitations to participate in trials significantly increases recruitment [370]. In EQUIP telephone follow-ups were conducted as and when necessary, thus not all clusters had the telephone follow-ups.

The primary outcome was selected to assess the effect of the recruitment intervention, without potential contamination of the telephone follow-ups. The primary outcome for the embedded recruitment trial was the proportion of patients in each group who were *consented and enrolled* into EQUIP after responding to the postal invitation - that is, the proportion of participants who responded and enrolled without the need for a telephone follow-up reminder. The denominator is the number of patients initially identified as eligible participants.

The following comprised the secondary outcomes:

1. The proportion of patients in each group who *positively responded*, without the need for a telephone follow-up reminder. This differs from the number actually consented and enrolled, due to, for example the host trial exclusion criteria
2. The total proportions of patients in each group who *positively responded*, including telephone follow-up of initial non-responders
3. The numbers of clusters in each group needing to conduct telephone follow ups due to low postal response. This outcome takes into account the potential resource implications of a mental health clinician or a trial recruiter telephoning patients who do not respond to the trial invitation

### **3.7.8.3 Sample size and power**

EQUIP aimed to recruit 36 mental health clusters and approach an average of 240 patients per cluster, in order to recruit a total of 480 participants. Thus the expected recruitment rate in EQUIP was approximately 5%.

As is usual with a trial embedded within a host trial, no formal power calculation was undertaken to determine the sample size [90]. This is because in the embedded trial the sample size was constrained by the number of patients being approached in EQUIP. The sample size for the embedded trial was the total number of patients invited to participate in EQUIP from the 34 available clusters at the time of implementing the embedded trial, which was 8182 patients.

Schulz and Grimes [580] argue that whilst trialists should make proper *a-priori* sample size calculations and adequately describe the key details in their published reports, *post-hoc* power calculations are a futile exercise, since the power of a trial is expressed in the confidence interval generated from the outcome analysis. However, for the purposes of this thesis, we estimate a *post-hoc* power calculation.

The denominator is the number of patients who were initially invited into EQUIP. This is a larger number than that normally required for power calculations of clinical outcomes within individually randomised trials. A base response rate of 50% to invitations in the non-PPIR arm was assumed. A significant improvement in recruitment rate was defined as an increase in response of 8%. Given that the embedded recruitment trial was cluster randomised, the sample size calculations needed to be inflated to accommodate the clustering or design effect [581]. We assumed a total sample size of 8182 patients across 34 clusters, with an average of 17 clusters per arm and approximately 240 patients per cluster. In this recruitment trial, individual patients (level-1) were clustered within mental health teams (level-2), which were clustered within paired mental health teams (level-3). Thus a level-3 design effect was initially assumed. However, given that the overall derived intra-cluster correlation coefficient (ICC) for our sample was very small at 0.006 we ignored the design effect imposed by the cluster pairs since it was negligible. This provides approximately >99% power for a minimally detectable difference of 8% between the intervention and control groups, assuming a 5% 2-sided alpha.

#### ***3.7.8.4 Randomisation***

The EQUIP host trial statisticians undertook the randomisation and were independent from the delivery of the interventions for both the host and embedded trial. Randomisation in EQUIP was stratified by cluster pairing, the site/region and caseload size of each cluster. The embedded recruitment trial used the same cluster pairing as the host trial. Thus the unit of randomisation for the embedded recruitment trial was the cluster pair. Each cluster pair was block-randomised using permuted block sizes of 2, 4 and 6. A computerised randomisation programme was utilised to undertake the randomisation. Patients did not know that they were part of a trial of a PPIR intervention so were blind to the study hypothesis. CSOs and Research Nurses undertaking trial recruitment and mental health team clusters were also blind to the group to which clusters were allocated. Allocation was also concealed from patients, mental health teams and trial recruiters.

#### ***3.7.7.5 Data management***

Data were entered and managed using Microsoft Excel [582]. Data were checked and validated, and discrepancies were checked with the EQUIP host trial team manager to resolve. Once discrepancies were dealt with the database was locked for analysis. This



means that the database was made read-only. To help identify problems with missing data, outlying values, or other errors, full descriptive statistics were produced for all variables in the database(s). The numbers for the available data for each analysis were reported.

#### ***3.7.8.6 Statistical Methods***

To undertake the statistical analysis, baseline data on cluster size (patient list size), deprivation, care quality rating and patient satisfaction with clinical care were obtained. Cluster size data were obtained from the EQUIP host trial team. Deprivation was determined using the Index of Multiple Deprivation rank, averaged across Lower-layer Super Output Areas located within each cluster's Clinical Commissioning Group [583]. Care quality and patient satisfaction data were obtained at the cluster level from the Care Quality Commission, which is the independent regulator of health and social care in England [584]. Patient satisfaction focused on the experiences of service users who receive care and treatment within the mental health teams. Baseline comparability of trial arms and representativeness of the sample in terms of the clusters and the overall eligible population were examined using preliminary tabular and graphical exploration of the data.

Patients from the same mental health team cluster were considered to be possibly correlated since their outcomes are more likely to be similar to each other [585]. Various options were considered for the statistical analyses. Standard logistic regression was not considered to be appropriate in this instance, given that the analysis needed to account for a multi-level structure involving individual patients, mental health clusters and cluster pairs. The generalised estimating equation (GEE) approach was considered as an option [586]. The GEE accounts for clustering and the cluster pair could have been treated as a fixed-effect, or a categorical covariate in the model; however, this would have had the undesired effect of limiting the generalisability of the effect estimate and underestimating its standard error.

Analysis therefore adjusted for the clustering variable and used generalised linear mixed models (GLMM) to estimate the effect of the recruitment intervention [587]. The 'mixed' model refers to the use of both fixed effects - parameters that would be used again if the trial was repeated; and random effects - parameters that have been randomly selected, for example, mental health teams. As the unit of randomisation was the cluster pair, a three-level random effects logistic model was fitted, which pertained to the individual patient (level-1), clustered within mental health teams (level-2), clustered within paired mental

health teams (level-3). Calculation of a cluster-marginal effect involved averaging over the random effects at level-2 (cluster) and 3 (cluster pair). This provided a measure of effect on the group (cluster) being randomised, rather than on the individuals within the clusters. The analysis adjusted for mental health team cluster size, levels of deprivation and care quality rating. Patient satisfaction with clinical care was not included in the model due to incomplete data. Standard errors and confidence intervals for cluster marginal effects were calculated using the delta method. Given that the EQUIP randomisation occurred after the embedded trial randomisation, there was no plausible causal effect of the EQUIP intervention on recruitment so no interaction between the EQUIP intervention and the recruitment intervention was tested for. To assist with interpretation, the output reports the marginal mean difference in proportions (that is, the effect in the cluster pair) as well as odds ratios (which provide a measure of association between being sent the recruitment intervention and enrolling in EQUIP).

Due to the small numbers of clusters, Fisher's exact test rather than a chi-squared test was used to test for association between recruitment trial arm and the need for telephone follow-up [588]. Fisher's test calculates an exact p-value by considering all possible configurations, hence its use in small samples, rather than an approximation which improves with increasing numbers. Analyses were in accordance with the intention-to-treat principle and were undertaken using Stata, version 14 [589]. Appendix reports the statistical analysis outputs.

#### ***3.7.8.7 Ethical Issues and trial registration***

NRES approval was obtained to conduct the EQUIP trial, using the recruitment method described above. Patients did not give informed consent to enter into the embedded recruitment trial. This was approved by NRES Committee Yorkshire and the Humber – South Yorkshire (REC Reference 11/YH/0271) on the basis that the embedded trial was not withholding information. The embedded trial has been registered by EQUIP as a sub-study [559], and as a 'Study Within a Trial' (SWAT) by the MRC Hubs for Trials Methodology Research (SWAT 26) [590]. A Research Passport and letters of access were obtained for all recruitment sites in EQUIP to enable the author to access the data.

### **3.8 Chapter Summary**

In this Chapter we have outlined the methodological basis of this thesis. We discussed the adoption of the MRC framework for the thesis and explained the rationale for using a mixed methods approach. This chapter also detailed each of the three studies, including the rationale for method selection, a description of the main features of the methods, and a discussion of the key strengths and limitations of each.

We have reported each study in publication format, which we present in the following three chapters (4-6).

# Results

---

The following three chapters (chapters 4-6) are results chapters from the three empirical studies.

## Chapter 4: Factors affecting recruitment into depression trials: Systematic review, meta-synthesis and conceptual framework

---

**Chapter type:** Journal Article

**Journal:** Journal of Affective Disorders

**Status:** Published

**Submission date:** 30<sup>th</sup> May 2014

**Published online:** 13<sup>th</sup> October 2014

**Reference:** Hughes-Morley, A., Young, B., Waheed, W., Small, N., & Bower, P. (2015). Factors affecting recruitment into depression trials: systematic review, meta-synthesis and conceptual framework. *Journal of affective disorders*, 172, 274-290.

**Awards:** Best Poster Presentation, NIHR Trainees Meeting 2013, Leeds

**Contributions:** AH-M conceived and designed the study. AH-M undertook the searches, eligibility selection, data extraction, synthesis and drafted the manuscript under the supervision of Bridget Young, Peter Bower and Waquas Waheed. Nicola Small undertook data extraction and eligibility selection. All authors contributed to the manuscript write up and approved the final article.





## Review

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



Adwoa Hughes-Morley <sup>a,\*</sup>, Bridget Young <sup>b</sup>, Waquas Waheed <sup>a</sup>, Nicola Small <sup>a</sup>, Peter Bower <sup>a</sup>

<sup>a</sup> NIHR School for Primary Care Research, Manchester Academic Health Science Centre, Centre for Primary Care, Institute of Population Health, The University of Manchester, Manchester, UK

<sup>b</sup> MRC North West Hub for Trials Methodology Research, Institute of Psychology, Health and Society, University of Liverpool, Liverpool, UK

## ARTICLE INFO

## Article history:

Received 30 May 2014

Received in revised form

1 October 2014

Accepted 3 October 2014

Available online 16 October 2014

## Keywords:

Systematic review

Depression

Patient recruitment

Meta-synthesis

Randomised controlled trials

Conceptual framework

## 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.

© 2014 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-SA license (<http://creativecommons.org/licenses/by-nc-sa/3.0/>).

## Contents

1. Introduction	275
2. Method	275
2.1. Systematic literature search	276
2.1.1. Inclusion and exclusion criteria	276
2.2. Quality appraisal	276
2.3. Literature synthesis	277
3. Results	277
3.1. Search results	277
3.2. Quality appraisal outcome	278
3.3. Literature synthesis: analysis and results	278
3.3.1. Health state	280
3.3.2. Attitudes towards research and trial interventions	281
3.3.3. Engaging the patient	282
4. Application of the synthesis to develop a conceptual framework of key factors involved in patients’ decision to participate in depression trials	284

\* Corresponding author. Tel.: +44 161 275 7632; fax: +44 161 275 7600.

E-mail address: [adwoa.hughes-morley@manchester.ac.uk](mailto:adwoa.hughes-morley@manchester.ac.uk) (A. Hughes-Morley).

5. Discussion .....	284
5.1. Summary of key findings .....	284
5.2. Comparison with existing literature .....	284
5.3. Research implications .....	285
5.4. Limitations .....	286
6. Conclusions .....	286
Ethics .....	286
Role of funding source .....	286
Conflict of interest .....	286
Acknowledgement .....	286
Appendix A. Search strategy – Medline .....	287
Appendix B. The papers excluded from the meta-synthesis, and reasons for exclusion.....	288
References .....	288

## 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 (Tenhaven 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; Hetherington 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 approach (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.

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

Inclusion	Exclusion
<p>Studies: Peer reviewed journal articles or conference papers published anytime up to April 2013.</p> <p>Articles in English language, published in any country</p> <p><b>Sample:</b> Patients with depression, professionals including clinicians, as well as researchers etc.</p> <p><b>Phenomenon of interest:</b> Recruitment of research participants</p> <p><b>Design:</b> 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</p> <p><b>Evaluation:</b> Any type of evaluation/outcome, including patient, clinician or researcher views</p> <p><b>Research type:</b> Qualitative and mixed methods studies that report on factors affecting recruitment into depression trials</p>	<p>Unpublished dissertations, book chapters or papers</p> <p>Studies with a majority (more than 50%) of participants under 18 years of age</p> <p>Studies that focus on attrition</p> <p>No qualitative analysis undertaken or primarily quantitative data reported. Questionnaire data were included in this classification</p> <p>Reports that focus on the feasibility of delivering interventions in depression trials, rather than on recruitment</p> <p>Studies of recruitment into depression research studies that are not randomised controlled trials</p>

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

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; Hetherington 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).

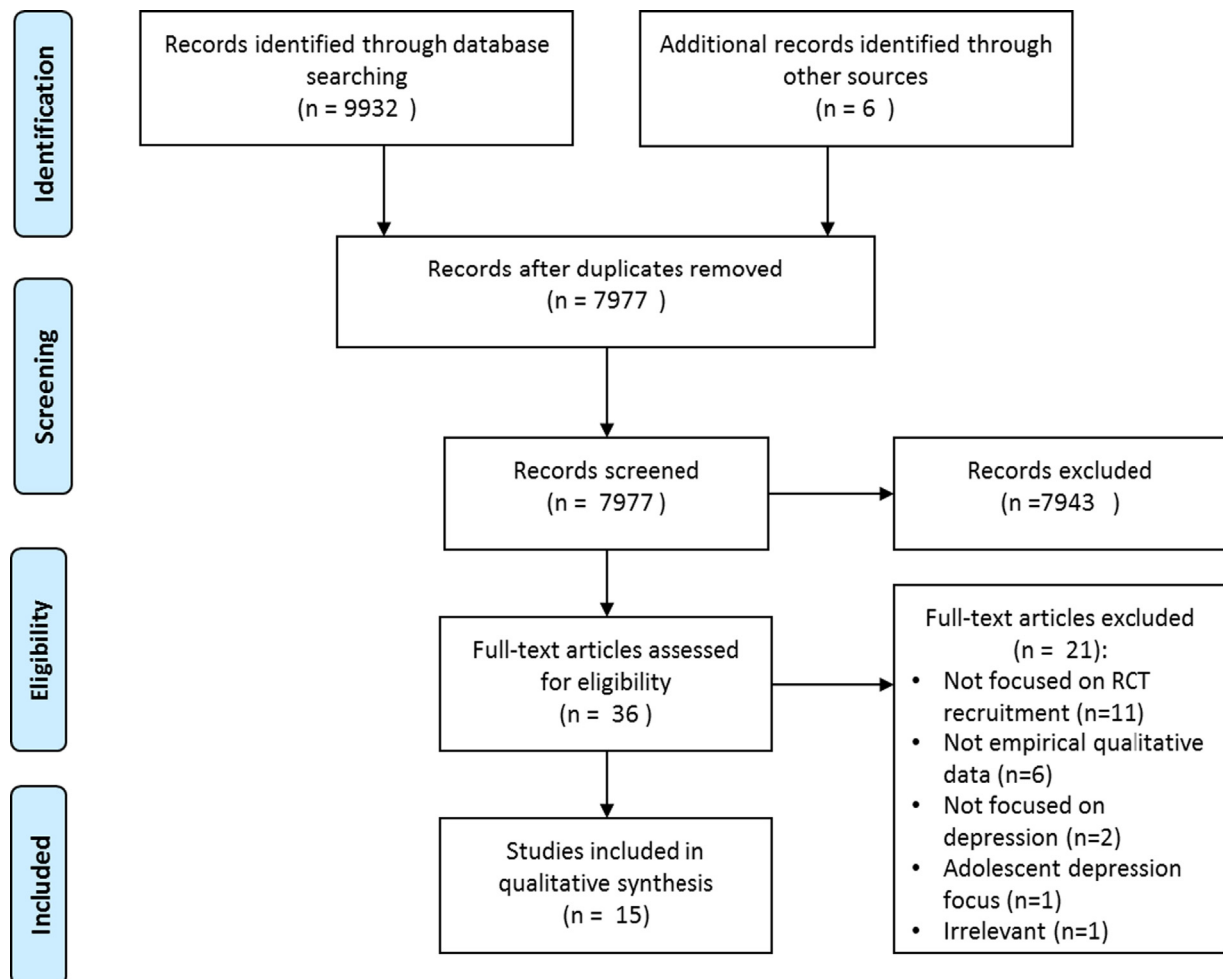


Fig. 1. Summary of literature search, adapted from PRISMA (Moher, 2009).

**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 <sup>a</sup> 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%)

<sup>a</sup> 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 present 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. Hetherington 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 Mokol (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 $\geq 75$ 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. Hetherington et al. (2004)	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	SAT
9. Hinton et al. (2006)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	KP
10. Mason et al. (2007)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	KP
11. Mendel et al. (2011)	✓	✓	✓	✓	✗	✓	✓	✓	✗	✓	✓	SAT
12. Schroer et al. (2009)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	SAT
13. Shellman (2010)	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	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 ( <i>Presentation, endorsement and impact of depression symptoms</i> )	Risk of trial to mental health ( <i>Fear of symptom exacerbation</i> )	Stigma ( <i>Perceived, self, double stigma</i> )	Protecting the vulnerable patient ( <i>Concerns about capacity and welfare of patients</i> )	Presenting depression trials to patients ( <i>Difficulties introducing research to patients with depression</i> )	Treatment preferences ( <i>Patient and clinician preferences for particular trial treatments</i> )	Views of trial processes and procedure ( <i>Inconvenience and burden</i> )
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. Hetherington 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; Hetherington 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. Hetherington 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 as 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 (Hetherington 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 (Hetherington 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; Hetherington 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
<i>"There's more shame associated with admitting to symptoms of depression, admitting to failure."</i> (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).	<b>Expression of depression symptoms</b>	<b>Health state</b> Consideration around the patient's health state is a key factor for both patients and referring clinicians.
<i>"Is this going to do my patient any good, or am I just doing it for the study's sake?"</i> (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).	<b>Risk of trial to mental health</b>	The diagnosis of depression often lends to patients being characterised as vulnerable, often leading to protectiveness on the part of the treating clinician
<i>"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?"</i> (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).	<b>Protecting the vulnerable patient</b>	
<i>"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"</i> (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).	<b>Burden</b>	
<i>"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</i> (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)	<b>Access to services to meet mental health needs</b>	<b>Attitude towards trial interventions</b> 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>"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."</i> (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).	<b>Treatment preferences</b>	
<i>"I guess I wanted to be part of something, to help out society ... I just thought it might help somewhere down the line."</i> (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).	<b>Altruism</b>	
<i>"[The randomization process] is the reason why they didn't get into the study in the first place. It stopped it".</i> (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)	<b>Randomisation</b>	
<i>"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.'"</i> (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)	<b>Stigma</b>	<b>Engaging the patient</b> 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
<i>"To raise the research seemed alien to the atmosphere of the consultation."</i> (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)	<b>Presenting depression trials to patients</b>	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
<i>"It must be said by a physician I visit regularly ... Then I would like to agree, because my physician tells me this"</i> (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)	<b>Trust</b>	
<i>"In my opinion, the issue is that older persons are not aware of clinical studies and researchers</i>		<b>Marketing</b>	



Table 7 (continued)

First order construct	Second order constructs	Sub-theme	Third order construct: Synthesis of main findings into an explanatory framework
<i>should make an effort to inform older persons. If older persons become more aware of the problem, they will get involved more easily.</i> (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).		
<i>"The (referral) form was so simple, it was no hassle to refer on."</i> (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).	<b>Trial processes</b>	

all: "To raise the research seemed alien to the atmosphere of the consultation" (Hetherington 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; Hetherington 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

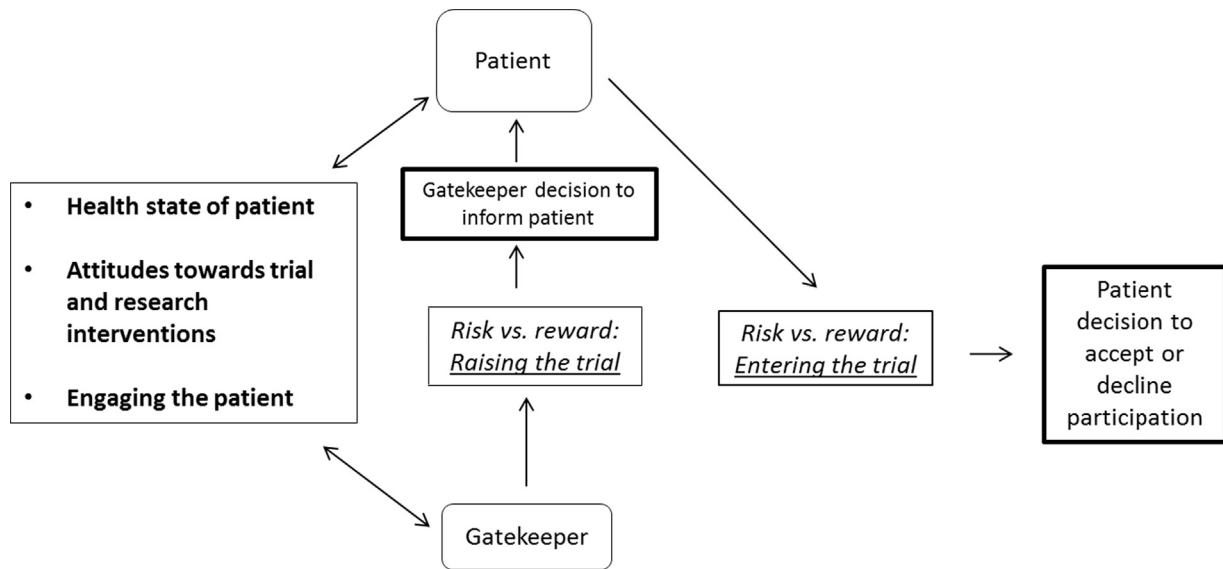


Fig. 2. Conceptual framework of factors influencing the decision to participate.

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 overstated 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 (Trewick 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 constraints 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.

## Acknowledgement

Adwoa Hughes-Morley is funded by the National Institute for Health Research (NIHR), through a Doctoral Research Fellowship (Award Reference number: DRF-2012-05-128). This article presents independent research funded by the NIHR. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. We are grateful to Dr. Gavin Daker-White, who read and provided very helpful comments on a draft of this manuscript.

**Table A1**  
Search strategy – Medline.

Search domains	Search terms used	Results in Medline (Search date 5th April 2013)
<b>Sample</b>	1. Depression/ 2. Depressive disorder/ 3. Dysthymic disorder/ 4. Mood disorder/ 5. or/1–4	1. 69,314 2. 55,773 3. 935 4. 10,109 5. 13,1621
<b>Phenomenon of interest:</b> 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/ 7. Patient participation/ 8. Patient selection/ 9. Enrol?*ab. /freq=2 10. recruit*.ab. /freq=2 11. Participat*.ab. /freq=2 12. Enlist*.ab. /freq=2 13. Informed consent.tw. 14. Informed consent/ 15. or/6–14	6. 4756 7. 16,563 8. 45,870 9. 18,050 10. 29,625 11. 37,227 12. 200 13. 19,713 14. 30,084 15. 17,9749
<b>Design, evaluation, research:</b> these three constructs have been combined to identify ANY research design that recruits patients with depression.	16. [Leave blank]  17. 5 and 15	16. [-]  17. 2262
<b>Limits</b>	18. limit 17 to (English language and humans)	<b>2097</b>

**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.
Gaudio 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 trial 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 enrolled 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.

## References

- Allen, M., Bromley, A., Kuyken, W., Sonnenberg, S.J., 2009. Participants' experiences of mindfulness-based cognitive therapy: It changed me in just about every way possible. *Behav. Cognit. Psychother.* 37 (4), 413–430.
- Andresen, E., Wilson, K., Castillo, A., Koopman, C., 2010. Patient motivation for participating in clinical trials for depression: validation of the motivation for clinical trials inventory-depression. *Int. Clin. Psychopharmacol.* 25, 7–16.
- Antman, E., Lau, J., Kupelnick, B., Mosteller, F., Chalmers, T., 1992. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts: treatments for myocardial infarction. *J. Am. Med. Assoc.* 268, 240–248.
- Appelbaum, P., Roth, L., Lidz, C., 1982. The therapeutic misconception: informed consent in psychiatric research. *Int. J. Law Psychiatry* 5, 319–329.
- Baquet, C., Henderson, K., Commiskey, P., Morrow, J., 2008. Clinical trials: the art of enrollment. *Semin. Oncol. Nurs.* 24, 262–269.
- Barbour, R., 2001. Checklists for improving rigour in qualitative research: a case of the tail wagging the dog? *Br. Med. J.* 322, 1115–1117.
- Barlow, D.H., 2010. Negative effects from psychological treatments: a perspective. *Am. Psychol.* 65, 13.
- Barnes, M., Wiles, N., Morrison, J., Kessler, D., Williams, C., Kuyken, W., Lewis, G., Turner, K., 2012. Exploring patients' reasons for declining contact in a cognitive behavioural therapy randomised controlled trial in primary care. *Br. J. Gen. Pract.* 62, e371–e377.
- Bartlam, B., Crome, P., Lally, F., Beswick, A.D., Cherubini, A., Clarfield, A.M., Edbrooke, D., Farre, A., Hertogh, C., Lesauskaite, V., Mills, G., Muller, M., Oristrell, J., Prada, G.I., Ruggiero, C., Sinclair-Cohen, J., Szczerbinska, K., Topinkova, E., Zalewski, Z., 2012. The views of older people and carers on participation in clinical trials: the PREDICT study. *J. Clin. Invest.* 2, 327–336.
- Barton, S., 2000. Which clinical studies provide the best evidence? the best RCT still trumps the best observational study. *Br. Med. J.* 321, 255.
- Beck, C.T., 2002. Postpartum depression: a metasynthesis. *Qual. Health Res.* 12, 453–472.
- Bevan, E., Chee, L., Mcghee, S., Mcinnes, G., 2012. Patients' attitudes to participation in clinical trials. *Br. J. Clin. Pharmacol.* 35, 204–207.
- Bonvicini, K.A., 1998. The art of recruitment: the foundation of family and linkage studies of psychiatric illness. *Fam. Process* 37, 153–165.
- Boote, J.D., Dalglish, M., Freeman, J., Jones, Z., Miles, M., Rodgers, H., 2014. But is it a question worth asking? A reflective case study describing how public involvement can lead to researchers' ideas being abandoned. *Health Expect* 17, 440–451.
- Bower, P., King, M., Nazareth, I., Lampe, F., Sibbald, B., 2005. Patient preferences in randomised controlled trials: conceptual framework and implications for research. *Soc. Sci. Med.* 61, 685–695.
- Bower, P., Wallace, P., Ward, E., Graffy, J., Miller, J., Delaney, B., Kinmonth, A.L., 2009. Improving recruitment to health research in primary care. *Fam. Pract.* 26, 391–397.
- Breland-Noble, A.M., et al., 2011. "Mama just won't accept this": adult perspectives on engaging depressed African American teens in clinical research and treatment. *J. Clin. Psychol. Med. Settings* 18 (3), 225–234.
- Britten, N., Campbell, R., Pope, C., Donovan, J., Morgan, M., Pill, R., 2002. Using meta ethnography to synthesise qualitative research: a worked example. *J. Health Serv. Res. Policy* 7, 209–215.
- Brown, G., Marshall, M., Bower, P., Woodham, A., Waheed, W., 2014. Barriers to recruiting ethnic minorities to mental health research: a systematic review. *Int. J. Methods Psychiatr. Res.* 23, 36–38.
- Caldwell, P.H., Murphy, S.B., Butow, P.N., Craig, J.C., 2004. Clinical trials in children. *Lancet* 364, 803–811.
- Caldwell, P.H.Y., Hamilton, S., Tan, A., Craig, J.C., 2010. Strategies for increasing recruitment to randomised controlled trials: systematic review. *PLoS Med.* 7, e1000368.
- Campbell, M., Snowdon, C., Francis, D., Elbourne, D., McDonald, A., Knight, R., Al, E., 2007. Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study. *Health Technol. Assess.* 11, iii, ix–105.
- Carey, M.P., Morrison-Beedy, D., Carey, K.B., Maisto, S.A., Gordon, C.M., Pedlow, C.T., 2001. Psychiatric outpatients report their experiences as participants in a randomized clinical trial. *J. Nerv. Ment. Dis.* 189, 299–306.
- Cassileth, B.R., Lusk, E.J., Miller, D.S., Hurwitz, S., 1982. Attitudes toward clinical trials among patients and the public. *J. Am. Med. Assoc.* 248, 968–970.
- Centerwatch, 2009. State of the Clinical Trials Industry 2009: A Sourcebook of Charts and Statistics. CenterWatch, Boston, USA.
- Centre for Reviews and Dissemination, 2009. Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care. CRD, University of York, York.
- Chamberlain, K., 2000. Methodology and qualitative health research. *J. Health Psychol.* 5, 285–296.
- Chew-Graham, C.A., Lovell, K., Roberts, C., Baldwin, B., Morley, M., Burns, A., Burroughs, H., 2007. Achieving target recruitment in a primary care trial: lessons from PRIDE. *Prim. Health Care Res. Dev.* 8, 264–270.
- Cox, K., 2000. Enhancing cancer clinical trial management: recommendations from a qualitative study of trial participants' experiences. *Psycho-Oncology* 9, 314–322.
- Cooke, Alison, Debbie Smith, and Andrew Booth. "Beyond PICO The SPIDER Tool for Qualitative Evidence Synthesis." *Qual. Health Res.* 22 (10), 2012, 1435–1443.
- Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., Petticrew, M., 2008. Developing and evaluating complex interventions: the new medical research council guidance. *Br. Med. J.* 337, a1655.
- Cramer, H., Salisbury, C., Conrad, J., Eldred, J., Araya, R., 2011. Group cognitive behavioural therapy for women with depression: pilot and feasibility study for a randomised controlled trial using mixed methods. *BMC Psychiatry* 11, 82.
- Criscione, L.G., Sugarman, J., Sanders, L., Pisetsky, D.S., St Clair, E.W., 2003. Informed consent in a clinical trial of a novel treatment for rheumatoid arthritis. *Arthritis Care Res.* 49, 361–367.
- Dixon-Woods, M., Tarrant, C., 2009. Why do people cooperate with medical research? Findings from three studies. *Soc. Sci. Med.* 68, 2215–2222.
- Dixon-Woods, M., Agarwal, S., Young, B., Jones, D., Sutton, A., 2004a. Integrative Approaches to Qualitative and Quantitative Evidence. Agency, H.D., London.
- Dixon-Woods, M., Shaw, R.L., Agarwal, S., Smith, J.A., 2004b. The problem of appraising qualitative research. *Qual. Saf. Health Care* 13, 223–225.
- Dixon-Woods, M., Cavers, D., Agarwal, S., Annandale, E., Arthur, A., Harvey, J., Hsu, R., Katbanna, S., Olsen, R., Smith, L., 2006. Conducting a critical interpretive synthesis of the literature on access to healthcare by vulnerable groups. *BMC Med. Res. Methodol.* 6, 35.
- Dixon-Woods, M., Sutton, A., Shaw, R., Miller, T., Smith, J., Young, B., Jones, D., 2007. Appraising qualitative research for inclusion in systematic reviews: a quantitative and qualitative comparison of three methods. *J. Health Serv. Res. Policy* 12 (1), 42–47.
- Dowrick, C.F., Hughes, J.G., Hiscock, J.J., Wigglesworth, M., Walley, T.J., 2007. Considering the case for an antidepressant drug trial involving temporary deception: a qualitative enquiry of potential participants. *BMC Health Serv. Res.* 7, 64.
- Drüeke, T.B., Descamps-Latscha, B., Locatelli, F., 2003. Stopping a medical research project for financial reasons. *Nephrol. Dial. Transplant.* 18, 1982–1983.
- Edge, D., 2008. 'We don't see Black women here': an exploration of the absence of Black Caribbean women from clinical and epidemiological data on perinatal depression in the UK. *Midwifery* 24 (4), 379–389.
- Edwards, A., Mrcgp, G.E., Hood, K., Rollnick, S., 2000. Judging the 'weight of evidence' in systematic reviews: introducing rigour into the qualitative overview stage by assessing signal and noise. *J. Eval. Clin. Pract.* 6, 177–184.
- Elliott, S., Brown, J., 2002. What are we doing to waiting list controls? *Behav. Res. Ther.* 40, 1047–1052.

- Emanuel, E.J., Patterson, W.B., 1998. Ethics of randomized clinical trials. *J. Clin. Oncol.* 16, 365–371.
- Fairhurst, K., Dowrick, C., 1996. Problems with recruitment in a randomized controlled trial of counselling in general practice: causes and implications. *J. Health Serv. Res. Policy* 1, 77–80.
- Fayter, D., Mcdaid, C., Eastwood, A., 2007. A systematic review highlights threats to validity in studies of barriers to cancer trial participation. *J. Clin. Epidemiol.* 60, 990–e1.
- Flemming, K., Briggs, M., 2007. Electronic searching to locate qualitative research: evaluation of three strategies. *J. Adv. Nurs.* 57, 95–100.
- Fletcher, B., Gheorghe, A., Moore, D., Wilson, S., Damery, S., 2012. Improving the recruitment activity of clinicians in randomised controlled trials: a systematic review. *Br. Med. J.* 2, e000496.
- Foy, R., Duggan, A., Delaney, B., Wilson, S., Lewin-Van Den Broek, N., Lassen, A., Vickers, L., Myres, P., 2003. How evidence based are recruitment strategies to randomized controlled trials in primary care? Experience from seven studies. *Fam. Pract.* 20, 83–92.
- Froelicher, E.S., Lorig, K., 2002. Who cares about recruitment anyway? *Patient Educ. Couns.* 48, 97.
- Garnham, J., Slaney, C., O'donovan, C., 2011. Depression trial subject exclusion characteristics. *Int. Clin. Psychopharmacol.* 26, e18.
- Gask, L., Macdonald, W., Bower, P., 2011. What is the relationship between diabetes and depression? A qualitative meta-synthesis of patient experience of comorbidity. *Chronic Illn.* 7, 239–252.
- Gaudio, B.A., et al., 2013. Patients' treatment expectancies in clinical trials of antidepressants versus psychotherapy for depression: a study using hypothetical vignettes. *Compr. Psychiatry* 54 (1), 28–33.
- Gorecki, C.A., Brown, J.M., Briggs, M., Nixon, J., 2010. Evaluation of five search strategies in retrieving qualitative patient-reported electronic data on the impact of pressure ulcers on quality of life. *J. Adv. Nurs.* 66, 645–652.
- Gough, D., 2007. Weight of evidence: a framework for the appraisal of the quality and relevance of evidence. *Res. Pap. Educ.* 22, 213–228.
- Grant, J., et al., 2009. Participants' perceptions of motivation, randomisation and withdrawal in a randomised controlled trial of interventions for prevention of depression. *J. Med. Ethics: J. Inst. Med. Ethics* 35 (12), 768–773.
- Higgins, J., Green, S. (Eds.), 2011. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration, Chichester, UK ([Updated March 2011]).
- Gross, C.P., Mallory, R., Heiat, A., Krumholz, H.M., 2002. Reporting the recruitment process in clinical trials: who are these patients and how did they get there? *Ann. Int. Med.* 137, 10–16.
- Haberfellner, E.M., 2000. Recruitment of depressive patients for a controlled clinical trial in a psychiatric practice. *Pharmacopsychiatry* 33, 142–144.
- Halpern, S., Karlawish, J., Berlin, J., 2002. The continuing unethical conduct of underpowered clinical trials. *J. Am. Med. Assoc.* 288, 358–362.
- Harveveld, F., Spijker, J., De Graaf, R., Nolen, W.A., Beekman, A.T., 2010. Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatr. Scand.* 122, 184–191.
- Hetherington, J., Matheson, A., Robson, M., 2004. Recruitment by GPs during consultations in a primary care randomized controlled trial comparing computerized psychological therapy with clinical psychology and routine GP care: problems and possible solutions. *Prim. Health Care Res. Dev.* 5, 5–10.
- Hinton, L., Zweifach, M., Oishi, S., Tang, L., Unutzer, J., 2006. Gender disparities in the treatment of late-life depression: qualitative and quantitative findings from the IMPACT trial. *Am. J. Geriatr. Psychiatry* 14, 884–892.
- Howard, L., Thornicroft, G., 2006. Patient preference randomised controlled trials in mental health research. *Br. J. Psychiatry* 188, 303–304.
- Hunt, C.J., Shepherd, L.M., Andrews, G., 2001. Do doctors know best? Comments on a failed trial. *Med. J. Aust.* 174, 144–146.
- Hussain-Gambles, M., 2004. South Asian patients' views and experiences of clinical trial participation. *Fam. Pract.* 21, 636–642.
- Jenkins, V., Fallowfield, L., 2000. Reasons for accepting or declining to participate in randomized clinical trials for cancer therapy. *Br. J. Cancer* 82, 1783.
- Jenkinson, C.E., Winder, R.E., Sugg, H.V.R., Roberts, M.J., Ridgway, N., Kuyken, W., Wiles, N., Kessler, D., Campbell, J., 2014. Why do GPs exclude patients from participating in research? An exploration of adherence to and divergence from trial criteria. *Fam. Pract.* 31, 364–370.
- Johnson, V.A., Powell-Young, Y.M., Torres, E.R., Spruill, I.J., 2011. A systematic review of strategies that increase the recruitment and retention of African American adults in genetic and genomic studies. *ABNF J.* 22, 84–88.
- Katz, T., Fisher, P., Katz, A., Davidson, J., Feder, G., 2005. The feasibility of a randomised, placebo-controlled clinical trial of homeopathic treatment of depression in general practice. *Homeopathy* 94, 145–152.
- Khan, N., Bower, P., Rogers, A., 2007. Guided self-help in primary care mental health: meta-synthesis of qualitative studies of patient experience. *Br. J. Psychiatry* 191, 206–211.
- King, M., Nazareth, I., Lampe, F., Bower, P., Chandler, M., Morou, M., Sibbald, B., Lai, R., 2005. Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials. *Health Technol. Assess.* 9, 1–186.
- Knowles, S., Toms, G., Sanders, C., Bee, P., Lovell, K., Rennick-Egglestone, S., Coyle, D., Kennedy, C., Littlewood, E., Kessler, D., Gilbody, S., Bower, P., 2014. Qualitative meta-synthesis of user experience of computerised therapy for depression and anxiety. *PLoS One* 9, e84323.
- Kokanovic, R., et al., 2009. The politics of conducting research on depression in a cross-cultural context. *Qual. Health Res.* 19 (5), 708–717.
- Lamb, J., Bower, P., Rogers, A., Dowrick, C., Gask, L., 2012. Access to mental health in primary care: a qualitative meta-synthesis of evidence from the experience of people from 'hard to reach' groups. *Health* 16, 76–104.
- Langer, S., Chew-Graham, C., Hunter, C., Guthrie, E.A., Salmon, P., 2013. Why do patients with long-term conditions use unsheduled care? A qualitative literature review. *Health Soc. Care Community* 21, 339–351.
- Lilienfeld, S.O., 2007. Psychological treatments that cause harm. *Perspect. Psychol. Sci.* 2, 53–70.
- Limkakeng, A., Phadtare, A., Shah, J., Vagharia, M., Wei, D.Y., Shah, A., Pietrobon, R., 2013. Willingness to participate in clinical trials among patients of Chinese heritage: a meta-synthesis. *PLoS One* 8, e51328.
- Locock, L., Smith, L., 2011. Personal benefit, or benefiting others? Deciding whether to take part in clinical trials. *Clin. Trials* 8, 85–93.
- Loraas, E.L., 2009. Patient motivation for participation in clinical trials for depression: development and validation of the motivation for clinical trials inventory-depression (MCTI-D). *Diss. Abstr. Int.* 69, 5038.
- Loue, S., Sajatovic, M., 2008. Research with severely mentally ill Latinas: successful recruitment and retention strategies. *J. Immigr. Minor. Health* 10 (2), 145–153.
- Malpass, A., Shaw, A., Sharp, D., Walter, F., Feder, G., Ridd, M., Kessler, D., 2009. "Medication career" or "moral career"? The two sides of managing antidepressants: a meta-ethnography of patients' experience of antidepressants. *Soc. Sci. Med.* 68, 154.
- Marshall, I.J., Wolfe, C.D.A., Mckevitt, C., 2012. Lay perspectives on hypertension and drug adherence: systematic review of qualitative research. *Br. Med. J.* 345, e9353.
- Mason, V., Shaw, A., Wiles, N., Mulligan, J., Peters, T., Sharp, D., Lewis, G., 2007. GPs' experiences of primary care mental health research: a qualitative study of the barriers to recruitment. *Fam. Pract.* 24, 518–525.
- Mays, N., Pope, C., 2000. Assessing quality in qualitative research. *Br. Med. J.* 1, 50–52.
- McFarland, C., et al., 2002. The establishment of a brain bank for the study of late-life depression: a feasibility study of factors facilitating consent. *CNS Spectr.* 7 (11), 816–821.
- Mccann, S., Campbell, M., Entwistle, V., 2013. Recruitment to clinical trials: a meta-ethnographic synthesis of studies of reasons for participation. *J. Health Serv. Res. Policy* 18, 233–241.
- Mccann, S.K., Campbell, M.K., Entwistle, V.A., 2010. Reasons for participating in randomised controlled trials: conditional altruism and considerations for self. *Trials* 11, 31.
- Mcdonald, A., Knight, R., Campbell, M., Entwistle, V., Grant, A., Cook, J., 2006. What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. *Trials* 7, 9.
- Mendel, P., Ngo, V.K., Dixon, E., Stockdale, S., Jones, F., Chung, B., Jones, A., Masongsong, Z., Khodyakov, D., 2011. Partnered evaluation of a community engagement intervention: use of a kickoff conference in a randomized trial for depression care improvement in underserved communities. *Ethn. Dis.* 21, S78–S88.
- Minas, H., Klimidis, S., Kokanovic, R., 2005. Mental health research in general practice. *Australas. Psychiatry* 13, 181–184.
- Minas, H., Klimidis, S., Kokanovic, R., 2005. Mental health research in general practice. *Australas. Psychiatry* 13 (2), 181–184.
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann. Int. Med.* 151, 264–269.
- Mullins, C.D., Vandigo, J., Zheng, Z., Wicks, P., 2014. Patient-centeredness in the design of clinical trials. *Value Health* 17, 471–475.
- National Collaborating Centre for Mental Health, 2009. Depression: the treatment and management of depression in adults. In: Excellence, N.I.O.H.A.C. (Ed.), *NICE Clinical Guideline 90*. National Institute of Health and Clinical Excellence, London.
- Noblit, G.W., Hare, R.D., 1988. *Meta-Ethnography: Synthesizing Qualitative Studies*. SAGE Publications, Incorporated, Newbury Park, CA, USA.
- Nutt, D.J., Sharpe, M., 2008. Uncritical positive regard? Issues in the efficacy and safety of psychotherapy. *J. Psychopharmacol.* 22, 3.
- O'Donnell, A.B., et al., 2007. Using focus groups to improve the validity of cross-national survey research: a study of physician decision making. *Qual. Health Res.* 17 (7), 971–981.
- Oxman, A., Guyatt, G., 1993. The science of reviewing research. *Ann. N.Y. Acad. Sci.* 703, 125–133.
- Parry, G. & Barkham, M., 2009. *Trials & tribulations: towards better design and practice in psychological therapy trials*. In: *Proceedings of the Society for Social Medicine Conference*. Sheffield, UK.
- Patel, M.X., Doku, V., Tennakoon, L., 2003. Challenges in recruitment of research participants. *Advances* 9, 229–238.
- Peters, S., 2010. Qualitative research methods in mental health. *Evid. Based Ment. Health* 13, 35–40.
- Peto, R., Baigent, C., 1998. Trials: the next 50 years: large scale randomised evidence of moderate benefits. *Br. Med. J.* 317, 1170.
- Petticrew, M., Egan, M., Thomson, H., Hamilton, V., Kunkler, R., Roberts, H., 2008. Publication bias in qualitative research: what becomes of qualitative research presented at conferences? *J. Epidemiol. Community Health* 62, 552–554.
- Pettigrew, M., Roberts, H., 2006. *Systematic Reviews in the Social Sciences: A Practical Guide*. Blackwell, Oxford.
- Prescott, R., Counsell, C., Gillespie, W., Grant, A., Russell, I., Kiauka, S., 1999. Factors that limit the quality, number and progress of randomised controlled trials. *Health Technol. Assess.* 3, 1–143.

- Rendell, J., Licht, R., 2007. Under-recruitment of patients for clinical trials: an illustrative example of a failed study. *Acta Psychiatr. Scand.* 115, 337–339.
- Rendell, J., Merritt, R., Geddes, J., 2007. Incentives and disincentives to participation by clinicians in randomised controlled trials. *Cochrane Database Syst. Rev.* 2, MR000021.
- Roberts, L.W., Kim, J.P., 2014. Do investigators understand ethically-important perspectives of clinical research participants? A 'piggy-back' study of attunement and alignment in serious illness research. *J. Psychiatr. Res.* 54, 36–43.
- Ross, M., Jeffords, K., Gold, J., 1994. Reasons for entry into and understanding of HIV/AIDS clinical trials: a preliminary study. *AIDS Care* 6, 77–82.
- Ross, S., Grant, A., Counsell, C., Gillespie, W., Russell, I., Prescott, R., 1999. Barriers to participation in randomised controlled trials: a systematic review. *J. Clin. Epidemiol.* 52, 1143–1156.
- Rost, K., Nutting, P.A., Smith, J., Werner, J.J., 2000. Psychiatry and primary care. Designing and implementing a primary care intervention trial to improve the quality and outcome of care for major depression. *Gen. Hosp. Psychiatry* 22 (2), 66–77.
- Ruddell, M., Spencer, A., Hill, K., House, A., 2007. Fluoxetine vs placebo for depressive symptoms after stroke: failed randomised controlled trial. *Int. J. Geriatr. Psychiatry* 22, 963–965.
- Sacks, H., Chalmers, T., Smith, H.J., 1982. Randomized versus historical controls for clinical trials. *Am. J. Med.* 72, 233–240.
- Salmon, P., Peters, S., Rogers, A., Gask, L., Clifford, R., Iredale, W., Dowrick, C., Morriss, R., 2007. Peering through the barriers in GPs' explanations for declining to participate in research: the role of professional autonomy and the economy of time. *Fam. Pract.* 24, 269–275.
- Salmon, P., Hill, J., Ward, J., Gravenhorst, K., Eden, T., Young, B., 2012. Faith and protection: the construction of hope by parents of children with leukemia and their oncologists. *Oncologist* 17, 398–404.
- Schroer, S., Macpherson, H., 2009. Acupuncture, or non-directive counselling versus usual care for the treatment of depression: a pilot study. *Trials* 10, 3.
- Schroer, S., Macpherson, H., Adamson, J., 2009. Designing an RCT of acupuncture for depression—identifying appropriate patient groups: a qualitative study. *Fam. Pract.* 26, 188–195.
- Schroer, S., Kanaan, M., Macpherson, H., Adamson, J., 2012. Acupuncture for depression: exploring model validity and the related issue of credibility in the context of designing a pragmatic trial. *CNS Neurosci. Ther.* 18 (4), 318–326.
- Sharp, L., Cotton, S., Alexander, L., Williams, E., Gray, N., Reid, J., 2006. Reasons for participation and non-participation in a randomized controlled trial: postal questionnaire surveys of women eligible for TOMBOLA (trial of management of borderline and other low-grade abnormal smears). *Clin. Trials* 3, 431–442.
- Shellman, J., Mokel, M., 2010. Overcoming barriers to conducting an intervention study of depression in an older African American population. *J. Transcult. Nurs.* 21, 361–369.
- Simpson, S., Corney, R., Fitzgerald, P., Beecham, J., 2000. A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression. *Health Technol. Assess.* 4 (36), 1–83.
- Sloane, P.D., Callahan, L., Kahwati, L., Mitchell, C.M., 2006. Development of a practice-based patient cohort for primary care research. *Fam. Med.* 38 (1), 50–58.
- Smith, C.T., Hickey, H., Clarke, M., Blazeby, J., Williamson, P., 2014. The trials methodological research agenda: results from a priority setting exercise. *Trials* 15, 32.
- Snowdon, C., Elbourne, D., Garcia, J., 2007. Declining enrolment in a clinical trial and injurious misconceptions: is there a flipside to the therapeutic misconception? *Clin. Ethics* 2, 193–200.
- Stack, R.J., Shaw, K., Mallen, C., Herron-Marx, S., Horne, R., Raza, K., 2012. Delays in help seeking at the onset of the symptoms of rheumatoid arthritis: a systematic synthesis of qualitative literature. *Ann. Rheum. Dis.* 71, 493–497.
- Steinman, L., et al., 2012. Implementation of an evidence-based depression care management program (PEARLS): perspectives from staff and former clients. *Prev. Chronic Dis.* 9, E91.
- Stek, M.L., Van Der Wurff, F.B., Uitdehaag, B.M.J., Beekman, A.T.F., Hoogendijk, W.J.G., 2007. ECT in the treatment of depressed elderly: lessons from a terminated clinical trial. *Int. J. Geriatr. Psychiatry* 22, 1052–1054.
- Stern, P.N., Harris, C.C., 1985. Women's health and the self-care paradox. A model to guide self-care readiness. *Health Care Women Int.* 6, 151–163.
- Sully, B.G., Julious, S.A., Nicholl, J., 2013. A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. *Trials* 14, 166.
- Tallon, D., Mulligan, J., Wiles, N., Thomas, L., Peters, T.J., Elgie, R., Sharp, D., Lewis, G., 2011. Involving patients with depression in research: survey of patients' attitudes to participation. *Br. J. Gen. Pract.* 61, 134–141.
- Tenhave, T.R., Coyne, J., Salzer, M., Katz, I., 2003. Research to improve the quality of care for depression: alternatives to the simple randomized clinical trial. *Gen. Hosp. Psychiatry* 25, 115–123.
- Timmerman, G.M., 1996. The art of advertising for research subjects. *Nurs. Res.* 45, 339–340 (344).
- Tong, A., Flemming, K., McInnes, E., Oliver, S., Craig, J., 2012. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. *BMC Med. Res. Methodol.* 12, 181.
- Torpey, D.C., Klein, D.N., 2008. Chronic depression: update on classification and treatment. *Curr. Psychiatry Rep.* 10, 458–464.
- Tramm, R., Daws, K., Schadewaldt, V., 2013. Clinical trial recruitment—a complex intervention? *J. Clin. Nurs.* 22, 2436–2443.
- Treweek, S., Lockhart, P., Pitkethly, M., Cook, J.A., Kjeldstrom, M., Johansen, M., Taskila, T.K., Sullivan, F.M., Wilson, S., Jackson, C., Jones, R., Mitchell, E.D., 2013. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. *Br. Med. J.* 3, e002360.
- Uebelecker, L.A., Marootian, B.A., et al., 2012. Barriers and facilitators of treatment for depression in a latino community: a focus group study. *Community Ment. Health J.* 48, 114–126.
- Uybico, S., Pavel, S., Gross, C., 2007. Recruiting vulnerable populations into research: a systematic review of recruitment interventions. *J. Gen. Intern. Med.* 22, 852–863.
- Van Der Wee, G.M., De Jong, R., De Waal, M.W., Spinhoven, P., Rooze, H.A., Reis, R., Assendelft, W.J., Gussekloo, J., Van Der Mast, R.C., 2012. Response to an unsolicited intervention offer to persons aged  $\geq 75$  years after screening positive for depressive symptoms: a qualitative study. *Int. Psychogeriatr.* 24, 270–277.
- Wasan, A.D., Taubenberger, S.P., Robinson, W.M., 2009. Reasons for participation in pain research: can they indicate a lack of informed consent? *Pain Med.* 10 (1), 111–119.
- Watson, J., Torgerson, D., 2006. Increasing recruitment to randomised trials: a review of randomised controlled trials. *BMC Med. Res. Methodol.* 6, 1–9.
- van Weel, C., van Weel-Baumgarten, E., Mold, J., 2006. The importance of longitudinal studies in family medicine: experiences of two practice-based research networks. *J. Am. Board Fam. Med.* 19 (1), 69–74.
- Wetterneck, C.T., Little, T.E., Rinehart, K.L., Cervantes, M.E., Hyde, E., Williams, M., 2012. Latinos with obsessive-compulsive disorder: mental healthcare utilization and inclusion in clinical trials. *J. Obsessive-Compuls. Relat. Disord.* 1, 85–97.
- Whiting, M., Leavey, G., Scammell, A., Au, S., King, M., 2008. Using acupuncture to treat depression: a feasibility study. *Complement. Ther. Med.* 16 (2), 87–91.
- Willison, D.J., et al., 2009. Consent for use of personal information for health research: do people with potentially stigmatizing health conditions and the general public differ in their opinions? *BMC Med. Ethics* 10, 1.
- Woodall, A., Morgan, C., Sloan, C., Howard, L., 2010. Barriers to participation in mental health research: are there specific gender, ethnicity and age related barriers? *BMC Psychiatry* 10, 103.
- Woodford, J., Farrand, P., Bessant, M., Williams, C., 2011. Recruitment into a guided internet based CBT (iCBT) intervention for depression: lesson learnt from the failure of a prevalence recruitment strategy. *Contemp. Clin. Trials* 32, 641–648.
- Woolfall, K., Young, B., Frith, L., Appleton, R., Iyer, A., Messahel, S., Hickey, H., Gamble, C., 2014. Doing challenging research studies in a patient-centred way: a qualitative study to inform a randomised controlled trial in the paediatric emergency care setting. *BMJ Open* 4, e005045.
- World Health Organisation, 2004. The Global Burden of Disease: 2004 Update. World Health Organisation, Geneva.
- World Health Organisation. 2013. Mental health: suicide prevention (SUPRE) [online]. ([http://www.who.int/mental\\_health/prevention/suicide/suicideprevent/en/](http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/)) (accessed 18.06.13.).
- Yastrubetskaya, O., Chiu, E., O'Connell, S., 1997. Is good clinical research practice for clinical trials good clinical practice? *Int. J. Geriatr. Psychiatry* 12, 227–231.
- Young, B., Shilling, V., Hickey, H., Sowden, E., Smyth, R.L., Williamson, P.R., 2011. What parents think about being approached about children's trials, how this differs from what practitioners expect, and what this tells us about enhancing recruitment. *Trials* 12, A116.





## Chapter 5: What can we learn from trial decliners about improving recruitment? Qualitative study

---

**Chapter type:** Journal Article

**Journal:** *Trials*

**Status:** Accepted, subject to minor revisions

**Submission date:** 17<sup>th</sup> June 2016

**Published online:** 12th October 2016

**Reference:** Hughes-Morley, A., Young, B., Hempel, R.J., Russell, I.T., Waheed, W., & Bower, P. (2016). What can we learn from trial decliners about improving recruitment? Qualitative study. *Trials*, 17 (1), 494

**Contributions:** AH-M led on the methods for the qualitative study, undertook the participant interviews, analysis and drafted the manuscript. Bridget Young, Peter Bower and Waquas Waheed supervised the study design, data collection, analysis and reporting.

Roelie J. Hempel (RJH) and Ian T. Russell (ITR) are members of the REFRAMED trial group. RJH was REFRAMED Trial Manager and led the ethics amendment and sub-study registration for conducting the qualitative study linked with the REFRAMED trial, as well as participant recruitment. ITR was involved in the REFRAMED trial design, including on methodological aspects of participant recruitment.

All authors commented on drafts of the paper and approved the final manuscript.



RESEARCH

Open Access



# What can we learn from trial decliners about improving recruitment? Qualitative study

Adwoa Hughes-Morley<sup>1,2\*</sup> , Bridget Young<sup>3</sup>, Roelie J. Hempel<sup>4</sup>, Ian T. Russell<sup>5</sup>, Waquas Waheed<sup>6</sup> and Peter Bower<sup>1,6</sup>

## Abstract

**Background:** Trials increasingly experience problems in recruiting participants. Understanding the causes of poor recruitment is critical to developing solutions. We interviewed people who had declined a trial of an innovative psychological therapy for depression (REFRAMED) about their response to the trial invitation, in order to understand their decision and identify ways to improve recruitment.

**Methods:** Of 214 people who declined the trial, 35 (16 %) gave permission to be contacted about a qualitative study to explore their decision. Analysis of transcripts of semi-structured interviews was informed by grounded theory.

**Results:** We interviewed 20 informants: 14 women and six men, aged 18 to 77 years. Many interviewees had prior experience of research participation and positive views of the trial. Interviewees' decision making resembled a four-stage sequential process; in each stage they either decided not to participate in the trial or progressed to the next stage. In stage 1, interviewees assessed the invitation in the context of their experiences and attitudes; we term those who opted out at this stage 'prior decliners' as they had an established position of declining trials. In stage 2, interviewees assessed their own eligibility; those who judged themselves ineligible and opted out at this stage are termed 'self-excluders'. In stage 3, interviewees assessed their need for the trial therapy and potential to benefit; we term those who decided they did not need the trial therapy and opted out at this stage 'treatment decliners'. In stage 4, interviewees deliberated the benefits and costs of trial participation; those who opted out after judging that disadvantages outweighed advantages are termed 'trial decliners'. Across all stages, most individuals declined because they judged themselves ineligible or not in need of the trial therapy. While 'prior decliners' are unlikely to respond to any trial recruitment initiative, the factors leading others to decline are amenable to amelioration as they do not arise from a rejection of trials or a personal stance.

**Conclusions:** To improve recruitment in similar trials, the most successful interventions are likely to address patients' assessments of their eligibility and their potential to benefit from the trial treatment, rather than reducing trial burden.

**Trial registration:** International Standard Randomised Controlled Trial Number: ISRCTN85784627. Registration date 10 August 2011.

**Keywords:** Randomised controlled trials, Non-participation, Depression, Qualitative research, Recruitment

\* Correspondence: [adwoa.hughes-morley@york.ac.uk](mailto:adwoa.hughes-morley@york.ac.uk)

<sup>1</sup>MRC North West Hub for Trials Methodology Research, Manchester Academic Health Science Centre, University of Manchester, Oxford Road, Manchester M13 9PT, UK

<sup>2</sup>York Trials Unit, Department of Health Sciences, University of York, York YO10 5DD, UK

Full list of author information is available at the end of the article



## Background

Randomised trials are strongly recommended for evaluating interventions, yet recruitment of participants is an increasing problem [1–3]. In developed countries, there have been considerable efforts to improve recruitment through legislation and infrastructure [4–6]. Recent reports in the United Kingdom (UK) suggest that more people than ever are being approached to participate in trials [6]; however the proportion of people who enrol is small and recruitment remains a problem, with between 45 % and 80 % of trials failing to meet recruitment targets [2, 7]. The difficulties may be even more pronounced when enrolling patients with depression, with many examples of trial failure due to poor recruitment [8, 9]. The challenges stem from sources including: the stigma of mental illness; poor identification of mental disorders by clinicians; diagnoses which adversely affect patients' ability and motivation to participate in research; and mistrust [10, 11]. Consequences of poor recruitment include increased costs, reduction in statistical power and continued use of interventions that are ineffective or harmful to patients [12, 13].

There is a dearth of evidence-based interventions for improving recruitment into trials, leading to calls for the development of '*a science of recruitment*' [1, 14]. Recruitment is now a methodological research priority for trials units in the UK [15], and systematic reviews have identified an urgent need for robustly evaluated interventions, particularly those tested in the real world [16, 17].

The Medical Research Council (MRC) Complex Interventions Framework provides a useful basis for developing and evaluating interventions to improve recruitment [18, 19]. Qualitative research has an important role to play in the development of interventions [20–22]. To improve recruitment, it is important that this development work is informed by the perspectives of people who decline trials. However, our meta-synthesis of factors affecting recruitment into depression trials [23] found that only one of the 15 studies included decliners [24]. The remaining studies all focused on the perspectives of staff, or of patients successfully recruited. Furthermore, all of the studies focused on respondents' reported reasons for their decision, but did not explore in detail their accounts of what happened when they received the invitation to join a trial. This may have elicited idealised justifications and failed to take into account *deliberation*, an important aspect of decision making identified by the 'deliberation and determination' framework [25, 26]. Understanding responses to the invitation to join a trial and how the decision to decline is reached may assist trialists to enhance recruitment by designing interventions to address shortcomings. By exploring this important gap in our understanding, we aimed to shed light on what has been termed a 'blind spot in the literature' on recruitment [27].

We therefore explored interviewees' accounts of what they did and what happened when they received the trial invitation. Rather than simply asking for reasons why they declined trial participation, which might elicit idealised justifications rather than deliberations and reasons, we explored informants' accounts of *how* they reached their decisions and the factors that affected them.

## Methods

### Setting: the REFRAMED trial

This qualitative study explored interviewees' responses to receiving an invitation to participate in the REFRAMED trial (REFRActory depression - Mechanisms and Efficacy of Dialectical Behaviour Therapy) [28]. REFRAMED evaluated the effectiveness of Radically Open Dialectical Behavioural Therapy (RO-DBT) [29] for treatment-resistant depression. It recruited trial participants through general practices and mental health services in Dorset and Hampshire in England and Gwynedd in North Wales. Those eligible were: aged over 18 years; had a current diagnosis of depression; and had not responded to antidepressants. All invited individuals received a 'summary participant information leaflet' (Additional file 1) and those who were interested took part in full eligibility assessments. Eligible individuals who consented were randomised to RO-DBT in addition to usual care and antidepressant medication, or to usual care and antidepressant medication. RO-DBT comprised 29 weekly individual therapy sessions lasting 50 minutes and 27 group skills sessions lasting 2.5 hours. While some components of RO-DBT are common to all behaviour therapies, RO-DBT uniquely targets social-signalling deficits, focuses on changing internal experience (for example emotion dysregulation, cognitive distortions and traumatic memories) and also teaches clients how to express emotions appropriate to context and use non-verbal social-signalling strategies known to enhance social connectedness. REFRAMED participants were assessed four times over 18 months – at baseline and after 7, 12 and 18 months; in addition RO-DBT participants completed monthly questionnaires over 18 months.

### Qualitative study

The qualitative study was informed by an epistemological standpoint of pragmatism, a perspective that embraces methodological pluralism and is increasingly used in health services research to inform the development and evaluation of interventions that are transferable and usable in real life [30, 31]. Pragmatism focuses on 'what works' and on generating solutions to existing problems by identifying and integrating effective strategies to build on the strengths and reduce the inherent flaws of each [32, 33]. Our pragmatic approach enabled us to use different methods of sampling, data collection and analysis to address our research aims, including techniques from

grounded theory [34]. Grounded theory aims to generate theories of social phenomena grounded in systematic analysis of data and is particularly appropriate for explaining social processes. We offered individuals who had declined the REFRAMED trial the choice between being interviewed by telephone or email. These options were informed by: advice from two patient and carer engagement groups – the UK Clinical Research Network Mental Health Service User Research Panel (SURP) and Primary care Research In Manchester Engagement Resource (PRIMER); advice from trialists who had worked with similar groups; literature suggesting that decliners would be reluctant to take part in face-to-face interviews [24]; and evidence that well-planned telephone and email interviews can gather the same data as interviews face to face [24, 35] and promote access to ‘isolated, geographically dispersed or stigmatised groups who are often overlooked or ignored’ [36, 37].

#### Sampling and recruitment

Most of the 1867 patients approached for REFRAMED were identified from electronic health records in general practices and community mental health teams by searching for patients diagnosed with depression who were receiving repeat prescriptions of antidepressants. Of the rest, a few referred themselves, but most were referred to REFRAMED by their general practitioners (GPs), care coordinators and psychiatrists. We could not access those who declined their clinicians’ invitations so our sampling for the qualitative study focused on the 214 patients who responded to postal invitations from general practices and community mental health teams by returning reply slips to decline REFRAMED, in particular the 35 who expressed interest in participating in the interviews and provided contact details.

We initially sampled 12 interviewees for maximum variation [38] in the following characteristics: age, gender and geographic location. In line with the principles of grounded theory, we then sampled theoretically [39], using information provided on decliners’ reply slips. We invited eight interviewees who gave different reasons for declining and who we therefore felt were ‘deviant’ or could provide accounts that would help us to develop our analyses further [34]. We continued sampling until we achieved data saturation; that is until no new themes emerged.

#### Data collection

One of us, AH-M, a health services researcher undertaking a PhD with training in qualitative interviewing, contacted those who expressed interest – by telephone or email according to their preferences – to discuss the qualitative study. Having had no prior contact with interviewees, she explained that she was linked to the REFRAMED team but

independent of both them and patients’ clinical teams, and sought consent from potential interviewees. Arrangements were made to conduct telephone or email interviews at a later date with those who consented. Audio interviews were recorded and professionally transcribed in an ‘efficient verbatim’ style, that is by transcribing content but not pauses or hesitations. AH-M checked transcripts for accuracy and pseudonymised them.

Recruitment to REFRAMED took place between March 2012 and May 2015 and the qualitative interviews took place between August 2013 and January 2015 – within 3 months of interviewees declining to participate in REFRAMED so as to minimise recall bias. To allow full exploration of topics, interviews were conversational and responsive to participants. To ensure consistency across interviews, questions followed a topic guide (Additional file 2), which was piloted and based on relevant literature and consultation with SURP and PRIMER, our patient and carer engagement groups. Interviews initially explored participants’ recollection of and thoughts about: being invited into the trial; making the decision to decline; understanding the research and trial interventions; and talking therapies, in particular RO-DBT. Interviews focused on the period when respondents first received the invitation into the REFRAMED trial, and asked them to describe in detail what they did, who they talked to, and what they thought. We made field notes during interviews and modified the topic guide in response to early interviews. To minimise interviewee burden, transcripts were not returned to respondents, nor were they asked to provide feedback on findings.

#### Data analysis

Analysis was interpretive and drew on constant comparison with grounded theory [34]. The iterative analysis process was led by AH-M who read and reread transcripts to develop preliminary codes to identify themes and theoretical categories [40], which we gradually developed into a conceptual framework. Coding was combined with a holistic consideration of transcripts to retain the context of participants’ accounts and identify and interpret aspects that participants were silent about or did not emphasise relative to the accounts of other participants, or which did not fit the rest of their account. In discussion with BY and PB, AH-M continually reviewed emerging themes and categories in the light of new data, modifying these to ensure they fitted the data whilst accounting for deviations. Some categories and themes arose from inductive analysis, while others drew more deductively on literature from our systematic review [23]. This flow from data to literature, and back to the data, refined the codes and the developing theoretical constructs [41]. The multi-disciplinary team developed the analysis and ensured its ‘trustworthiness’ [42, 43]

in a process of investigator triangulation. Analysis was assisted by NVivo 10.

To illustrate our interpretations we include selected quotations from our data. These are broadly representative of the key themes, whilst also reflecting a range of views. Quotation labels indicate participants' age, gender, identification number and stage at which they declined; for example '67F01S03' indicates a 67-year-old female who was our first participant and declined at stage 3. Text within square brackets [] indicates clarifications that we have inserted; ellipses '...' indicate pauses by respondents; and ellipses within square brackets [...] indicate omitted text.

## Results

### Participant characteristics

Of the 35 patients initially expressing interest, two declined to be interviewed when contacted and eight did not respond to our attempts to contact them. The remaining five were not interviewed as we had reached theoretical saturation. We undertook 20 interviews with 14 females and six males – 18 by telephone, one by email and one by both telephone and email. Apart from the interviewee and the researcher, no other persons were present during the interviews. Telephone interviews lasted between 16 and 76 minutes with a mean of 30 minutes. The email interview took place over the course of one week; and for the combined interview the telephone interview occurred first, followed by one day's email correspondence. The mean age of the 20 who participated in the qualitative study was 57 years; the mean age of the 252 who participated in REFRAMED was 45 years and that of the 214 who declined was 50 years. Of the 20 interviewees, 18 described themselves as 'white British', one as 'white other' and another as 'Asian British'. Ten were retired, six were unemployed, three were employed full time and one was a full-time student. Ten interviewees had prior experience of being invited to participate in a trial. Table 1 lists the characteristics of interviewees.

### Overview of informants' decision making

Ten interviewees read the trial invitation with experience of having made trial participation decisions in the past. Our analysis of their accounts of their response to receiving the trial invitation indicated that they passed through up to four sequential stages in making the participation decision: (1) assessing the nature of the invitation; (2) assessing their own eligibility; (3) assessing their own need for trial therapy and potential to benefit; and (4) comparing the risks with the rewards of participation. While all informants engaged in stage 1, two described opting out of the trial at this stage without further deliberation. Of those progressing to stage 2, nine declined at this stage, seven at stage 3, and two progressed to stage 4 before

finally declining. Thus while two progressed through all four stages of this process, the majority reached their decision earlier. However, the content of informants' deliberations did not always reflect this sequential order, for example some considered the potential to benefit from the therapy (stage 3) before assessing their eligibility (stage 2). In reporting their accounts, we characterise different 'types' of decision makers to distinguish the decisions that interviewees made at each stage of the process of responding to the REFRAMED invitation.

### Stage 1: assessing the nature of the invitation

In the REFRAMED trial GPs and mental health teams sent invitation letters to potential participants without prior notice. Informants generally reported opening the letter without delay and reading it with the trial response form. Some reported that they briefly glanced through the accompanying REFRAMED summary leaflet or did not read it, while others described reading the leaflet in detail. With one exception, informants reported that: they approved of being sent the trial invitation; the letter format was appropriate; and being invited in this way was good because it enabled them to make decisions in their own time:

*'The letter is a good idea...I mean if they sign you up you have to decide very quickly and you don't have time to chew over the information, so having a letter makes sense, you can sit and think about it and decide what to do.'* (66M12S2)

The exception was an interviewee widowed one year before receiving the trial invitation. She reported that, given her personal circumstances, she would have expected her GP to have removed her name from the list of patients to be sent the invitation. However, she acknowledged that for people experiencing 'normal depression', being sent such an invitation was not only appropriate, but would actually be positive:

*'It probably is a good thing really, if I'm honest. I mean, it's the only way you get to know things, isn't it?... Like, say, I'd got some illness, I suppose it's the only way you're going to find out things isn't it, what tablets I'm on, whether they work and all that sort of thing. I think perhaps if I'd been depressed normally, like, I mean, a lot of people are, aren't they, and they're on depression tablets for a while. I can understand that.'* (70F08S2)

The other interviewees expressed positive views about research and the trial specifically, particularly the need to improve health services and advance knowledge through such endeavours:

**Table 1** Characteristics of study participants

Participant number	Age	Site	Gender	Highest educational qualification
1	67	England	F	Secondary school
2	18	Wales	F	Secondary school
3	67	Wales	M	Secondary school
4	54	England	F	University degree or higher
5	74	England	F	Secondary school
6	59	England	M	Secondary school
7	62	Wales	M	University degree or higher
8	70	England	F	Secondary school
9	44	England	F	Secondary school
10	73	England	F	Secondary school
11	77	England	F	University degree or higher
12	66	Wales	M	University degree or higher
13	63	England	M	Secondary school
14	69	England	F	Secondary school
15	40	England	F	University degree or higher
16	46	Wales	F	University degree or higher
17	61	England	F	Secondary school
18	50	England	F	Secondary school
19	38	England	M	University degree or higher
20	45	Wales	F	University degree or higher

*'Without research no-one would ever get anywhere, would they? So even if it didn't help me, it would still help, you know, others wouldn't it?'* (44F09S3)

Many respondents reported that they supported REFRAMED's aim to evaluate a new treatment for depression, and were comforted to know *'that somebody was doing something about it'* (67F01S3).

For ten informants this was not the first time they had been invited by letter to participate in research. Of these, eight reported having accepted at least one invitation. Three of these were trials of psychological therapy for depression; one a psychological experiment including mood assessment; two studied bowel cancer; one respiratory illness; and one vision. Being sent such letters was seen as a necessary part of the research process, regardless of whether the invitation was declined or accepted. Crucially, interviewees felt able to make whatever decision felt right for them, including declining, so did not mind being invited:

*'I didn't mind actually because I know that the [general practice] was very into research and I believe that the surgery itself was one of the best in the country for research. I had been sent them on, I think, about bowel cancer and, I can't remember, two or*

*three other things and I must admit that my reaction was just the same.'* (74F05S1)

This interviewee, whom we categorised as a 'prior decliner', reported that REFRAMED was one of several trials that she had declined owing to concerns about confidentiality. The other 'prior decliner', who reported having declined all invitations, was the oldest of our interviewees, and cited her advanced age as the reason for not accepting trial invitations:

*'I'm 77...when you get to this age, you realise that you just take every day at a time, and I don't want anything that I haven't got to have, because I've had two hip replacements, I've had an operation on my back, and to be quite honest, as I say, I don't want anything that isn't necessary. I don't think that at this stage in my life, [trials] apply to me, really.'* (77F11S1)

Thus these two 'prior decliners' had made prior decisions not to participate in trials for different reasons – confidentiality and being 'too old'. Yet both accounts centred on their personal circumstances and their policy of declining all trial invitations, and both declined very quickly and with little deliberation, as they had established a precedent.

In contrast most interviewees reported making decisions that took account of the features of each trial presented to them. The remaining 18 interviewees, including eight who had previously participated in research, made decisions specific to the REFRAMED trial. These interviewees approached the REFRAMED decision with positive attitudes despite perceiving mixed outcomes from that previous research:

*'It was excellent... And it's been the greatest help I've ever had actually. I mean, 40 years I've been suffering with depression but this came at a latter stage of my life obviously and I took it.'* (62M07S3)

Whilst others found it to be of less direct benefit:

*'I think the person that was doing [the study] got more benefit than I did. I was just helping that person out, which I didn't mind doing.'* (54F04S2)

Interviewees with no experience of trials often recounted experiences of close family members who had made decisions to enrol in trials, described supporting their family members' decisions, and displayed positive opinions and detailed knowledge of those trials:

*'One of my husband's problems is that he now has end-stage kidney failure, and has had for the last 8 years. When he was initially diagnosed with chronic renal failure [pharmaceutical company] were instigating a massive worldwide research into statins and the effect on renal failure. My husband agreed to enter into that and I appreciate that they basically give people either a placebo or the real drug[...]And it was perfectly obvious from my husband's statins – prior to taking the drug, his cholesterol was six-something and 3 months after it had gone down to two. So it was pretty obvious that he didn't have the placebo.'* (74F05S1)

Thus interviewees were universally positive about the trial, even the 'prior decliners'.

### **Stage 2: determining own eligibility**

With the exception of prior decliners, all respondents described engaging with trial eligibility on reading the letter. Interviewees described: the trial eligibility criteria; their perceptions of their eligibility for the trial; and their identification by clinical teams who sent them the trial invitation. Their accounts revealed differences in the interpretation of the diagnosis and management of depression. Nine interviewees described using the trial information and eligibility criteria to decide how to respond to the invitation in light of their personal circumstances. They fell into two broad 'self-excluding'

categories: those who judged that they were ineligible because they were not taking antidepressants prescribed by their clinical teams (though they may have been considered eligible by those teams); and those who described themselves as 'not depressed enough'.

The trial eligibility criteria required patients to have a current diagnosis of major depressive disorder, to have been prescribed antidepressants, and not to have responded to these within the current episode. All participants in this qualitative study had been identified by their clinical teams as matching these criteria. Six interviewees reported that, when invited into REFRAMED, they had never taken their prescribed antidepressants, or soon stopped doing so, without informing their doctors. They had decided not to participate in the trial, perceiving that they were ineligible for the trial, rather than rejecting the trial itself. One reported that doctors had prescribed him antidepressants on several occasions, but he had always refused to take them, because he felt strongly that he did not need them to manage his mood, and worried about the effects of long-term antidepressant use on his health:

*'I really do believe going onto antidepressants, particularly long-term, is not a good thing.'* (62M07S3)

Other interviewees, who had initially taken their prescribed antidepressants, reported that they had stopped taking them without consulting their doctors when they felt they no longer needed medication, or they did not 'like taking them' (59M06S2). Several interviewees reported side effects from the antidepressants, which they had managed by stopping their medication. Another interviewee described asking her GP to stop antidepressants immediately as her mood had improved, but her GP had insisted on reducing the dose gradually:

*'She wanted me to wind it down...she made me have one more lot.'* (70F08S2)

Thus respondents pointed to differences between themselves and their treating clinicians in perceptions of the diagnosis of depression and its management. Some managed these differences by doing what felt right, often without consulting their doctors.

Other interviewees had been taking their antidepressants but considered themselves ineligible because their depression was not severe enough to meet the inclusion criteria in the trial invitation. These respondents reported that: they were 'not very depressed'; they were on maintenance doses of antidepressants; their antidepressants were for comorbid conditions like anxiety; their depression was not the main



problem; or their mood had improved as a result of taking antidepressants:

*'The thing was I'd been on tablets but they seemed to have worked'.* (69F14S2)

Some interviewees reported that, to be of use to the trial, they needed to be much more unwell than they were:

*'I didn't think you'd learn anything from me'.* (73F10S2)

Thus respondents and their clinical teams differed in their interpretation of eligibility for the trial. The fluidity of the diagnosis of depression may have allowed these differing interpretations that led to interviewees excluding themselves from the trial. The imprecision of the initial screening process via electronic health records may have given further scope for interviewees to exclude themselves and not progress to the full assessment of eligibility (by a member of the REFRAMED team). As one participant commented:

*'Our GP practice must have sent the letter to everyone with the word "depression" in their records rather than going for the precise criteria'.* (66M12S2)

In summary the term 'self-excluders' describes the nine respondents who labelled themselves as ineligible after reading the initial invitation. Typically they did not deliberate on the decision, but soon returned the 'opt-out' form to the trial team.

### **Stage 3: assessing own need for trial therapy and potential to benefit**

Other participants focused their decision making on the trial therapy. This is distinct from stage 2, in that informants who progressed to stage 3 considered the trial's potential to benefit their health, rather than their potential to benefit the trial. They viewed the trial as offering an adjunct to current treatment, and focused their decision making on whether they were likely to benefit from the trial therapy. These seven interviewees, whom we term 'treatment decliners' indicated that once they had assessed that they did not need the trial therapy they decided to decline:

*'I don't need it. If I did need it, then yes, it's good'.* (67F01S3)

These informants saw the trial invitation as offering help to manage their depression. Whilst they acknowledged that they were depressed, some described their

depression as not as severe as others', and therefore in less need of help:

*'I don't think that I'm that ill enough to warrant anything a great deal anyway, if you know what I mean. There are people far more depressed than what I am and need more help than I do'.* (67F01S3)

Other interviewees compared their present state with past episodes of depression. Several claimed they were better able to 'cope' with their present state than with past episodes, and therefore did not feel in need of the trial therapy:

*'I thought, well I'm not actually, I mean, I'm bumping along on a low dose of antidepressants, I've retired from work, things are going reasonably'.* (66M12S2)

Despite the trial invitation stressing randomisation, all interviewees assumed they would receive the trial therapy. They made their decision by focusing on what would happen should they receive the trial therapy, rather than on the uncertainty of receiving one of two possible allocations. Some did go on to reflect on the difficult situation that could arise if a hypothetical depressed person focused their decision on their need for the treatment but was randomised to 'usual care'. Informants emphasised how help was often lacking for people with depression and people were sometimes 'desperate' for treatment. In this context, one informant talked of how it was '*almost cruel*' to offer people the chance to enrol into a trial but then not provide the trial treatment, and advised that people could experience feelings of frustration and rejection:

*'People are sometimes desperate for something new or different that will get rid of the pain...for people with mental health issues where feelings of suicide pop up now and again it can be almost cruel if you were not to be chosen[...]Feelings of distress and frustration can be ever so amplified. You can feel so disheartened'.* (46F16S4)

Similarly, another interviewee who had participated in a trial of psychological therapy for depression (which he had completed not long before being invited into REFRAMED) described how he had enrolled in the previous trial because he had wanted help for his depression; and he had declined to participate in REFRAMED because his depression was much improved as a consequence of receiving the active psychological intervention in the previous trial. He recognised there was a chance he might not receive the psychological intervention in the previous

trial; however he had enrolled with the clear aim of being assigned to psychological therapy:

*'That was my target. I aimed to get the assessments right, so they would put me on the [trial therapy], because I wanted something to help me. No question of it, that was my goal. I never thought any different.'* (62M07S3)

Thus there was also a belief that the randomisation outcome depended on the baseline assessments.

This and other accounts saw trials as providing access to potentially life-prolonging and life-enhancing treatment not otherwise available. The perception was that trials are fulfilling health needs, rather than providing an impartial mode of resolving clinical uncertainty. Thus not to receive the trial treatment was problematic for people seeking novel healthcare where few other options were available. In declining REFRAMED, however, patients did not feel they 'needed' the trial therapy to manage their depression. However, it is clear from these accounts that, if interviewees had felt they needed the therapy, they would have considered enrolling in the trial with the aim of accessing the trial therapy to manage their depression.

#### **Stage 4: deliberating burdens and benefits of trial participation**

The remaining two interviewees deliberated about the costs and benefits of trial participation, but only after deciding that they could benefit from the trial therapy. We describe them as 'trial decliners'. They considered the burden of the research procedures and the commitment required to participate. Personal circumstances, like caring and work responsibilities, were key considerations alongside the distance and time from home to therapy and other inconveniences caused by participation.

Interviewees expressed this in terms of comparing burdens and rewards. The burdens arose from the time commitment, both to therapy and research follow-up; one focused on the number and length of therapy sessions, regarded as time-consuming and 'intense', whilst the other focused on the follow-up period of 18 months:

*'The long-term commitment was a nightmare for me as I was looking for work, going for interviews and not really knowing what I would be doing or where I would be over the next 18 months.'* (46F16S4)

This debate was important only to the two people who judged that they were eligible and could benefit from the trial therapy – the 'trial decliners'. Most interviewees decided to opt out of the trial earlier in the deliberation process and did not consider inconvenience as a primary

reason for not participating; for them eligibility and need for the trial therapy trumped inconvenience.

## **Discussion**

### **Summary of main findings**

The 20 interviewees had positive views of research and of the aims of the REFRAMED trial in particular. Many had experience of research participation. The interviews enabled us to identify four stages in the process of deciding whether or not to participate in the REFRAMED trial. At each stage some respondents concluded their deliberation and opted out. In stage 1 the '*prior decliners*' opted out, who have an established position of declining trial participation, stemming from personal circumstances, for example viewing themselves as 'too old'. In stage 2, the '*self-excluders*' who use the trial eligibility criteria to declare themselves ineligible opted out; they see their illness and its management differently from the clinical team who invited them to participate. In stage 3 the '*treatment decliners*' opted out, who perceive that they may be eligible, but focus on their health needs and decide that they do not need the trial therapy. In stage 4 the '*trial decliners*' opted out, who perceive that they may be eligible and in need of the trial therapy, but focus on the burden of trial participation and decide that that outweighs potential benefits.

### **Strengths and limitations**

Our study adds to the very sparse literature on non-participation in randomised trials. To our knowledge this is the first qualitative study to explore explicitly how decisions to decline invitations to mental health trials were made and to present the results in a conceptual framework of decision making.

There are gender and age differences in the presentation and diagnosis of depression [44, 45], and most primary care depression trials enrol many more females than males [46]. Our sample of 14 (70 %) women and six (30 %) men, with ages ranging from 18 to 77 years, reflects the demographics of depression trials and is a strength of this study.

We used telephone and e-mail interview methods and it is possible that, compared with face-to-face interviews, these may compromise rapport, probing and interpretation of interview responses [47]. However, using these methods enabled us to interview a hard-to-reach group who otherwise may not have engaged [48, 49] and to achieve a degree of anonymity which arguably helped interviewees to disclose their experiences.

It is possible that interviewees present themselves as rational deliberators in studies of this sort, because that is what they perceive is expected of them. We minimised this risk by asking interviewees simply to report what happened when they received the trial invitation, rather

than to provide detailed elaborations of their decision making process and some – the ‘prior decliners’ who had previously made similar decisions to decline other trials – clearly reported that they made the decision with little deliberation. Some interviews occurred months after the initial refusal. While some respondents had difficulty recalling details, most recalled the invitation and decision process in detail and provided vivid accounts.

As in all studies of volunteers, informants selected themselves. However, participants represented only 16 % of decliners, which may limit the transferability of our findings. Interviewees expressed very positive views of research, presumably because, like other studies of non-participation, we could not access those averse to research. However, we doubt whether research-averse individuals could help to enhance recruitment, as they would not respond to recruitment interventions.

Patients who declined after being directly approached by clinicians to participate in REFRAMED also could not contribute to this study. Such patients may have offered different views, particularly around eligibility and self-exclusion issues, since clinicians were perhaps more likely to approach those whom they were confident would meet the trial eligibility criteria.

Whilst we undertook purposive sampling, the small numbers of patients who responded limited the scope of that. Despite this we did reach data saturation with those interviewed. Finally, the novel treatment in REFRAMED was aimed at patients with refractory depression and was particularly intense, so findings may not be transferable to other depression trials.

### Comparison with existing literature

Our meta-synthesis [23] shows that patients’ decisions to enter depression trials depend on: their health at the time of the invitation; their attitudes towards the research and trial interventions; and the demands of the trial. Our conceptual framework describes how decisions to participate require judgment between ‘risk and reward’. This qualitative study supports that meta-synthesis by showing that in making their decisions, respondents balanced their current health and whether they would benefit from the trial therapy against the burden of participating in the therapy including travel and time. In planning this study, we sought to contribute to existing knowledge. For example, we focused on patients under-represented in the previous literature by exploring how those who opted out of REFRAMED made their decisions.

Our findings reflect the wider decision-making literature, in particular the ‘deliberation and determination’ framework [25]. This framework differentiates between the pre-decisional process of deliberation, the act of determination and post-decisional outcomes. Our findings and the stages appear to match this process of ‘deliberation,’ in

which the person considers the invitation in light of their eligibility, experiences and need; and determination, which is the act of choosing to not participate. Our classification of individuals as ‘prior decliners,’ ‘self-excluders,’ ‘treatment decliners’ and ‘trial decliners’ appears to reflect the ‘determination’ phase of the deliberation and determination framework.

Our findings in this subgroup contrast with the general literature which suggests that altruism is a major reason for research participation [50–52]. Our respondents initially assessed their eligibility for the trial, then focused on their need for the trial therapy, and their potential to benefit. There is evidence that perceived ineligibility can lead people with depression to decline trial participation [24], and that patients participating in trials focus on the therapy under review and consider personal benefits from it [53–57]. The term ‘conditional altruism’ describes willingness to help others that inclines people to participate in trials, but does not clinch trial participation unless they judge that this will benefit them personally [57]. Whilst interviewees appeared to understand that randomisation meant that those who enrol might not receive the trial intervention, their accounts revealed the perception of randomisation in treatment trials as fundamentally unfair, even ‘cruel’ in cases where people may be seeking treatment through trial participation. Thus our group of decliners demonstrated similar attitudes to those who enrol to gain therapeutic benefit from trial participation. A relevant concept is the *therapeutic misconception* – a blurring of research and treatment, and thus a threat to understanding the trial and its risks [58–61]. There is some evidence that patients who decline participation often misunderstand the nature of the research [62, 63]. More pertinent to our interviewees, however, may be the concept of the *therapeutic misestimation*, which misunderstands the likelihood of risks and benefits rather than the general purpose of trials [64].

We found that interviewees had positive attitudes to research and the trial. This contrasts with some literature on non-participation which reports that decliners are less supportive of research [65–67]. Despite not participating, our interviewees generally did not mind being invited and felt free not to participate. There is evidence that most patients with mental health problems approve of psychiatric research [50], and that non-participation does not reflect objection to research in principle [63, 68]. Patients who opt out of trials have reported that they do not object to being asked to participate, nor do they feel any pressure to do so [69].

### Implications for recruitment practice and future research

Our findings have several implications for trial recruitment and ethical and methodological research on it. First it is important to recognise that those whom we

term ‘prior decliners’ are unlikely to respond to any recruitment initiative as they have an established stance of declining all trial invitations. However, other factors leading patients to opt out of trials may be open to amelioration as they do not arise from a rejection of trials or personal stances of declining such invitations.

To improve responses to postal invitations in similar trials, the most successful interventions are likely to address patients’ assessments of their eligibility and their potential to benefit from the trial treatment, rather than reducing the burden of that treatment. Trialists can influence patients’ assessments of eligibility by exploring methods of:

- (a) managing electronic patient records to estimate eligibility more precisely;
- (b) influencing patients’ own assessment of eligibility and their judgments of their potential to benefit from the trial treatment; and
- (c) drafting trial invitations, for example to minimise the risk of excluding themselves as ineligible.

The wording of invitations could be evaluated to examine the effect of conveying broader criteria on the numbers initially expressing interest, and ultimately enrolled. It is unclear whether ‘self-excluders’ make the same decisions that the trial team would, and whether the trial team would also have excluded them as not meeting the inclusion criteria. Thus trialists could evaluate a trial invitation letter which lists the precise inclusion and exclusion criteria against a comparator invitation which lists only the condition under investigation (e.g. ‘depression’), to estimate how many people initially respond in each arm, how many are excluded by the trial team and how many are ultimately enrolled. While eligibility issues are complex, there may be a case for accepting the risk of attracting more patients who turn out to be ineligible rather than being too restrictive. However, our findings caution against raising patients’ expectations in a way that would be unrealistic.

We know from our study that most patients focus on their need for the trial therapy when deciding whether to participate, whatever their final decision. Thus Miller and Brody [70] and Schlichting [71] have argued for trials to serve health needs, by abandoning the traditional commitment to clinical equipoise and conducting research ‘with therapeutic intent’. This approach replaces the ethical framework of equipoise with that of non-exploitation, so as to achieve the goals of patients, clinicians and researchers [71]. Though detailed examination of this ethical dilemma is beyond the scope of this study, trialists should know that our respondents effectively supported this radical proposal. The implication of accepting the principle of research ‘with therapeutic intent’ is that

trials should aim, not only for a favourable benefit-risk ratio for society, but also to avoid an unfavourable benefit-risk ratio for each trial participant [72, 73]. Our qualitative study suggests that trialists should prospectively monitor patients’ expectations of their trials and use that to inform design and delivery. Better, patient-centred explanations of the potential benefits of trial treatments may help [74]. Engaging service users and members of the public in the design and conduct of trials alongside qualitative research may be the key to this [75]. For example, qualitative research could explore patient treatment preferences [76, 77]. Thus a priority for future research is the presentation and provision of accurate and effective trial information in which patients and the public play a seminal role [78]. Retrospective but timely feedback from patients who opt out of trials can assess the acceptability of the treatment being evaluated [24]. Early inclusion of such feedback into trial recruitment procedures can increase participation rates [79]. However, all such interventions require robust evaluation, ideally through embedded randomised trials.

## Conclusions

We have studied how patients invited into a randomised trial in mental health decided not to participate. They opted out in a sequence of four stages: first, the ‘prior decliners’ who have an established position of declining trial participation; second, the ‘self-excluders’ who judge that they are ineligible; third, the ‘treatment decliners’ who decide that they do not need the trial therapy; and finally the ‘trial decliners’ who decide that the burden of trial participation outweighs potential benefits. These findings have positive implications for improving trial recruitment, because trialists can address most of these issues.

## Additional files

**Additional file 1:** Summary participant information leaflet. Description of data: a copy of the trial participant information that was posted to interviewees along with the trial invitation letter. (PDF 279 kb)

**Additional file 2:** Interview with decliners in a depression trial - topic guide. Description of data: the topic guide used to interview participants. (DOCX 28 kb)

## Abbreviations

GP: General Practitioner; MCR: Medical Research Council; NHS: National Health Service; NIHR: National Institute for Health Research; PRIMER: Primary Care Research in Manchester Engagement Resource; REC: Research Ethics Committee; RO-DBT: Radically Open Dialectical Behavioural Therapy; SURP: Service User Research Panel

## Acknowledgements

We thank the UK Clinical Research Network Mental Health’s Service User Research Panel (SURP) and Primary Care Research in Manchester Engagement Resource (PRIMER) for their support and feedback on the study. Special thanks to Tim Rawcliffe for his support, detailed feedback on the interview schedule, and eager participation in ‘role playing’ the interview. We also thank the REFRAMED trial investigators, especially Chief Investigator Professor Thomas

Lynch, for giving us access to participants for this study. Finally, this study would not have been possible without the contributions of our 20 interviewees, each of whom took the time to revisit a difficult decision they had made. In doing so, each person made an invaluable contribution to this study. Thank you all!

#### Funding

We are grateful to the Efficacy and Mechanism Evaluation (EME) Programme, a partnership between the MRC and NIHR, for funding the REFRAMED trial; and to the NIHR itself for funding Adwoa Hughes-Morley through a Doctoral Research Fellowship (NIHR DRF 2012 051128). This article presents independent research funded by the MRC and NIHR. The views expressed are those of the authors and not necessarily those of the MRC, the NIHR, the NHS or the Department of Health.

#### Availability of data and materials

The transcripts for this manuscript will not be shared. The transcripts contain sensitive information around people's experiences of mental health problems and their decision to decline a trial. We also did not obtain ethical permission from participants for their interview transcripts to be shared.

#### Authors' contributions

RJH and ITR are members of the REFRAMED trial group. RJH was REFRAMED Trial Manager and led the ethics amendment and sub-study registration for conducting this qualitative study, as well as participant recruitment. ITR contributed to REFRAMED trial design, including methodological aspects of participant recruitment. AH-M led on the methods for the qualitative study, undertook the participant interviews, analysis and drafted the manuscript. BY, PB and WW supervised the study design, data collection, analysis and reporting. All authors commented on drafts of the manuscript and approved the final manuscript.

#### Competing interests

The authors declare that they have no competing interests.

#### Consent for publication

Written informed consent was obtained from the participants for publication of their individual details in this manuscript. The consent form is held by the authors and is available for review by the Editor-in-Chief.

#### Ethics approval and consent to participate

The National Research Ethics Service Committee South Central - Southampton A (REC reference 11/SC/0146) granted approval for the whole REFRAMED trial including a linked qualitative study to explore the decision making of patients who declined to participate in REFRAMED. We informed all potential participants in the qualitative study of its purpose and assured them that participation was voluntary and we would pseudonymise their data to keep them confidential. These potential participants opted into the qualitative study by providing written consent, but received no payment for their participation.

#### Author details

<sup>1</sup>MRC North West Hub for Trials Methodology Research, Manchester Academic Health Science Centre, University of Manchester, Oxford Road, Manchester M13 9PT, UK. <sup>2</sup>York Trials Unit, Department of Health Sciences, University of York, York YO10 5DD, UK. <sup>3</sup>MRC North West Hub for Trials Methodology Research, Department of Psychology, Institute of Psychology, Health and Society, University of Liverpool, Liverpool, UK. <sup>4</sup>School of Psychology, University of Southampton, Southampton SO17 1BJ, UK. <sup>5</sup>Swansea University Medical School, Swansea University, Swansea SA2 8PP, UK. <sup>6</sup>NIHR School for Primary Care Research, Manchester Academic Health Science Centre, The University of Manchester, Williamson Building, Manchester M13 9PT, UK.

Received: 21 June 2016 Accepted: 28 September 2016

Published online: 12 October 2016

#### References

- Bower P, Wallace P, Ward E, Graffy J, Miller J, Delaney B, Kinmonth AL. Improving recruitment to health research in primary care. *Fam Pract*. 2009;26(5):391–7.
- Sully BG, Julious SA, Nicholl J. A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. *Trials*. 2013;14(1):166.
- Carlisle B, Kimmelman J, Ramsay T, MacKinnon N. Unsuccessful trial accrual and human subjects protections: an empirical analysis of recently closed trials. *Clin Trials*. 2015;12(1):77–83.
- Darbyshire JH. The UK Clinical Research Network—building a world-class infrastructure for clinical research. *Rheumatology*. 2008;47(6):745.
- Zerhouni E. Medicine. The NIH roadmap. *Science*. 2003;302(5642):63–72.
- National Institutes of Health. About NIH. 2015. Available at: <http://www.nih.gov/about/>. Accessed 1 Mar 2016.
- CenterWatch. State of the clinical trials industry 2009: a sourcebook of charts and statistics. Boston: CenterWatch; 2009.
- Bryant K, Wicks MN, Willis N. Recruitment of older African American males for depression research: lessons learned. *Arch Psychiatr Nurs*. 2014;28(1):17–20.
- Olsen K, Howell D, Barber R, Ford GA, Gallagher P, McAllister-Williams RH, Nilsson J, O'Brien J, Parker J, Thomas A. Lessons from a pilot and feasibility randomised trial in depression (Blood pressure Rapid Intensive Lowering And Normal Treatment for Mood and cognition in persistent depression (BRILiant mood study)). *Pilot Feasibility Stud*. 2015;1(1):1–11.
- Woodall A, Morgan C, Sloan C, Howard L. Barriers to participation in mental health research: are there specific gender, ethnicity and age related barriers? *BMC Psychiatry*. 2010;2:10–103.
- Brown G, Marshall M, Bower P, Woodham A, Waheed W. Barriers to recruiting ethnic minorities to mental health research: a systematic review. *Int J Methods Psychiatr Res*. 2014;23(1):36–48.
- Halpern SD, Karlawish JHT, Berlin JA. The continuing unethical conduct of underpowered clinical trials. *JAMA*. 2002;288:358–62.
- Drueke TB, Descamps-Latscha B, Locatelli F. Stopping a medical research project for financial reasons. *Nephrol Dial Transplant*. 2003;18(10):1982–3.
- Adamson J, Hewitt CE, Torgerson DJ. Producing better evidence on how to improve randomised controlled trials. *BMJ*. 2015;351:h4923.
- Smith CT, Hickey H, Clarke M, Blazeby J, Williamson P. The trials methodological research agenda: results from a priority setting exercise. *Trials*. 2014;15(1):32.
- Watson JM, Torgerson DJ. Increasing recruitment to randomised trials: a review of randomised controlled trials. *BMC Med Res Methodol*. 2006;9:1–9.
- Treweek S, Lockhart P, Pitkethly M, Cook JA, Kjeldstrom M, Johansen M, Taskila TK, Sullivan FM, Wilson S, Jackson C, Jones R, Mitchell ED. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. *BMJ*. 2013;3(2):e002360.
- Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. 2008;337:a1655.
- Tramm R, Daws K, Schadewaldt V. Clinical trial recruitment—a complex intervention? *J Clin Nurs*. 2013;22(17–18):2436–43.
- Howard L, de Salis I, Tomlin Z, Thornicroft G, Donovan J. Why is recruitment to trials difficult? An investigation into recruitment difficulties in an RCT of supported employment in patients with severe mental illness. *Contemp Clin Trials*. 2009;30(1):40–6.
- Donovan JL, Lane JA, Peters TJ, Brindle L, Salter E, Gillatt D, Powell P, Bollina P, Neal DE, Hamdy FC, ProtecT Study Group. Development of a complex intervention improved randomization and informed consent in a randomized controlled trial. *J Clin Epidemiol*. 2009;62(1):29–36.
- O' Cathain A, Thomas KJ, Drabble SJ, Rudolph A, Hewison J. What can qualitative research do for randomised controlled trials? A systematic mapping review. *BMJ Open*. 2013;3(6):e002889.
- Hughes-Morley A, Young B, Waheed W, Small N, Bower P. Factors affecting recruitment into depression trials: systematic review, meta-synthesis and conceptual framework. *J Affect Disord*. 2015;172C:274–90.
- Barnes M, Wiles N, Morrison J, Kessler D, Williams C, Kuyken W, Lewis G, Turner K. Exploring patients' reasons for declining contact in a cognitive behavioural therapy randomised controlled trial in primary care. *Br J Gen Pract*. 2012;62(598):e371–7.
- Elwyn G, Miron-Shatz T. Deliberation before determination: the definition and evaluation of good decision making. *Health Expect*. 2010;13(2):139–47.
- Gillies K, Elwyn G, Cook J. Making a decision about trial participation: the feasibility of measuring deliberation during the informed consent process for clinical trials. *Trials*. 2014;15(1):307.

27. Snowden C, Elbourne D, Garcia J. The decision to decline to enrol in a clinical trial: a blind spot in the literature on decision-making for research participation. In: Corrigan O, McMillan J, Liddell K, Richards M, Weijer C, editors. *The limits of consent: a socio-ethical approach to human subject research in medicine*. Oxford: Oxford University Press; 2009. p. 57.
28. Lynch TR, Whalley B, Hempel RJ, Byford S, Clarke P, Clarke S, Kingdon D, O'Mahen H, Russell IT, Shearer J, Stanton M, Swales M, Watkins A, Remington B. Refractory depression: mechanisms and evaluation of radically open dialectical behaviour therapy (RO-DBT) [REFRAMED]: protocol for randomised trial. *BMJ Open*. 2015;5(7):e008857.
29. Lynch TR. Radically open dialectical behavior therapy for disorders of overcontrol. New Harbinger Publications Inc.: Oakland; 2017. in press.
30. Cornish F, Gillespie A. A pragmatist approach to the problem of knowledge in health psychology. *J Health Psychol*. 2009;14(6):800–9.
31. O' Cathain A, Murphy E, Nicholl J. Why, and how, mixed methods research is undertaken in health services research in England: a mixed methods study. *BMC Health Serv Res*. 2007;7(1):85.
32. Patton MQ. *Qualitative evaluation and research methods*. SAGE: Newbury Park; 1990.
33. Tashakkori A, Teddlie C. *Mixed methodology: Combining qualitative and quantitative approaches*. Thousand Oaks: Sage; 1998.
34. Glaser B, Strauss A. *The discovery of grounded theory: strategies for qualitative research*. Chicago: Aldine; 1967.
35. Taylor AW, Wilson DH, Wakefield M. Differences in health estimates using telephone and door-to-door survey methods—a hypothetical exercise. *Aust N Z J Public Health*. 1998;22(2):223–6.
36. McCoyd JLM, Kerson TS. Conducting intensive interviews using email: a serendipitous comparative opportunity. *Qual Soc Work*. 2006;5(3):389–406.
37. Hamilton RJ, Bowers BJ. Internet recruitment and e-mail interviews in qualitative studies. *Qual Health Res*. 2006;16(6):821–35.
38. AncaVitu EL, Vitcu L, Marcu A. Multi-stage maximum variation sampling in health promotion programs' evaluation. *J Prev Med*. 2007;15:5–18.
39. Coyne IT. Sampling in qualitative research. Purposeful and theoretical sampling; merging or clear boundaries? *J Adv Nurs*. 1997;26(3):623–30.
40. Morse JM. Confusing categories and themes. *Qual Health Res*. 2008; 18(6):727–8.
41. Strauss A, Corbin JM. *Basics of qualitative research: Grounded theory procedures and techniques*. Thousand Oaks: Sage; 1990.
42. Denzin NK. *The research act: a theoretical introduction to sociological methods*. New Brunswick: Transaction; 1970.
43. Madill A, Jordan A, Shirley C. Objectivity and reliability in qualitative analysis: Realist, contextualist and radical constructionist epistemologies. *Br J Psychol*. 2000;91(1):1–20.
44. Bertakis KD, Helms LJ, Callahan EJ, Azari R, Leigh P, Robbins JA. Patient gender differences in the diagnosis of depression in primary care. *J Womens Health Gend Based Med*. 2001;10(7):689–98.
45. Sherbourne C, Schoenbaum M, Wells KB, Croghan TW. Characteristics, treatment patterns, and outcomes of persistent depression despite treatment in primary care. *Gen Hosp Psychiatry*. 2004;26(2):106–14.
46. Chan KS, Bird CE, Weiss R, Duan N, Meredith LS, Sherbourne CD. Does patient-provider gender concordance affect mental health care received by primary care patients with major depression? *Womens Health Issues*. 2006;16(3):122–32.
47. Novick G. Is there a bias against telephone interviews in qualitative research? *Res Nurs Health*. 2008;31(4):391–8.
48. Ison NL. Having their say: email interviews for research data collection with people who have verbal communication impairment. *Int J Soc Res Methodol*. 2009;12(2):161–72.
49. Hunt N, McHale S. A practical guide to the e-mail interview. *Qual Health Res*. 2007;17(10):1415–21.
50. Schafer I, Burns T, Fleischhacker W, Galderisi S, Rybakowski JK, Libiger J, Rossler W, Molodynski A, Edlinger M, Piegari G, Hrnčiarova J, Gorna K, Jaeger M, Fett A-K, Hissbach J, Naber D. Attitudes of patients with schizophrenia and depression to psychiatric research: a study in seven European countries. *Soc Psychiatry Psychiatr Epidemiol*. 2011;46(2):159–65.
51. Tallon D, Mulligan J, Wiles N, Thomas L, Peters TJ, Elgie R, Sharp D, Lewis G. Involving patients with depression in research: a survey of patients' attitudes to participation. *Br J Gen Pract*. 2011;61(585):134–41.
52. Grant J, Mackinnon A, Christensen H, Walker J. Participants' perceptions of motivation, randomisation and withdrawal in a randomised controlled trial of interventions for prevention of depression. *J Med Ethics*. 2009;35(12):768–73.
53. Kim SY, De Vries R, Holloway RG, Wilson R, Parnami S, Kim HM, Frank S, Kiebertz K. Sham surgery controls in Parkinson's disease clinical trials: views of participants. *Mov Disord*. 2012;27(11):1461–5.
54. Wasan AD, Taubenberger SP, Robinson WM. Reasons for participation in pain research: can they indicate a lack of informed consent? *Pain Med*. 2009;10(1):111–9.
55. Locock L, Smith L. Personal experiences of taking part in clinical trials - a qualitative study. *Patient Educ Couns*. 2011;84(3):303–9.
56. Madsen SM, Holm S, Riis P. Attitudes towards clinical research among cancer trial participants and non-participants: an interview study using a grounded theory approach. *J Med Ethics*. 2007;33(4):234–40.
57. Mccann SK, Campbell MK, Entwistle VA. Reasons for participating in randomised controlled trials: conditional altruism and considerations for self. *Health Technol Assess (Rockv)*. 2010;11:31.
58. Appelbaum PS, Roth LH, Lidz C. The therapeutic misconception: informed consent in psychiatric research. *Int J Law Psychiatry*. 1982;5(3–4):319–29.
59. Benson PR, Roth LH, Winslade WJ. Informed consent in psychiatric research: preliminary findings from an ongoing investigation. *Soc Sci Med*. 1985;20(12):1331–41.
60. Appelbaum PS, Roth LH, Lidz CW, Benson P, Winslade W. False hopes and best data: consent to research and the therapeutic misconception. *Hastings Cent Rep*. 1987;17(2):20–4.
61. Wilcox S, Dowda M, Griffin SF, Rheame C, Ory MG, Leviton L, King AC, Dunn A, Buchner DM, Bazzarre T, Estabrooks PA, Campbell-Voytal K, Bartlett-Prescott J, Dowdy D, Castro CM, Carpenter RA, Dziewaltowski DA, Mockenhaupt R. Results of the first year of Active for Life: translation of 2 evidence-based physical activity programs for older adults into community settings [corrected] [published erratum appears in *Am J Public Health* 2006 Nov;96(11):1901]. *Am J Public Health*. 2006;96(7):1201–9.
62. Robinson EJ, Kerr CE, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, Beck SR, Rowley MG. Lay public's understanding of equipoise and randomisation in randomised controlled trials. *Health Technol Assess*. 2005;9(8):1–192. iii–iv.
63. Williams B, Irvine L, McGinnis AR, McMurdo ME, Crombie IK. When 'no' might not quite mean 'no': the importance of informed and meaningful non-consent: results from a survey of individuals refusing participation in a health-related research project. *BMC Health Serv Res*. 2007;7:59.
64. Horng S, Grady C. Misunderstanding in clinical research: distinguishing therapeutic misconception, therapeutic misestimation, and therapeutic optimism. *IRB Ethics Hum Res*. 2003;25(1):11–6.
65. Snowden C, Elbourne D, Garcia J. Declining enrolment in a clinical trial and injurious misconceptions: is there a flipside to the therapeutic misconception? *Clin Ethics*. 2007;2(4):193–200.
66. Sharp L, Cotton SC, Alexander L, Williams E, Gray NM, Reid JM. Reasons for participation and non-participation in a randomized controlled trial: postal questionnaire surveys of women eligible for TOMBOLA (Trial Of Management of Borderline and Other Low-grade Abnormal smears). *Clin Trials*. 2006;3(5):431–42.
67. Madsen SM, Mirza MR, Holm S, Hilstedt KL, Kampmann K, Riis P. Attitudes towards clinical research amongst participants and nonparticipants. *J Intern Med*. 2002;251(2):156–68.
68. Stevens T, Ahmedzai SH. Why do breast cancer patients decline entry into randomised trials and how do they feel about their decision later: a prospective, longitudinal, in-depth interview study. *Patient Educ Couns*. 2004;52(3):341–8.
69. Shilling V, Williamson PR, Hickey H, Sowden E, Smyth RL, Young B. Processes in recruitment to randomised controlled trials of medicines for children (RECRUIT): a qualitative study. *Health Technol Assess*. 2011;15(15):1–116.
70. Miller FG, Brody H. A critique of clinical equipoise: therapeutic misconception in the ethics of clinical trials. *Hastings Cent Rep*. 2003;33(3):19–28.
71. Schlichting DE. Destabilizing the 'equipoise' framework in clinical trials: prioritizing non-exploitation as an ethical framework in clinical research. *Nurs Philos*. 2010;11(4):271–9.
72. Emanuel EJ, Wendler D, Killen J, Grady C. What makes clinical research in developing countries ethical? The benchmarks of ethical research. *J Infect Dis*. 2004;189(5):930–7.
73. Jansen LA. A closer look at the bad deal trial: beyond clinical equipoise. *Hastings Cent Rep*. 2005;35(5):29–36.
74. Relton C, Torgerson D, O' Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial". *BMJ*. 2010;340:c1066.

75. Barber R, Boote J, Parry G. Can the impact of public involvement on research be evaluated? A mixed methods study. *Health Expect*. 2012;15(3):229–41.
76. de Salis I, Tomlin Z, Toerien M, Donovan J. Using qualitative research methods to improve recruitment to randomized controlled trials: the Quartet study. *J Health Serv Res Policy*. 2008;13 Suppl 3:92–6.
77. Mills N, Donovan JL, Wade J, Hamdy FC, Neal DE, Lane JA. Exploring treatment preferences facilitated recruitment to randomized controlled trials. *J Clin Epidemiol*. 2011;64(10):1127–36.
78. Evans BA, Bedson E, Bell P, Hutchings H, Lowes L, Rea D, Seagrove A, Siebert S, Smith G, Snooks H. Involving service users in trials: developing a standard operating procedure. *Trials*. 2013;14(1):1–7.
79. Martin A, Negron R, Balbierz A, Bickell N, Howell EA. Recruitment of Black and Latina women to a randomized controlled trial. *J Health Care Poor Underserved*. 2013;24(3):1102–14.

Submit your next manuscript to BioMed Central  
and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at  
[www.biomedcentral.com/submit](http://www.biomedcentral.com/submit)





## **REFRAMED:** REFRActory depression - Mechanisms and Efficacy of Radically Open Dialectical Behaviour Therapy

We are conducting a research study asking the question **“Does Radically Open Dialectical Behaviour Therapy reduce depression symptoms better than Standard Clinical Care such as antidepressant medication?”** and are looking for people to take part

Depression is an extremely common mental health problem that is most commonly treated with antidepressant drugs. Unfortunately, some people continue to feel depressed even though they have taken antidepressants for a while.

Recently, a new type of therapy has been developed, called Radically Open Dialectical Behaviour Therapy (RO-DBT). In order to find out whether RO-DBT can reduce depression symptoms, we need to compare two approaches to treating depression by carrying out what is called a randomised controlled trial. In this study, we will compare antidepressant medication alone with antidepressant medication plus RO-DBT.

We are hoping to include 276 people in this study.



## What's the Research about?

Standard DBT has proved to be effective for borderline personality disorder or people who harmed themselves. Radically Open Dialectical Behaviour Therapy (RO-DBT), a new treatment approach with strong roots in standard DBT, has demonstrated promise for patients with difficult-to-treat depression and related overcontrolled disorders.

We want to know if RO-DBT together with antidepressant medication is better than antidepressant medication alone by asking a lot more people to take part and checking back with these people a year after they've finished their treatment to see how they are doing.

In order to work out which is the best way to help people who suffer from depression, we will organise people into two groups. One group will continue to take their antidepressants as usual (the Standard Care group) and the other group will take part in a course of RO-DBT in addition to taking their medications.

As part of the research we will ask all participants from both groups to chat, privately, with a researcher several times over the next 12, and if possible 18, months. The researcher will ask you questions about how you have been feeling and look for any signs of low mood or depression. You will never have to answer any question you don't want to.

Because we also want to know *how* this therapy might work, we will further ask people to complete a questionnaire every month during the first year, and if possible, once more 6 months later.

## **What is RO-DBT and what will happen if I am in the RO-DBT Group?**

RO-DBT is a type of talking therapy that is based on the idea that the way people think and behave affects how they feel. During RO-DBT sessions, the patient and therapist discuss difficulties the patient is experiencing and how their thoughts and feelings affect the problem. The patient and therapist then work together to find ways of helping the person cope with their depression.

If you are in this group, you will be invited to take part in a RO-DBT programme run by a trained and closely supervised therapist. The duration of the therapy is approximately 29 weeks. The RO-DBT treatment involves 1 hour weekly individual sessions and 2.5-hour weekly group sessions. As part of this process, you may be asked to think about some of the issues discussed between sessions and you are asked to keep a diary.

## **What will happen if I am in the Standard Care group?**

If you are in this group, we would prefer you to continue to take your prescription for the duration of the study in the way you and your GP decide is appropriate. This is currently the recommended treatment for people who suffer from depression. However, taking part in this study does not mean you would *have* to continue to take your medication; if you and your GP decided it was the right time for you to stop, we would support that decision. We will regularly ask you how you are getting on. We will also not discourage you from seeking other types of treatment, such as psychotherapy.

## **Who can take part?**

We are looking for people who:

- ✓ Are 18 or over
- ✓ Are currently depressed
- ✓ Have been taking antidepressant medication for at least 6 weeks during their current episode. This means you do not have to be taking them at the moment, as long as you have tried them for at least 6 weeks.

## **Will my taking part in this study be kept confidential?**

Yes, all information collected about you during the course of the research will be kept confidential in line with the normal NHS and clinical research policies.

## **How do I find out more?**

This is a very short summary about the study, if you would like to find out more then you can do so by

- returning the enclosed ready prepared letter,
- telephoning 01202 492126 ;
- or emailing [reframed.dorset@dhuft.nhs.uk](mailto:reframed.dorset@dhuft.nhs.uk)

Someone working on the study will then send you more information about this study and arrange a time to meet you to answer any questions that you may have.

Thank you for reading this and for considering taking part in this study.

**[www.REFRAMED.org.uk](http://www.REFRAMED.org.uk)**

# Additional file 2

## Interview topic guide

The beginning of the interview covered introducing the researcher and research, agreeing appropriate time for the interview, obtaining consent for the interview, to audio record the interview and confidentiality.

### Questions

7  
'k-7k° U -)' @  
)  
@  
'k-7k° U -)' @@  
'k-7k° U -)'  
@ 'k-7k° U -)'  
'k-7k° U -)'

*If yes, PROBE*

### PROBES

7  
@  
@  
‡ =\ ‡  
@

### PROBES

‡  
)  
.  
‡  
)  
)  
)  
)  
=  
= ‡

o

8h

=

#

#

'feel'

=

**If not already known**

‡

@

‡

‡

u

u

u

‡

**(If they read the information sheet)**

u

\

)

"

u

u

)

"

u

**If applicable**

‡

=

=

)

"

u

'randomly'

#

=

**(If applicable)**

j

@

o

u ..... )  
" u

*(If applicable)* ‡ ..... )  
" u

u ..... @ @

-----End by thanking participant-----



# **Chapter 6: The impact of advertising patient and public involvement on trial recruitment: embedded cluster randomised recruitment trial**

---

**Chapter type:** Journal Article

**Journal:** Trials

**Status:** Under review

**Submission date:** 29<sup>th</sup> June 2016

**Published online:** 8th December 2016

**Reference:** Hughes-Morley, A., Hann, M., Fraser, C., Meade, M., Lovell, K., Young, B., Roberts, C., Cree, L., More, D., O'Leary, N., Callaghan, P., Waheed, W., & Bower, P. (2016). The impact of advertising patient and public involvement on trial recruitment: embedded cluster randomised recruitment trial. *Trials*

**Contributions:** AH-M led on the methods and the development of the recruitment intervention, worked with the EQUIP Trial group to develop the embedded study protocol, data sharing agreement, substantial amendment and embedded study registration materials, undertook the analysis under the supervision of MH with input from CR and NO'L, and drafted the manuscript. AH-M, PB MH, BY and WW all commented on drafts of the paper. All authors read and approved the final manuscript.

CF was EQUIP programme manager and led the ethics amendment and sub-study registration for conducting the embedded START trial within the EQUIP Study, as well as recruitment. NO'L and CR were statisticians and were involved in trial design and randomisation of both the EQUIP trial and the embedded recruitment trial. KL is the chief investigator for the EQUIP research programme and has overall responsibility for the design and implementation of the EQUIP trial. CF, KB, KL, LC, DM, PB, PC, N'OL, CR, OM all commented on a draft of this paper.






RESEARCH

Open Access



# The impact of advertising patient and public involvement on trial recruitment: embedded cluster randomised recruitment trial

Adwoa Hughes-Morley<sup>1,2\*</sup> , Mark Hann<sup>2</sup>, Claire Fraser<sup>3</sup>, Oonagh Meade<sup>4</sup>, Karina Lovell<sup>3</sup>, Bridget Young<sup>5</sup>, Chris Roberts<sup>2</sup>, Lindsey Cree<sup>3</sup>, Donna More<sup>3</sup>, Neil O'Leary<sup>6</sup>, Patrick Callaghan<sup>7</sup>, Waquas Waheed<sup>2</sup> and Peter Bower<sup>8</sup>

## Abstract

**Background:** Patient and public involvement in research (PPIR) may improve trial recruitment rates, but it is unclear how. Where trials use PPIR to improve design and conduct, many do not communicate this clearly to potential participants. Better communication of PPIR might encourage patient enrolment, as trials may be perceived as more socially valid, relevant and trustworthy. We aimed to evaluate the impact on recruitment of directly advertising PPIR to potential trial participants.

**Methods:** This is a cluster trial, embedded within a host trial ('EQUIP') recruiting service users diagnosed with severe mental illness. The intervention was informed by a systematic review, a qualitative study, social comparison theory and a stakeholder workshop including service users and carers. Adopting Participatory Design approaches, we co-designed the recruitment intervention with PPIR partners using a leaflet to advertise the PPIR in EQUIP and sent potential participants invitations with the leaflet (intervention group) or not (control group). Primary outcome was the proportion of patients enrolled in EQUIP. Secondary outcomes included the proportions of patients who positively responded to the trial invitation.

**Results:** Thirty-four community mental health teams were randomised and 8182 service users invited. For the primary outcome, 4% of patients in the PPIR group were enrolled versus 5.3% of the control group. The intervention was not effective for improving recruitment rates (adjusted OR = 0.75, 95% CI = 0.53 to 1.07,  $p = 0.113$ ). For the secondary outcome of positive response, the intervention was not effective, with 7.3% of potential participants in the intervention group responding positively versus 7.9% of the control group (adjusted OR = 0.74, 95% CI = 0.53 to 1.04,  $p = 0.082$ ). We did not find a positive impact of directly advertising PPIR on any other outcomes.

**Conclusion:** To our knowledge, this is the largest ever embedded trial to evaluate a recruitment or PPIR intervention. Advertising PPIR did not improve enrolment rates or any other outcome. It is possible that rather than advertising PPIR being the means to improve recruitment, PPIR may have an alternative impact on trials by making them more attractive, acceptable and patient-centred. We discuss potential reasons for our findings and implications for recruitment practice and research.

(Continued on next page)

\* Correspondence: [adwoa.hughes-morley@york.ac.uk](mailto:adwoa.hughes-morley@york.ac.uk)

<sup>1</sup>York Trials Unit, Department of Health Sciences, University of York, York YO10 5DD, UK

<sup>2</sup>Division of Population Health, Health Services Research and Primary Care, University of Manchester, Williamson Building, Manchester M13 9PL, UK

Full list of author information is available at the end of the article



(Continued from previous page)

**Trial registration numbers:** ISRCTN, ISRCTN16488358. Registered on 14 May 2014.  
Study Within A Trial, SWAT-26. Registered on 21 January 2016.

**Keywords:** Recruitment, Patient and public involvement, Research methodology, Randomised controlled trial, Service user involvement, Study within a trial, *Mesh:* embedded trial

## Background

Randomised controlled trials are the ‘gold standard’ for evaluating treatments, yet recruitment into trials remains a great challenge, with approximately 45% of publicly funded and 80% of industry-funded trials failing to meet their recruitment targets [1, 2]. Mental health disorders are the leading cause of disability among adults worldwide [3]; however, trials enrolling patients with mental health problems experience even greater recruitment challenges [4–7]. These challenges stem from various sources including stigma [8] and issues related to the diagnosis adversely impacting on the patient’s ability and motivation to participate in research [9]. Inability to recruit into a trial adversely impacts trials by reducing the total sample size (which limits internal validity) and the proportion of eligible participants who are recruited (which limits external validity).

Thus there is a need to develop and test interventions to improve recruitment. One method is to ‘embed’ trials of recruitment interventions in ongoing trials; however, such trials are rare. Systematic reviews of trial recruitment interventions have highlighted the need for more embedded recruitment trials [10, 11]. Recent initiatives have also increasingly called for the development and evaluation of interventions for recruiting and retaining participants in trials [11–16].

We have developed methodological, logistical and reporting frameworks for embedded recruitment trials [12, 17] and assessed their feasibility using interventions such as an improved Participant Information Sheet and a multimedia decision aid [18, 19]. The eventual aim is to make delivery of embedded recruitment trials a routine activity, to assist the rapid development of recruitment to meet health and policy goals [20].

Patient and public involvement in research (PPIR), also known, among other terms, as ‘user involvement’, is research being carried out ‘with’ or ‘by’ patients and/or members of the public rather than ‘to’, ‘about’ or ‘for’ them [21]. This definition of PPIR is broad and involves patients, all groups who represent patients, as well as members of the public taking roles in the development, conduct and governance of research [22–24]. PPIR is thought to be crucial because it produces ‘better’ patient-focussed research by offering unique, invaluable insights into its prioritization, design, implementation and evaluation, making trials more effective and credible

[25, 26]. PPIR is well-established as public policy in the United Kingdom (UK) and other developed countries and is increasingly mandated for publicly funded trials [27–30]. However, quantitative evidence around its impact is sparse, and that which exists is of poor quality and lacking in rigour [31]. There is a need to assess the effectiveness, cost-effectiveness and ethical impacts of PPIR through high-quality methodological research [31–37].

We recently reported a systematic review and meta-synthesis of factors affecting the recruitment of participants into depression trials [38] to help us to develop and evaluate an intervention for recruiting participants into mental health trials, using the Medical Research Council (MRC) complex interventions framework [39]. We developed a conceptual framework, which highlighted that the decision by patients to enrol as subjects in trials involves a difficult deliberation involving ‘risk’ [38]. This includes potential risks of stigma, of ‘losing out’ by being randomised to the ‘wrong’ intervention arm, or of encountering adverse effects of trial involvement, against potential rewards such as a personal need to access treatment and support. Outside of the mental health context, perceptions of risk have also been shown to impact on patients’ decision to enrol in trials [40–44]. We have also undertaken a qualitative study with patients who declined to participate in a trial, which highlighted the need to research the presentation and provision of accurate and effective trial information in which patients and the public play a seminal role [45].

There is some emerging observational evidence that mental health trials with more PPIR are associated with an increased likelihood of achieving their recruitment targets [46], although studies in other clinical settings have had variable outcomes [47]. PPIR may have a role in reducing patient perception of risk in trials and, as a consequence, may increase trial enrolment. Patients may perceive trials with PPIR to be improved methodologically or ethically, or to be more relevant and, therefore, more likely to influence practice in ways that are important to them and other patients [25, 26, 48]. Additionally, the concept of ‘social validation’ suggests that people may be more willing to comply with a request to enrol in a trial if they believe that others are already engaged in a trial, as people tend to compare and base their beliefs, attitudes and actions on similar others [49–51].

A survey of public attitudes to research suggests that PPIR may increase confidence and trust in a trial, if potential participants are reassured that other patients have advised its design [52, 53]. The authors concluded that: *'if health researchers communicate the fact that patients and the public have been involved in the design of their research when approaching potential study participants, it might help to boost recruitment'* [52, 53]. However, to achieve these effects, it is necessary that PPIR is communicated to patients, but this does not always seem to be the case as researchers tend not to routinely advertise PPIR [54, 55]. We aimed to test this hypothesis about the effects of PPIR on recruitment using a rigorous evaluation. In this paper, we describe the development and evaluation of an intervention directly advertising PPIR in a mental health trial to potential participants.

### Objectives

Our objectives were to work with PPIR stakeholders to develop an intervention directly advertising PPIR in the design and conduct of a host trial, the 'Enhancing the Quality of User Involved care Planning in mental health services' ('EQUIP') trial, which was recruiting people with a diagnosis of severe mental illness; and to evaluate its effectiveness on recruitment by undertaking a randomised controlled trial, embedded in the EQUIP host trial.

### Methods

We report the development of the intervention in line with the Criteria for Reporting the Development and Evaluation of Complex Interventions (CReDECI 2) [56] and its evaluation in line with the 'guidelines for reporting embedded recruitment trials' [17].

#### Trial design: the EQUIP host trial

The EQUIP trial aimed to recruit 480 service users with diagnoses of severe mental illness to evaluate the cost-effectiveness of a training intervention for mental health professionals in enhancing user involvement in care planning. EQUIP had significant high-quality PPIR and was awarded the 2014 UK Mental Health Research Network Prize for 'Outstanding Carer Involvement' [57].

EQUIP is a multicentre cluster randomised trial, where 36 community mental health teams in the Midlands and the North of England were randomly allocated to training or to usual care. In EQUIP mental health team clusters were 'paired' at the recruitment stage (based on size and geographic location) and randomised using minimisation in pairs to training or the control arm. Recruitment in the paired clusters then operated in parallel.

EQUIP used existing registers maintained by community mental health teams to recruit service users. Recruitment was undertaken by the UK Clinical Research Network Mental Health (CRN MH) clinical studies

officers (CSOs) and research nurses, who, in conjunction with service users' care coordinators, were responsible for accessing service user details, determining eligibility and mailing trial invitations. Invitations were posted to patients before randomisation of mental health teams occurred in EQUIP. To be eligible, patients had to be: aged 18 years or older; under the care of the community mental health team; have capacity to provide fully informed consent; and judged by their care coordinator to be well enough to complete study assessments. The research team did not have access to service users' details until service users returned the 'Consent to Contact' Form. In the majority of mental health teams, potential participants who did not respond to the initial invitation letter were telephoned by a CSO or a member of their mental health team to determine whether they had received the trial invitation and whether they were interested in taking part. Recruitment and baseline assessment of participants within each cluster occurred within a 6-week period, before the training was delivered to the mental health clusters in the intervention arm. The EQUIP team aimed to recruit a minimum of 10 participants per cluster (no upper limit was specified). Details of the EQUIP trial design have been reported elsewhere [58].

#### Trial design: the embedded recruitment trial

Recruitment into the embedded trial occurred over an 18-month period (June 2014 to December 2015) until recruitment into the host trial ceased. A patient-level randomised controlled trial would have been the most efficient design for the embedded recruitment trial; however, this was not practical as it was logistically burdensome for the EQUIP host trial team to administer. We therefore adopted a cluster randomised design for the recruitment trial, using the same mental health team clusters as in the EQUIP host trial. This had two methodological implications. First, due to the relatively small numbers of clusters ( $n = 36$ ), there was a possibility of imbalance between the patients in the two arms of the embedded trial. Second, there was also a potential risk to the validity of the host trial: if the PPIR recruitment intervention were successful there could be differences between arms in the numbers and types of patients enrolled into the host trial.

We therefore adopted a cross-factorial, embedded randomised controlled trial design with the EQUIP host trial intervention allocation, using pairwise allocation. In the embedded trial, the same cluster pairs as in the EQUIP host trial were presented for randomisation; however, we randomised *both* clusters to receive the PPIR intervention, or *both* to the control arm (as opposed to *one* cluster being assigned to the intervention arm, and the *other* to the control arm). The priority was to ensure the integrity of the host trial. Pairwise

allocation guaranteed that we achieved balance of cluster allocations between intervention and control arms for both the EQUIP host trial and for the embedded recruitment trial; this allocation method also ensured the validity of both the host and embedded recruitment trial interventions.

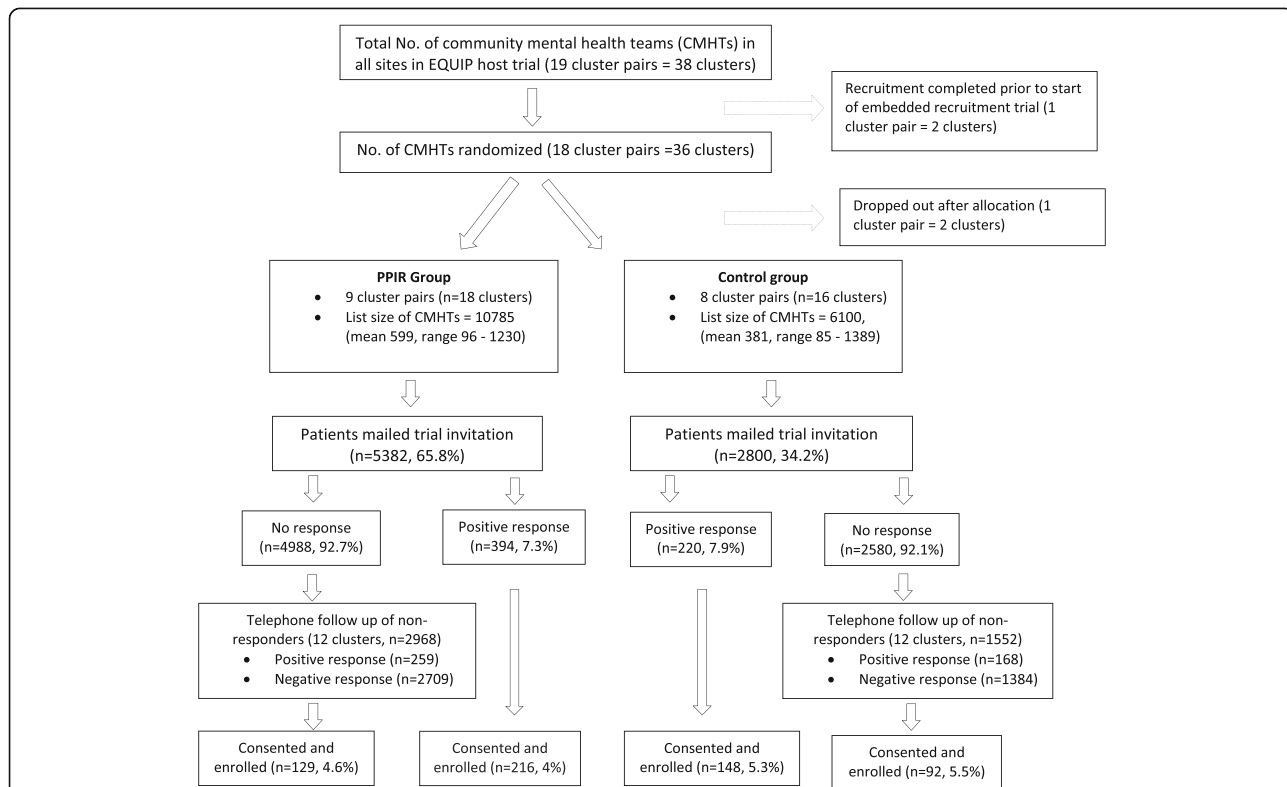
Clusters were randomly allocated for their patients to be sent one of two interventions: the standard invitation (control group); or the PPIR intervention in addition to the standard invitation (intervention group). The PPIR intervention was sent in the same envelope as the EQUIP trial invitation, which also contained a cover letter, a Participant Information Sheet, a ‘Consent to Contact’ Form and stamped addressed envelope. The embedded recruitment trial thus measured the incremental benefit of being sent the recruitment intervention. Figure 1 outlines the recruitment flowchart for the embedded recruitment trial.

**Eligibility criteria for participants: embedded recruitment trial**

The recruitment trial included all patients identified as potentially eligible for the EQUIP host trial: there were no additional inclusion or exclusion criteria.

**The recruitment intervention: the PPIR communication and its development**

We developed a recruitment intervention communicating PPIR guided by the MRC complex interventions framework [39], informed by Participatory Design approaches with end users [59, 60]. As described earlier, the hypothesised mechanism was reducing the perception of risk in trial enrolment, informed by our prior systematic review [38] and qualitative study [45]; ‘social validation’, emerging from social comparison theory [49, 51] and survey evidence [52, 53]. We searched the latest Cochrane systematic reviews to determine frequently used recruitment and retention interventions [11, 61]. We reviewed the EQUIP host trial recruitment strategy and held discussions with the EQUIP team to determine a simple, systematic, feasible and acceptable method of delivering the PPIR intervention. Given that the recruitment occurred through mental health teams and patients were being approached to enter the host trial by postal invitations, we selected a leaflet format as the delivery mechanism to communicate PPIR. We then organised an expert workshop involving 27 key stakeholders including 10 service users with severe mental illness and two carers of people with severe mental illness, who were either EQUIP PPIR members or belonged to the



**Fig. 1** Flow diagram for the embedded recruitment trial. An overview of the flow of mental health teams and their patients in the embedded trial, based on the ‘guidelines for reporting embedded recruitment trials’, which adapts Consolidated Standards of Reporting Trials (CONSORT) for embedded recruitment trials [17]

EQUIP trial target population. Other stakeholders present were: five principal investigators/researchers with expertise in undertaking mental health trials; three patients with physical health problems; two researchers with expertise in PPIR; two mental health trial recruiters; two Research Ethics Board members and a consultant psychiatrist.

During this workshop, stakeholders endorsed the use of the of the leaflet format for advertising PPIR with the aim of improving recruitment. Working in small breakout groups (each group comprised of a mix of researchers and PPIR members), and then reconvening, stakeholders discussed and agreed seven 'core principles' for the leaflet advertising PPIR to potential trial participants (see Table 1).

In line with the principles of Participatory Design, participants were asked to design their ideal PPIR leaflet according to the 'core principles' in four breakout groups using appropriate materials. Each of the four groups presented their prototype leaflets to the wider group, including the key elements of the design. Members then voted for which of the four leaflets they thought was best overall for attracting potential participants. The top-rated leaflet contained similar elements to the other leaflets, including: making a clear and direct appeal for potential participants to join the trial; positive photographs of people with mental health problems which avoided the typical media image of people holding their heads in their hands, which members discussed as stigmatising [62]; highlighting benefits to future patients and convenience; the option to withdraw from the trial without giving a reason; and approval by an independent Research Ethics Committee.

Two of the PPIR members of EQUIP who were present at the workshop (LC and DM) – one a carer and the other a service user – volunteered to be photographed and featured in the EQUIP PPIR leaflet. Both PPIR members had active and ongoing involvement in EQUIP, one as a co-applicant and a member of the Trial Management Team; and both as part of the training

team who delivered the user-involvement training intervention to the host trial intervention clusters. We worked closely with LC and DM to develop a bespoke leaflet for the EQUIP host trial, in line with the 'core principles' and taking into account key elements from the four leaflets created during the workshop. Once the initial version was developed, we asked for contributions from the EQUIP host trial researchers (chiefly to check for accuracy); their input did not change the content or format of the leaflet. The leaflet was then sent to a professional graphic designer in a company with significant expertise in designing patient communication materials ([www.makingsense.co.uk](http://www.makingsense.co.uk)). The design brief highlighted the agreed 'core principles' (Table 1) and related solely to the visual presentation of the leaflet and not the content. Two versions of the leaflet were initially designed and presented to the EQUIP team and PPIR members, who voted on their preferred design. Voting gave priority to PPIR members, who also provided comments in three rounds of iterations before the final design was agreed. These comments related to the colours and visual presentation, and the content did not change. Table 2 outlines the presentation and content of the final leaflet, which is also attached as Additional file 1.

#### Outcome measures

In the EQUIP host trial, CSOs or mental health teams telephoned patients who did not initially respond to the postal invitation in poor recruiting clusters. There is evidence that telephone follow-up prompting of patients who do not respond to invitations to participate in trials significantly increases recruitment [11]. The host trial recruiters undertook telephone follow-ups as, and when, necessary which meant that not all clusters had the telephone follow-ups.

Our pre-planned primary outcome was, therefore, chosen to assess the effect of the PPIR leaflet, without potential contamination of the telephone follow-ups. The primary outcome for our embedded recruitment trial was the proportion of participants in each group who were *consented and enrolled* into the EQUIP host trial after responding to the postal invitation (i.e. the proportion of participants who responded and enrolled without the need for a telephone follow-up reminder).

The secondary outcomes were:

1. The proportion of patients in each group who *positively responded* without the need for a telephone follow-up reminder (note this differs from the number actually consented and enrolled, due to for instance, the EQUIP trial exclusion criteria)
2. The total proportions of patients in each group who were *consented and enrolled*, including telephone follow-up of initial nonresponders

**Table 1** Core components of the patient and public involvement in research (PPIR) communication leaflet intervention

1. The intervention advertising PPIR was in a leaflet format
2. The leaflet was in a booklet style
3. The leaflet was written in plain language, with an informal, conversational style
4. The leaflet included photographs of the PPIR patients and carers, who in their own voice describe *how* they were involved in the trial and what their impact has been
5. The leaflet included photographs of the research team
6. The leaflet aimed to show that PPIR was taken seriously and was not tokenistic, and aimed to provide an honest account of PPIR
7. The leaflet aimed to be eye catching: bold, bright print, large font, colourful

**Table 2** Content and layout of the finalised patient and public involvement in research (PPIR) leaflet

Presentational elements	Content
<ul style="list-style-type: none"> <li>• Four-page booklet format</li> <li>• Photographs of the EQUIP trial team together with PPIR members on the front and back pages</li> <li>• Written in plain language; informal, conversational style</li> <li>• Contained several photographs of the PPIR members, including one of them designing the leaflet</li> <li>• Quotations written by PPIR members</li> <li>• Use of large font sizes and bright colours</li> </ul>	<ul style="list-style-type: none"> <li>• Front and back pages advertised award of 'outstanding carer involvement' to EQUIP</li> <li>• Front page stated that 'real patients and carers' had informed in the design of the study, and asked patients to consider taking part in EQUIP</li> <li>• Middle pages of the leaflet contained photographs of PPIR members</li> <li>• Quotations by PPIR members described why they thought the study was important</li> <li>• A section highlighting issues felt to be important to patients including: helping future patients, convenience, confidentiality, approval by a Research Ethics Committee</li> <li>• Quotation by EQUIP chief investigator about close working with PPIR members</li> <li>• Contained contact details of the study team</li> </ul>

3. The numbers of clusters in each group needing to conduct telephone follow-ups due to low postal response. This outcome takes into account the potential resource implications of a mental health clinician or a trial recruiter telephoning patients who do not respond to the trial invitation

#### Sample size calculation

The sample size calculations for the EQUIP trial have been published in the original protocol [58].

As is usual with a trial embedded within a host trial, we did not undertake a formal power calculation to determine the sample size [15], since the sample size was constrained by the number of mental health teams and patients being approached in the EQUIP host trial. Our sample size was the total number of service users invited to participate in EQUIP from the 34 available clusters at the time of implementing the embedded trial, which was 8182 potential participants. We did not undertake a post-hoc power calculation as this is arguably a futile exercise, since the power of a trial is expressed in the confidence interval generated from the outcome analysis [63] (see 'Results' section).

#### Randomisation

Randomisation was undertaken by the host trial statisticians (NO'L and CR), who were independent from the delivery of the trial interventions for both the host and embedded recruitment trials. Randomisation in the EQUIP host trial was stratified by cluster pairing, the site/region of each cluster and the caseload size of each cluster. For the recruitment trial, we used the same cluster pairing as the host trial and allocated each cluster pair by block-randomisation with permuted block sizes of 2, 4 and 6, using a computerised randomisation programme. Service users did not know that they were part of a trial of a recruitment intervention so were blind to the study hypothesis. CSOs and research nurses undertaking trial recruitment and mental health team

clusters were also blind to the group to which clusters were allocated.

#### Statistical methods

We obtained baseline data on cluster size (patient list size), deprivation, care quality rating and patient satisfaction with clinical care. Deprivation used the Index of Multiple Deprivation (IMD) rank averaged across Lower-layer Super Output Areas for each cluster's Clinical Commissioning Group [64]. Care quality and patient satisfaction data were obtained at the cluster level from the Care Quality Commission which is the independent regulator of health and social care in England [65]. Patient satisfaction focussed on the experiences of service users who receive care and treatment within the mental health teams. Preliminary graphical and tabular examination of the data explored baseline comparability of trial arms and representativeness of the sample in terms of the clusters and the overall eligible population.

Data analysis used generalised linear mixed models [66] to estimate the effect of the recruitment intervention. As the unit of randomisation was the cluster pair, we fitted a three-level, random effects logistic model which pertained to the individual patient, clustered within mental health teams, and clustered within paired mental health teams. We adjusted for mental health team cluster size, levels of deprivation and care quality rating (we did not include patient satisfaction with clinical care in the model due to incomplete data). We present the marginal mean difference in proportions, as well as odds ratios (ORs), to assist with interpretation. Standard errors and confidence intervals for cluster marginal effects were calculated using the Delta Method. Given that the EQUIP randomisation occurred after the embedded trial randomisation, there was no plausible causal effect of the EQUIP intervention on recruitment so we did not test for an interaction between the EQUIP intervention and the recruitment intervention. Fisher's exact test was used to test for association between

recruitment trial arm and the need for telephone follow-up. Analyses used the intention-to-treat principle and were conducted using Stata, version 14 (Stata Corp., College Station, TX, USA).

## Results

Thirty-eight community mental health team clusters were recruited and randomised. One cluster pair (two clusters) could not be included as the EQUIP recruitment started before the embedded trial could begin. Another cluster pair withdrew from the EQUIP trial after randomisation, but prior to the mailing of invitation letters to their patients, and so are not included in the analysis. Eight thousand one hundred and eighty-two patients in 34 clusters were sent the standard EQUIP trial invitation letter or the addition of the PPIR intervention – see Fig. 1, flow diagram for the embedded recruitment trial. Table 2 outlines the characteristics of the mental health clusters and patients. Comparison of cluster baseline characteristics showed that clusters in the intervention arm were larger (544 mean patient list size versus 323); located in more deprived areas (IMD quintile median 1.5 versus 2.5); and had fewer mental health team clusters rated as ‘good’ for care quality (11.1% versus 18.8%). Patients in the intervention and control arms were broadly similar in age and gender distribution.

### Primary outcome

For the primary outcome of the proportions consented and enrolled into the EQUIP trial, 4% of patients sent the PPIR communication were enrolled compared with 5.3% of the control group (Table 3). Mixed-effects logistic regression showed that the recruitment intervention was not effective for improving recruitment rates [OR = 0.75, 95% CI = 0.53 to 1.07,  $p = 0.113$ ]. The average marginal effect of the intervention on the probability of enrolment was  $-0.0123$  [95% CI =  $-0.0282$  to  $0.0036$ ].

### Secondary outcomes

1. Responding positively to the invitation, without telephone follow-up: there was no difference between the intervention and control groups, with 7.3% of potential participants sent the recruitment intervention responding positively, compared with 7.9% in the control group: adjusted OR = 0.74, 95% CI = 0.53 to 1.04,  $p = 0.082$ . The average marginal effect of the intervention on the probability of positive response was  $-0.0208$  [95% CI =  $-0.0451$  to  $0.0035$ ].
2. All positive response (including telephone follow-up): there was no difference between the intervention and control groups, with 9.2% of the intervention group responding positively, compared with 10.0% in the

**Table 3** Baseline information for mental health cluster teams and patients, by allocation

Mental health team cluster Baseline factors	PPIR group	Control group
List size, mean (SD)	544 (273)	323 (191.6)
IMD quintile, median (range) [1 = most deprived; 5 = least deprived]	1.5 (1–4)	2.5 (1–5)
Care Quality Commission rating		
Good, $n$ (%)	2 (11.1%)	3 (18.8%)
Requires improvement, $n$ (%)	8 (44.4%)	6 (37.5%)
Rating suspended, $n$ (%)	8 (44.4%)	4 (25%)
Not yet inspected, $n$ (%)	0 (0%)	3 (18.8%)
Patient satisfaction with care <sup>a</sup> , mean (SD) [10 = highly satisfied]	6.6 (0.3)	6.9 (0.2)
Patients expressing interest <sup>b</sup> :		
Male, $n$ (%)	151 (38.9%)	81 (36.8%)
Female, $n$ (%)	237 (61.1%)	139 (63.2%)
Patients enrolled <sup>b</sup> :		
Male, $n$ (%)	76 (36.2%)	49 (36%)
Female, $n$ (%)	134 (63.8%)	87 (64%)
Mean age, years (SD)	48.5 (12.8)	45.5 (9.3)

IMD Index of Multiple Deprivation, PPIR patient and public involvement in research, SD standard deviation

<sup>a</sup>Patient satisfaction survey score data available for 32 clusters

<sup>b</sup>Baseline information only available for observed sample and not for entire cluster

control group: adjusted OR = 0.74, 95% CI = 0.51 to 1.09,  $p = 0.125$ . The average marginal effect of the intervention on the probability of all positive response was  $-0.0343$  [95% CI =  $-0.0795$  to  $0.0108$ ].

3. Number of clusters requiring telephone follow-up of nonresponsive patients: this showed that there was no association between the recruitment trial arm and the need for a telephone reminder, with 66.7% in the PPIR group, compared with 75% of control group: Fisher’s exact test  $p$  value = 0.715.

### Harms

We tested a two-tailed hypothesis, which accepted that sending the recruitment intervention to potential participants could cause benefit or loss to recruitment for the host trial. Patients not being recruited presents a loss to the host trial; however, for the patient, not being enrolled into the trial may not be harmful and may in fact be the best thing for them to make an informed decision that suits them without encountering the potential inconvenience or negative consequences of trial participation. The primary and secondary outcomes were designed to demonstrate any potential harms to the EQUIP host trial in terms of reduced enrolment in the intervention group. The results demonstrate that the recruitment intervention was ineffective for increasing



enrolment rates for all outcomes measured. A second potential harm to the host trial was the potential differences in the numbers and types of patients enrolled into the host trial between the intervention and control groups. We sought to minimise this potential harm by adopting the cross-factorial design, and making baseline comparisons between the intervention and control groups. Baseline comparison of the intervention and control groups found no differences. We did not measure other potential harms, such as perceptions of increased pressure to participate in the intervention group.

## Discussion

### Summary of main findings

We undertook an embedded trial to evaluate the effectiveness on recruitment of directly advertising PPIR to potential trial participants. In this group of patients with severe mental health problems, the overall rates of response and participation were low, although this was in line with similar studies [18]. For our primary outcome, we found that being sent the intervention was not effective for improving recruitment rates. Our secondary outcomes found that directly advertising PPIR did not make a positive difference to any other outcomes.

### Strengths and limitations

To our knowledge, this multicentre trial involving 8182 patients is the largest-ever trial embedded in an ongoing trial to have been undertaken to evaluate the effectiveness of an intervention on trial recruitment [11] as well as the largest to evaluate the impact of patient and public involvement [31, 47]. Recruitment trials embedded within host trials are often plagued by the problem of small sample sizes as embedded trials are reliant upon the numbers of patients approached by the host trial. These numbers are not usually sufficient to show small but important differences in recruitment [11, 15].

The EQUIP host trial had award-winning high-quality PPIR. Additionally, the development of the recruitment intervention and its evaluation involved close collaboration with PPIR members. Both PPIR and recruitment are considered complex interventions [55, 67]. In our trial we used the MRC complex interventions framework to systematically develop a theory-informed recruitment intervention and evaluate it in a rigorous way, using real patients being approached to make a real decision about participation in an ongoing trial. With increasing calls and now guidance for measuring the impact of PPIR [68, 69], our work provides randomised evidence in a field that is very much lacking such evidence.

Cluster randomised designs are often used to evaluate the effectiveness of recruitment interventions [70–72], as they are often the most logistically feasible way to deliver recruitment interventions embedded in ongoing

host trials. We recognise that cluster randomised trials can be susceptible to a range of methodological problems [73, 74]. Due to logistic and operational reasons, it was not possible to undertake a patient-level randomised trial, so we adopted a cluster randomised trial design, which was a design agreeable to the host trial team, and protected the host trial from potential biases introduced by the recruitment intervention such as differential recruitment and imbalance in the characteristics of patients recruited into the host trial as a consequence of the PPIR intervention. The outcome of the random allocation led to there being more and larger clusters in the intervention arm of the recruitment trial. However, this imbalance was a result of the random allocation and occurred by chance. This was a compromise and without this design we would not have been able to conduct the embedded recruitment trial, and we later adjusted for cluster size in the analyses. The randomisation of matched cluster pairs also has some potential problems, such as some pairs of clusters being more closely matched than others, so minimisation in this instance may have been a better option. However, again it was not feasible to undertake the minimisation because logistically, the least burdensome option for the host trial team was to use the same cluster pairs that they were using in the host trial.

There is an argument that the impact of involvement *within any particular project* is somewhat unpredictable, and that there is a need to provide details of context in accounts of PPIR [75]. Furthermore, there is also a need to understand how context and mechanism influence the impact of PPIR [75]. We did not have sufficient resources to undertake formal qualitative interviews to understand the mechanism of impact. However, we are currently undertaking two other embedded trials of this intervention directly advertising PPIR to potential trial participants to better understand the context and mechanism of impact. In one of these linked trials, we are undertaking user-testing of the PPIR recruitment intervention with patients and families to enable the revision and refining of the intervention to make it more appropriate to their context. We are also undertaking qualitative interviews with people who enter the host trial to explore their views of the PPIR intervention and determine its impact on their decision-making.

### Comparison with existing trial literature

Our findings contrast with a survey where 44% members of the British public responding to a hypothetical question indicated that they would be more likely to enrol in a trial if they found that patients had advised in its design [53]. The authors of this survey reported that very few people thought that PPIR would reduce their confidence in a trial. We found that patients actually invited to enter a real trial were no more likely to enrol when

they were sent a leaflet about PPIR. Research investigating hypothetical and actual willingness to enrol in a trial found that only 20% of participants stating hypothetical willingness to enter a trial actually enrolled and that statements of hypothetical willingness to participate in future trials may overestimate true enrolment [76].

A systematic review to assess the impact of PPIR on recruitment and retention in trials has found that while PPIR is consistently associated with improved retention, the evidence for impact on enrolment is variable and inconsistent [47]. A number of studies identified by this review found either no significant positive effect of PPIR on trial recruitment, or in one case involving the recruitment of African-Americans being recruited through three different sources, that the non-PPIR arm was more effective at improving recruitment [77]. Our present findings are, therefore, in line with the trial literature evaluating the impact of PPIR on recruitment.

#### **Explaining our findings and potential mechanisms of action**

Beyond advertising PPIR intervention simply being ineffective for improving trial recruitment and response rates, there are a range of other possible reasons for our present findings. First, it is possible that people in the PPIR arm did not read the leaflet. The leaflet was sent by post in a large recruitment pack with several other documents. Those sent the recruitment pack may not have opened it, and those who did may not have read the PPIR recruitment leaflet. We were not able to determine how many people read the recruitment leaflet and our intention-to-treat analysis may have underestimated the effects of the active intervention components.

Second, it is also not clear whether those sent the leaflet, and who read it, understood the message in the leaflet and what PPIR meant for the trial that they were being asked to enrol into. Conversely, there is some research evidence indicating that patients receiving supplementary written information about a trial in the form of a booklet or leaflet have improved knowledge about the trial [78, 79]. It is possible that those who read the leaflet were more likely to make a more informed decision about not enrolling in the trial, which would have been a good decision for the patient, but a bad outcome for the trial. Unfortunately, in this population it was not possible to obtain estimates of the effect of the recruitment intervention for those who were randomised to receive the leaflet, who also actually read it, and how they interpreted the message.

Third, there are a range of mechanisms by which PPIR might influence recruitment, including on the trial design and trial conduct. Thus, the role of PPIR might lead to sensitive issues being handled better [80] or enhance trial quality and appropriateness, making them more effective [25, 35]. These mechanisms call into question the mechanism used in our trial, which is that advertising

PPIR might improve recruitment. Additionally, the high-quality PPIR in EQUIP may have meant that the PPIR benefits may have been already optimised in EQUIP. The addition of the PPIR recruitment intervention may, therefore, have been irrelevant since the PPIR undertaken in EQUIP may have been sufficient to promote participant recruitment. However, the overall enrolment rates in EQUIP were low, with rates similar to other trials recruiting from similar populations [18, 81], so this does not suggest that the significant PPIR in EQUIP improved recruitment when compared with other trials. This contrasts with an observational study which found that studies that involved patients to a greater extent were more likely to have achieved recruitment targets [46].

Fourth, we developed our conceptual framework around the decision to enter trials using depression as the case exemplar, yet our recruitment intervention, informed by the conceptual framework, was evaluated in a population of patients with severe mental illness (who may or may not have had depression). Depression is the leading cause of disease burden worldwide [82, 83], and when we initiated our programme of work we anticipated that we would develop and then test the recruitment intervention using a depression trial. However, we found it impossible to recruit a host depression trial in order to evaluate the recruitment intervention, despite directly contacting 14 potential host trials registered on the National Institute for Health Research (NIHR) trials portfolio, seeking support from the Clinical Research Network Mental Health, which contacted trials on our behalf, and advertising for host trials via the UK Trial Managers' Network. The main reason why a depression host trial was not forthcoming was due to a mismatch between the recruitment timelines of potential host trials and that of the embedded recruitment trial: the majority of host trials approached were either close to finishing participant recruitment, or were in the early phase of set-up, meaning that it was not possible to align host trial participant recruitment with the embedded recruitment trial. Two other depression trials reported that they already intended to advertise their PPIR activities to potential participants. This failure to recruit a depression trial may have impacted on the embedded trial outcomes as the intervention may not have been as relevant for the population in the EQUIP trial of people with severe mental illness. However, approximately 47% of the EQUIP population had comorbid depression. Additionally, mental health disorders in general have the strongest established history of PPIR in the UK [84–86], and there is some evidence that the use of PPIR is significantly associated with successful recruitment across a range of mental health trials, including severe mental illness, psychoses and depression [87, 88]. Furthermore, the Health Research Authority survey suggesting direct

communication of PPIR to potential participants indicated that this approach could be used in all disease areas [52, 53]. We developed the PPIR intervention closely with the EQUIP trial and the use of the intervention was strongly endorsed by stakeholders.

Fifth, we used the concept of social validation to inform our recruitment intervention. The concepts of risk and social validation exist across all disease areas, however, not just depression. Social validation has also been used successfully as a trial recruitment intervention, with an embedded recruitment trial of text messages containing quotes from existing participants significantly increasing randomisations [89]. However, in our trial, social validation came from patients as *research partners*, rather than from patients as *trial participants*. This may have had an influence on our findings.

Finally, informal discussions of our findings with stakeholders suggested that the stigma associated with mental illness may have led to a negative impact of the PPIR intervention. Stigma, both towards others with mental health problems, as well as mental health stigma 'internalised' towards the person's own self are well-documented and can deter people with mental health problems from seeking health care [90–92]. In our recruitment trial, stigma may have meant that awareness that EQUIP had significant PPIR from individuals with mental health problems may have made some people reluctant to enrol. Additionally, there may have been a perception of a lack of 'professionalism' in trial design and conduct, suggested by the significant involvement of patients and carers, as opposed to the trial being wholly conducted by 'trained professional researchers'. Stigma and a perceived lack of professionalism may have combined to make some people disinclined to enrol in the trial. Other PPIR members and stakeholders involved in other trials suggested that the leaflet lacked representativeness and commented that the images of people in the leaflet were not representative of them, that: '*the people in this leaflet do not look like me*'. Diversity in representativeness of PPIR members has been discussed in the trial literature, and arguments have been made for the need to engage with PPIR representatives who reflect the diversity of the study population [93]. Due to resource constraints, we were unable to undertake qualitative interviews with the people sent the PPIR communication in order to explore and understand patient views of the intervention.

#### **Implications for recruitment practice, public policy and research**

It is important to highlight here that while we found that directly communicating PPIR using a leaflet to potential trial participants was not effective for improving trial recruitment, this is not the same as PPIR being ineffective

or harmful to trials *in general*. Our experience in undertaking this trial, and that of the EQUIP host trial, is that PPIR is very effective for developing interventions that can be delivered and evaluated in trials. However, we did not actually evaluate this, as the recruitment intervention was about direct communication of PPIR to potential participants. It is quite possible that rather than directly communicating PPIR to potential participants, what PPIR achieves in terms of making a trial and its interventions more attractive, acceptable and patient-centred is what is important in terms of its impact. More rigorous trials are needed to evaluate the impact of PPIR. Here, our findings point to a direction of focus for evaluating the impact of PPIR in trials, in informing the design and conduct of trials, but not as a means for direct recruitment. Policy-makers should be aware that PPIR is not a panacea and should fund more systematic evaluations of the impact of PPIR. Findings from this research will be sent to the authors of the Cochrane systematic review of interventions to improve recruitment to trials, for inclusion in future systematic reviews [11].

There is some evidence to suggest that PPIR may be effective for improving retention in trials [47]. Participants in EQUIP are currently in the follow-up phase. We aim to determine whether direct communication of PPIR improves retention in EQUIP. It is unclear to what extent different versions of this intervention might have had different impacts in different trial contexts and patient populations. For example, while the PPIR intervention was developed with PPIR partners, it was not user-tested with potential trial participants. There is some evidence that performance-based user-testing of trial information can identify strengths and weaknesses in trial information materials and make them fit for purpose [94, 95]. Here, the usability, acceptability and accessibility can be improved using semistructured interviews and iterative testing cycles [96]. A user-tested version of the intervention may have impacted on how potential participants responded. A user-tested version of the PPIR intervention is currently being evaluated in the Culturally-adapted Family Intervention (CaFI) study recruiting African-Caribbean people diagnosed with schizophrenia [97]; another version of the intervention is currently being evaluated in a study investigating early signs of dementia. Our broad aim is to aggregate the results across the different trials to obtain a more precise estimate of effect, as well as to explore the effectiveness of the intervention across different research contexts and patient populations.

Our trial highlights the potential benefits of process evaluation in embedded recruitment trials by adopting qualitative methods to explore patients' use and views of recruitment interventions. This would make it necessary for trialists to obtain the necessary ethical permissions to approach people sent such recruitment materials to

gain insights into the mechanisms and contexts of these interventions [98]. There are potential problems, as process evaluation would add significant costs to embedded trials and may add significant complexity to the process of embedding a trial, which might act as a barrier to adoption. In addition, however, our prior work with people who declined to enter a trial highlights that even those who declined to enter a trial reported that they do not mind being approached and, in addition, were happy to explore their trial participation decisions [45]. We are currently undertaking an additional qualitative study to explore the views of people who are sent a similar PPIR recruitment intervention as part of the trial embedded in the CaFI study [97].

## Conclusions

This embedded recruitment trial found no benefits of directly communicating PPIR on response, consent or enrolment rates. Further embedded trials of these materials are being conducted to explore how the impact of the intervention may vary by intervention type, trial context and patient population. A more comprehensive cohort of embedded trials of recruitment interventions across the trials portfolio could lead to a rapid development of the evidence base around recruitment to make trials more acceptable and accessible to patients.

## Additional file

**Additional file 1:** Recruitment intervention advertising patient and public involvement in research. A copy of the recruitment intervention which was mailed to potential trial participants. (PDF 2112 kb)

## Abbreviations

CaFI: Culturally-adapted Family Intervention; CMHT: Community Mental Health Team; CSO: Clinical studies officer; EQUIP: Enhancing the Quality of User Involved care Planning in mental health services; IMD: Index of Multiple Deprivation; ISRCTN: International Standard Randomised Controlled Trial Number; NHS: National Health Service; NIHR: National Institute for Health Research; NRES: National Research Ethics Service; OR: Odds ratio; PPIR: Patient and public involvement in research; UK: United Kingdom

## Acknowledgements

We wish to acknowledge the support of the National Institute of Health Research Clinical Research Network (NIHR CRN), which supported both the EQUIP and the embedded recruitment trials. In addition to those listed as authors on this paper, EQUIP is led by Penny Bee, Anne Rogers, Patrick Cahoon, Linda Davies, Richard Drake, Andrew Grundy, Caroline Sanders, Lauren Walker, Susan Beatty, Helen Brooks, Chris Gibbons, Matthew Hamilton and Nicola Ollevent.

We would also like to acknowledge the contribution of Sandra Eldridge and Vichitrhranie Madurasinghe who designed the data analysis as part of the wider MRC START programme grant (MRC START Grant Reference: G1002325) which aims to test interventions to improve trial recruitment. Our thanks go to Making Sense Design who worked with AHM to graphically design the advertisement, and to Judith Hogg and Ailsa Donnelly from PRIMER (the Primary Care Research in Manchester Engagement Resource) who contributed patient and public involvement to the work of the MRC START Study team. Last but not least, we thank all the patients, carers, trialists, Research Ethics Board members and trial recruiters who attended the intervention development workshop – your input was invaluable.

## Funding

The EQUIP programme grant is funded by the National Institute for Health Research (NIHR)'s Programme Grants for Applied Research (RP-PG-1210-12007). Adwoa Hughes-Morley is funded by the NIHR on a Doctoral Research Fellowship (NIHR DRF 2012-05-1128), which funded the embedded trial. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

## Availability of data and materials

The datasets analysed during the current study is available from the corresponding author on reasonable request.

## Authors' contributions

The following are members of the EQUIP Trial Group: Claire Fraser, Karina Lovell, Lindsey Cree, Donna More, Peter Bower, Patrick Callaghan, Neil O'Leary, Chris Roberts and Oonagh Meade. CF was EQUIP programme manager and led the ethics amendment and substudy registration for conducting the embedded START trial within the EQUIP Study, as well as recruitment. NOL and CR were statisticians and were involved in trial design and randomisation of both the EQUIP trial and the embedded recruitment trial. KL is the chief investigator for the EQUIP research programme and has overall responsibility for the design and implementation of the EQUIP trial. CF, KL, LC, DM, PB, PC, NOL, CR and OM all commented on a draft of this paper. Adwoa Hughes-Morley led on the methods and the development of the recruitment intervention, worked with the EQUIP Trial Team to develop the embedded study protocol, data sharing agreement, substantial amendment and embedded study registration materials, undertook the analysis under the supervision of MH with input from CR and NOL, and drafted the manuscript. AHM, PB MH, BY and WW all commented on drafts of the paper. All authors read and approved the final manuscript.

## Authors' information

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

## Consent for publication

Written informed consent was obtained from the patients for publication of their individual details and accompanying images in this manuscript. The 'Consent to Contact' Form is held by the authors' institution and is available for review by the editor-in-chief.

## Ethics approval and consent to participate

UK National Research Ethics Service (NRES) approval was obtained to conduct the EQUIP Study, using the recruitment method described above on 8 August 2014 (NRES Committee North West Lancaster, REC Reference 14/NW/0297; IRAS Project ID 125899). No consent was needed for patients to participate in the embedded trial, on the basis that the embedded trial was not withholding information: we obtained approval for the embedded trial and to not consent patients from NRES Committee Yorkshire and the Humber – South Yorkshire (REC Reference 11/YH/0271). The embedded trial has been registered by EQUIP as a substudy [58], and as a 'Study Within a Trial' by the MRC Hubs for Trials Methodology Research. The protocol for the embedded trial can be found here – (SWAT-26).

## Author details

<sup>1</sup>York Trials Unit, Department of Health Sciences, University of York, York YO10 5DD, UK. <sup>2</sup>Division of Population Health, Health Services Research and Primary Care, University of Manchester, Williamson Building, Manchester M13 9PL, UK. <sup>3</sup>Division of Nursing, Midwifery and Social Work, University of Manchester, Jean McFarlane Building, Manchester M13 9PL, UK. <sup>4</sup>School of Health Sciences, Queen's Medical Centre, The University of Nottingham, Nottingham NG7 2HA, UK. <sup>5</sup>MRC North West Hub for Trials Methodology Research, Institute of Psychology, Health and Society, University of Liverpool, Liverpool, UK. <sup>6</sup>HRB Clinical Research Facility, National University of Ireland Galway, Galway, Republic of Ireland. <sup>7</sup>School of Health Sciences and Institute of Mental Health, The University of Nottingham, Jubilee Campus, Nottingham NG7 2TU, UK. <sup>8</sup>MRC North West Hub for Trials Methodology Research, Manchester Academic Health Science Centre, University of Manchester, Williamson Building, Manchester M13 9PT, UK.

gain insights into the mechanisms and contexts of these interventions [98]. There are potential problems, as process evaluation would add significant costs to embedded trials and may add significant complexity to the process of embedding a trial, which might act as a barrier to adoption. In addition, however, our prior work with people who declined to enter a trial highlights that even those who declined to enter a trial reported that they do not mind being approached and, in addition, were happy to explore their trial participation decisions [45]. We are currently undertaking an additional qualitative study to explore the views of people who are sent a similar PPIR recruitment intervention as part of the trial embedded in the CaFI study [97].

## Conclusions

This embedded recruitment trial found no benefits of directly communicating PPIR on response, consent or enrolment rates. Further embedded trials of these materials are being conducted to explore how the impact of the intervention may vary by intervention type, trial context and patient population. A more comprehensive cohort of embedded trials of recruitment interventions across the trials portfolio could lead to a rapid development of the evidence base around recruitment to make trials more acceptable and accessible to patients.

## Additional file

**Additional file 1:** Recruitment intervention advertising patient and public involvement in research. A copy of the recruitment intervention which was mailed to potential trial participants. (PDF 2112 kb)

## Abbreviations

CaFI: Culturally-adapted Family Intervention; CMHT: Community Mental Health Team; CSO: Clinical studies officer; EQUIP: Enhancing the Quality of User Involved care Planning in mental health services; IMD: Index of Multiple Deprivation; ISRCTN: International Standard Randomised Controlled Trial Number; NHS: National Health Service; NIHR: National Institute for Health Research; NRES: National Research Ethics Service; OR: Odds ratio; PPIR: Patient and public involvement in research; UK: United Kingdom

## Acknowledgements

We wish to acknowledge the support of the National Institute of Health Research Clinical Research Network (NIHR CRN), which supported both the EQUIP and the embedded recruitment trials. In addition to those listed as authors on this paper, EQUIP is led by Penny Bee, Anne Rogers, Patrick Cahoon, Linda Davies, Richard Drake, Andrew Grundy, Caroline Sanders, Lauren Walker, Susan Beatty, Helen Brooks, Chris Gibbons, Matthew Hamilton and Nicola Ollevent.

We would also like to acknowledge the contribution of Sandra Eldridge and Vichitrhranie Madurasinghe who designed the data analysis as part of the wider MRC START programme grant (MRC START Grant Reference: G1002325) which aims to test interventions to improve trial recruitment. Our thanks go to Making Sense Design who worked with AHM to graphically design the advertisement, and to Judith Hogg and Ailsa Donnelly from PRIMER (the Primary Care Research in Manchester Engagement Resource) who contributed patient and public involvement to the work of the MRC START Study team. Last but not least, we thank all the patients, carers, trialists, Research Ethics Board members and trial recruiters who attended the intervention development workshop – your input was invaluable.

## Funding

The EQUIP programme grant is funded by the National Institute for Health Research (NIHR)'s Programme Grants for Applied Research (RP-PG-1210-12007). Adwoa Hughes-Morley is funded by the NIHR on a Doctoral Research Fellowship (NIHR DRF 2012-05-1128), which funded the embedded trial. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

## Availability of data and materials

The datasets analysed during the current study is available from the corresponding author on reasonable request.

## Authors' contributions

The following are members of the EQUIP Trial Group: Claire Fraser, Karina Lovell, Lindsey Cree, Donna More, Peter Bower, Patrick Callaghan, Neil O'Leary, Chris Roberts and Oonagh Meade. CF was EQUIP programme manager and led the ethics amendment and substudy registration for conducting the embedded START trial within the EQUIP Study, as well as recruitment. NOL and CR were statisticians and were involved in trial design and randomisation of both the EQUIP trial and the embedded recruitment trial. KL is the chief investigator for the EQUIP research programme and has overall responsibility for the design and implementation of the EQUIP trial. CF, KL, LC, DM, PB, PC, N'OL, CR and OM all commented on a draft of this paper. Adwoa Hughes-Morley led on the methods and the development of the recruitment intervention, worked with the EQUIP Trial Team to develop the embedded study protocol, data sharing agreement, substantial amendment and embedded study registration materials, undertook the analysis under the supervision of MH with input from CR and N'OL, and drafted the manuscript. AHM, PB MH, BY and WW all commented on drafts of the paper. All authors read and approved the final manuscript.

## Authors' information

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

## Consent for publication

Written informed consent was obtained from the patients for publication of their individual details and accompanying images in this manuscript. The 'Consent to Contact' Form is held by the authors' institution and is available for review by the editor-in-chief.

## Ethics approval and consent to participate

UK National Research Ethics Service (NRES) approval was obtained to conduct the EQUIP Study, using the recruitment method described above on 8 August 2014 (NRES Committee North West Lancaster, REC Reference 14/NW/0297; IRAS Project ID 125899). No consent was needed for patients to participate in the embedded trial, on the basis that the embedded trial was not withholding information: we obtained approval for the embedded trial and to not consent patients from NRES Committee Yorkshire and the Humber – South Yorkshire (REC Reference 11/YH/0271). The embedded trial has been registered by EQUIP as a substudy [58], and as a 'Study Within a Trial' by the MRC Hubs for Trials Methodology Research. The protocol for the embedded trial can be found here – (SWAT-26).

## Author details

<sup>1</sup>York Trials Unit, Department of Health Sciences, University of York, York YO10 5DD, UK. <sup>2</sup>Division of Population Health, Health Services Research and Primary Care, University of Manchester, Williamson Building, Manchester M13 9PL, UK. <sup>3</sup>Division of Nursing, Midwifery and Social Work, University of Manchester, Jean McFarlane Building, Manchester M13 9PL, UK. <sup>4</sup>School of Health Sciences, Queen's Medical Centre, The University of Nottingham, Nottingham NG7 2HA, UK. <sup>5</sup>MRC North West Hub for Trials Methodology Research, Institute of Psychology, Health and Society, University of Liverpool, Liverpool, UK. <sup>6</sup>HRB Clinical Research Facility, National University of Ireland Galway, Galway, Republic of Ireland. <sup>7</sup>School of Health Sciences and Institute of Mental Health, The University of Nottingham, Jubilee Campus, Nottingham NG7 2TU, UK. <sup>8</sup>MRC North West Hub for Trials Methodology Research, Manchester Academic Health Science Centre, University of Manchester, Williamson Building, Manchester M13 9PT, UK.

Received: 1 July 2016 Accepted: 19 November 2016

Published online: 08 December 2016

## References

- Sully BG, Julious SA, Nicholl J. A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. *Trials*. 2013;14(1):166.
- CenterWatch. State of the clinical trials industry 2009: a sourcebook of charts and statistics. Boston: CenterWatch; 2009.
- Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T. The global burden of mental, neurological and substance use disorders: an analysis from the global burden of disease study 2010. *PLoS One*. 2015;10(2):e0116820.
- Olsen K, Howel D, Barber R, Ford GA, Gallagher P, McAllister-Williams RH, Nilsson J, O'Brien J, Parker J, Thomas A. Lessons from a pilot and feasibility randomised trial in depression (Blood pressure Rapid Intensive Lowering And Normal Treatment for Mood and cognition in persistent depression (BRILIANT mood study)). *Pilot Feasibility Stud*. 2015;1(1):1–11.
- Adams CE. Many more reasons behind difficulties in recruiting patients to randomized controlled trials in psychiatry. *Epidemiol Psychiatr Sci*. 2013; 22(04):321–3.
- Leeson VC, Tyrer P. The advance of research governance in psychiatry: one step forward, two steps back. *Epidemiol Psychiatr Sci*. 2013;22(04):313–20.
- Bryant K, Wicks MN, Willis N. Recruitment of older African American males for depression research: lessons learned. *Arch Psychiatr Nurs*. 2014;28(1):17–20.
- Woodall A, Morgan C, Sloan C, Howard L. Barriers to participation in mental health research: are there specific gender, ethnicity and age related barriers? *BMC Psychiatry*. 2010;2:10–103.
- Serretti A, Artioli P. Ethical problems in pharmacogenetic studies of psychiatric disorders. *Pharmacogenomics J*. 2006;6(5):289–95.
- Watson JM, Torgerson DJ. Increasing recruitment to randomised trials: a review of randomised controlled trials. *BMC Med Res Methodol*. 2006;6:34.
- Treweek S, Lockhart P, Pitkethly M, Cook JA, Kjeldstrom M, Johansen M, Taskila TK, Sullivan FM, Wilson S, Jackson C, Jones R, Mitchell ED. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. *BMJ*. 2013;3(2):e002360.
- Rick J, Graffy J, Knapp P, Small N, Collier D, Eldridge S, Kennedy A, Salisbury C, Treweek S, Torgerson D, Wallace P, Madurasinghe V, Hughes-Morley A, Bower P. Systematic techniques for assisting recruitment to trials (START): study protocol for embedded, randomized controlled trials. *Trials*. 2014;15(1):407.
- Smith V, Clarke M, Devane D, Begley C, Shorter G, Maguire L. SWAT 1: what effects do site visits by the principal investigator have on recruitment in a multicentre randomized trial? *J Evid Based Med*. 2013;6(3):136–7.
- Treweek S. Trial forge: a systematic approach to making trials more efficient. *Trials*. 2013;14 Suppl 1:O121.
- Adamson J, Hewitt CE, Torgerson DJ. Producing better evidence on how to improve randomised controlled trials. *BMJ*. 2015;351:351.
- Anonymous. Education section—studies within a trial (SWAT). *J Evid Based Med*. 2015;8(3):165.
- Madurasinghe VW, Eldridge S, on behalf of the MRC START Group and Gordon Forbes on behalf of the START Expert Consensus Group. Guidelines for reporting embedded recruitment trials. *Trials*. 2016;17:27.
- Man MS, Rick J, Bower P. Improving recruitment to a study of telehealth management for long-term conditions in primary care: two embedded, randomised controlled trials of optimised patient information materials. *Trials*. 2015;16:309.
- Bower P, Collier D, Eldridge S, Graffy J, Kennedy A, Knapp P, Hughes-Morley A, Rick J, Salisbury C, Small N. A multimedia intervention to enhance recruitment to clinical trials in primary care and community settings: process of development and evaluation. *Trials*. 2013;14 Suppl 1:90.
- National Institute for Health Research. Embedding health research: National Institute for Health Research Annual Report 2009/10. London: Department of Health; 2010. Crown Copyright.
- INVOLVE. Defining patient and public involvement. 2015.
- Stewart D, Wilson R, Selby P, Darbyshire J. Patient and public involvement. *Ann Oncol*. 2011;22 Suppl 7:vii54–6.
- Arnstein SR. A ladder of citizen participation. *J Am Inst Plann*. 1969;35(4): 216–24.
- Tritter JQ, McCallum A. The snakes and ladders of user involvement: moving beyond Arnstein. *Health Policy (New York)*. 2006;76(2):156–68.
- Entwistle VA, Renfrew MJ, Yearley S, Forrester J, Lamont T. Lay perspectives: advantages for health research. *BMJ*. 1998;316(7129):463–6.
- Staley K. Exploring impact: public involvement in NHS, public health and social care research. Eastleigh: National Institute for Health Research; 2009.
- Ives J, Damery S, Redwood S. PPI, paradoxes and Plato: who's sailing the ship? *J Med Ethics*. 2013;39(3):181–5.
- Boote J, Telford R, Cooper C. Consumer involvement in health research: a review and research agenda. *Health Policy (New York)*. 2002;61(2):213–36.
- Gross D, Fogg AL. Clinical trials in the 21st century: the case for participant-centered research. *Res Nurs Health*. 2001;24(6):530–9.
- Gagnon M-P, Desmartis M, Lepage-Savary D, Gagnon J, St-Pierre M, Rhoads M, Lemieux R, Gauvin F-P, Pollender H, Légaré F. Introducing patients' and the public's perspectives to health technology assessment: a systematic review of international experiences. *Int J Technol Assess Health Care*. 2011;27(01):31–42.
- Mockford C, Staniszewska S, Griffiths F, Herron-Marx S. The impact of patient and public involvement on UK NHS health care: a systematic review. *Int J Qual Heal Care*. 2012;24(1):28–38.
- Evans D. Patient and public involvement in research in the English NHS: a documentary analysis of the complex interplay of evidence and policy. *Evid Policy A J Res Debate Pract*. 2014;10(3):361–77.
- Forbat L, Hubbard G, Kearney N. Patient and public involvement: models and muddles. *J Clin Nurs*. 2009;18(18):2547–54.
- Brett J, Staniszewska S, Mockford C, Herron-Marx S, Hughes J, Tysall C, Suleman R. A systematic review of the impact of patient and public involvement on service users, researchers and communities. *Patient*. 2014;7(4):387–95.
- Brett J, Staniszewska S, Mockford C, Herron-Marx S, Hughes J, Tysall C. Mapping the impact of patient and public involvement on health and social care research: a systematic review. *Heal Expect*. 2014;17(5):637–50.
- Barber R, Boote J, Parry G. Can the impact of public involvement on research be evaluated? A mixed methods study. *Heal Expect*. 2012;15(3):229–41.
- Staniszewska S, Adebajo A, Barber R, Beresford P, Brady L, Brett J. Developing the evidence base of patient and public involvement in health and social care research: the case for measuring impact. *Int J Consum Stud*. 2011;35(6):628–32.
- Hughes-Morley A, Young B, Waheed W, Small N, Bower P. Factors affecting recruitment into depression trials: systematic review, meta-synthesis and conceptual framework. *J Affect Disord*. 2015;172C:274–90.
- Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. 2008;337:a1655.
- Reynolds WW, Nelson RM. Risk perception and decision processes underlying informed consent to research participation. *Soc Sci Med*. 2007;65(10):2105–15.
- Deakin CT, Alexander IE, Kerridge I. Accepting risk in clinical research: is the gene therapy field becoming too risk-averse? *Mol Ther*. 2009;17(11):1842–8.
- Appelbaum PS, Lidz CW, Grisso T. Therapeutic misconception in clinical research: frequency and risk factors. *IRB*. 2004;26(2):1–8.
- Snowdon C, Elbourne D, Garcia J. Declining enrolment in a clinical trial and injurious misconceptions: is there a flipside to the therapeutic misconception? *Clin Ethics*. 2007;2(4):193–200.
- Eborall HC, Stewart MC, Cunningham-Burley S, Price JF, Fowkes FGR. Accrual and drop out in a primary prevention randomised controlled trial: qualitative study. *Trials*. 2011;12:7.
- Hughes-Morley A, Young B, Hempel R, Russell I, Waheed W, Bower P. What can we learn from trial decliners about improving recruitment? Qualitative study. *Trials*. 2016;17(494).
- Ennis L, Wykes T. Impact of patient involvement in mental health research: longitudinal study. *Br J Psychiatry*. 2013;203(5):381–6.
- Crocker J, Hughes-Morley A, Petit-Zeman S, Rees S. Assessing the impact of patient and public involvement on recruitment and retention in clinical trials: a systematic review. *Trials*. 2015;16 Suppl 2:O91.
- Oliver SR, Rees RW, Clarke-Jones L, Milne R, Oakley AR, Gabbay J, Stein K, Buchanan P, Gyte G. A multidimensional conceptual framework for analysing public involvement in health services research. *Heal Expect*. 2008;11(1):72–84.
- Groves RM, Cialdini RB, Couper MP. Understanding the decision to participate in a survey. *Public Opin Q*. 1992;56(4):475–95.
- Free CJ, Hoile E, Knight R, Robertson S, Devries KM. Do messages of scarcity increase trial recruitment? *Contemp Clin Trials*. 2011;32(1):36–9.
- Festinger L. A theory of social comparison processes. *Hum Relations*. 1954; 7(2):117–40.
- Hunn A. Survey of the general public: attitudes towards research. Ipsos MORI and NHS Health Research Authority; 2013. Available at: <http://www.hra.nhs.uk/documents/2013/11/survey-general-public-attitudes-towards-health-research.pdf>. Accessed 1 Dec 2013.

53. Health Research Authority. Patient involvement increases public confidence in health research. 2013. [Online]. Available at: <http://www.hra.nhs.uk/blog/news/2013/11/22/patient-involvement-increases-public-confidence-health-research/#sthash.rjPNrw7W.dpuf>. Accessed 1 Dec 2013.
54. Chambers R, O'Brien LM, Linnell S, Sharp S. Why don't health researchers report consumer involvement? *Qual Prim Care*. 2004;12(2):151–7.
55. Brett J, Staniszewska S, Mockford C, Seers K, Herron-Marx S, Bayliss H. The PIRICOM Study: a systematic review of the conceptualisation, measurement, impact and outcomes of patients and public involvement in health and social care research. 2010.
56. Möhler R, Kopke S, Meyer G. Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare: revised guideline (CREDECI 2). *Trials*. 2015;16:204.
57. National Institute for Health Research. NIHR HS&DR study wins national award for involving service users and carers. 2014.
58. Bower P, Roberts C, O'Leary N, Callaghan P, Bee P, Fraser C, Gibbons C, Ollevent N, Rogers A, Davies L, Drake R, Sanders C, Meade O, Grundy A, Walker L, Cree L, Berzins K, Brooks H, Beatty S, Cahoon P, Rolfe A, Lovell K. A cluster randomised controlled trial and process evaluation of a training programme for mental health professionals to enhance user involvement in care planning in service users with severe mental health issues (EQUIP): study protocol for a randomised co. *Trials*. 2015;16(1):348.
59. Sanders EB-N. Generative tools for co-designing. In: Scrivener SAR, Ball LJ, Woodcock A, editors. Collaborative design: proceedings of codesigning 2000. London: Springer London; 2000. p. 3–12.
60. Sanders EB-N, Stappers PJ. Co-creation and the new landscapes of design. *CoDesign*. 2008;4(1):5–18.
61. Brueton VC, Tierney JF, Stenning S, Meredith S, Harding S, Nazareth I, Rait G. Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis. *BMJ Open*. 2014;4(2).
62. Time to Change. Get the picture. 2016. [Online]. Available at: <http://www.time-to-change.org.uk/getthepicture>. Accessed 1 June 2016.
63. Schulz KF, Grimes DA. Sample size calculations in randomised trials: mandatory and mystical. *Lancet*. 2005;365(9467):1348–53.
64. Department for Communities and Local Government. English indices of deprivation 2015. England: Department for Communities and Local Government; 2015.
65. Care Quality Commission. Community Mental Health Survey 2015. 2015. [Online]. Available at: <http://www.cqc.org.uk/content/community-mental-health-survey-2015>. Accessed 21 Oct 2015.
66. Breslow NE, Clayton DG. Approximate inference in generalized linear mixed models. *J Am Stat Assoc*. 1993;88(421):9–25.
67. Tramm R, Daws K, Schadewaldt V. Clinical trial recruitment—a complex intervention? *J Clin Nurs*. 2013;22(17-18):2436–43.
68. Bagley HJ, Short H, Harman NL, Hickey HR, Gamble CL, Woolfall K, Young B, Williamson PR. A patient and public involvement (PPI) toolkit for meaningful and flexible involvement in clinical trials—a work in progress. *Res Involv Engagem*. 2016;2(1):15.
69. Stocks SJ, Giles SJ, Cheraghi-Sohi S, Campbell SM. Application of a tool for the evaluation of public and patient involvement in research. *BMJ Open*. 2015;5(3):e006390.
70. Coyne CA, Xu R, Raich P, Plomer K, Dignan M, Wenzel L, Fairclough D, Habermann T, Schnell L, Quella S, Cella D, E. C. O. Group. Randomised, controlled trial of an easy-to-read informed consent statement for clinical trial participation: a study of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2003;21:836–42.
71. Liénard J-L, Quinaux E, Fabre-Guillevin E, Piedbois P, Jouhaud A, Decoster G, Buyse M. Impact of on-site initiation visits on patient recruitment and data quality in a randomized trial of adjuvant chemotherapy for breast cancer. *Clin Trials*. 2006;3(5):486–92.
72. Kimmick GG, Peterson BL, Kornblith AB, Mandelblatt J, Johnson JL, Wheeler J, Heinze R, Cohen HJ, Muss HB. Improving accrual of older persons to cancer treatment trials: a randomized trial comparing an educational intervention with standard information: CALGB 360001. *J Clin Oncol*. 2005;23(10):2201–7.
73. Hahn S, Puffer S, Torgerson DJ, Watson J. Methodological bias in cluster randomised trials. *BMC Med Res Methodol*. 2005;5:10.
74. Donner A, Klar N. Pitfalls of and controversies in cluster randomization trials. *Am J Public Health*. 2004;94(3):416–22.
75. Staley K, Buckland SA, Hayes H, Tarpey M. The missing links: understanding how context and mechanism influence the impact of public involvement in research. *Heal Expect*. 2014;17(6):755–64.
76. Buchbinder SP, Metch B, Holte SE, Scheer S, Coletti A, Vittinghoff E. Determinants of Enrollment in a preventive HIV vaccine trial: hypothetical versus actual willingness and barriers to participation. *JAIDS J Acquir Immune Defic Syndr*. 2004;36(1):604–12.
77. Wisdom K, Neighbors K, Williams VH, Havstad SL, Tilley BC. Recruitment of African Americans with type 2 diabetes to a randomized controlled trial using three sources. *Ethn Health*. 2002;7(4):267–78.
78. Graham AC, Raisch DW, Fye CL, Sather MR. Assessment of the impact of a patient clinical trials handbook among pharmacy students. *Clin Ther*. 2005;27(2):238–45.
79. Kruse AY, Kjaergard LL, Krogsgaard K, Gluud C, Mortensen EL, Gottschau A, Bjerg AM. A randomised trial assessing the impact of written information on outpatients' knowledge about attitude toward randomised clinical trials. The INFO trial group. *Control Clin Trials*. 2000;21:223–40.
80. Snape D, Kirkham J, Britten N, Gradinger F, Looban F, Popay J. Exploring perceived barriers, drivers, impacts and the need for evaluation of public involvement in health and social care research: a modified Delphi study. *BMJ Open*. 2014;4(6):e004943.
81. Burns T, Catty J, Becker T, Drake RE, Fioritti A, Knapp M, Lauber C, Rössler W, Tomov T, van Busschbach J, White S, Wiersma D. The effectiveness of supported employment for people with severe mental illness: a randomised controlled trial. *Lancet*. 2007;370:1146–52.
82. World Health Organization. Mental Health Action Plan 2013–2020. Geneva: World Health Organization; 2013.
83. World Health Organization. Mental health: suicide prevention (SUPRE). 2013.
84. Gamble C, Dudley L, Allam A, Bell P, Goodare H, Hanley B, Preston J, Walker A, Williamson P, Young B. Patient and public involvement in the early stages of clinical trial development: a systematic cohort investigation. *BMJ Open*. 2014;4(7):e005234.
85. Staley K. An evaluation of service user involvement in studies adopted by the Mental Health Research Network. MHRN. 2012. available at: [http://www.twocanassociates.co.uk/perch/resources/files/MHRN%20Service\\_user\\_involvement\\_evaluation.pdf](http://www.twocanassociates.co.uk/perch/resources/files/MHRN%20Service_user_involvement_evaluation.pdf). Accessed 4 Dec 2016.
86. Patterson S, Trite J, Weaver T. Activity and views of service users involved in mental health research: UK survey. *Br J Psychiatry*. 2014;205(1):68–75.
87. Larkey LK, Staten LK, Ritenbaugh C, Hall RA, Buller DB, Bassford T, Altamari BR. Recruitment of Hispanic women to the Women's Health Initiative: the case of Embajadoras in Arizona. *Control Clin Trials*. 2002;23(3):289–98.
88. Ennis L, Wykes T. Impact of patient involvement in mental health research: longitudinal study. *Br J Psychiat*. 2013;203(5):381–86.
89. Free C, Hoile E, Robertson S, Knight R. Three controlled trials of interventions to increase recruitment to a randomized controlled trial of mobile phone based smoking cessation support. *Clin Trials*. 2010;7(3):265–73.
90. Corrigan PW, Watson AC. The paradox of self-stigma and mental illness. *Clin Psychol Sci Pract*. 2002;9(1):35–53.
91. Rüsçh N, Angermeyer MC, Corrigan PW. Mental illness stigma: concepts, consequences, and initiatives to reduce stigma. *Eur Psychiatry*. 2005;20(8):529–39.
92. Clement S, Schauman O, Graham T, Maggioni F, Evans-Lacko S, Bezborodovs N, Morgan C, Rüsçh N, Brown JSL, Thornicroft G. What is the impact of mental health-related stigma on help-seeking? A systematic review of quantitative and qualitative studies. *Psychol Med*. 2014;45:1–17.
93. Wilson P, Mathie E, Keenan J, McNeilly E, Goodman C, Howe A, Poland F, Staniszewska S, Kendall S, Munday D, Cowe M, Peckham S. ReseArch with Patient and Public involvement: a RealisT evaluation – the RAPPORt study. *Heal Serv Deliv Res*. 2015;3(38):1–176.
94. Knapp P, Raynor DK, Silcock J, Parkinson B. Performance-based readability testing of participant materials for a phase I trial: TGN1412. *J Med Ethics*. 2009;35(9):573–8.
95. Raynor DK, Knapp P, Silcock J, Parkinson B, Feeney K. 'User-testing' as a method for testing the fitness-for-purpose of written medicine information. *Patient Educ Couns*. 2011;83(3):404–10.
96. Durand M-A, Alam S, Grande SW, Elwyn G. Much clearer with pictures': using community-based participatory research to design and test a Picture Option Grid for underserved patients with breast cancer. *BMJ Open*. 2016;6(2):e010008.
97. Edge D, Degnan A, Cotterill S, Berry K, Drake R, Baker R, Barrowclough C, Hughes-Morley A, Grey P, Bhugra D, Cahoon P, Tarrier N, Lewis S, Abel K. Culturally-adapted Family Intervention (CaFI) for African-Caribbeans diagnosed with schizophrenia and their families: a feasibility study protocol of implementation and acceptability. *Pilot Feasibility Stud*. 2016;2(1):39.
98. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, Moore L, O' Cathain A, Tinati T, Wight D, Baird J. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ*. 2015;350:h1258.

Take part  
in an  
award-winning  
study!

To find out  
more about the  
EQUIP study:  
Telephone:  
0161 306 7863  
Email:  
equip@manchester.ac.uk

**NHS**  
National Institute for  
Health Research

Real patients  
and carers like you  
have helped to  
design this study

We are running a research  
study called EQUIP. Our study team  
includes real patients and carers,  
as well as researchers

Outstanding  
Carer  
Involvement  
Award winning  
study

We hope you will consider  
taking part in the EQUIP study

Professor Karina Lovell,  
EQUIP study lead, and  
Lindsey Cree, a carer and  
member of the study team,  
received the award from  
the Mental Health Research  
Network on behalf of the  
EQUIP study team.



“ I used to think  
research was just for  
academics, but since  
I’ve been involved in  
EQUIP I’ve realised  
how much my  
opinions matter and  
are taken on board ”

*Lindsey, Carer*

“ We have worked  
closely with patients  
and carers and are  
delighted that this has  
been recognised ”

*Professor Karina Lovell*

**MANCHESTER**  
1824  
The University of Manchester

**EQUIP**  
Enhancing the quality of user involved  
care planning in mental health services  
The EQUIP project is funded by the National Institute for Health  
Research's Programme Grants for Applied Research Programme

**MRC** | Hubs for Trials  
Methodology Research





## What do real patients and carers say about the EQUIP study?

“As a patient, I think this study is very important because patients need to have more of a voice and involvement in the decisions about their own future well-being.”

*Donna, Patient*

**Donna is a patient.** As part of EQUIP she trains mental health professionals to better involve patients and carers in care planning.



## Real patients and carers say that by taking part in this study, you can help make a difference

Donna, a patient, and Lindsey, a carer, say their involvement in the EQUIP study is to focus on the needs of real patients and carers. They also helped to design this leaflet.

**Lindsey is a carer.** She helped to apply for funding for EQUIP and is part of the study management team. She also trains mental health professionals to better involve patients and carers in care planning as part of EQUIP.



“As a carer, I feel I am making a difference towards change in mental health care. If we don't get involved in research, other people will be making decisions that can affect the future of people we care about. By taking part, I am making a difference to the future and there is no better feeling than that.”

*Lindsey, Carer*

### Important things that we think you should remember:

- If you decide to take part in this study, you will be helping other patients in the future.
- The study appointments will be arranged at a time to suit you.
- You can pull out of the study at any time if you no longer want to take part, without giving a reason.
- EQUIP has been approved by an independent research ethics committee, to make sure patients taking part in it will not be harmed.
- We are asking you to consider taking part in this study because your care team think that you may be interested in taking part.





# **Chapter 7: Overall discussion and conclusions**

---

## **7.1 Overview**

The purpose of this concluding chapter is to examine the implications of the empirical findings from the previous chapters, to relate these findings to the current literature and to suggest future directions for trial recruitment practice and research.

In this chapter we will:

1. Briefly revisit our aims and objectives
2. Provide a statement of principal findings from the three studies
3. Interpret our findings in the context of the wider literature
4. Examine the overall methodological strengths and limitations of the thesis
5. Hypothesise how possible implementation, mechanism and contextual factors may have led to our observed findings
6. Discuss some of the challenges encountered in conducting the research in this thesis
7. Reflect on the contribution made by this thesis
8. Reflect on the overall implications of the findings for recruitment practice and make recommendations for future research
9. Present overall conclusions
10. Describe the ongoing work emerging from the thesis

## **7.2 Revisiting thesis aims and objectives**

The thesis aimed to systematically develop an intervention for recruiting participants into mental health trials and evaluate its effectiveness, guided by the MRC framework for complex interventions [164]. The research was guided by four objectives:

1. To undertake a systematic review, meta-synthesis and conceptual framework of empirical qualitative evidence of influences on recruitment into depression trials
2. Identify potential components of a possible recruitment intervention, drawing on findings from qualitative interviews with patients who declined to participate in a depression trial
3. To develop the recruitment intervention, using Participatory Design methods

4. To determine the effectiveness of the recruitment intervention, using a randomised controlled trial design embedded in an ongoing trial involving patients with mental health problems

## **7.3 Overview of studies and principal findings**

### **7.3.1 Summary of main findings: Study One**

In Study One (Chapter 4), we undertook a systematic review, meta-synthesis and conceptual framework of empirical qualitative evidence of influences on recruitment into depression trials. Findings indicated that the decision to enter a depression trial was made by patients and gatekeepers based on the patients' 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 became engaged with the trial. We developed a conceptual framework of factors influencing the decision to participate. This highlighted that the decision to participate by both the patient and the gatekeeper involved a judgement between risk and reward. The findings suggested that advertising PPIR to prospective trial participants might help to reduce such perceived risk. The findings also identified a need for further qualitative work to understand the decision making from the perspective of patients who declined to enrol.

### **7.3.2 Summary of main findings: Study Two**

In Study Two (Chapter 5), we undertook semi-structured qualitative interviews with 20 patients who declined to participate in a trial to understand the process of declining trial participation. Findings indicated that the decision making process involved four stages, each of which was associated with a different type of non-participation decision. Stage 1 was associated with the 'prior decliner', who had an established position of declining trials, which they did after *assessing the nature of the invitation*. Stage 2 was associated with the 'self-excluder' who focused on the trial eligibility criteria and interpreted that they were ineligible *after determining their own eligibility*. Stage 3 was associated with the 'treatment decliner' who was eligible, but took a treatment decision about not needing the trial treatment after *assessing their own need for trial therapy and potential to benefit from the treatment*. Stage 4 involved *deliberating burdens and benefits of trial participation*, and was associated with the 'trial decliner', who declined after deliberating about the burdens versus the benefits of participation. Patients had positive views of the trial and often had

prior experience of research participation. Trial demands were considered only after patients assessed themselves as eligible and also in need of the trial treatment. Most did not participate because they considered that they did not need the trial treatment, or judged themselves as ineligible for the trial. Findings indicated that while 'prior decliners' are unlikely to respond to trial recruitment interventions, many of the other factors leading to non-participation can be addressed, as these are a result of situational and process factors rather than a rejection of trials. A number of possible recruitment interventions were identified, including the use of PPIR to inform the design and delivery of trials.

### **7.3.3 Summary of main findings: Study Three**

In Study Three (Chapter 6), we developed an intervention advertising PPIR to potential participants, and determined its effectiveness using a cluster randomised trial embedded in an ongoing mental health trial (The EQUIP Trial). Development of the recruitment intervention was guided by Participatory Design approaches. The principles underlying the intervention were informed by the meta-synthesis (Study One), the qualitative study (Study Two), social comparison theory and a workshop involving mental health service users, trialists and members of research ethics committees. We co-designed the recruitment intervention with PPIR partners using a leaflet as the delivery mechanism to advertise PPIR. Patients invited into the EQUIP trial were sent the recruitment intervention (intervention group), or not (control group). The primary outcome was the proportion of patients consented and enrolled in EQUIP. Thirty-four mental health team clusters containing 8182 patients were randomised. For the primary outcome, 4% of patients in the intervention group were enrolled compared with 5.3% of the control group. Analysis showed that the PPIR intervention was not effective for improving trial recruitment rates (adjusted OR= 0.75, 95% CI= 0.53 to 1.07, p=0.113). Directly advertising PPIR using a leaflet demonstrated no benefits for improving participant recruitment into EQUIP, or on any other outcome.

### **7.3.4 What does this research add?**

To our knowledge, this is the first piece of work to have systematically developed and evaluated a recruitment intervention for mental health trials using a trial embedded within an ongoing trial. Recruiting patients into trials has been described as a complex intervention [461]. However, in the literature there is a clear absence of studies that

systematically adopt a complex interventions framework to develop and evaluate a recruitment intervention. A lack of robust theory to guide intervention development has also been a key limitation of the existing literature. Additionally, there is an absence of solutions that have been empirically evaluated for effectiveness. Furthermore, explanations of recruitment processes in the literature have rarely been subjected to formal examination [188].

This thesis contributes to the trial recruitment evidence base by combining theory-informed intervention development with randomised evaluation in an ongoing trial recruiting real patients with mental health problems. The combination of intervention development and rigorous evaluation is a distinctive feature of this thesis. In the latest Cochrane systematic review of recruitment interventions, the sample sizes of the identified studies ranged between six and 2561 participants. With a sample size of 8182, this thesis also presents the largest ever trial embedded in an ongoing trial to evaluate the effectiveness of an intervention for trial recruitment [370].

Whilst PPIR is well-established in the UK and elsewhere, quantitative impact on its effectiveness is lacking. By developing and evaluating a recruitment intervention advertising PPIR, the thesis also makes a contribution to the evidence base for the impact of PPIR. Based on existing systematic reviews of PPIR, the embedded trial also represents the largest ever trial to evaluate the impact of PPIR [351], [591]. In Study Three (Chapter 6) we adopted the Participatory Design method, which is rarely used in the context of trial recruitment, to successfully co-design the recruitment intervention with PPIR members and other stakeholders, informed by the findings from studies one and two. We directly evaluated a recommendation made by the HRA in a press release that *'if health researchers communicate the fact that patients and the public have been involved in the design of their research when approaching potential study participants, it might help to boost recruitment'* [334] and found that direct communication of PPIR is ineffective for improving recruitment rates, at least in this particular context.

The systematic review and meta-synthesis (Chapter 4) enabled the development of a conceptual framework and identified that the enrolment decision actually involves two weighing up decisions by the patient and gatekeeper, rather than either the patient or gatekeeper alone. The conceptual framework highlighted that there were clear tensions between the assessment of risk and reward. The review highlighted the important role that gatekeepers play in the recruitment of patients into depression trials, as well as the protective biases in predicting the vulnerabilities of patients with depression. The review also identified a strong theme that patients predominantly enrol in depression trials to

access services to meet mental health needs, which contrasted with the literature and suggested that altruism is rather the key reason for taking part. This conceptual framework highlighted a number of mechanisms which could be evaluated to determine their impact on trial recruitment.

Research on the patient decision to decline trial participation has been described as a 'blind spot' in the literature [512]. Study Two (Chapter 5) focused on a group of patients under-represented in the meta-synthesis and the wider literature, by qualitatively exploring in depth the accounts of those who declined trial participation in order to understand the process involved in their decision making. This thesis presents the first qualitative study to focus on the decision making process (rather than simply the reasons) for patients who opt out of participating in depression trials. Findings from the qualitative study supported the meta-synthesis in Chapter 4 by highlighting that in making the participation decision, patients considered their current health state and whether they would benefit from the trial therapy, against the burden posed by participation in the therapy and other inconvenience. Whilst a lot of prior research has focused on trial demands as a barrier to participation, we found this to be of much less consideration than patients' own assessment of eligibility for the trial and their perceived need for the treatment. We also found patients' attitudes to research and the trial to be positive, which contrasts with some literature suggesting that patients who do not participate are less supportive of research.

## **7.4 Interpreting findings in the context of the wider literature**

In Chapters 4, 5 and 6 we compare the findings of the individual studies with the wider literature. This section provides an overview of how the thesis findings overall compare with the wider literature.

This thesis builds on the work of the START programme which aimed to support the routine adoption of embedded trials to test standardised recruitment interventions across ongoing host trials [572]. Using the START methodology, we successfully evaluated our recruitment intervention developed for mental health trials in the context of an ongoing mental health trial, and reported findings using guidelines for reporting embedded recruitment trials developed as part of START [553]. To date, four trials have completed in START: published findings suggest limited benefits of optimised patient information materials on recruitment rates (RR 1.08, 95% CI 0.95 to 1.23,  $I^2 = 0$ ) [592], [593]. Thus the work in this thesis supports the aims of START by demonstrating that it is possible to

embed trials of recruitment interventions across ongoing host trials, providing a model for rapid improvement of the evidence base.

Our findings from Study Two links in with the wider decision making literature, in particular the 'deliberation and determination' framework by Elwyn & Miron-Shatz (2010) [532], which proposes that decision making comprises a pre-decisional process and an act of decision determination. This model distinguishes between the pre-decisional deliberation process, the act of determination and post-decisional outcomes. Our findings and the stages appear to match this process of 'deliberation', in which the person considers the invitation in light of their eligibility, experiences and need; and determination, which is the act of choosing to not participate. Here, our classification of individuals, such as 'prior decliners', 'self-excluders', 'treatment decliner' and 'trial decliner' appears to synchronise with the 'determination' phase of the deliberation and determination framework. Whilst other potentially theories and frameworks exist - including prospect theory [594] and expected utility theory [595] - the deliberation and determination framework is particularly pertinent because it has been used in the trial participation literature to evaluate patients' decision making about trial enrolment [596].

Although a wide range of benefits have been suggested about the impact of PPIR, very little quantitative evidence exists in the literature; mainly because objective methods for assessing its impact and influences remain elusive in a process that is fundamentally relational, subjective and socially constructed [354]. In this thesis, we found that advertising PPIR to potential trial participants in a mental health trial was not effective for improving recruitment. Our findings, based on a sample of patients being recruited into an ongoing mental health trial contrasts with the findings from the HRA survey, in which 44% members of the British public responding to a hypothetical scenario indicated that they would be more likely to enrol in a trial if they found that real patients had advised in its design [333], [334]. From their findings, the HRA recommended that if trialists advertised PPIR to potential participants, it might boost recruitment. In our embedded trial patients invited to enter a real trial were no more likely to enrol when they were sent a leaflet advertising the PPIR in the trial. Our findings also contrast with an embedded trial which evaluated the impact of text messages containing quotes from existing trial participants on recruitment. Sending text messages containing quotes from existing participants increased randomisations, with 3.5% of the intervention group and 0% of the control group randomised into the host trial, risk difference 3.5 (95% CI 1.7-5.2) [577]. This text message trial also utilised the concept of social validation; however unlike our



intervention, the social validation in their trial came from existing participants rather than PPIR partners, which may account for the differences in findings.

Our finding receives support from the wider literature, where a study investigating hypothetical and actual willingness to enrol in a trial found that only 20% of participants stating hypothetical willingness to enter a trial actually enrolled and that statements of hypothetical willingness to participate in future trials may overestimate true enrolment [597]. This may account for the differences between ours and the HRA findings. Another cross-sectional survey investigating the impact of PPIR compared public interest in research participation in studies overall, with studies explicitly designed with PPIR [598]. In that study 5% of respondents had either been previously involved as PPIR contributors themselves or knew someone who had; findings showed there was no association between prior personal PPIR or knowing someone who had and willingness to engage in research. The authors concluded that PPIR in study design may not affect overall rates of participation [598]. While this was a cross-sectional hypothetical survey of healthy members of the US population, the findings are similar to ours in that knowledge of PPIR did not affect reported willingness to enrol in research. In another observational study by Wisdom *et. al.* (2002) involving the recruitment of African-Americans being recruited through three different sources, the non-PPIR arm was more effective for improving recruitment [599]. Whilst these are observational studies, the findings from the thesis are in line with this literature evaluating the impact of PPIR on recruitment.

Since starting the research in this thesis, Edelman and Barron (2015) have argued that the way in which PPIR has been evaluated as a complex intervention is the reason why evaluation has proved difficult, consequently derailing the development of a meaningful and robust evidence base [347]. They maintain that PPIR cannot, and indeed should not, be evaluated as an intervention but rather as part of the research process. Edelman and Barron offer alternative constructions of PPIR from the deontological and consequentialist perspectives, which respectively construct PPIR as a contribution of expertise and advocacy, equitable to the contribution of clinicians and statisticians; or as a methodological activity to improve research quality. Here, they assert that PPIR should not be tested against pre-determined outcomes in the same manner that a complex intervention would be evaluated. Rather, they state evaluation should focus on process. In this thesis we have successfully adopted a complex intervention approach to evaluate the impact of a PPIR intervention on recruitment. Thus our findings suggest that PPIR can indeed be successfully evaluated as a complex intervention, in a systematic and robust way. Our approach to evaluating PPIR is supported by other authors, who have argued

that the lack of an evidence base for PPIR is a consequence of this focus on process, which often leads to the exclusion of defining or measuring the outcomes of PPIR [600]. Moreover, it has also been suggested that defining PPIR outcomes solely in terms of research quality ignores the rights of those being researched or likely to benefit from the research to be involved in how it is defined and executed [601] -p36.

Recently, others have paid attention to using the complex interventions framework to develop and evaluate a trial retention intervention. Duncan *et. al.* (2015) adopted the complex interventions framework and behaviour change theory to develop a cover-letter to improve trial follow-up questionnaire response rates and evaluate its impact in an embedded trial. Findings from their trial showed questionnaire return rate was significantly higher in the group receiving the theoretically informed letter than the group who received the original cover letter (73.0% vs. 66.8%, difference +6.2%, [95% CI +1.0% to +11.4%]) [602]. The authors are now encouraging the evaluation of their intervention in other contexts, using the SWAT platform [603].

## **7.5 Key methodological strengths and limitations**

In this section we will examine the methodological strengths and limitations of the thesis. A critical assessment of each study's methodological strengths and limitations can be found in Chapter 3 and as part of the individual manuscripts (Chapters 4-6). Findings from this thesis should be interpreted in context of the following strengths and limitations. Firstly, the findings may not generalise from the contexts of the REFRAMED and EQUIP trials to other trials conducted nationally or internationally. The findings may not translate to recruiting participants in other contexts; such as in other disease areas outside of or even within mental health; outside of the NHS; or in other healthcare contexts. These findings are most likely to apply to trials sharing similar demographics to our study populations and using similar recruitment methods.

### **7.5.1 Rigour**

As noted earlier, this thesis used best practice guidelines to develop, evaluate and report an intervention for recruiting participants into mental health trials. The science of intervention development is still in its infancy [461]. Few studies report the development process, giving the impression that interventions emerge 'out of thin air' and proceed straight to trial [188]. Working alongside START, which developed methodological,

logistical and reporting frameworks for embedded recruitment trials and assessed their feasibility, the author systematically developed a recruitment intervention using the evidence base and published theory, and evaluated its effectiveness using the gold standard of a randomised controlled trial. The MRC framework was adopted to identify the evidence base and develop a conceptual framework to inform the mechanism of the intervention; qualitative interviews with a hard-to-reach group of patients who declined trial participation were undertaken to understand the process of decision making; additional components of the PPIR intervention were identified using an existing theory and existing research evidence; and the recruitment intervention was co-designed with end-users. The recruitment intervention was evaluated in a large trial embedded within an ongoing multi-centre trial recruiting patients from routine mental health settings, which is the most robust test of effectiveness [554]. Outcomes were reported in collaboration with PPIR partners and used best practice in accordance with published reporting guidelines [553], [604][605][478].

In Chapter 3 we outlined how reflexivity and triangulation are important to ensuring rigour in qualitative research. Below, we describe how this was achieved in the thesis.

### **7.5.2 Reflexivity and triangulation**

Whilst reflexivity and data triangulation are important for the quality of qualitative research [522], such processes do not guarantee quality [606]. Nevertheless, for the purposes of transparency, it is important to reflect on how the researcher's position as a health services researcher may have impacted on the qualitative research undertaken within this thesis. Researchers' flexibility and adaptability is important during the research process, particularly in ensuring that we do not become constrained by our own preconceptions [607]. The author aimed to enforce this throughout the conduct of the qualitative research; however it must be acknowledged that her background as a health services researcher and previous experiences of recruiting people with mental health problems into trials may have shaped the interpretation of the findings. Integrating reflexivity and triangulation into the process meant that whilst the potential influence of those experiences was acknowledged, she maintained a 'field diary' and consciously returned to the data to verify and ensure her interpretation of data was not unduly influenced. Additionally, the meta-synthesis and conceptual framework (Study One) may have influenced personal perceptions and interpretation of interviewee accounts in the qualitative study (Study Two). It was therefore important to guard against this prior

experience and knowledge constraining our analysis and interpretation. This was achieved through actively seeking out deviant cases - that is, pursuing cases and accounts that did not fit with the emerging findings.

In terms of triangulation, the author's supervisory team and collaborators were from multiple disciplines, covering health services research, psychology, psychiatry and clinical trials. As such, during the interpretation and write up she sought their contributions in order to help to develop both depth and range of meaning in the data, and to assure the trustworthiness of the analysis [523], [524]. For example, the supervisory team engaged with the data during the analysis process by reading a proportion of the transcripts and drafts of the manuscripts using extensive quotations from participants' accounts. During the analyses for both studies one and two, the appropriateness of the fit of the data mapped to the themes and stages were discussed during supervisory meetings. As part of this process, some themes and categories were renamed to more accurately reflect the content or grouped with other categories or themes. Audit-trail records of the developing analyses for studies one and two were maintained, including definitions of the key theoretical categories. For Study Two, the author also examined links between emergent findings and theoretical ideas in the wider literature to test the quality of the developing analysis in terms of its coherence, theoretical validity and potential to inform practice. These strategies contributed to ensuring rigour in the qualitative studies.

### **7.5.3 Adopting a mixed-methods approach**

The three studies were designed to build on each other; for findings from each to inform the next study. Furthermore, adopting pragmatism as a philosophical perspective enabled the use of a combination of quantitative, qualitative and Participatory Design methods, which ensured robustness and comprehensiveness, allowing for a wider range of questions to be answered than each method can individually allow. This addressed the deficits of either method alone in addressing the complex issues around trial recruitment. For example, the meta-synthesis and qualitative study in studies one and two provided an in-depth exploration of the issues affecting recruitment and the decision to decline participation. Using quantitative methods for studies one and two would have provided summary data of limited insight into the issues. Conversely, the use of qualitative methods to evaluate the recruitment intervention would not have permitted a robust estimation of the effectiveness of the recruitment intervention. The focus on actual, rather than

hypothetical decisions also ensured that we evaluated the recruitment intervention under the conditions in which it would be applied in practice.

In Chapter 3 we highlighted the strengths and limitations of mixed methods research. In mixed methods research the result of a qualitative phase of research can inform the quantitative phase and theory can be generated and tested. Using mixed methods research enabled us to generate a conceptual framework from our meta-synthesis; which informed the development of the recruitment intervention; which was then tested in a trial. One challenge with mixed methods research is that findings from a qualitative study may not always translate easily into an intervention that can be evaluated. A second challenge of this mixed methods approach in this thesis was the need to learn multiple methods in detail concurrently, in order to deliver the work: however, this added to the breadth of skills of the researcher, who is now using the skills in her current role.

#### **7.5.4 Patient, public and stakeholder involvement**

In this section we will examine the PPIR in the thesis as a whole. A critical assessment of PPIR in the development and evaluation of the recruitment intervention has been reported in Chapters 3 and 6.

There is an argument that despite the policy emphasis on PPIR, some professionals have not embraced the idea of partnerships with patients and even feel threatened by the notion of active involvement [322][336]. PPIR was necessary and fundamental to the development and evaluation of a recruitment intervention advertising PPIR in a mental health trial. Using the Participatory Design approach, we worked with the patients and professionals who were best placed to know what works, engaging with PPIR members in a way that went '*beyond the role of passive suppliers of opinion, to a role of active negotiators for change*' [608]. Treating research as a shared exercise between researcher and patients, carers and other stakeholders aimed to shift the balance of power so all actors were on a more equal footing [609]. For example, in developing the leaflets, the PPIR partners took the lead and the research team was not asked for their opinion until the leaflet was drafted. Priority in voting for the preferred leaflet was also given to PPIR partners, which aimed to provide authenticity to the intervention.

The PPIR within this thesis was facilitated by the SURP and PRIMER. Involvement from both PPIR groups strengthened the work in this thesis by bringing forth different

perspectives and drawing on the strengths of each group. The research presented was well received by PPIR members and suggestions were implemented (Table 19).

**Table 19: Suggestions by PPIR groups for the research and action taken**

<b>Suggestions by PPIR groups</b>	<b>Response</b>
Timing of telephone calls for qualitative should be conducted from late morning to early evenings	All telephone interviews conducted between 11am-8pm
Role play the qualitative interview with a service user prior to interviews	Role play undertaken with a service user from SURP prior to start of interviews
Important to consider how suicide risk might be managed in undertaking telephone interviews with people with low mood	Protocol for managing suicide risk implemented (see Appendix C)

EQUIP as a host trial had strong, award-winning PPIR: among the grant holding team were PPIR members; and the trial intervention training team was led by service users and/or carers. Thus at the time of undertaking the work within this thesis, we used the best example of a trial with authentic PPIR that was available to develop and evaluate our recruitment intervention. Lindsey Cree and Donna More, EQUIP PPIR partners, are co-authors on Study Three (Chapter 6). We therefore co-developed, co-produced and co-delivered a recruitment intervention with significant input from those to whom the intervention directly relates.

It is important to acknowledge that in undertaking the PPIR in the thesis, the focus and direction of the research was set by the researcher; the PPIR partners did not have input into all aspects of the research or decision making, so the ‘control’ the PPIR partners had on the research was bounded. Thus, despite the extensive PPIR in the thesis, it did not amount to user-control. Doing PPIR also requires more resources. Whilst the author had a generous budget allocated for PPIR through her funding from the NIHR, this is not a typical resource available to most doctoral-level researchers. Working with PPIR members and trialists/research professionals and managing a broad range of abilities can also be challenging. For example, in the workshop to develop the recruitment intervention a balance had to be struck between engaging with PPIR stakeholder who had no experience of trial recruitment and trialist/researcher stakeholders with significant experience. A lot of context had to be provided in the presentation and attendees were encouraged to ask questions and seek clarification. Since it was important to ensure that all stakeholders present could contribute, for some researcher attendees the pace might have been slower

than they may have preferred. However, the workshop was successful in achieving all its aims and informal feedback from participants was very positive.

The work within this thesis was nominated by PRIMER for best 'Public Engagement' at the Greater Manchester Clinical Research Awards 2015.

### **7.5.5 Part of a wider endeavour to develop an evidence base for recruitment**

A key strength of this thesis is that the development, implementation evaluation and reporting of the recruitment intervention has been part of a wider research endeavour, designed to rapidly and systematically develop an evidence base for trial recruitment interventions. Here, the recruitment endeavour is a core part of improving overall trial efficiency, through marginal but incremental gains in all aspects of trials, with the aim of making gains that are 'greater than the sum of its parts' [357].

As described earlier, this thesis links in with the work of START. The author collaborated closely with the START team throughout the PhD programme, to shadow and gain valuable insights from START, as well as to actively contribute to START, in order to inform the development and evaluation of a separate recruitment intervention for mental health trials. Working closely with the START team, the author actively contributed to the START protocol [572]; to the development and testing of the START recruitment interventions in ongoing host trials [592][557], [610]; and to the development of guidelines for reporting embedded recruitment trials [553]. This active collaboration and contribution to the START programme is evidenced in multiple co-authored publications arising from START [307], [553], [572], [592].

Thus a strength of this thesis is its links with the wider evidence based trial recruitment endeavour, which ensured a broad overview of the clinical trial enterprise. Working with different trial teams to deliver the work in this thesis illuminated different aspects of trial methodology research, ensured the consideration of different recruitment contexts, and led to the development of an intervention with the potential application to a range of trials, not just in mental health. Furthermore, being part of this endeavour means findings and outcomes from the thesis can make its own clear contribution, through for example, the registration of the work in this thesis as a SWAT [590], which encourages other trialists to adopt or adapt the recruitment intervention from this thesis to undertake their own embedded methodology research. Here, this thesis will serve to provide a worked example, from intervention development through to rigorous evaluation, for others to

learn from and adapt. Improving recruitment is one aspect of improving efficiency in the conduct of trials, where resources can be wasted because of limited evidence upon which to base many aspects of design, conduct, analysis, and reporting of trials [357].

#### **7.5.6 Failure to recruit a host depression trial to evaluate the intervention**

Depression is the most common mental health problem, thus when we initiated the PhD programme of Research, the author anticipated that the thesis would most likely focus on depression as there were numerous trials evaluating interventions to manage depression. Studies one and two were therefore undertaken using depression as a case exemplar, with the expectation of continuing to develop and evaluate the recruitment intervention in the context of a depression trial. However, at the time of developing our intervention, the author was unable to recruit a depression trial. We sought support from the CRN Mental Health, who contacted trial teams on our behalf. We advertised for host trials in *Trials and Tribulations*, the Magazine for the UK Trial Managers' Network. We also directly contacted trialists undertaking current mental health trials, as well as those listed on the UK Clinical Trials Gateway as having mental health trials in 'set up' or 'recruiting'. However we were unsuccessful. Therefore, having developed the recruitment intervention using depression as the case exemplar, we were unable to conduct the evaluation in a depression trial. The intervention developed using depression as a case exemplar may not have been as relevant for the population in the EQUIP trial of people with SMI. This may have impacted on the embedded trial outcomes. Table 20 outlines the commonalities and differences between depression and SMI.



**Table 20: A comparison of depression and SMI, data from Rajji (2009)[611], Messias (2007)[612], Kessler (2011)[613], Gelder (2012)[614]**

	<b>Depression</b>	<b>SMI</b>
<b>Patient populations</b>	Higher prevalence in females. Age of onset 25 years	Higher prevalence in males. Age of onset: 18 years in men; 25 years in women
<b>Symptoms</b>	Difficulties in thinking and concentration, loss of energy, social withdrawal, self-neglect	Difficulties in thinking and concentration, loss of energy, social withdrawal, self-neglect  Hallucinations, delusions, disorders of the form and flow of thought, lack of insight
<b>Illness course</b>	Relapsing-remitting	Relapsing-remitting
<b>Sequelae</b>	Suicidality, infections (communicable diseases such as HIV/AIDS hepatitis), endocrine, cardiovascular, cerebrovascular, respiratory and gastrointestinal disorders, secondary substance abuse disorders.	Suicidality, infections (communicable diseases such as HIV/AIDS hepatitis), endocrine, cardiovascular, cerebrovascular, respiratory and gastrointestinal disorders, secondary substance abuse disorders.
<b>Impact on decision making</b>	Approximately 52% of patients had impaired capacity	Approximately 22% of patients had impaired capacity
<b>Treatment - typical</b>	Pharmacological (Antidepressants); psychological or combined; disease management programs	Pharmacological (Antipsychotics); psychological or combined; disease management programs; social occupational and educational interventions

From Table 19, it is evident that there are significant overlaps between SMI and depression. This overlap has given rise to a debate in the literature about the relationship between psychotic and affective symptoms and whether they should be classified along a continuum, or as discrete conditions [27] [615]. Whilst data from EQUIP is not yet available to determine to what extent depression was prevalent in that population of patients with SMI, there is clear evidence that depression comorbidity is high in SMI, with an estimated 50% of patients with SMI also experiencing comorbid depression [27]. Conversely, depressive episodes can also evolve into psychosis [27]; indeed, it is estimated that between 14% and 19% of patients experience psychosis during the course of a depressive episode [27]. The initial symptoms of both conditions reflect a core psychopathology common to the early stages of both [27]. There are also commonalities in their treatment, with CBT for example being recommended by NICE to manage both

depression and SMI [31], [34]. However, there are also key differences such as the presence of delusions, hallucinations, disordered thinking and lack of insight in SMI [614]. In terms of decision making – which is particularly pertinent to the trial enrolment decision – impairment in capacity is also more common in SMI with 52% of patients assessed as having impaired capacity in general, compared with 22% of patients with depression [616]. There is evidence that outpatients diagnosed with depression have few impairments in their decision-making capacities related to research [617]. Individuals diagnosed with schizophrenia on the other hand have shown heterogeneity in performance on measures of decision making capacity for research [618]. However, it is noteworthy that patients diagnosed with schizophrenia tend to respond to interventions to improve decisional capacity for consenting to research; and that such patients also retain the information necessary for informed consent during trials [619]. Current trials in both depression and SMI tend to investigate pharmacological and psychological interventions [166][64][168]; however, for SMI there also tends to be more trials evaluating service level interventions such as liaison psychiatry, care planning or systemic therapies, which might reflect greater need for services as well as the impact of SMI on families and loved ones [620]. Thus whilst there are significant differences between SMI and depression, there are also some overlaps in presentation, disease management and evaluation of potential treatments.

Mental health research has a very strong history of PPIR in the UK [621], [622] and there is some evidence that the use of PPIR is significantly associated with successful recruitment in different mental health trials, including depression and SMI [332]. The concepts of risk and social validation used to develop the recruitment intervention exists across all disease areas however, not just depression, and it is possible that our findings would have been similar had we evaluated the intervention in a depression trial. Social validation has also been used successfully as a trial recruitment intervention, with an embedded recruitment trial of text messages containing quotes from existing participants significantly increasing randomisations [626]. Moreover, the HRA survey advocating the direct advertising of PPIR to prospective trial participants indicated that this approach could be used in all disease areas [333][333]. Finally, the PPIR intervention was strongly endorsed by stakeholders at the workshop and was developed in close collaboration with the EQUIP trial team and stakeholders, who also endorsed its use.

### **7.5.7 The role of the qualitative study**

With the benefit of hindsight, the core findings of the qualitative study (Chapter 5) could have played a more prominent role in the recruitment intervention. Whilst the systematic review and the PPIR literature made a strong case for developing a PPIR intervention, the small number of ‘decliners’ opting into the qualitative study meant that the study took longer than anticipated to be completed. Additionally, the timings of the EQUIP recruitment phase meant that the recruitment intervention had to be ready for evaluation before the qualitative study was finalised. This meant that whilst emergent findings from the qualitative study informed the intervention (which highlighted eligibility issues and the need for more effective trial information), the analysis was completed after the intervention had already been designed, meaning it was not fully utilised in the intervention design. When completed, the full qualitative analysis suggested other mechanisms could be targeted. Thus earlier completion of the qualitative study might have led to the development of a different intervention, or a variation on the current intervention, which may have made more use of the findings from the qualitative study. These other options are discussed in the ‘Recommendations’ section later in this chapter.

It is important to briefly reflect here on the relative contribution that findings from qualitative research can make to trials, versus the knowledge that can be gained from PPIR. A key distinction in terms of their contribution to trials is that whilst qualitative research is generally recommended in the early stages of complex interventions development, PPIR can occur at any or all stages of the research process. PPIR involves patients, carers and members of the public as partners in research and is a two way exchange of knowledge that can influence trial design, treatment, trial conduct and implementation. Qualitative research on the other hand involves the collection of participant data to address research questions, predominantly for advancing understanding related to trial design, treatment, findings or implementation issues. Thus it involves the researchers being informed by the participants [627]. Overlaps exist where in both qualitative research and PPIR individuals can be asked to comment on how their experience might improve trial conduct or the patient experience in trials, or to suggest research questions or priorities. Undertaking PPIR and qualitative research synergistically can be powerful, particularly in accessing hard-to-reach groups [627], which we successfully did in this thesis, through PPIR consultations with SURP and PRIMER, which led to suggested changes being implemented in the qualitative study.

### **7.5.8 Optimisation of the PPIR leaflet**

Ideally, the recruitment intervention would have been user tested. The intervention was not user tested, due to time constraints and the need to assimilate with the host trial and ensure the intervention was ready for randomisation. We are currently evaluating the impact of a user tested version of the recruitment intervention in a study of culturally adapted family intervention for African Caribbean people with schizophrenia and their family. While the wording of the recruitment intervention was approved by both the host trial and PPIR partners, in hindsight the leaflet may have been optimised and modifications to the wording made. The leaflet was also only delivered in the English language, which may have impacted on those not able to read in English; however, the host trial only recruited participants who could complete the study procedures in English, therefore attempting to develop the leaflet in any other language would have constituted a waste of resources since non-English speaking patients could not have been enrolled.

### **7.5.9 Cluster randomisation**

Patient level randomisation would have been the most efficient method for ensuring adequate power for testing the PPI leaflet intervention in the embedded trial in Study Three (Chapter 6), and we had originally aimed to adopt this approach. It was not possible to undertake patient level randomisation for the embedded trial however, as this was logistically burdensome and not acceptable to the trial team. Cluster randomisation enabled the embedded trial to be implemented in EQUIP and random assignment in the embedded recruitment trial and reduced the burden on the host trial. However, this design reduced the power of the trial and introduced imbalance issues which had to be addressed methodologically and in the statistical analysis.

### **7.5.10 Absence of a formal process evaluation**

Whilst we developed, implemented and evaluated a recruitment intervention in a trial embedded in an ongoing host trial, we did not undertake a formal process evaluation, which would have offered a greater insight into our findings. The MRC guidance for developing and evaluating complex interventions recognised the importance of process evaluations within trials [164]; and recently guidance on the process evaluation of complex interventions have been published [628]. We lacked the time within the time-frame of the PhD to undertake a process evaluation to explain our findings, which we acknowledge to be a limitation of the work presented. However, undertaking such a study is also not

straightforward and would have required significant resources. Whilst process evaluations are required for trials in general, there is arguably less of a need for them in embedded trials, given the constraints imposed by the host trials. Indeed, such process evaluations may only be justified with very high cost and high impact interventions, such as Donovan *et. al.*'s Quintet Recruitment Intervention, a complex intervention which uses a combination of qualitative research methods with quantification to understand recruitment and identify sources of difficulties [629]. Furthermore, there are limitations set by embedded trials which work well with minor changes to trial procedures which have limited impact on trial teams, but gives less scope for major impactful changes. This is a limitation of all embedded trials, but is relevant to the work presented in this thesis.

## **7.6 The lack of effectiveness observed in the recruitment intervention**

It is important to revisit why, given the systematic development of the recruitment intervention, it was found to be ineffective for all outcomes measured. Here, we remind the reader that the intervention evaluated advertising PPIR to potential trial participants, rather than evaluating the impact of PPIR in terms of improving the trial. In the previous section we discussed the lack of process evaluation in the thesis arising from limited resources, and how this is a limitation. In this section we attempt to hypothesise about the possible causes leading to the lack of effectiveness in the recruitment intervention, using the format for process evaluation of complex interventions outlined by the MRC [628]. The framework for process evaluation focuses on three key areas: 1) implementation; 2) mechanism; and 3) context. We use these to frame our discussion.

### **7.6.1 Implementation**

The process evaluation guidelines emphasise that an intervention may have limited impact because it is not implemented as intended. Capturing fidelity, that is, whether the intervention was delivered as intended is considered important to developing an understanding of what works.

For the embedded trial a robust and auditable randomisation process, packaging and delivery system of the patient recruitment packs was employed. There was no indication that implementation of the recruitment did not occur as it should and that patients

randomised to the leaflets were not sent them. Thus it is likely that the intervention was implemented as intended - that is, posted to potential participants in the invitation packs.

## **7.6.2 Mechanism**

Investigating the mechanisms through which interventions deliver change is highlighted by the process evaluation guidelines as vital to discerning how the effects of the intervention are manifested.

### **7.6.2.1 Risk**

The meta-synthesis identified the consideration of risk as an important issue in the participation decision. Issues of risk may be less important than other mechanisms identified in the qualitative work in this thesis, such as patients self-excluding themselves as ineligible. Alternatively, risk may be important, but written information is not a good method of addressing it.

### **7.6.2.2 Social validation**

To inform the recruitment intervention, the concept of social validation was utilised. It has been suggested that the concept of social validation can be applied in trials across all disease areas, with an embedded recruitment trial of text messages containing quotes from existing participants significantly increasing randomisations in a trial of smoking cessation support [626]. However, in our trial, social validation came from a service user and a carer who were *research partners*, rather than *trial participants*. This may have impacted on our findings.

### **7.6.2.3 Use of the leaflet as the delivery mechanism**

Whilst the leaflet format was chosen for ease of implementation and compatibility with the host trial recruitment, it is important to acknowledge that the use of the leaflet as the delivery mechanism may have adversely affected the impact of the intervention. Alternative delivery mechanisms for communicating risk and social validation such as text messages, email or telephone calls may have resulted in a more positive impact. Furthermore, an alternative format, for example, comprising of two rather than the booklet format of four pages, may have elicited a more positive response. There may also have been a ceiling effect associated with the use of the leaflet, since there is some

evidence to suggest that there is little additional benefit to using supplementary information such as leaflets when recruiting participants [370].

#### ***7.6.2.4 Content of the leaflet***

In terms of the presentational elements of the leaflet, the content and wording was based on the core principles agreed from the workshop and elements deemed by workshop attendees and the EQUIP PPI partners to be important. Whilst the content of the leaflet was written in close collaboration with PPIR partners and was intended to be written in clear, plain language, we did not assess its readability, undertake user testing, nor did we seek an external assessment of how clear the 'plain language' used in the leaflet was, for example, via the 'Crystal Mark' seal of approval for the clarity of understanding [632]. In line with the core principles identified from the workshop, the leaflet aimed to be eye catching: bold, bright print, large font and colourful. Whilst this was achieved, visual appeal of the leaflet may have been achieved with an alternative use of some colour with good contrast [633]. The provision of structured, evidence-based guidance to PPIR members on the leaflet content may have resulted in a leaflet that had greater potential to positively impact on response rates [634].

#### ***7.6.2.5 Media***

Whilst the information design of the leaflet such as the information architecture and typography of the leaflet was undertaken by a professional graphic designer in a company with significant expertise in developing and printing patient leaflets for the NHS, the leaflet design was bounded by the principles developed from the workshop and the steer of PPIR partners. The use of numerous images in the leaflet may have affected how the leaflet was perceived. The paper density of the printed leaflet and the glossy finish used may have also impacted on how it was perceived. Again, more structured guidance based on evidence-based leaflet design for PPIR partners may have resulted in a leaflet that had greater potential to positively impact on response rates.

#### ***7.6.2.6 Exposure to the intervention***

It is possible that people in the intervention arm did not read the recruitment leaflet. The intervention was sent by post in a large recruitment pack with several other documents. Those sent the recruitment pack may not have opened it, and those that did may not have

read the recruitment leaflet. We were not able to determine how many people read the recruitment leaflet, and our intention to treat analysis may have underestimated the effects of the active intervention components.

#### ***7.6.2.7 Interpretation of the recruitment intervention***

It is not clear whether patients who received the recruitment intervention leaflet and read it understood and appreciated the message it attempted to convey, and what PPIR meant for EQUIP, which they were being asked to enrol into. On the other hand there is some research evidence suggesting that patients reading supplementary written information about a trial in booklet or leaflet format have enhanced knowledge about the trial [630], [631]. It is likely that those who read the leaflet may have been more likely to make a more informed decision about declining to enrol the trial, which, although a good decision for the patient, constituted an adverse outcome for the trial. It was not possible however to obtain estimates of the effectiveness of recruitment intervention for patients who were allocated to receive the intervention, who also read the leaflet, and how they received and interpreted the content of the leaflet.

### **7.6.3 Context**

The process evaluation guidelines highlight the importance of considering how context can affect implementation of the intervention and outcomes. This includes anything external to the intervention that may act as a barrier or facilitator to its implementation, or its effects.

#### ***7.6.3.1 Lack of representativeness***

Informal discussions of our findings with stakeholders and PPIR contributors to other trials suggested that the recruitment intervention leaflet lacked appeal to the target group in terms of the representativeness in the images used. Some remarked that the images of people in the leaflet did not represent them, that: '*the people in this leaflet do not look like me*'. As previously noted, lack of diversity of PPIR members has been highlighted in the literature, and it has been proposed that there is a need to engage with PPIR contributors who reflect the diversity of the study's target population [326]. Unfortunately, we were unable to gather biographical data for all patients approached or undertake qualitative



interviews with the people sent the recruitment intervention in order to explore and understand patient views of the intervention.

### **7.6.3.2 *The host trial***

There are a range of mechanisms by which PPIR might influence recruitment, including on the trial design and trial conduct. Thus the role of PPIR might lead to sensitive issues being handled better [635] or enhance trial quality and appropriateness, making them more effective [322], [353]. These mechanisms call into question the mechanism used in our trial, which is that advertising PPIR might improve recruitment. Additionally, the high-quality PPIR in EQUIP may have meant that the PPIR benefits may have been already optimised in the host trial. The addition of the PPIR recruitment intervention may therefore have been irrelevant.

The meta-synthesis and qualitative study identified issues around individual patients making individual decisions about their participation in trials and patients' consideration about the treatments they might receive. These two studies highlighted the issues around patient-level randomised trials that evaluate patient focused treatments. The EQUIP trial in hindsight did not fit this model, and this may have contributed to the lack of effect. EQUIP was cluster randomised; and the intervention being evaluated was at the service level of the mental health teams, rather than being patient focused. Patients themselves did not receive an intervention and were therefore not making a decision around whether or not they were in need of a trial treatment. While patients may have benefited from the EQUIP intervention, this would have been an indirect benefit and therefore the hypothesised mechanism around risk reduction may not have been as strong in EQUIP as it would have been in a patient-level randomised trial.

As previously discussed, the recruitment intervention was developed using depression as the exemplar, however it was tested in a group of patients with SMI, who may or may not have had comorbid depression. This may have impacted on the findings as the intervention may not have been as relevant for the SMI population in EQUIP as it would have for a trial recruiting patients with depression. Since we have already outlined the issues elsewhere in this discussion, we will not repeat them, other than to reiterate that in evaluating the intervention in EQUIP, the context in was different to than envisioned when developing the intervention, which might have adversely impacted on the outcomes observed.

## 7.7 Challenges

In this section we discuss the challenges in undertaking the work in this thesis, and the approaches we took to managing these challenges.

This thesis, particularly studies two and three (Chapters 5 and 6) is the result of a collaborative endeavour. Collaborations are formed when two or more stakeholders invest their resources (e.g., talent, information, data), to solve problems that they could not solve as individuals [636]. There are a number of significant advantages to interdisciplinary collaboration, including enhanced access to other knowledge [637]. Collaborations occurred in this thesis through a nested qualitative study in an ongoing host trial (Chapter 5), and through the embedded trial to evaluate the effectiveness of the recruitment intervention (Chapter 6). Prior research exploring issues around embedded recruitment trials identified that while there was broad support for such studies from key stakeholders, there were concerns around challenges to implementation, for both the host and embedded trials [554]. Challenges for host trials included increased complexity and management burden; compatibility between the host and embedded trial; and the impact of the embedded trial on trial design and relationships with collaborators. For embedded trials, there were concerns that host trial investigators might have strong preferences, limiting the embedded study investigators' control over their research, and also concerns about sample size which might limit statistical power [554]. These concerns were raised for embedded recruitment trials, however these also relate equally to the qualitative study nested within REFRAMED. During the course of the work undertaken in this thesis, the author encountered a number of these challenges, which we discuss below.

### 7.7.1 *Increased complexity and management burden*

Undertaking the embedded recruitment trial raised significant methodological and logistical challenges (discussed in Chapter 3), which had to be resolved prior to implementing the embedded trial in EQUIP. By working closely within the host trial team we were able to reduce the burden of implementing the embedded recruitment trial. We also brought added value to the EQUIP trial team by providing additional resource to the host trial; this closer collaboration also expedited the collection, analysis and reporting of data for the embedded recruitment trial, thus benefitting both trial teams. This approach

recognised that implementing an embedded trial presents an additional burden to the host trial team.

In order to undertake both the embedded qualitative study in REFRAMED and the embedded trial in EQUIP, the author was required to have research contracts with the academic institutions as well as letters of access to all recruiting sites. Whilst there were processes in place to support this, this was nonetheless an additional administrative burden to the host trials.

### ***7.7.2 Compatibility between the host and SWAT***

To ensure compatibility with the EQUIP trial, The recruitment intervention and embedded recruitment trial were designed around EQUIP. There were a number of issues around compatibility. We were restricted in the method of delivering the recruitment intervention by the recruitment methods utilised in EQUIP. EQUIP used a postal recruitment method, which meant that we had to align the recruitment intervention with this. Due to the potential burden posed by patient level-randomisation, we were also restricted in the design of the embedded recruitment trial to cluster randomisation. Cluster randomisation in the embedded recruitment trial created additional challenges which had to be managed. This illustrates that to ensure the success of embedded recruitment trials, the design of the host trial and its recruitment processes will dictate to a large extent the design and delivery of the recruitment intervention, as well as the design of the embedded recruitment trial. Here, it is possible and feasible to undertake embedded recruitment trials, however there must be careful consideration of the host trial to ensure there is alignment of the embedded recruitment trial, without risking the host trial, or compromising the embedded recruitment trial too much.

### ***7.7.3 Regulatory approval delays and addition of new sites in host trial***

Aside from the challenges presented above, we faced additional challenges not previously identified in the literature. Due to delays in gaining NHS ethics permission to undertake the embedded trial, the mailing out of invitations to the first two clusters in the EQUIP trial occurred before NHS ethics approval was received to undertake the embedded trial. This meant that instead of testing the recruitment intervention in all EQUIP clusters, the first two EQUIP clusters could not be included in the embedded recruitment trial. In all

such issues, the host trial was always the priority and therefore could not be delayed whilst approval was pending for the SWAT.

The EQUIP team found recruiting adequate numbers of patients in the limited recruitment window to be challenging. Additionally, fewer numbers of recruited patients than anticipated within each of the clinical team clusters led to slower than anticipated recruitment, and meant that the EQUIP team found it necessary to extend recruitment from the original planned clusters of 24 community mental health teams to 36 teams. This created additional logistical challenges for the embedded trial. Here, additional clusters recruited were required to be randomised to the embedded trial within tight timelines; there was a need to organise the supply of additional intervention leaflets to the trial team and to assist with the packing of the trial invitation packs; and additional Research Letters of Access had to be sought for each additional site.

## **7.8 Dissemination of findings: impact**

The mere existence of relevant research is insufficient to inform evidence based practice or policy [638]. A frequent finding in health services research is the gap between scientific evidence and actual practice [639], [640]. Whilst the UK is a global leader in delivering excellent research, there are clear gaps in the translation of research findings into practice, meaning that research is not fully utilised [641]. The primary motivation for submitting this thesis in the alternative format was to ensure timely dissemination of findings to maximise their utility.

We are now in the era that Arnold Relman predicted as the ‘third revolution’ in medical care, which is that of ‘assessment and accountability’ [642], where research funders and research organisations are actively seeking to determine whether and how they are making a difference [643]. This difference has been described as ‘research impact’, and in the UK and internationally, there is an increasing requirement for researchers to describe the impact of their work [644]. Whilst the assessment of impact can be subject to distortions as well as being administratively burdensome, impact remains a measure of research quality, nowhere more so than the UK [645].

Research Councils UK distinguish between academic, and economic and societal impacts of research. Here, academic impact is defined as:

*'The demonstrable contribution that excellent research makes to academic advances, across and within disciplines, including significant advances in understanding, methods, theory and application.'* [646]

Economic and societal impact on the other hand is defined as:

*'The demonstrable contribution that excellent research makes to society and the economy. Economic and societal impacts embraces all the extremely diverse ways in which research-related knowledge and skills benefit individuals, organisations and nations by: fostering global economic performance, and specifically the economic competitiveness of the United Kingdom; increasing the effectiveness of public services and policy; and enhancing quality of life, health and creative output.'* [647]

Researchers are encouraged to engage with potential users of their research throughout the lifetime of their project and beyond. Users of the research in this thesis are patients with and without mental health problems, carers, trialists, CRNs, funding bodies, policy makers, the commercial pharmaceutical industry, and clinical and contract research organisations. Thus this thesis has the potential to make an academic as well as an economic and societal impact.

In terms of academic impact, findings from this thesis have been disseminated through open-access sources and national and international conference presentations, thus it has the potential to reach a wider audience more rapidly than a 'publish-at-the-end' approach. Tables 21 and 22 outline the publications and presentations arising from or contributed by this thesis. These have arisen through a combination of direct dissemination of findings as well as collaborating with others during the course of the thesis.

**Table 21: Peer-reviewed publications and contributions arising from the thesis**

Reference	Contribution
<b>Published journal articles</b>	
Hughes-Morley, A., Hann, M., Fraser, C., Meade, O., Lovell, K., Young, B., Roberts, C., Cree, L., More, D., O’Leary, N. and Callaghan, P., (2016). The impact of advertising patient and public involvement on trial recruitment: embedded cluster randomised recruitment trial. <i>Trials</i> , 17(1), p.586.	Lead author
Hughes-Morley, A., Young, B., Hann, M., Waheed, W., Bower, P. (2015). SWAT 26: Improving trial recruitment with a leaflet advertising patient and public involvement. <a href="#">SWAT Repository Store</a>	Lead author
<b>Hughes-Morley, A.</b> , Young, B., Hempel, R.J., Russell, I.T., Waheed, W., & Bower, P. (2016).What can we learn from trial decliners about improving recruitment? Qualitative study. <i>Trials</i> , 17(1), p.494	Lead author
Edge, D., Degnan, A., Cotterill, S., Berry, K., Drake, R., Baker, J., Barrowclough, C., <b>Hughes-Morley, A.</b> , Grey, P., Bhugra, D. and Cahoon, P., (2016). Culturally-adapted Family Intervention (CaFI) for African-Caribbeans diagnosed with schizophrenia and their families: a feasibility study protocol of implementation and acceptability. <i>Pilot and Feasibility Studies</i> , 2(1), p.39.	Conception and design of embedded recruitment trial
Madurasinghe, V.W. and Eldridge, S. on behalf of <b>MRC START Group*</b> and Forbes, G. on behalf of the START Expert Consensus Group (2016). Guidelines for reporting embedded recruitment trials. <i>Trials</i> 217:27.  *Named as group author	Contributed to consensus meetings and discussions; reviewed and commented on the checklist and drafts of the manuscript; and contributed to organising consensus meetings
<b>Hughes-Morley, A.</b> , Young, B., Waheed, W., Small, N. and Bower, P., (2015). Factors affecting recruitment into depression trials: systematic review, meta-synthesis and conceptual framework. <i>Journal of affective disorders</i> , 172, pp.274-290.	Lead author
Man, M.S., on behalf of the Healthlines Study Group, Rick, J. and Bower, P., on behalf of the <b>MRC-START Group</b> (2015). Improving recruitment to a study of telehealth management for long-term conditions in primary care: two embedded, randomised controlled trials of optimised patient information materials. <i>Trials</i> , 16(1), p.1.  *Named as group author	Provided comments on drafts of the manuscript
Waheed, W., <b>Hughes-Morley, A.</b> , Woodham, A., Allen, G. and Bower, P., 2015. Overcoming barriers to recruiting ethnic minorities to mental health research: a typology of recruitment strategies. <i>BMC psychiatry</i> , 15(1), p.1.	Contributed to matching of strategies and to manuscript writing
Rick, J., Gaffy, J., Knapp, P., Small, N., Collier, D.J., Eldridge, S., Kennedy, A., Salisbury, C., Treweek, S., Torgerson, D., Wallace, P., Madurasinghe, V.W., <b>Hughes-Morley, A.</b> , Bower, P. (2014). Systematic techniques for assisting recruitment to trials (START): study protocol for embedded, randomized controlled trials. <i>Trials</i> , 15(1), p.1.	Provided comments on drafts of the manuscript

**Table 22: Presentations arising from the thesis**

Title	Conference
<b>Oral presentations</b>	
Improving trial recruitment through improved communication about patient and public involvement: an embedded cluster randomised recruitment trial	Society for Social Medicine Conference, University of York, September 2016
The need to undertake embedded recruitment and retention trials	Invited Presentation. University of Oxford. June 2016
Trials, recruitment and mental health	Invited Presentation. York Trials Unit, University of York March 2016
Assessing the impact of patient and public involvement on recruitment and retention in clinical trials: a systematic review	3rd International Clinical Trials Methodology Conference, Glasgow, 15-17 November 2015. Abstract published in: <i>Trials</i> 2015, 16(Suppl 2):O91 (16 November 2015)
Improving trial recruitment by developing an evidence base	Grünenthal GmbH, Aachen, Germany
Recruiting to mental health trials: how can we make it evidence-based?	8th Annual Optimizing Clinical Trials Summit. Barcelona, Spain, October 2014.
Recruiting to mental health trials: how can we make it evidence-based?	Mental Health Research Network Annual Scientific Conference. Liverpool: Mental Health Research Network. March 2014
Factors affecting recruitment into depression trials: systematic review and meta-synthesis of qualitative evidence	Scope Summit: Enrolment Planning and Patient Recruitment, 4-6 <sup>th</sup> February 2014, Miami, Florida
Systematic techniques for assisting recruitment to trials (START): developing the science of recruitment <a href="https://doi.org/10.1186/1745-6215-14-S1-O61">DOI: 10.1186/1745-6215-14-S1-O61</a>	2 <sup>nd</sup> International Clinical Trials Methodology Conference, Edinburgh, 18-19 November 2013. Abstract published in: <i>Trials</i> 2013, 14(Suppl 1): O61 (29 November 2013)
<b>Poster Presentations</b>	
Advertising patient and public involvement in trials as a way of improving participant recruitment: development of an intervention and its evaluation <a href="https://doi.org/10.1186/1745-6215-16-S2-P100">DOI: 10.1186/1745-6215-16-S2-P100</a>	3rd International Clinical Trials Methodology Conference, Glasgow, 15-17 November 2015. Abstract published in: <i>Trials</i> 2015, 16(Suppl 2):P100 (16 November 2015)
Testing the effectiveness of user-tested patient information on recruitment rates across multiple trials: meta-analysis of data from the START programme <a href="https://doi.org/10.1186/1745-6215-16-S2-P84">DOI: 10.1186/1745-6215-16-S2-P84</a>	3rd International Clinical Trials Methodology Conference, Glasgow, 15-17 November 2015. Abstract published in: <i>Trials</i> 2015, 16(Suppl 2):P100 (16 November 2015)
Factors affecting recruitment into depression trials: systematic review and meta-synthesis of qualitative evidence	NIHR Trainees Meeting 2013, Leeds * Poster Prize Competition Winner
Factors affecting recruitment into depression trials: systematic review and meta-synthesis of qualitative evidence <a href="https://doi.org/10.1186/1745-6215-14-S1-P82">DOI: 10.1186/1745-6215-14-S1-P82</a>	2 <sup>nd</sup> International Clinical Trials Methodology Conference, Edinburgh, 18-19 November 2013. Abstract published in: <i>Trials</i> 2013, 14(Suppl 1):P82 (29 November 2013)
A multimedia intervention to enhance recruitment to clinical trials in primary care and community settings: process of development and evaluation <a href="https://doi.org/10.1186/1745-6215-14-S1-P90">DOI: 10.1186/1745-6215-14-S1-P90</a>	2 <sup>nd</sup> International Clinical Trials Methodology Conference, Edinburgh, 18-19 November 2013. <i>Trials</i> 2013, 14(Suppl 1):P90 (29 November 2013)

This thesis has gained local, national and international attention from a range of stakeholders. The publication arising from Study One (Chapter 4) is placed in the top 25% of all research output scored by Altmetric, the multi-platform web-tool which monitors the reach and influence of research [648]. Studies Two (Chapter 5) and Three (Chapter 6) are placed in the top 5% of all research outputs scored by Altmetric. Study Three has also been formally peer-reviewed and registered online as part of the SWAT ([SWAT 26](#)) programme [590]. The SWAT programme is identifying methods for trials about which there is sufficient uncertainty to justify research to support well-informed decision making. The programme provides a library of these methodology studies and a repository for people using the designs to log their study and deposit their findings, to contribute to meta-analyses of the individual SWAT.

Emerging from the thesis, the author was invited to meet with researchers embarking on a newly funded project on trials engagement in children [649] to help inform their project by sharing experiences and findings from the thesis. She was also invited to formally collaborate with the University of Oxford's Patient Experience Institute to develop a PPIR intervention to enhance recruitment and retention in surgical trials. Study Three is being incorporated in a systematic review being undertaken as part of this collaboration, which is assessing the impact of PPIR on recruitment and retention [591].

Findings from this thesis have also been presented at three invited international conferences to audiences comprising of commercial pharmaceutical companies and clinical research and contract research organisations. Here, several companies expressed a keen interest in the findings and methods, and resulted in further invitations, including to collaborate and to visit the headquarters of one company in Germany and one in the UK. As a result of these international presentations, the author was also invited to join the Recruitment Group of the Clinical Trials Transformation Initiative (CTTI), a multi-national collaboration of academia, funders and the commercial sector founded by the US Federal Drug Administration (FDA) and Duke University. The focus of the CTTI Recruitment Group is to develop and publish recommendations and solutions for effective recruitment into trials being undertaken across academia and industry, with support from the FDA, a major funder and policy maker.

This thesis has the potential to impact on how PPIR is done, since its findings challenge the existing axiom that PPIR will always have a positive impact on research. Conversely, PPIR is also a valid and important route to impact; however demonstrating the impact of PPIR can be challenging [650]. PPIR has been essential to this thesis. Collaboration with PPIR members ensured the success of this embedded recruitment trial, by supporting



timely development of the recruitment intervention, which allowed its evaluation. Furthermore, PPIR has supported interpretation of our findings and dissemination of results through co-authorship of academic articles with PPIR partners. Our work is a case study of how PPIR can be effectively utilised to develop and evaluate interventions. Early dissemination involved presenting findings from Study One at the Annual Meeting of the Mental Health Research Network, where the audience comprised of patients, clinicians, trial recruiters and mental health trialists, amongst others. However, there is still progress to be made in this important impact pathway. More benefit may have been derived if studies two and three were published earlier. This would have strengthened the impact of the thesis to date. Future focus of economic and societal impact will include the dissemination of findings to the HRA, CRN Mental Health, INVOLVE and other PPIR partners, using plain language summaries, in-person presentations and social media. The main challenges to future PPIR will be a lack of time and resources, particularly since the author is now employed full-time and the research funding period for the thesis has now concluded. In terms of future academic impact, findings from the thesis will be shared with the authors of the Cochrane systematic review of recruitment interventions, which is currently being updated [651].

Thus this thesis has already made significant progress in terms of academic and economic impact, with additional plans made for future dissemination.

## **7.9 Ongoing research linked to this thesis**

There are four key pieces of work which build on the findings presented in this thesis and will help to develop further knowledge in the area. The first two involve evaluating the PPIR recruitment intervention in other mental health research contexts.

Whilst the evidence from our embedded trial of the recruitment intervention indicated that it did not have a positive effect on recruitment, it is important to obtain a clearer assessment of the general utility of the recruitment intervention, and its sensitivity to contextual factors such as clinical populations, and interventions under test, setting, or time [90]. The following are future and additional directions of research emerging from this work.

There is a need to understand how context and mechanism influencing the impact of PPIR [652]. We are currently undertaking two linked embedded trials of the recruitment intervention to provide further evidence of its effectiveness in other mental health studies,

and to better understand the context and mechanism of impact. We are undertaking a third evaluation to assess the impact of the intervention on participant retention.

### **7.9.1 Assessing effectiveness of the recruitment intervention in the Culturally-adapted Family Intervention for African Caribbean people Diagnosed with Schizophrenia study**

We are currently evaluating the recruitment intervention in a study of a Culturally-adapted Family Intervention for African Caribbean people Diagnosed with Schizophrenia and their families (CaFI) [653]. CaFI is a feasibility study with strong and ongoing PPIR, and was awarded the 2014 Mental Health Research Network Prize for 'Outstanding Service-User Involvement' [654]. CaFI is a feasibility study where all patients enrolled are offered the family intervention, therefore there is no risk of patients 'losing out' by not receiving the study intervention. We have developed a recruitment intervention, using the intervention development process developed in the thesis. To optimise the intervention, we undertook user-testing of the recruitment intervention with patients and families to refine it and make it more appropriate to their context. Secondly, we are undertaking qualitative interviews with people who enrol in CaFI to explore their views of the recruitment intervention and determine its impact on their decision making. This will enable us to gain a better understanding of the mechanism of the intervention's impact, which we were not able to do within EQUIP. The embedded recruitment trial in CaFI adopts patient-level randomisation. We aim to complete this project in 2017.

### **7.9.2 Assessing effectiveness of the PPIR intervention in the Software Architecture for Mental health Self-management study**

In seeking to determine the effectiveness of the recruitment intervention across different contexts, we are also undertaking an evaluation of the recruitment intervention in the Software Architecture for Mental health Self-management (SAMS) study. SAMS is an observational study investigating cognitive decline and dementia using software and has adopted PPIR to inform the development of both its software and study design. Thus we will evaluate whether the effectiveness of the intervention varies where there is no 'risk' of randomisation. We have developed the PPIR leaflet intervention using the same process developed within the thesis for developing the recruitment intervention. SAMS adopts patient level randomisation. We aim to complete this study in 2017.

### **7.9.3 Meta-analysis to evaluate the effectiveness of the PPIR leaflet on recruitment and retention**

The purpose of undertaking the three linked studies in EQUIP, CaFI and SAMS is to explore variability of the interventions' effectiveness across different host studies. There is emerging evidence that PPIR may have a more positive impact on retention [591]. Our aim is to combine results on the effectiveness of the PPIR intervention on patient recruitment and retention.

To pool the effectiveness of the intervention across different trials, we will explore this in a meta-analytic framework, following the START model [655]. In line with the START meta-analysis model, the proportions of invited patients recruited into each trial will be entered into a meta-analysis, and the heterogeneity of the intervention effect across trials will be assessed using the  $I^2$  statistic. If there is significant heterogeneity, an exploration of the differences between trials might be undertaken to explain the variation. Due to the small number of trials, the power of any such analyses will be limited; however we will explore this issue qualitatively using data collected on the trial, the patient population, and the context of the study. A pre-specified analysis plan will guide the analysis. We plan to publish this meta-analysis. Subsequently, data will be captured and reported by the existing Cochrane reviews of recruitment and retention interventions [370][656]. We aim to complete the meta-analysis in 2018.

### **7.9.4 Development of a PPIR intervention for surgical trials**

This work is led by Mr. Richard Bulbulia and Dr. Joanna Crocker, at the University of Oxford.

PPIR has the potential to enhance recruitment and retention in clinical trials, but there have been few attempts to investigate this experimentally. The aim of this project is to develop a PPIR intervention aimed at improving recruitment and/or retention in surgical trials. The project will consist of 4 stages:

- (1) Mapping current PPIR practice in UK surgical trials through a survey and analysis of NRES data;
- (2) Focus groups with key stakeholders (surgical trial investigators, administrators, PPIR co-ordinators and patients or members of the public involved in surgical trials) to explore the needs and challenges associated with PPIR in surgical trials, perceived barriers to effective recruitment and retention in surgical trials, possible

components of a PPIR intervention, and participants' views about PPIR impact on recruitment and retention in surgical trials;

- (3) A survey of stakeholders' views on the possible components of the PPIR intervention and the importance of the identified barriers to recruitment and retention;
- (4) A consensus workshop with a purposive sample of stakeholders to determine the most suitable PPIR intervention for implementation and evaluation.

The project will lead to a robust, evidence based PPIR intervention to be implemented and experimentally evaluated in surgical trials. Other anticipated outputs include two open-access peer-reviewed journal articles, a lay summary report to be published on numerous online platforms, conference papers, and dissemination activities at surgical trial centres across the UK.

The author is involved in this project as a collaborator, and has provided and will continue to provide advice to the project.

## **7.10 Recommendations for recruitment practice, policy and research**

The findings presented in this thesis evidence a need for further research. Recommendations specific to each study have been reported in the relevant chapter (Chapters 4-6). In the following section we report overarching recommendations from the thesis overall. For each recommendation, the required 'action', key actors and a timeframe for completion are specified.

### **7.10.1 Recommendation 1: An urgent need to investigate patient centred-trial designs to aid recruitment**

**Why this is important:** It is clear from the findings within this thesis that further research is needed to explore how best to match the way patients perceive trials as serving a health need, with trial recruitment efforts. Different trial designs have been proposed to tackle some of the problems of patient preferences and poor recruitment, including patient preference and the cohort multiple randomised controlled trial designs. Such designs can be challenging to implement, however, a consequence of which is perhaps their infrequent use, particularly in the context of mental health trials. There is a need for

methodological innovation to enable patient-centred trial recruitment, particularly how to achieve greater synergy between the patients' aims and the aims of the trial. The concept of 'patient-centred trials' has the potential to resolve the issue of withholding treatment (through randomisation to non-preferred interventions) from patients who are seeking treatment.

**Action:** The ethical, methodological and practical elements of patient-centred design approaches need to be explored to take account of the patient focus on receiving the trial intervention and potentially feeling disappointed if they agree to enter a trial and are subsequently randomised to the non-preferred arm. Whilst some work has already been undertaken in this area [657], this has been limited to the context of face-to-face recruitment. Research is required from the trials community to resolve issues around these existing patient-centred trial designs. Here, findings from the thesis suggest that alternatives to the equipoise framework should be prioritised.

**Responsibility of:** Trial Methodologists, trialists, funders, ethicists

**Timeframe:** Immediately and ongoing

### **7.10.2 Recommendation 2: A focus on eligibility is required**

**Why this is important:** The qualitative study identified that the majority of interviewees had declined to participate in REFRAMED did so after determining that they were ineligible. To improve responses to postal invitations in similar trials, it is important to explore issues around patients' assessment of eligibility and to address these with recruitment interventions where such issues can be ameliorated. An efficiency argument can be made for understanding and optimising the eligibility screening process. Measures of success might include increased proportions of patients approached who are enrolled.

**Action:** This is relevant to everyone engaged in the patient recruitment process. Trialists can aim to influence patients' assessments of eligibility by exploring methods including:

1. organisational changes related to electronic patient records to estimate eligibility more precisely
2. Influencing patients' own assessment of eligibility and their judgments of their potential to benefit from the trial treatment
3. The wording of trial invitations, for example to minimise the risk of excluding themselves as ineligible.

Here, it is important to consider cost effectiveness of proposed interventions, since some strategies such as listing fewer exclusion criteria on trial invitations may lead to increase workload, through increased numbers of ineligible patients opting in, without an associated increase in enrolment rates.

**Responsibility of:** CRNs, trial Methodologists, trialists, clinical teams and other gatekeepers

**Timeframe:** Ongoing

### **7.10.3 Recommendation 3: Further rigorous evaluations of impacts of PPIR is required**

**Why this is important:** This thesis demonstrates that it is possible to rigorously evaluate the impact of PPIR. There is a need for further robust quantitative evidence to assess PPIR impact on recruitment. Whilst there may be a limit in that not all assessments of PPIR require an embedded trial design - indeed qualitative research has generated good-quality evidence about PPIR [652], [658] - a need remains for robust quantitative evidence.

**Action:** A priority for future research is to focus on the provision and presentation of suitable and effective trial information. The involvement of patients and the public in the design of trial invitation materials may refine and optimise trial communication to be more in line with how patients make the participation decision. Involving patients and the public in the design and execution of trials may also enhance both the perception and communication around the need for the trial treatment.

**Responsibility of:** Trialists, trials units, trial methodologists, funders

**Timeframe:** Ongoing, especially during the course of PPIR activities

### **7.10.4 Recommendation 4: Embedding trials of recruitment interventions routinely within ongoing mental health trials**

**Why this is important:** Despite the policy and infrastructure drive, mental health trials continue to fail [213], [659]. Very few trials are embedded in host mental health trials. We have demonstrated that it is possible to develop a recruitment intervention for mental health trials and evaluate effectiveness in ongoing trials. Whilst embedded trials can be

challenging to implement and may require additional resources, they are arguably the most important way to generate an evidence base for trial recruitment.

**Action:** Both those that are interested in trials methodology research and those undertaking trials. This is often an inexpensive way of conducting a trial and adding to the evidence base [90]. Trials should plan these well in advance of starting recruitment. One way would be to routinely embed recruitment (and retention) trials in feasibility studies or the pilot phase of trials, where the focus tends to be to obtain robust estimates of recruitment and retention rates. Trialists should build these embedded recruitment trials within grant applications, and funders should consider routinely funding these trials. This will quickly and systematically build up the evidence base.

**Responsibility of:** Trialists, trials units, trial methodologists, funders

**Timeframe:** Immediately and ongoing, with special consideration during feasibility and pilot phases of trials

#### **7.10.5 Recommendation 5: Dissemination of effective and ineffectiveness recruitment interventions**

**Why this is important:** Despite emerging evidence, the practice of recruiting participants into trials continues to be viewed by many trialists as an ‘art’ rather than a ‘science’. For example, some trial teams are reluctant to alter their recruitment practices because they ‘know’ that an intervention is effective in improving recruitment or retention, since they have used it for years [90]. Thus there is a need for a step change in recruitment practices to ensure that findings from embedded recruitment trials are implemented by trial teams, and that valuable research effort is not wasted. Here, it is equally important to highlight where interventions have been shown to be ineffective.

**Action:** There is an onus on methodologists undertaking embedded recruitment and retention trials to disseminate findings to the trial community, whether positive, negative or inconclusive, beyond systematic reviews which are updated only every five years. There is a particular role for the CRNs, which support trial recruitment, the UK Clinical Research Collaboration Clinical Trials Unit Network (UK CRC CTU)[90], [357] who deliver trials and the UK Trial Managers’ Network, whose members manage trials.

**Responsibility of:** Trial Methodologists, trialists, CRNs, UK CRC CTU, TMN

**Timeframe:** Immediately and ongoing

### 7.10.6 Recommendation 6: Retention needs attention

#### **Why this is important:**

*'Retention can sometimes seem like Cinderella, left alone and neglected in favour of the ugly sister that recruitment can turn into.'* [660]

Recruitment is crucial, however, once the patient is in the trial they need to remain in the trial in order for the research question to be answered. A focus on participant retention is therefore equally critical. Trials with greater than expected attrition are underpowered, have limited impact and may even be unethical. If attrition is not at random, especially in trials aiming to demonstrate disease modification, outcome data analyses may result in erroneous conclusions.

**Action:** Trialists and trial methodologists. This is often another inexpensive way of conducting a trial and adding to the evidence base. Trials should plan these well in advance of starting follow-up. Trialists should build these embedded retention trials within grant applications, and funders should consider routinely funding these trials. This will quickly and systematically build up the evidence base.

**Responsibility of:** Trial Methodologists, trialists, funders

**Timeframe:** During the planning stages of a trial



## 8. Conclusions

---

- Mental health trials are a leading cause of disease burden, giving rise to a need for new interventions that have been robustly evaluated in the context of randomised controlled trials
- Recruiting participants into mental health trials is known for being ‘notoriously difficult’, highlighting a clear need to improve participant recruitment. A key criticism of the existing literature is the absence of scientific evidence for trial recruitment
- A key policy drive in the conduct of trials in the UK and other developed nations is PPIR; however little is known about the impact of PPIR, and there have been increasing calls to assess its effectiveness through robust methodological research
- This thesis adopted the MRC complex interventions framework to systematically develop an intervention for recruiting patients into mental health trials
- A systematic review of factors affecting recruitment into depression trials was undertaken, which led to the development of a meta-synthesis and conceptual framework. This identified that ‘risk’ was a key factors in the decision making process for patients and suggested that PPIR may have a role to play in reducing the perception of risk
- We undertook a qualitative study to understand the decision making of patients who had declined trial participation. The process of the decision making was mapped. This identified that patients who declined the trial were not necessarily rejecting the trial, and that such individuals may respond to recruitment efforts in the future, particularly where such efforts focus on patients’ assessment of their own eligibility or on their mental health needs.
- Using Participatory Design methods, we developed a recruitment intervention which involved advertising PPIR in a trial. We evaluated its effectiveness in a large trial embedded within an ongoing mental health trial. We found this intervention to be ineffective for improving recruitment for all outcomes measured
- The research in this thesis identified other mechanisms which can be used to develop other recruitment interventions
- We discuss the lack of effectiveness in the recruitment intervention and hypothesise about possible causes leading to the lack of effectiveness, using the format for process evaluation of complex interventions outlined by the MRC
- We discuss dissemination and the impact of findings to date

- Further work is currently underway to assess the effectiveness of the intervention across different contexts, and to understand the mechanism of impact
- We make recommendations for future research and recruitment practice

## 9. References

- Kleinman, M. W. (1987). *Educ. Res.*
- Kleinman, M. W., & Kleinman, M. W. (1987). *BMJ*
- Morgan, T. J. L., & Morgan, T. J. L. (1987). *JAMA*.
- Kleinman, M. W., & Kleinman, M. W. (1987). *The Lancet*
- Fergusson, D. M., & Fergusson, D. M. (1987). *PLoS Med.*
- @# (1987). *BMJ Br. Med. J.*
- † = \ @ U = † = \
- U h † h o o U U KU U k h k 8  
V Lancet
- ) = V ) = O
- 7 h u k ) oU @ uk Text
- ) " h Philos. Q.
- ° h Diagnostic and statistical manual of mental disorders :  
DSM-5 † h
- ‡ = \ International Statistical Classification of Diseases and Related  
Health Problems (International Classification of Diseases)(ICD) 10th Revision
- # o - # k - ) U k " o = ° -  
Transcult. Psychiatry
- ° " ) U @ h @ Midwest Sociol.
- k U U = U @ o h ) #

7 *Philosophy of Science*

) 8 o *British Journal of Psychiatry*

) " # *J. Ment. Health*

K# ‡ u *World Psychiatry*

" K) u *Clinical Psychology Review*

h ° u *Sociological approaches to mental illness.*

Mo M - U h @ *Am. J. Psychiatry*

k - M u *British Journal of Psychiatry* 7-

V 7 " U *J. Eval. Clin. Pract.*

° h ° ° @) °) oU *American Psychological Association*

h u ° ° °) oU °) *Adv. Psychiatr. Treat.*

h 7 " " K U °) ° O °) K# h *Schizophr. Bull.*

u @ " # U 8 k = °) ° h Mj # ° h ‡ k k) # *Am. J. Psychiatry*

" V # u k @ u k) # *BMC Med.*

= ° ‡ °) K k ° K " ° K 7 = - - 7 K # k - V °) 7 V K k " # K O U u † 8 8 " °) o *Lancet*

V # # U = °) u V@- # 8 V @ = # - O

U k °) *Br. J. Psychiatry*

° h # " U k ° O U O o *Soc. Psychiatry Psychiatr. Epidemiol.*

V # # U = h  
NICE 7 7 # 8

K'h K'o o@o MIM - @ o'h u'h  
u = K = u'M u = o'M K'O  
O @ Arch.  
Gen. Psychiatry

‡ = \ ) 7  
<http://www.who.int/mediacentre/factsheets/fs369/en/> ‡ =  
\

° K'7 ° K'o ° K" k'V o" h u't = °  
‡ 8 Psychol. Med.

) K'o " @V " # ) U - y = K- K'U k'8 " k K'  
8 ) U U = @) V # K'h'h h yM"  
# PLoS One

= ° ‡ ° K'7 O) † 7 u't u  
PLoS One

o'o ) # K'‡ K'U 8  
PLoS Medicine

K" M ° - u K# # U ) K K" k U U  
h" K @ PLoS ONE

° K'7 7 K# k - V o" h 8 7 # K'OU u't  
= ° ‡ " ) ) # o °  
7 8 " ) o PLoS Med.

# K'OU ° O The Global Burden of Disease: a comprehensive assessment  
of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to  
2020 8 ‡ = \ = o h  
=

o # ) ° k # U \ h U =  
h @ Cent. Ment. Heal. U

h U # o) ° h U M o'O o h  
Br. J. Psychiatry

‡ k = K o K \ ° k k o  
Eur. Neuropsychopharmacol.

o" U M # U = @ u  
Br. J. Psychiatry

# U u" k 7 t h o h o  
# Br. J. Psychiatry

o - y " #  
o - y

\ V o - K U

M † V M o  
yMV # @ o Br. Med. Bull.

M ° h O = # U  
International Encyclopedia of Housing and Home

U # ° o ) h  
Acta Psychiatrica Scandinavica

# = h † MO 8 u U  
# Br. J. Psychiatry oyhhO

‡ = \ Mental Health Action Plan 2013-2020 8 ‡ =  
\

U 7 Birth of Biopolitics (Michel Foucault: Lectures at the College De France)

K U o u u  
V@- ° ) =) Anthropol. Med.

# K ) = @# ° U # " @ #  
#) Cochrane Database Syst. Rev.

o K h K U M K k - 7 k o M k O #  
Br. J. Psychiatry

o O ° # O o ) U ) a 7 k U o # " k  
k - K k 8 ‡ M U h o " O 8 o K U )  
# Lancet

° 7 o # ‡ MU # ) ° h ° K  
# ‡ J. Affect. Disord.

- K h K V = K K U 8 o o U @ K † K  
U Schizophr. Bull.

Ukro = K - U ‡ hU uM  
BMJ

Ko ‡ o # O= " K° # U K°U ‡  
h  
Canadian Journal of Psychiatry

Kk8 oU # # ) u° 7 ) KM - 7 8 U  
8 k  
Lancet

MuU 7) ) Oh K- # h  
Annu. Rev. Clin. Psychol.

) U " " Qual Saf Heal. Care

KO A Treatise on the Scurvy: In Three Parts, Containing an Inquiry Into the Nature, Causes, an Cure, of that Disease, Together with a Critical and Chronological View of what Has Been Published on the Subject. O #

U k # # Lancet

K7K# O Med. J. Aust.

° O # Effectiveness and efficiency: random reflections on health services  
O k o U h

@# u  
Treating  
individuals: from randomised trials to personalised medicine h k O

) Oo ‡ U k \ Heal.  
Econ

8 = 8 - ACP J. Club

o- o ‡ o k h 8 k " = Evidence based medicine:  
how to practice and teach it # O

k " = h K) 8 = 8 #  
Evid. Based Med.

o- o ‡ o k h 8 k " = -  
- " U

" u = V h O Oh = V u O V = ° u ) V U ‡ = V u =  
u = 7 k V M° ) = V u = M = k  
u - " U ° K k U  
h ) PLoS One

k h - ) V ° k " ° U #  
J. Eval. Clin. Pract.

- " U ‡ 8  
 JAMA

K‡ u Adv. Psychiatr. Treat.

k O U 7 u Med.  
 Hypotheses

K 8 \ Evid. Based. Med.

o U O @ 7 o U # o @  
 ‡ British Journal of Psychiatry U ° k#=

K 8 - Evidence-based practice O  
 u o k - " o O

u o @# u yM# # V=o#  
 V=o k )  
 Heal. Econ

) = j V=o )  
 = O

K " ‡ = U #

o o U k # -

K ° # - = ) K u h  
 Bmj

k # - Nurse  
 Res.

U k o o O = K O - u K M 8 O o O h o k ° #  
 7 o @ U # o  
 J. Contin. Educ. Nurs.

U ) ‡ o h 8 ° # K U M = 7  
 h " K \ o BMC  
 Med. Educ.

‡ = \ @ U = ‡ = \

# h k u  
 Health:

U h M @ = K = u 8 u  
 BMC Med. Ethics

u 8 K = V U -  
 Bmj



Khoo @ † PLoS Med.

u8 † J. Prim. Health Care

Khoo @ - " U = " = " k )  
o J. Clin. Epidemiol.

K8 o # k Canadian  
Journal of Psychiatry

Khoo @ - " U = " = " k )  
o J. Clin. Epidemiol.

7 V " 7 k " ) = =  
Intern. Emerg. Med.

) K# k K 8 = 8 # K #  
= k # # 8 J Intensive Care Med

† o k U # † K V k o = u  
Am. Coll. Physicians J. Club

† U k K) O k o 8 ) ) o @  
J R Coll Physicians L.

Kh # = K) k U u #)  
Cochrane database Syst. Rev. Online

K- Ko h 7 u u  
Fam. Med.

8 K K U ) u M U \ " ) \  
7 Cochrane  
Database Syst Rev #)

h" k k M# u O -  
" U Plast Reconstr Surg

u U † k u -  
BMC Med. Res.  
Methodol.

K h u = o 8 # = o k  
@ † U u # #

) u # K # o Experimental and quasi-experimental designs for  
research # @k U V #

# u 7 h = - u  
# u 7 h = - Can Med Assoc J

h'8 K'h† @#  
Bmj

8 = 8 ) 'O'o K# o k = ) K# k K# y  
JAMA

y o h o u 7 y d u 7 8 y o h  
o u 7 † † "

V=Uk# # # #u

K) M† k o K8 V † U M =  
J. Clin. Epidemiol.

o @8 V o @8 V o @8 V

\#-"U u \ O - \ # - "

V@- V@- 8 ) U V @ # -  
O

o † o - # O o k u 8

= ) O

8 u " " k  
Am. J. Occup. Ther.

" " o " ) " 8 U ) U M V M U  
U V Mk † k U o † o = u "  
† h u h k # )  
h \ u Ergoscience

# K" Randomised Controlled Clinical Trials o V ' o yo

U U O 8 o Hematology/Oncology Clinics of North America

k M 8 - † ) \ k  
Cochrane Database Syst. Rev. Uk

# k ) u k Bmj

M 7 o ) 8 "  
Lancet

" o U k y †  
BMJ Br. Med. J.

) O o † U # k K U 8 k " = † o k  
Br. Med. J.

= o u # # = K o k  
*Am J Med*

o " † u k#u  
*Bmj*

# † # U k# *Bmj*

V @ = V@

# @ = k # u *Canadian Institutes of Health Research*  
 K \

† = \ u † = \

yM# k # yM= k

) "

u o 8 ) @ k o  
 8 = o # k o

= @U ) = U U o # o " h 8 # h - k )  
 u U k yo @ # *J. Am. Med. Assoc.*

= V Kh " @ = *Annu. Rev. Pharmacol. Toxicol.*

= V o ) @ *BMJ*

U ) U " k # h - U k # *Int. J. Pharm. Healthc. Mark.*

V @ = k 8 V@k

V @ = k @ *Website* \
 K

M 7 o @# k K = ) 8 -  
*JAMA*

) U k K 8 V U h h u o †  
*Control. Clin. Trials*

) U k K h u  
 # *Int. J. Technol. Assess. Health Care*

M = U h K # K U - j  
JAMA

# " U # o - k = ) U @ \ k h ) k M7  
o ) o ) 7 o @  
u # \ Vo \ ku JAMA

) U M7 o ) ° # 8 u # \ Vo \ ku  
k JAMA

M7 o ) 8 ° ) U # \ Vo \ ku o  
Br. Med. J.

U M# ) k - ) 8 ° # \ Vo \ ku  
Bmj

U M# 8 h ) k - ) 8 ° #  
Bmj

U - o u K 8 ) ° o u " = ° \ )  
U @ # \ Vo \ ku  
BMJ.

O u O o ) 8 ° M7 o ) U )  
# \ Vo \ ku o #  
Syst. Rev.

k U " ) U = h o M h  
Journal of Clinical Epidemiology

8 ° k  
BMJ.

U o o h Br.  
J. Psychiatry

K 8 7 K U u K  
Perspect. Biol. Med.

o 8 h † @  
Br. J. Psychiatry

h # h ) o U o U @ V U h )  
U k #  
BMJ K

K 8 u  
Adv. Psychiatr. Treat.

h # u ° 7 Mo U = = @ M @ ) U #

† = k # j  
J. Affect. Disord.

" u # #  
BMJ \

K U # - # j # u  
o \ Schizophr Bull

# u u # U ClinicalTrials.gov \  
K

@k#uV @k#uV BioMed Central \

# O # # k # u #-Vuk° O Cochrane  
Library \

o 8 h " U M # ) k - k  
BJOG

) U # o ) 8 † o  
JAMA

U M V ° h h Nat.  
Methods

M o " K h @ # U " V K 7 - o K k U k  
U h  
Nat. Rev. Neurosci.

o k K Emerg. Med. J.

# h 8 k U = = U M k  
Ann Int Med

K 8 @ Principles and Practice of Clinical  
Trials - = K 7 - - # O

K " k O † 8 U  
Biometrics note

K 7 # † \ † ) 8 † o 7 " # M h  
Stat Med.

# - @ h  
Cutting Edge Information \  
K

# † h @ @  
Global News \

° K

V = yM Bmj

U M# #o ) 7 ) - U U ) k M †  
 - K8 @k 8 k  
 u ou-ho Health Technol. Assess.  
 (Rockv).

" 8 o o° K KV yM  
 Trials

" M - - K' " 'u k'o u  
 " KKU U o M \ u @V # O U  
 7 oU U ) U - ) " K † @7 8 7  
 O ° V † 8 = k O U k k o - o  
 o o Æ h \ † " # K U † " " U  
 o O 8 = = # " 8 = 8 U " h  
 JAMA

# † State of the Clinical Trials Industry 2009: A Sourcebook of Charts and  
 Statistics # †

h " † # " # 8 o u # u o " ' h  
 † @

k 7 Kh ° ) " ) o † V O " ° O O  
 † h U =  
 Fam. Pract.

° U U ) k # M U M# † - ° U 8 K # ) k  
 - ) 7 K8 @k # o † yM  
 Trials K

M" O) #  
 BMC Med. Res. Methodol.

° " h @ o

) 7 # U ) -  
 Journal of Clinical Epidemiology

k o° † - U ° @  
 Am. J. Drug Alcohol Abuse

# 7 M) h  
 Journal of Health Services &  
 Research Policy

y o " h o° \ " k

*Psychiatr. Bull.*

M" u k *Family Process*

# K' = O'U o 8 ) # *Med. J. Aust.*

M° h° ° K'V k - # O k *Gerontologist*

K' = ° U U k k 8h *Prim. Health Care Res. Dev.*

V U † U ) h" MO ) k # k *Psychol. Med.*

K' = O o @u - u 8 ) † k#u *Contemporary Clinical Trials*

° † # U # o O = " *BMC Psychiatr*

K † h 7 U " # † k #u #u *Contemp Clin Trials*

K' 8 # o # \ ) *Int Clin Psychopharmacol*

- = k *Pharmacopsychiatry*

u M h 7 ° M K ) 8 7 u *Homeopath. J. Fac. Homeopath.*

= U o M k M U *Australas Psychiatr*

U O o 7 " † " U K y u 7 " † K' 8 = -#u O *Int J Geriatr Psychiatry*

\ " - # o \ # @ *Int J Geriatr Psychiatry*

O" V # = 8 MJ 7 k *Journal of Telemedicine & Telecare*

M" U V ‡ V ‡ k \ " " U  
 ) k O O Arch. Psychiatr. Nurs.

M\ ) = k " 8 ° 7 h 8 k = U ° ‡ K  
 V K \ " K h u O k @ O V  
 u U "k@ Vu  
 Pilot Feasibility Stud.

8 u # ° 7 ° 8 " 7 # k # k U  
 - k Br. Med.  
 J.

o o k # h 7 K"  
 Health Technol. Assess.

† ‡ k - # k # # u  
 ) ) # Public Engagement and Clinical Trials: New Models  
 and Disruptive Technologies - Workshop Summary

U = 8 O # V h  
 J. Epidemiol.  
 Community Health

" o V u O u K # 8 O V ‡ M u  
 h Fam. Pract.

K k O ‡ ‡ u) " h  
 American  
 Journal of Psychiatry

° 7 K # U M ° K U h  
 Psychol Med

U - - ° ) U 7 ° = 8 M k o # 8  
 ‡ ‡ ‡ 7 Psychiatry Res.

) u K U V ‡ O u u K h k - ) o 8 O  
 @ Br. J. Gen. Pract. @

o U k o k † o † k U O U M k k  
 American Journal of Psychiatry

o k ° 8 # # ‡ 8 @ k k h "  
 J. Clin. Epidemiol.

8 O o " Ethn. Dis.



8 " U U h " † † " Int J Methods Psychiatr Res

o 8 V ) MV o k " 7 U k h @ Am. J. Public Health

# = K - " " K ) V h K - ) O U M † h M o Contemp Clin Trials

" 7 o 8 ) U o † o ) @ Bmj

# † = O U " 8 h 8 h o International Review of Psychiatry

8 " U U h " † † " Int. J. Methods Psychiatr. Res.

O † U # o # = " k BMC Psychiatry

o † # U # o O = " BMC Psychiatry

U U U O † o U U MV M h Hosp. Community Psychol.

h † # ) O h ) u J. Ment. Heal.

h # = Am. Psychol. Am. Psychol.

V k U # h † # U # Eur. Psychiatry

U # = U u Acta Psychiatr. Scand.

O = - 8 K = o O † # J. Cross. Cult. Gerontol.

@ 7 = # # o ) k " - o Contemp. Clin. Trials V

# U # " o o " = V O 7 #

Alzheimer Dis. Assoc. Disord.

@

O# "KU 8 -Oh k# M †

Journal of the American

Academy of Psychiatry & the Law

) O" U o U - U u † † K - † =  
- h # o

) Dement Geriatr Cogn Disord

° 7K ° - M h ° K = # " k h h U

Med. J. Aust.

o K" O † k O o U h # U K -u M"  
‡ ‡ J.

Gen. Intern. Med.

U @\ V h V # ) 8 =

Br. J. Psychiatry

M" o o o = o h 7 U 8 7 yMo

Br.

J. Psychiatry

# U k U 8 = = " MU h 7 h

Br. J.

Psychiatry

# U h ) MU h K 8 = K O k Uykk°' h  
7° k\ V 7 -o\h

World Psychiatry

K 7" U K = V h ) k k † † O h

Gen. Hosp. Psychiatry

- = ° k y U @ h # h V  
= - # # Arch. Fam. Med.

MM ° u † ° K) u - \ @ # @  
h ) u U ) h # ° # k

O Psychosomatics

Uk# U k # k U = k k o  
k 8 U k #

k U † " O # u k " o ° U † V@

J. Womens. Health Gen. Based. Med.

‡ u # k k # o

Schizophr. Res.

7 # U K'o k U k ) k u † k - o h " " ) U Psychol. Med.

h # † u K 8 KU O ° # j # ° # kk " KK M K ) Archives of General Psychiatry

k U N. Engl. J. Med.

K U \ o = o K ) h V " # Arch. Gen. Psychiatry

) † K # ° ) " † h U Schizophr Bull

O ° ho k # Archives of General Psychiatry

U ° O O 8 ) J. Am. Geriatr. Soc.

K - " o # k Cogn. Emot.

# - # Arch. Gen. Psychiatry

O ) O h K ) h K 7 ° O u J Nerv Ment Dis

K o - U 7 " ) K M # = " k † 8 O " ) # J Nerv Ment Dis

= y † 7 K o Eur. Neuropsychopharmacol.

k # M " K # K 8 8 K \ M ° U O M k U U h ) o h OKk K o = y † ° U - u Depress. Anxiety

u † - † k h U ) - V † # = k O o 8 au @ o \ V ° k - Vu \ V h u k - k u " ° k V - o # " - V # = = U @ ) O u \ V V † k @ = u o h u - ko \ V † o = V ° = V V o - @ - † k @ = u # 7 k ) # Br. J. Psychiatry o

h 7 " h Journal of Clinical Psychiatry oyhhO

" ) O K'Oh @ h  
*Schizophr. Bull.*

U - # k @=  
*Br. Med. J.*

° M O† k K'O" @  
*Ethics Behav*

- - u = † V # U K'o K k  
k h # - k k  
y h = *J. Consult. Clin. Psychol.*

K° U U # " Mo'h ° V " MO† "  
k Acad.  
*Psychiatry*

# †  
*Stat Med*

K'U † ) K'u @  
*BMC Med. Res. Methodol.* K

o ) = K = u M K° " u  
*JAMA*

) " = # ) K'Oh k  
*Control. Clin. Trials*

o o o )

K'o u M° U M O'o h  
k o O # u u (EV) \ o o - *Control.*  
*Clin. Trials*

k " 8 h ° # K  
*J. Clin. Nurs.* K

u " y  
*N Engl J Med*

u " ) " ) O 7 O o  
*Nephrol Dial Transpl.*

U 8 Ok @# o U ) ) ) k " U O k  
o h *BMC Med. Res. Methodol.*

h U k u @ - †  
u *Lancet*

U - # k @=  
*Br. Med. J. (Clinical Res. Ed.)*

= 8 # † o u M k 7 - JAMA J. Am. Med. Assoc.

8 k ) 8 u k Alzheimer Dis. Assoc. Disord. oyhhO

o" Ku # " u O 8 V h U = K 7 8 O k † - " ) Cancer

U - u U U = k o h V † = U # 8 o K K 8 o \ U M - ) h - # ) @ Age and Ageing

U M # # o ) 7 ) - U U ) k M † - K 8 @ k 8 k u ou-ho Heal. Technol Assess

U k V " V " - = k " O † k # u J. Heal. Care Poor Underserved

" 8 ) 8 h h = ) M h M - 7 ) h @ @ Clin. Trials

V @ = V@

o - u k k # k k M h @ ) Soc. Stud. Sci.

U K U U U ) k o 8 @ Igarss 2014

K = K Bad Blood: The Tuskegee Syphilis Experiment V u 7 h

= " o # k u J. Health Serv. Res. Policy

8 O u O 8 Ku o" # " k 7 † U † = U # 8 u h u V k h Clin. Trials

K 8 7 U † = 8 O u O 8 o" U # 8 Ku # " u h u k 7 † " Cancer

K M # M " o # 7 U ) # U M U U O M

o K j h M 7 ‡  
*Transl. Behav. Med.*

) k - U @o " O 8 8 j  
*Contemp Clin Trials*

) \ = - = k V @ =  
k ° k # # h #\@ =  
) =

V @ = k V@k  
# O # ) = k ) o ‡ ° O - O U " J.

*Clin. Epidemiol.*  
) O o " *J. Chronic Dis.*

K k h " ) # o - K 8 ° M h M ° = U  
# o V o o  
α ku *Trials* o \

K " o o # U M o o = U = " u  
h @ \ U o

@ † \ O - )  
o k ° *J. Am. Inst. Plann.*

K j u ° U # u U  
*Health Policy (New. York).*

K " k u # # #  
*Health Policy (New. York).*

K ‡ K " @ *Issues in Mental Health Nursing*

) k h 7 h o h  
*Int. J. Soc. Psychiatry*

- 7 # *The consumer and the health care system: social and management perspectives* = k K U o O - V o

K @ o ) o k hh@ h J  
*Med Ethics*

K " k u # # #  
*Health Policy (New. York).*

) 8 i O 7 7 k U # u #

u # h # k Res. Nurs. Health  
U h 8 U ) ) O o K 8 U o h U k k  
O 7 h 8 = h 7 O @

*Int. J. Technol. Assess. Health Care*

V @ = k 7 h @  
Funding \

Mo o M- V=o  
@ \ O -

† - U K k o K 7 u O O  
Bmj

Mo - @ h V=o  
V @ = k -

u ) ) U " K @ " h - O 8 \ )  
h k 8 k = V

*Health Expectations*

8 V K \ M 8 K O V U † U  
h k o = U \ h  
# o Am. J. Community Psychol.

h † - U K M - U V # 8 = 7 h o  
o o M ) U U # o h k h  
h \ k u k ° hh \ ku Heal. Serv. Deliv.  
Res.

K " o o # U U  
Heal. Expect

K " o o # U o = U K = # u k  
o o o k @ h h @  
o y k # Patient

K " o o # U o = U K = # u k  
o U  
Heal. Expect

K h ) 8 h u - - † U V V o h  
BMC Heal. Serv Res

- V = U U K o \ \ U  
k Cochrane database Syst. Rev.

#)

O - u † @  
Br. J. Psychiatry

=  
o

@ U\k@ V=o= k  
 = k h  
 k # 'OU \ " 'o'O 'o'o ‡  
*Qual. Prim. Care*  
 K\ 'k'U 7  
*BMJ Qual. Saf.*  
 o'o 'k "' 'h "' 'O"' 'K"' )  
*Int J Consum Stud*  
 K'O 'u = '@ = 'o"' ) 'o ) 'h '@  
 'k 'k 'k 'k )  
 j 'k *Public Health Genomics*  
 h "'  
 O'7 '8 = 'V M 'h 'U  
*J. Clin. Nurs.*  
 O'7 '8 = 'V M 'h  
*J. Clin. Nurs.*  
 o'o 'K"' #'U 'k"' 'u '8k@h  
*Int. J. Technol. Assess. Health Care*  
 - K #' k  
*Int. J. Consum. Stud.*  
 h U ‡ 'h 'y M 'o  
*Heal. Soc. Care Community*  
 Mo '@ 'U  
*Res. Invol. Engagem.*  
 Mo 'o "' '= = 'U u u  
*Heal. Expect*  
 V - ) "' -  
*J. Health Serv. Res. Policy*  
 - O 'U - - 'U  
*J. Comp. Eff. Res.*  
 V ) o 'K'h ) '8 '8 K'h 'O - ‡ 'u ° - 'U  
 V h  
*Heal. Expect*  
 - O 'U - - 'U  
*J. Comp. Eff. Res.*



# U o o 7 8 o = U u  
yMV=o Int J Qual Heal. Care

) - h - V=o  
Pract. Evid. Policy A J. Res. Debate

K" o o # U o = U K= # u U  
Heal. Expect

k " K" 8 h #  
Heal. Expect.

8 k O K 7 h h U 7  
Sci. Technol. Human Values

U 8 U t o K 8 k K U M 7 o ) U  
7 " K 8 7 # 8 # 8 # 7 # 8 U U 7  
U - U o V ‡ 7 h " U h = V o V  
o U k o V O o K k u ) K t t - 7  
- K" o  
h Heart Fail. Rev.

o u ) 8 ° h " U # @ # o # h # )  
# h ) ) U  
u 7 Trials

k K h # - # o k k ) 7  
Health Technol. Assess. (Rockv).

h " † " # 8 o u # o " † h †  
@ Trials

" ° " = O O = 8 u † V U  
J. Womens. Health Gen. Based.  
Med.

8 U u u Nurs. Res.

# k " M = h # K V U #  
Semin. Oncol. Nurs. V

- o 7 M O † Patient Educ  
Couns

h " h † - † K 8 K U " ) O M  
@ Fam. Pract.

h " h † - † K 8 K U " ) O M

@ \ *Fam. Pract.*

k 7 Kh ) " ) o † VuO † ) " O O  
† h U = *Fam. Pract.*

7

K U † ) Ku @ *BMC Med. Res. Methodol.*

K U ) - @k o *Cochrane Database Syst. Rev.* Uk K

h = ' # o = u K # # o *PLoS Med*

o u h O U h K ° # U M U K u Mu  
7 U o o † # K k K - ) U U  
#  
*Bmj*

h V M " = u *J. Clin. Epidemiol.*

O u O @ " @ *J. Med. Ethics*

° ° U 8 U U 8 8 U h U M # U ° U 8  
u  
*Clin. Trials*

† † ° ° = U ° † 8 ° h " \ *BMC Psychiatry*

o Ky " o h # h 8 k *J. Gen. Intern. Med.*

h = ' # h V " K # # h *J. Pediatr.*

@V U K ° ) K O ) o - *Qual. Prim. Care*

K U k k ) U K k 8 @ *Cochrane Database Syst. Rev.*  
Uk

@K † h ' U u -k o

k *ABNF Journal*  
 # u o = = U # K" h ‡ u *Trials*  
 h " h ‡ - ‡ K'8 K'U " ) O'M *Fam. Pract.*  
 @  
 K' - ) U @8 k o *Cochrane Database Syst. Rev.* U k  
 K'8 h " - ‡ h ‡ " ) O'M ) # K' *BMC Med. Res. Methodol.* K  
 U u k  
 K'k K'8 h'M V o ) K# o - o *Trials.* ou' ku  
 7 # ) 77 U = o K *J. Health Care Poor Underserved*  
 ‡ V k K' ) O" u ) o M'k o *Soc. Sci. Med.*  
 U  
 O7 *Hum. Relations*  
 k U 8 k " # U h # y *Public Opin. Q.*  
 @° *From intentions to actions: A theory of planned behavior* o  
 8 h j # O'h M" 8 † ) # " h u'k *J. Cancer Educ.*  
 o # \ o - K'† # ‡ 8" O  
 O ‡ 8 U ‡ M *Health promotion planning: an educational and environmental approach* U † #° U h  
 ° U U ) o u = o # 7 k M # o U M# *Trials*  
 y  
 k ‡ k o'h ) h  
 o - O " k O h 7 ‡ u *Recruit. Retent. Minor. Popul. Lessons Learn. Conduct. Res. Heal. Promot. Minor. Aging*  
 ) 7 @k ) k - = o k # M K'8 # o †

U U ) U 8 U M# U  
*Trials* K

MO 7 u - Am J  
*Sociol*

o" ‡ V ) 7 = U - 8 " o = 7 o  
7 k k o *Ethn. Dis.* K = o

u # " @ # u † - *Psychological*  
*Foundations of Attitude* 8 8 u # " u U \ - V  
h

# K 7 - = k M o k MU ) )  
*Contemp. Clin. Trials* K

K \ h ‡ 7 † u  
*Am. J. Heal. Promot.*

= - h *Interpersonal relations in nursing: A conceptual frame of reference for*  
*psychodynamic nursing* V " 8 h h o

o h U " h U # - 7 @  
h  
*Nurs. Sci. Q.*

O" ) V - 8 @  
*JAMA J. Am. Med. Assoc.*

@k ) h o " 7 K ‡ 8 O -  
U k # # k ° o = *Lancet*

K 7 " " " " *Reinventing Patient Recruitment: Revolutionary*  
*ideas for clinical trial success* h #

@° U 7 @° - ° u 7 u # u = - \ k ' \ 7  
k - ° o \ V - ) # u @ V u = - \ k ' \ 7 h O V V - ) - = † @ k *Soc. Psychol. (Gott).*

@° u *Organ. Behav. Hum. Decis. Process.*

8 h j # O h M" 8 † ) # " h u k  
o # \ o - K † # † O  
*J. Cancer Educ.*

# K ° U #  
*Br. J. Soc. Psychol.*

O 8 k M o k - = \ \ ) O 7 # 7 y  
*Trials*

U 8 = - yM Research methods in health: investigating health and health services

) = k u Qualitative research methods in mental health and psychotherapy: A guide for students and practitioners K ‡ o

\ h Int. J. Soc. Res. Methodol.

U o o h Choosing methods in mental health research: Mental health research from theory to practice k

o U # U O K M j K U u Qual. Health Res.

u o M u o

- 8 8 o O # Handb. Qual. Res.

U = u - \ V k h o o Life Sci. J.

# u 7 U U o u ‡ - J. Mix. Methods Res.

V " o M 8 The Practice of Nursing Research: Conduct, Critique, and Utilization o O - o

) 7 h # u " h = Essentials of Nursing Research: Methods, Appraisal and Utilization - h O ‡ ‡

o h j Evid Based Ment Heal.

" o U # o Soc Sci Med

- 8 8 o h o O Fourth Generation Evaluation # O V )

U ) ‡ o " ) K o @

V U # h j Bmj

' o O - 8 8 - u Naturalistic Inquiry

o o Educ. Inf.

U j h - Health Serv. Res. h

8. U # U " U J.  
*Adv. Nurs.*

U = @ = " Qualitative Research Methods u \ #°  
o

k - # u 7 ) O k -  
*Br. J. Clin. Psychol.*

h U h † *Qual. Health Res.*

O 7 \ *Qual. Health Res.*

O M k *The American journal of occupational therapy.: official publication of the American Occupational Therapy Association*

K k " 8 h k = o k *Qual. Health Res.*

o V = " h O *The Practice of Qualitative Research* u \ #°  
o

U ) *Nurse Res.*

O 7 " 8 *Reflexivity: A Practical Guide for Researchers in Health and Social Sciences*

M V O ) U o = *Heal. Serv Res*

° \ # - U K V † *BMC Health Serv. Res.*

U " U ° U = ) u *Educ. Res.*

# = j *URL <http://tinyurl.com/bmztxp8>*

U = u h † *Br. J. Sociol. Educ.*

V O 8 u h † u ° = o k *Educ. Res.*

° u # u U #

M k = *Educ. Res.*

U j h *Qualitative evaluation and research methods* o 8- h

8 " k " O † V #  
*Eval. Rev.*

K † # *Research design: Qualitative, quantitative, and mixed methods approaches* O

° " *Quantity and quality in social research* O k

K # 8 † K # † 7 8 u  
*Educ. Eval. Policy Anal.*

° u # u *SAGE Handbook of Mixed Methods in Social & Behavioral Research* O

K U U h  
*Handbook of mixed methods in social and behavioural research*

° \ # - U K V u  
*BMJ*

K # 8 † K # † 7 8 u  
*Educ. Eval. Policy Anal.*

8 " k " O † V " "  
*Qual. Quant.*

# u ° u # # # # U U  
k k # @ # 8 # *Am. Behav. Sci.*

° K \ k " K u † @ U k *Res. Sch. Mid-South Educ. Res. Assoc.*

U k # *A framework for the development and evaluation of randomised controlled trials for complex interventions to improve health* O  
U k #

k u M ) † o #  
*J Clin Nurs*

° U # †  
u *Soc. Sci. Med.*

- U o u # h ° U 7 O " # ) u 7 ° M  
7 U # \ ) V  
*BMC Med.*

h = ° o u k #  
*BMJ Br. Med. J.*

" " U J.  
*Adv. Nurs.*

K) U h # BMC Public Health

# k ) Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care #k) y

k ) o V O U Control. Clin. Trials

) ‡ o ) U a-s J. Adv. Nurs.

U h = k Systematic Reviews in the Social Sciences U U

8 ‡ V k ) = Meta-ethnography: Synthesizing qualitative studies o 8- h @

) U O K u ) 8 ° 8 h k @ U ° h h k @ U ° ° BMJ

K " # K 8 U o K U h 7 h O K # u West. J. Nurs. Res.

o U O u # ° o Health Libr. Rev.

° " o Syst. Rev.

U o @ o K U 8 @ 8 8 y U - ) @ - # @ = O Journal of Clinical Epidemiology

° # ) o ° " " h @ \ u d h @ - k u j Qual. Health Res.

O ° U ) u K ° ) 8 u h k @ U ° 8 h k ) @ o k U ° u h k @ U ° o PLoS Med.

# ° 8 K U " U " K V - J Adv Nurs

° U U o # # # 8 k U V o # o h @ \ h @ \ o d h @ - k BMC Health Serv. Res.

o o ‡ V O ‡ k " = ) U - ) @ - Medinfo

V U # h Bmj



) K# " 7# - *Ann. Fam. Med.*

7u Mo V° U" - # K° M" u *BMC Med. Res. Methodol.*

k# h h U U 8) ‡ V" k h O' # h *Evaluating meta-ethnography: systematic analysis and synthesis of qualitative research* h h O

U ) ‡ ° o k o u U K o " " o " ° " *J. Health Serv. Res. Policy*

O o 8" *Quality in Qualitative Evaluation: A framework for assessing research evidence* 8 # o k \ # \

#° oh yM # ° o h #° oh j k # *J. Eval. Clin. Pract.*

U ) ‡ k O o ° ° K ° o u *Qual Saf Heal. Care*

k o " U " *J. Eval. Clin. Pract.*

U ) ‡ ) # ° ° - ° ° K = k = o *BMC Med Res Methodol*

M k \ O o #

K u ° = U *BMC Med. Res. Methodol.*

h V o # # = ‡ self-care *Health Care Women Int.*

U ° U k K U u 7 # U *Int. J. Clin. Pharm.*

U o o ) # - 7 j *Res. Nurs. Heal.*

o - M 8 u # o h " MO o k - ) # # U *PLoS One*

M - O ) M o 8 h " j

o ) " # = K U 8 K U o 8 o *J. Reprod. Infant Psychol.*

° O ° h K o U ‡ ) ° ‡ ° o k h *PLoS One*

‡ h # u h # = ° U

o *PLoS One*

o U # U # † - k *J Heal. Serv Res Policy*

V " k # # h K) U U k h y *J Heal. Serv Res Policy*

# u " h *Qual Heal. Res*

V U # h K h o *J Heal. Serv Res Policy*

K V K h h M = j # *Cochrane Handb. Syst. Rev. Interv.*

k o ) # h V o j *Comple. a Qual. Proj. Details dialogue*

° - " k O o K U 8 † *Soc. Sci. Med.*

) O 7 U u *Qual. Health Res.*

) O U h O h k U @ # j j U *J. Mix. Methods Res.*

U U = *Qualitative Data Analysis: an Expanded Sourcebook* O o

K U # 7 *Qualitative Research Design: An Interactive Approach*

- 7 # = 7 U ) O ) y *Aust. N. Z. J. Psychiatry*

U " V † K U ) M # † † M 8 O M u *Br J Gen Pr.*

# o ) - K 8 u *Limits Consent A Socio-ethical Approach to Hum. Subj. Res. Med.*

u k O " † k K = o " h # o # ) M = \ U @ u k K o U o U o † " k k k \ ) " u k - 7 k U - ) *BMJ Open*

) O U *Integrating qualitative and quantitative methods : a pragmatic approach* o h @

K) = † u John Dewey: The Later Works, 1925-1953

77 o A Handb. Res. methods Clin. Heal. Psychol.

K O U U # u o M # @ @ y -  
o # \ Qual. Soc. Work

k K= " K" @  
Qual. Health Res.

o - " k - =  
Res. Methods Rev. Pap. Natl. Cent.

- O ° † O † ° ° U U o U † o  
= h h - J. Prev. Med.

@ u # o h  
J. Adv. Nurs.

° o K U # Basics of qualitative research: Grounded theory procedures  
and techniques o h @

V M) The research act: A theoretical introduction to sociological methods  
u

° U ° K # o \  
k Br. J. Psychol.

j dk @ V † o † j dk  
@ h O

V U ° ° ) k † k U  
° U ° ) † Feminist Dilemmas in Qualitative Research

" 8 ° o u ) 8 u j  
k

h V o 8 Image (IN).

# h V U k  
BMJ Br. Med. J.

K U U # Qual. Health Res.

° = U " † † V o h " 7  
J Affect Disord #

8 - u U o )

K - - J. Adv. Nurs.

8 V @ Res. Nurs. Health

V = o U = Qual. Health Res.

K - o M K = # Qual. Res.

O - u † @ Br J Psychiat

) 8 ° K U " u Bmj

- O 8 † # u @ o Encyclopedia of Statistics in Behavioral Science " - ) = - † "

K = † U " = h u 8 " h # N Engl J Med.

) O o # U h = Clin Trials

) o K O - J. Chronic Dis.

O u K M O ) O † # O U # k = h # = h Trials

M - u U - ° ) \ o u # ) 7 ) 8 ° o u - " @ = ) K U M # hk-#@ J. Clin. Epidemiol.

8 u M o † # - ° h Dialogues Clin Neurosci

u M K O K ° M U o h hk-#@ J. Clin. Epidemiol.

) K u # Bmj

o h ) K u K † # J. Eval. Clin. Pract.

° ) V M Design and analysis of cluster randomization trials in health research

k K= o" o  
*Int. J. Epidemiol.*

o K O- ) " k K O K o  
*Br Med J*

o h ) u K †  
*Bmj*

† † U U k # o 8 o - o - # 8 8  
7 8  
*Trials*

K 8 h" - † h † " ) M ) # K U  
u k  
*BMC  
Med. Res. Methodol.*

o u - U U h K # U M u u U K 7  
o o † # K k K o  
k  
*Library (Lond).*

† U o- 8 7 U k # o )  
*Trials* o \

h" ) # o- K 8 M h M = U K k  
# o V o  
*Trials* o h

U o U K k h" @  
*Trials*

h" # k V \ O h # h" # 7 # 8 V \  
° k O) k ) # o \ U 8 O † O # M  
" = " o" h # k MO  
-j y @  
*Trials*

V @ = k V @ k = o ) k

7 M K" h @ *Comput. Support.  
Coop. Work*

- " V o h K o #  
*CoDesign*

- " V o 8 u # *Collaborative Design:  
Proceedings of CoDesigning 2000* o k o O K"  
O o O

) o : V h ) h h System

8 † k O K 8 U K h OzCHI 2013

h = h # U Participatory Design of evidence-based online youth mental health promotion, intervention and treatment

o M \ o O † U † 8 U K M † k ) 8  
 o 8 o ) o h # V h k  
 \ h h o k # @ )  
 u " U = † " @ JMIR Hum. Factors

h " 8 k - Qual. Saf. Heal. Care

h - h Conf. Particip. Des.

- o V = u U U K o \ ) \ U  
 Cochrane Database Syst Rev

h M ) M k K o " h # BMC Med.

K k K 8 h M V o ) # o - M # o o  
 u ) u h † † U = U h "  
 o ou ku Trials

# 7 K 8 # Proc. 11th Int. Conf. Interact. Des. Child. - IDC '12

h - U M # # U = 7 Des.  
 Work

o = U " † † V o h " 7  
 o J. Affect. Disord.

o = U " " k = @k † † j h " † Trials

# 7 - = o k k M u Clin Trials

† # " K u o o o = o U @V 8 k  
 o Cochrane Database Syst Rev  
 U k

u # 8 h \

M7 o ) 8 o U  
*Lancet*

U M# K U 8 V o o  
*J. Heal. Serv. Res. Policy*

U # U - U #

) # O 8 -  
 ) # O 8 -

# j # # U = o \

U M# K U V o K U 8 U -  
*Fam. Pract.*

M' O o O - O  
*Biometrika*

V - " ) 8 # @ 8 O U  
 U *J. Am. Stat. Assoc.*

k 7 \ @ # u  
 # h *J. R. Stat. Soc.*

o # o o o k 2015

= U o t u @  
*North. Irel. Netw. Trials Methodol. Res.*

K # = U o h - o k  
*Trials* o \ \

U o U K k h " # u O - U # o )  
 # o - K 8 = U M h M @  
 u  
*Trials*

h " K k M # o ) # ) u K 8 o u o  
 - t U h M = U V o u o  
*Trials* o

h h

) M u h u ) k  
*Econometrica*

h U - *Handbook of Economic Methodology*

M 8 8 - K # U

*Trials*

o h " " U o - = o o # - †  
) h = † u = †  
‡ h JAIDS J. Acquir. Immune Defic. Syndr.

- # ° 8 ) o U ) h @ U k  
h ) @U h # U = = )  
o Clin. Transl. Sci.

M † MV † = † o O = " # u k

*Ethn. Health*

o ° M h Can. Public Adm.

- U h † 7 h - U V ° = o o U # )  
U # 8 # ° yM  
Int. J. Consum. Stud.

° ) ) " K # # k @  
Trials

° ) ) " K # # k o † ° u y  
The  
Northern Ireland Network for Trials Methodology Research \

u V @ V u U k  
7 o 7

k U o M ° 8 U # k )  
- # @ #k ) -#@ Trials

° u h o K # #  
#\k-j Int. J. Qual. Heal.  
Care

k " #  
Bmj

V 8 8 = - # o k o k y  
BMC Med. Res.  
Methodol.

) h † ° Q k \ V ° o Q ' y  
= J. Ment. Heal.

K \ k U 7  
BMJ Qual. Saf. U

h " K k ° M # o ) # ) u K 8 o u o  
- † U h M ° = U V o # k = k  
- k u



Trials

Br. J. Psychiatry

Psychiatric Clinics of North America

BMC Med. Clin. N. Am. Annu Rev Public Heal. Author Manuscr. Annu Rev Public Heal.

New Oxford textbook of psychiatry

World J. Biol. Psychiatry

Br. J. Psychiatry

Am. J. Psychiatry

Behav. Sci. Law

J. Clin. Psychiatry

UK Clinical Trials Gateway

Methods

Psychol. Med.

BMJ Open

Br. J. Psychiatry

*Clin. Trials*

= U 8 u V # 7 ) h = # hh@

*Res. Involv. Engagem.*

8 7 U o U " O " # " † = O U  
 \ # u u ) † K " h  
 U k # Bmj

K O ) O k U K ) - K † M V U # † o  
 h K U " \ j  
 k @ j k @ Trials

° # 8 ) † k # O 7 U k o

*Clin Ther*

° M O O M M M # 8 - O U ° 8  
 U " u @ 7 7

*Control Clin Trials*

h - # # U Services \ K

) ) ) Mk U ) h Patient Educ. Couns.  
 y

O O = h U ) )  
 Inf. Des. J.

) o K M V " 7 8 7 O K h -  
 ) BMJ Open

U ) k K # o h 7 = - =kj O  
 # † h Contract

K M = M 8 h M K K o K O )  
 Implement. Sci.

o k = U ° 8 " U K " U M u  
 Policy Syst. Heal. Res.

k 8 U † † " o o  
 Med. J. Aust.

k 8 K 8 7  
 Lancet

o ) # yM HMSO )

J Heal. Serv Res Policy

Website  
K

Website

BMC Health Serv. Res.

BMJ Open

Pilot

Feasibility Stud.

Trials

BMJ Open

J. Clin.

Epidemiol.

h @ j o h k #  
k # u PLoS One  
8 = # - ) K U @ o O † o  
u - # k @  
" #k@  
Pilot Feasibility Stud.  
o u k \

## **10. Appendices**

---

## Appendix A: REFRAMED trial ethical approval letter

AMENDED 07.07.11



**National Research Ethics Service**

**NRES Committee South Central - Southampton A**

Level 3, Block B  
Whitefriars  
Lewins Mead  
Bristol  
BS1 2NT

Telephone: 0117 342 1381

Facsimile: 0117 342 0446

20 June 2011

Prof. Thomas R Lynch  
Professor of Clinical Psychology  
University of Exeter  
Psychology, CLES  
Washington Singer Laboratories  
Perry Road, Exeter  
EX4 4QG

Dear Prof. Lynch

**Study title:** REFRAMED: REFRActory depression - Mechanisms and  
Evaluation of Dialectical behaviour therapy  
**REC reference:** 11/SC/0146  
**Protocol number:** DBT2011

Thank you for your letter of 13 June 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

### Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

### Ethical review of research sites

#### NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

#### Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as

soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

#### *Conditions of the favourable opinion*

*The favourable opinion is subject to the following conditions being met prior to the start of the study.*

*Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.*

*Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.*

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

*Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of approvals from host organisations*

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

#### **Approved documents**

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Advertisement	Recruitment flyer; v1.1	25 March 2011
Advertisement	Recruitment poster; v1.1	25 March 2011
Covering Letter		29 March 2011
Evidence of insurance or indemnity		27 July 2010
GP/Consultant Information Sheets	Clinician cover letter; v1.1	22 March 2011
GP/Consultant Information Sheets	Clinician info leaflet; v1.1	22 March 2011
GP/Consultant Information Sheets	Non-referring GP info leaflet; v1.1	22 March 2011
GP/Consultant Information Sheets	Non-referring GP outcome randomisation; v1.1	22 March 2011
Interview Schedules/Topic Guides	Telephone screening script; v1.1	25 March 2011
Interview Schedules/Topic Guides	Telephone	25 March 2011

	screening scoring sheet; v1.1	
Interview Schedules/Topic Guides	SCID 1 screening interview; v1	25 March 2011
Interview Schedules/Topic Guides	SCID 2 screening interview; v1	25 March 2011
Interview Schedules/Topic Guides	AdSUS interview; v1	28 March 2011
Interview Schedules/Topic Guides	CAM-PROM PT brief description; v1.1	25 March 2011
Investigator CV		29 March 2011
Letter from Sponsor		28 March 2011
Letter of invitation to participant	Participant letter as from GP; v1.2	31 May 2011
Letter of invitation to participant	Participant reply form; v1.1	22 March 2011
Other: Letter from funder EME		04 November 2010
Participant Consent Form: Pre-Trial Consent Form	1.1	22 March 2011
Participant Consent Form: Participant Consent Form	1.1	22 March 2011
Participant Consent Form	1.1	22 December 2010
Participant Information Sheet: Pre-Trial Information Sheet	1.1	22 March 2011
Participant Information Sheet: Participant Summary Pamphlet with GP invite	1.1	22 March 2011
Participant Information Sheet: Participant Information Sheet	1.1	22 March 2011
Participant Information Sheet: Participant DBT leaflet	1.1	22 March 2011
Participant Information Sheet: Pre Trial	1.2	31 May 2011
Participant Information Sheet: Leaflet	1.2	31 May 2011
Protocol	1.1	23 March 2011
Questionnaire: SCID 2 Screening Questionnaire		
Questionnaire: Invalidating Childhood Environment Scale		
Questionnaire: NEO-FFI Conscientiousness subscale		
Questionnaire: Frost Multidimensional Perfectionism scale		
Questionnaire: Schwartz Values Scale		
Questionnaire: Urgency Premeditation Perseverance Sensation Seeking		
Questionnaire: Measure of Parenting Style		
Questionnaire: Hamilton Rating Scale for Depression		
Questionnaire: Suicidal Behaviour Questionnaire		
Questionnaire: Modified Scale for Suicide Ideation		
Questionnaire: LIFE-RIFT		
Questionnaire: EQ-5D		
Questionnaire: Client Satisfaction Questionnaire		
Questionnaire: Inventory of Interpersonal Problems - Personality Disorders		
Questionnaire: Dialectical Behaviour Therapy Ways of Coping		



Checklist		
Questionnaire: White Bear Suppression Inventory		
Questionnaire: Ambivalence Over Emotional Expressiveness		
Questionnaire: Social Support Questionnaire		
Questionnaire: Patient Health Questionnaire		
Questionnaire: Positive and Negative Affect Scale		
Questionnaire: Emotional Approach Coping		
Questionnaire: Credibility/Expectancy Questionnaire		
Questionnaire: California Psychotherapy Alliance Scale - patient version		
Questionnaire: Outcome Rating Scale		
Questionnaire: Session Rating Scale		
Questionnaire: DBT for ECD diary card	1.1	25 March 2011
Questionnaire: Automated Telephone Questionnaire	1.1	25 March 2011
Questionnaire: Automated Telephone Conscientiousness check	1.1	25 March 2011
REC application		28 March 2011
Referees or other scientific critique report	Funder Reviewer Report (i)	02 September 2010
Referees or other scientific critique report	Funder Reviewer Report (ii)	02 September 2010
Referees or other scientific critique report	Funder Statistician Report	02 September 2010
Response to Request for Further Information		13 June 2011

### Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

### After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email [referencegroup@nres.npsa.nhs.uk](mailto:referencegroup@nres.npsa.nhs.uk).

**11/SC/0146**

**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely



PP

**Dr Iain MacIntosh**  
**Chair**

Email: [scsha.SWHRECA@nhs.net](mailto:scsha.SWHRECA@nhs.net)

*Enclosures:* "After ethical review – guidance for researchers"

*Copy to:* *Dr Roelie J Hempel*  
*Dr Tim Hollingbery, Dorset HealthCare University NHS Foundation*

## Appendix B: Reply form for patients declining participation in the REFRAMED trial

Source: GP surgery

UNIVERSITY OF  
Southampton



Dorset HealthCare University   
NHS Foundation Trust

### REFRAMED REPLY FORM

Thank you for taking the time to read the REFRAMED trial summary pamphlet. We appreciate that this is a short summary of the trial and you will need to have more information to make an informed choice. We would like to call you to discuss the trial further, but understand that you may have already made your decision. If you know that you would like to find out more, or if you are certain you would not like to take part in this trial, then it would greatly help us if you can either

1. Return one of the letters below (i.e. either the one saying that you are interested in finding out more, or the one saying that you are not interested in finding out more); or
  2. Email or telephone us, leaving your contact details.
- Trial Email: [reframed.dorset@dhuft.nhs.uk](mailto:reframed.dorset@dhuft.nhs.uk)
  - Telephone number: 01202 492126. An answer phone will be in operation out of hours

Thank you for your time

---

Telephone: 01202 492126  
Email: [reframed.dorset@dhuft.nhs.uk](mailto:reframed.dorset@dhuft.nhs.uk)  
Web: [www.reframed.org.uk](http://www.reframed.org.uk)

ISRCTN85784627  
South Central REC: 11/SC/0146  
Version 1.0 Date: 27-02-2012



**I am interested in finding out more about REFRAMED**

I confirm that I have read and understand the summary pamphlet for the REFRAMED trial and would like a researcher to contact me to discuss it further. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected in any way.

Name: \_\_\_\_\_

Address: \_\_\_\_\_  
\_\_\_\_\_

Preferred telephone numbers: \_\_\_\_\_ / \_\_\_\_\_

It is OK to leave an answer phone message on this number?; YES / NO

When is the best time to call?; \_\_\_\_\_

Email address (optional): \_\_\_\_\_

Signature \_\_\_\_\_

It helps us to plan research in the future if we know the reasons that this trial appeals to you. We would be very grateful if you could write these reasons below, but we want to stress that this is not something you have to do; we respect that this may be a private decision that you do not want to share.

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_



**I am not interested in finding out more about REFRAMED**

---

I have read the summary pamphlet for the REFRAMED trial and have decided that I definitely would **NOT** like any further information and **do not** want to be contacted about this trial again.

NAME: \_\_\_\_\_

Signature: \_\_\_\_\_

GP Surgery: \_\_\_\_\_

It helps us to plan research in the future if we know the reasons that this trial did not appeal to you. We would be very grateful if you could write these reasons below, but we want to stress that this is not something you have to do; we respect that this may be a private decision that you do not want to share.

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

We would also like to contact a small number of people, about 20, to talk in more detail over the telephone about their thoughts on the trial and their reasons for declining.

Would you be interested in talking over the telephone about these reasons? YES / NO

If yes, please put your telephone number here: \_\_\_\_\_

---

It is important for us to know that the people who do take part are representative of the general population. To check this we compare some basic details about those who chose to take part with those who choose not to. For this reason it would be very helpful if you could fill out the below details. You do not have to fill out these details, but if you do, we would remove this section so that it is not possible to tell who you are. Your name and signature will be securely shredded so that it would never be possible for anyone to identify you.

Your Age: \_\_\_\_\_ Your Gender: Male / Female

Your marital status: \_\_\_\_\_

What's the highest qualification you have?

What's your current job?

## **Appendix C: REFRAMED RISK assessment procedures**

### **REFRAMED**

#### **PROTOCOL FOR ASSESSING AND REPORTING RISK**

The following principles and procedures govern risk assessment and reporting in the REFRAMED study. REFRAMED members do not manage risk themselves.

#### **General principles**

Site PIs are responsible for risk assessment in their treatment programmes. The Trial Management Team is responsible for risk assessment during research assessments. This includes ensuring that staff, students and interns working with them receive adequate induction and training prior to participant contact in which risk could be disclosed and ongoing supervision during their research work.

#### **General procedures**

Background training materials are available on the website. All staff should attend training in the use of this protocol as soon as is reasonably possible. If they undertake any work where risk may be an issue prior to receiving formal training, it is the PI's / Trial Management Team's responsibility to ensure that they have reviewed all the materials and have received bespoke training.

Risk Assessment: Whenever any significant risk is identified a risk assessment should be completed and (counter-) signed by the responsible member of staff. If at all possible this should be done at the time of the assessment, or as soon afterwards as possible. This record should be kept on file in line with the study's data storage procedures.

Reporting Risk: Any significant, but not imminent risk should be reported to the person's GP and, if appropriate, other health care professionals, as soon as is reasonably possible. The Trial Management Team should ALWAYS be notified of any risk assessments that have taken place. Please use Appendix I to write a brief report and send this to the Trial Team.

For research outside of the local area, PIs / supervisors should familiarise themselves with the local providers' risk procedures, and researchers should hold the relevant contact details needed in the case of immediate risk.

When clinical staff is not available they should ensure appropriate cover is arranged for any risk issues that might arise in their absence.

When conducting telephone interviews in which risk may be disclosed, the interviewer should establish the telephone number and location of the participant at the start of the call, and clarify the boundaries of confidentiality (as per trial / clinic protocol).

#### **Local emergency contact numbers**

**Prof Peter Bower (Primary Supervisor): 0161 275 7638/[mobile number redacted]**

## Bournemouth / Poole

Community Mental Health Teams (Adult) - Bournemouth, Poole and SE Dorset

Monday – Friday, 8.30am – 5pm. At evenings or weekends please contact the Crisis Team directly on 01202 652000.

## Southampton/Winchester

<u>Access and Assessment Team - Southampton</u>	Adult Mental Health	College Keep, Terminus Terrace, Southampton, SO14 3DT	02380 717204
---	---------------------	---	--------------

<u>Access and Assessment Team - East Hampshire</u>	Adult Mental Health	Osborn Centre, Osborn Road, Fareham, PO16 7ES	01329 288331
--	---------------------	---	--------------

<u>Access and Assessment Team - North Hampshire</u>	Adult Mental Health	Church Square Resource Centre, 49 Church Square, Basingstoke, 7SN	01256 346616
---	---------------------	---	--------------

<u>Access and Assessment Team - West Hampshire</u>	Adult Mental Health	Old School House, Southampton Road, Cadnam, SO40 2NF	02380 816650
--	---------------------	--	--------------

## Bangor/ North Wales

Nant y Glyn Community Mental Health Team, Telephone 01492 532164.

Roslin Community Mental Health Team, Telephone 01492 860926.

Flintshire	NE Wales	North Delyn	Pwll Glas Resource Centre Pwll Glas Road Mold, CH7 IRA	01352 750252
------------	----------	-------------	--	--------------

Flintshire	NE Wales	Mold	Pwll Glas Resource Centre Pwll Glas Road Mold, CH7 IRA	01352 750252
------------	----------	------	--	--------------

Flintshire	NE Wales	Deeside	Aston Plough House, Aston, Deeside, Flintshire, CH5 IXS	01244 834921
------------	----------	---------	---	--------------

Wrexham	Central	Wrexham	16 Grosvenor Road, Wrexham, LL11 1BU	01978 355783
---------	---------	---------	---	--------------

Wrexham	Rural	Wrexham	16 Grosvenor Road, Wrexham, LL11 1BU	01978 366867
---------	-------	---------	---	--------------

Denbigh	Conwy Denbigh	& South	Oakleigh, Glyndwr Abbey Llangollen, LL20 8SS	Road,	01978 860707
Denbigh	Conwy Denbigh	& Dyffryn Clwyd	Tim Duffryn Noddfa, Middle Denbigh, Clwyd, LL6 3UR	Clwyd, Lane,	01745 813138
Denbigh	Conwy Denbigh	& Rhuddlan	Hafod, Beechwood Rhyl, LL18 3EU	Road,	01745 443050
Conwy	Conwy Denbigh	& Colwyn	Nant-y-Glyn Nant-y-Glyn Colwyn	Resource Centre, Road,	01492 532164
Conwy	Conwy Denbigh	& Aberconwy	Roslin Community Health Nant y Gamar Craig y Llandudno Conwy LL30 IYE	Mental Team Road Don	01492 860926
Ynys Mon	NW Wales	Ynys Mon	Bryn Y Hospital, Llanfairfechan, Conwy, LL3 5DH	Neuadd	01248 682508
Gwynedd	NW Wales	Dwyfor	Cilan, Penlan Pwllheli, Gwynedd, LL53 5NI	Street,	01758 614647
Gwynedd	NW Wales	Arfon	Hergest Ysbyty BANGOR Gwynedd LL57 2PW	Unit Gwynedd	01248 363470
Gwynedd	NW Wales	Meirionydd	Plas Dolgallau, Gwynedd, LL40 IDU.	Brith,	01341 422122



## Exploring Risk in Research Interviews

### THOUGHTS

*“I see that you’ve said / you mentioned that..... These are thoughts / feelings that people suffering from depression often have, but it’s important to make sure you are receiving the right kind of support. So if it’s OK, I would now like to ask you some more questions that will explore these feelings in a little more depth.”*

#### PLANS

1 Do you know how you would kill yourself? Yes / No

If yes – details

---

2 Have you made any actual plans to end your life? Yes / No

If yes – details

---

#### ACTIONS

3 Have you made any actual preparations to kill yourself? Yes / No

If yes – details

---

4 Have you ever attempted suicide in the past? Yes / No

If yes – details

---

#### PREVENTION

5 Is there anything stopping you killing or harming yourself  
at the moment? Yes / No

If yes – details

---

6 Do you feel that there is any immediate danger that you  
will harm or kill yourself? Yes / No

Details:

---

FOLLOW-UP FROM PREVIOUS CONTACT

**7** If Action B was enacted at previous assessment and level B risk is identified at current assessment: Last time we met I suggested that you spoke to your GP about these thoughts, and I also wrote to your GP about this. Have you been able to speak with your GP about these thoughts since we last met? Yes / No

**See risk table overleaf for appropriate actions**

## Researcher Risk Protocol

To be used following any indication of risk from questionnaire items, responses to interview questions or any other sources. Look at answers from the sheet to determine the level of risk, A B or C:

### Actions by Researcher

### Tell Participant

All answers 'no' apart from Q5 'yes':

A

↓

|

→

*I can see that things have been very difficult for you, but it seems to me these thoughts about death are not ones you would act on – would this be how you see things? (if they say yes) I would advise you to make an appointment to see your GP to talk about these feelings (as per trial protocol).*

'Yes' for any **one** of Qs 1-4; plus 'yes' for Q5 and 'no' for Q6

B1

↓

|

→

*Things seem to be very hard for you right now and I think it would help if you were to speak to your GP about these feelings. I will be writing to your GP to tell them that you have been here today and have been having some troubling thoughts. I would also advise you to make an appointment to see your GP to talk about these feelings. (as per trial protocol).*

*I think it's important that your GP knows how difficult things are for you right now. I will be telephoning your GP to speak with him/her and suggest that you meet with one another. I also advise that you make an appointment to see your GP to talk about these feelings. (as per trial protocol).* N.B: telephone call to GP to be followed up by letter. The letter should include the statement "the clinical management of this patient remains your responsibility, but it is part of our protocol to inform you of any risks disclosed to ourselves so that you can take account of them in your care plan."

'Yes' for any **one** of Qs 1-4; plus 'yes' for Q5 and 'no' for Q6 **and** 'no' to Q7

B2

↓

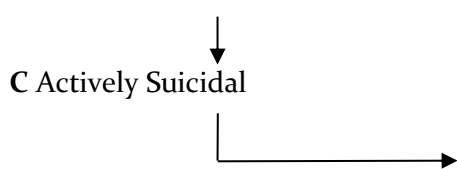
|

→

Scoring 'yes' to Q6

Scoring 'no' to Q5 **and** 'yes' to Qs 1-4 or 6

*I am very concerned about your safety at this moment, I am not a clinician but I would like you to*



*talk to one right now. I am going to make some telephone calls now to arrange for your GP Care Co-ordinator / Crisis Management team/the emergency services to let them know how you are feeling and to arrange for you to receive immediate help.*

Action to take in the case of immediate risk:

Participant needs immediate help – **do not leave them alone, or if on telephone, do not hang up.** Follow your trial's chain of supervisory clinical contact in order to involve supervisory clinician right away. Then (with clinician if possible) follow the chain of contact below:

1. GP / out of hours GP; if not
2. Crisis team; if not
3. Clinician accompanies to A&E; if not (or interview is over telephone)
4. Call ambulance.

**Appendix 1**

**Risk Report**

Patient ID: \_\_\_\_\_

DOB: \_\_\_\_\_

*Suicide risk information:*

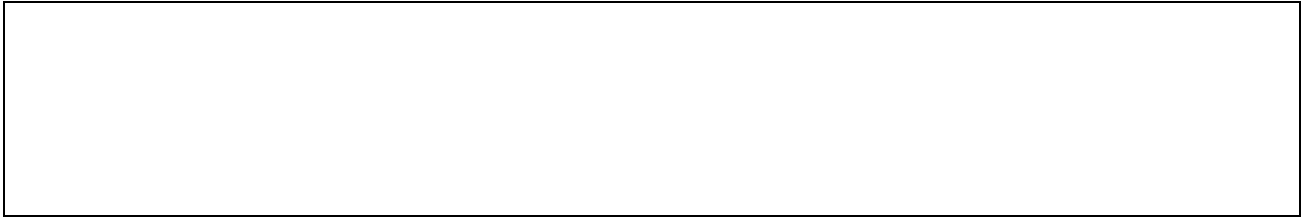
- *Suicidal ideation severity, frequency, whether longstanding/recent/fluctuating.*
- *Any history of suicide attempts? (State if no history)*
- *Any history of self-harming behaviour without intent to die? (State if none)*
- *Is there a plan? (State if no plan)*
- *Are there the means? (State if no means)*
- *Any protective factors? (State if none)*
- *Any other relevant information, such as precipitating environmental factors (i.e. impending divorce, for example)?*
- *Relevant inventory scores and their meanings where appropriate*
- *Are those within the patient's care network (GP, psychiatrist, etc.) aware of the behaviour?*

*Date reported: \_\_\_/\_\_\_/\_\_\_*

*Additional notes / actions taken:*

*As part of the REFRAMED risk protocol, suicide risk is **managed** by the patient's GP or their Research Therapist.*

*Date action taken: \_\_\_/\_\_\_/\_\_\_*



Researcher / assessor: \_\_\_\_\_ Signed: \_\_\_\_\_ Date: \_\_\_/\_\_\_/\_\_\_

Supervisor: \_\_\_\_\_ Signed: \_\_\_\_\_ Date: \_\_\_/\_\_\_

## Appendix D: START ethics amendment letter



### Health Research Authority

#### NRES Committee Yorkshire & The Humber - South Yorkshire

Unit 002, JARROW Business Centre  
Rolling Mill Road  
Jarrow  
Tyne and Wear  
NE32 3DT

Tel: 0191 428 3561

29 May 2014

Professor Peter Bower  
Professor of Health Services Research  
University of Manchester  
Centre for Primary Care, Institute for Population Health  
5th Floor, Williamson Building  
University of Manchester, Manchester  
M13 9PL

Dear Professor Bower

**Study title:** Systematic Techniques for Assisting Recruitment to Trials (START): a study of the feasibility of testing recruitment interventions by nesting across multiple trials in primary care and community settings

**REC reference:** 11/YH/0271

**Amendment number:** Substantial Amendment 3

**Amendment date:** 08 May 2014

**IRAS project ID:** 63122

The above amendment was reviewed the Sub-Committee in correspondence.

#### Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The sub committee did not raise any ethical issues.

#### Approved documents

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering letter on headed paper [Letter from Peter Bower]	Letter from Peter Bower	15 May 2014
Notice of Substantial Amendment (non-CTIMP) [Substantial Amendment 3]	Substantial Amendment 3	08 May 2014
Research protocol or project proposal [Protocol]	Version 2.0	14 May 2014

A Research Ethics Committee established by the Health Research Authority

### Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

### R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

### Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

11/YH/0271:	Please quote this number on all correspondence
-------------	--

Yours sincerely

pp



Mr Neil Marsden  
Chair

E-mail: [nrescommittee.yorkandhumber-southyorks@nhs.net](mailto:nrescommittee.yorkandhumber-southyorks@nhs.net)

*Enclosures: List of names and professions of members who took part in the review*

*Copy to: Ms Rachel Georgiou, Greater Manchester Primary Care Research Governance Partnership (ReGroup)  
Ms Lynne Macrae, University of Manchester*



**NRES Committee Yorkshire & The Humber - South Yorkshire**

**Attendance at Sub-Committee of the REC meeting via correspondence.**

**Committee Members:**

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
Professor Nigel Beail	Consultant Clinical Psychologist & Professor of Psychology	Yes	
Mr Neil Marsden	Police Staff	Yes	

**Also in attendance:**

<i>Name</i>	<i>Position (or reason for attending)</i>
Miss Kerry Dunbar	Assistant Coordinator

## Appendix E: EQUIP ethics amendment letter



**Health Research Authority**  
**National Research Ethics Service**

### NRES Committee North West - Lancaster

Barlow House  
3rd Floor  
4 Minshull Street  
Manchester  
M1 3DZ

Tel: 0161 625 7109  
Fax: 0161 625 7919

02 July 2014

Professor Karina Lovell  
Professor of Mental Health  
University of Manchester  
School of Nursing, Midwifery & Social Work  
Room 6.322a Jean McFarlane Building, Oxford Road  
Manchester  
M13 9PL

Dear Professor Lovell

**Study title:** Enhancing the quality of user involved care planning in mental health services (EQUIP): Clinical randomised control trial and process evaluation  
**REC reference:** 14/NW/0297  
**Amendment number:** 1  
**Amendment date:** 18 June 2014  
**IRAS project ID:** 125899

#### A. Changes to the Protocol:

- 1) Changing the method of randomisation
  - 2) For CSO's to follow up non responders to the invitation to take part with one telephone call.
- B. Addition of standard correspondence (15 additional letter/emails) for service users, carers and professionals.
- C. Minor Amendments to the outcome measures pack
- D. To Run an additional trial as a sub-study, entitled MRC START in EQUIP

The above amendment was reviewed on 02 July 2014 by the Sub-Committee in correspondence.

#### Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

#### Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Copies of advertisement materials for research participants [PPI Flyer-text images and logos]	1	09 June 2014
Letters of invitation to participant [Postal Completion consent forms letter]	1	09 June 2014
Letters of invitation to participant [Confirmation of appointment letter]	1	09 June 2014

A Research Ethics Committee established by the Health Research Authority

Letters of invitation to participant [Postal completion covering letter]	1	09 June 2014
Letters of invitation to participant [Voucher covering letter]	1	09 June 2014
Letters of invitation to participant [Carer follow up reminder letter]	1	09 June 2014
Letters of invitation to participant [Carer Follow up Letter covering letter]	1	09 June 2014
Letters of invitation to participant [Postal Completion follow up letter]	1	09 June 2014
Letters of invitation to participant [Carer voucher covering letter]	1	09 June 2014
Letters of invitation to participant [Cohort Voucher covering letter]	1	09 June 2014
Letters of invitation to participant [Confirmation of FU appointment letter]	1	09 June 2014
Notice of Substantial Amendment (non-CTIMP)	1	18 June 2014
Other [Calling Card Text]	1	09 June 2014
Other [CMHT withdrawal letter]	1	09 June 2014
Other [CMHT ineligible letter]	1	09 June 2014
Other [SU not eligible letter]	1	09 June 2014
Other [Email Approach]	1	09 June 2014
Other [Telephone follow up script]	1	16 June 2014
Other [Thank you card text]	1	09 June 2014
Research protocol or project proposal [MRC START in EQUIP Protocol Cluster RCT]	2	25 June 2014
Research protocol or project proposal [CRCT and PE Protocol]	8	11 June 2014

#### Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

#### R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

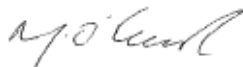
#### Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

<b>14/NW/0297:</b>	<b>Please quote this number on all correspondence</b>
--------------------	---

Yours sincerely



pp  
Dr Lisa Booth  
Chair

E-mail: [nrescommittee.northwest-lancaster@nhs.net](mailto:nrescommittee.northwest-lancaster@nhs.net)

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Ms Lisa Dowell, Manchester Mental Health and Social Care Trust  
Dr Andy Mee,*

**NRES Committee North West - Lancaster**

**Attendance at Sub-Committee of the REC meeting on 02 July 2014**

**Committee Members:**

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
Dr Lisa Booth	Senior Lecturer / Chair	Yes	Expert in the Chair
Professor Jois Stansfield	Professor of Speech Pathology	Yes	Vice Chair

**Also in attendance:**

<i>Name</i>	<i>Position (or reason for attending)</i>
Miss Margaret O'Connor	REC Assistant

## Appendix F: EQUIP trial invitation cover letter



The EQUIP project is funded by the National Institute for Health Research's Programme Grants for Applied Research [Programmes](#).

### Enhancing the quality of user involved care planning in Mental Health Services (EQUIP)

**Dear service user**

We would like to invite you to take part in our research study being carried out at the Universities of Manchester and Nottingham.

**What is the study about?** The EQUIP project aims to increase service user involvement in planning their own care. We are trying to do this by training mental health workers. Our training is run by service users and carers. We want to test whether this training makes a difference. We are testing it by training some mental health teams but not others. We will then speak to service users to see if our training makes any difference to the care they receive.

**Why have I been invited?** You have been invited because you receive support from a mental health team that is taking part in our study.

**Do I have to take part?** No. It is up to you to decide. If you take part we ask you to sign a consent form.

**What will happen to me if I take part?** You would take part in two meetings with a researcher. These last about an hour and a half. The meeting would be arranged at a time and place to suit you. During the first meeting you fill in a survey about your mental health and care. After six months we ask you to do the survey again to see if anything has changed.

**Is there any payment?** You will receive a £10 high street voucher at the second meeting.

**Will I benefit from taking part?** This study will probably not help you personally, but the results might help improve mental health services in future.

**Will my taking part in the study be kept confidential?** Yes. All information about you will be kept confidential.

**If you would like to know more then please read the attached information sheet. If you decide to take part, please complete the enclosed form and return it to the research team using the enclosed prepaid envelope. A researcher will then contact you.**

Yours sincerely

**Professor Karina Lovell**

## Appendix G: EQUIP Participant information sheet

# Enhancing the quality of user involved care planning in Mental Health Services (EQUIP)

## Participant Information Sheet (Service users)

†

**What is the purpose of the study?**

U

u -j y @

@ -j y @

---

h -j y @

†

†

u **'Evaluation of the efficacy and cost effectiveness of user/carer involved care planning'.**

**How is it decided which mental health team receives the new training package?**

u

u

u

**Why have I been invited?**

†

### Do I have to take part?

V @ @

### What will happen to me if I take part?

@  
y U V V=O#  
o \ # o \ u  
V=O u  
# u

u y 7 u

" # #  
‡

### Expenses and payments

-

### What are the possible disadvantages and risks of taking part?

u u \ @  
V=O  
U M O y

The EQUIP project is funded by the National Institute for Health Research's Programme Grants for Applied Research Programme.

### Will my taking part in the study be kept confidential?

u  
@  
y V  
†  
@

### What if there is a problem?

@  
h U # 7 M  
O @  
k h 8 #  
u k h 8 # k \  
# " u y U \ k U U hO

The following services are also available for help and advice should you require it:

### Manchester Mental Health and Social Care Trust Patient Advice and Liaison Service (PALS)

U U = o # u h ° O o  
7 = u  
# †  
U U 8j  
u  
U  
- h° O



## Appendix H: EQUIP trial 'Consent to Contact' form



The EQUIP project is funded by the National Institute for Health Research's Programme Grants for Applied Research Programme.

### Enhancing the quality of user involved care planning in Mental Health Services (EQUIP)

#### Service User Consent to Contact form

If you think you would like to take part in the EQUIP study: Evaluation of the efficacy and cost effectiveness of user/carer involved care planning, please use this form to let us know. Please send it back to the research team using the pre-paid envelope provided.

A member of the research team will then contact you to discuss the study and if you wish to participate, will arrange an appointment to see you. There is no obligation to take part in this study by completing this form; you are simply providing your consent to be contacted. We will not pass your details to anyone outside of the EQUIP team.

If you would prefer to talk to the research team before completing this form, please contact:

EQUIP Programme Managers: Kathryn Berzins, tel: 0161 306 7893

(Kathryn.Berzins@manchester.ac.uk) or Claire Fraser, tel: 0161 306 7882

(Claire.Fraser@manchester.ac.uk),

Address: School of Nursing, Midwifery & Social Work, University of Manchester, Jean McFarlane Building, Oxford Road, Manchester, M13 9PL

<b>I would like to be contacted about taking part in the EQUIP study: Evaluation of the efficacy and effectiveness of user/carer involved care planning</b>		
Name:		
Postal address:		
Post Code:		
Telephone number:		
Email:		
What is it best time to contact you? (please indicate preference)	Morning/Afternoon/ Evening/ Don't Mind	
I would like to receive a summary of the results of this study	Yes please	No thank you

EQUIP/WS2/CRCT/SU/Cohort/Consent to Contact form/V2/08.04.14

## Appendix I: statistical analysis (Study Three)

**Primary outcome=Proportions of patients consented and enrolled by post.**

Generalized linear mixed models. Fitting a 3-level model (individuals within teams within EQUIP cluster-pairs). Also fitting Trial Arm from embedded trial + IMD + cluster Size + CQC rating:

melogit Enrol\_Post i.Trial\_Group ib3.IMD\_Tri i.CQC\_Rating size || Clus\_pair\_ID: || Clustr\_ID:, or

Mixed-effects logistic regression Number of obs = 8,182

Group Variable	No. of Groups	Observations per Group		
		Minimum	Average	Maximum
Clus_pair_ID	17	137	481.3	942
Clustr_ID	34	36	240.6	591

Integration method: mvaghermite Integration pts. = 7

Wald chi2(7) = 13.30

Log likelihood = -1476.1329 Prob > chi2 = 0.0651

Enrol_Post	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
1.Trial_Group	.7538554	.1342442	-1.59	0.113	.5317515	1.068729
IMD_Tri						
1	.7051063	.1532955	-1.61	0.108	.4604653	1.079723
2	.9109685	.1717482	-0.49	0.621	.6295399	1.318207
CQC_Rating						
2	1.186988	.3171949	0.64	0.521	.7030443	2.004058
3	1.319031	.3309923	1.10	0.270	.8065991	2.157009
4	.7204256	.2737801	-0.86	0.388	.3420667	1.517286
size	.9999334	.0003167	-0.21	0.833	.9993128	1.000554
_cons	.0565882	.014587	-11.14	0.000	.0341435	.0937872
Clus_pair_ID						
var(_cons)	.0016799	.0381299			8.04e-23	3.51e+16
Clus_pair_ID>Clustr_ID						
var(_cons)	.0472755	.0530549			.0052406	.4264768

LR test vs. logistic model: chi2(2) = 3.74 Prob > chi2 = 0.1544

Note: LR test is conservative and provided only for reference.

Adjusted rate difference between arms, with standard error

margins, dydx(Trial\_Group) predict( mu ) atmeans

Conditional marginal effects Number of obs = 8,182
Model VCE : OIM

Expression : Marginal predicted mean, predict(mu)
dy/dx w.r.t. : 1.Trial\_Group
at : 0.Trial\_Gr~p = .3422146 (mean)
1.Trial\_Gr~p = .6577854 (mean)
1.IMD\_Tri = .4531899 (mean)
2.IMD\_Tri = .2286727 (mean)
3.IMD\_Tri = .3181374 (mean)
1.CQC\_Rating = .1239306 (mean)
2.CQC\_Rating = .4489122 (mean)
3.CQC\_Rating = .3802249 (mean)
4.CQC\_Rating = .0469323 (mean)
size = 560.0114 (mean)

Table with 7 columns: Variable, dy/dx, Std. Err., z, P>|z|, and [95% Conf. Interval]. Row 1: 1.Trial\_Group, -.0123001, .0080873, -1.52, 0.128, -.0281509, .0035506.

Note: dy/dx for factor levels is the discrete change from the base level.

**Secondary outcome 1: Patients in each group responding positively to the intervention without prompting**

melogit Res\_Post i.Trial\_Group ib3.IMD\_Tri i.CQC\_Rating size || Clus\_pair\_ID: || Clustr\_ID:, or

Mixed-effects logistic regression Number of obs = 8,182

Group Variable	No. of Groups	Observations per Group		
		Minimum	Average	Maximum
Clus_pair_ID	17	137	481.3	942
Clustr_ID	34	36	240.6	591

Integration method: mvaghermite Integration pts. = 7

Log likelihood = -2157.2469 Wald chi2(7) = 20.85  
 Prob > chi2 = 0.0040

Res_Post	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
1.Trial_Group	.7418651	.1273249	-1.74	0.082	.5299499	1.038521
IMD_Tri						
1	.8265146	.1529593	-1.03	0.303	.5750725	1.187896
2	.9070903	.1479264	-0.60	0.550	.6589285	1.248713
CQC_Rating						
2	1.53116	.3842891	1.70	0.090	.936239	2.504115
3	1.877934	.4442961	2.66	0.008	1.181126	2.985823
4	.6757969	.2488886	-1.06	0.287	.3283431	1.390927
size	1.00037	.0002775	1.33	0.182	.9998264	1.000914
_cons	.055636	.0134888	-11.92	0.000	.0345927	.0894803
Clus_pair_ID						
var(_cons)	.0191073	.0304919			.0008372	.4360853
Clus_pair_ID>Clustr_ID						
var(_cons)	.0310417	.0349283			.0034211	.2816579

LR test vs. logistic model: chi2(2) = 7.81 Prob > chi2 = 0.0202

*Adjusted rate difference between arms, with standard error*

margins, dydx(Trial\_Group) predict( mu ) atmeans

Conditional marginal effects    Number of obs        =        8,182  
 Model VCE        : OIM

Expression        : Marginal predicted mean, predict(mu)  
 dy/dx w.r.t.    : 1.Trial\_Group  
 at                : 0.Trial\_Group        =        .3422146 (mean)  
                   1.Trial\_Group        =        .6577854 (mean)  
                   1.IMD\_Tri           =        .4531899 (mean)  
                   2.IMD\_Tri           =        .2286727 (mean)  
                   3.IMD\_Tri           =        .3181374 (mean)  
                   1.CQC\_Rating       =        .1239306 (mean)  
                   2.CQC\_Rating       =        .4489122 (mean)  
                   3.CQC\_Rating       =        .3802249 (mean)  
                   4.CQC\_Rating       =        .0469323 (mean)  
                   size                    =        560.0114 (mean)

	Delta-method					
	dy/dx	Std. Err.	z	P> z	[95% Conf. Interval]	
1.Trial_Group	-.0207967	.0124178	-1.67	0.094	-.0451352	.0035418

Note: dy/dx for factor levels is the discrete change from the base level.

## Secondary outcome 2: All patients in PPIR vs. control group responding positively, including telephone follow up

Mixed-effects logistic regression Number of obs = 8,182

Group Variable	No. of Groups	Observations per Group		
		Minimum	Average	Maximum
Clus_pair_ID	17	137	481.3	942
Clustr_ID	34	36	240.6	591

Integration method: mvaghermite Integration pts. = 7

Log likelihood = -3072.1275 Wald chi2(7) = 6.75  
 Prob > chi2 = 0.4556

Respond	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
1.Trial_Group	.7426489	.1438592	-1.54	0.125	.5080383	1.085602
IMD_Tri						
1	1.057513	.2020863	0.29	0.770	.727151	1.537966
2	1.135655	.200433	0.72	0.471	.803557	1.605003
CQC_Rating						
2	1.093842	.338904	0.29	0.772	.5959748	2.00762
3	1.421866	.4236537	1.18	0.237	.7929352	2.549643
4	1.125651	.4798092	0.28	0.781	.4881783	2.595546
size	.999773	.0003017	-0.75	0.452	.9991818	1.000365
_cons	.1563284	.047586	-6.10	0.000	.0860863	.2838846
Clus_pair_ID						
var(_cons)	.0667136	.064817			.009936	.4479368
Clus_pair_ID>Clustr_ID						
var(_cons)	.0475296	.0429158			.0080982	.2789572

LR test vs. logistic model: chi2(2) = 43.35 Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.



**Secondary outcome 3: clusters in both arms needing telephone follow up. Fisher's exact test**

. tabi 12 6 \ 12 4, chi2 exact row expected

Key
<i>frequency</i>
<i>expected frequency</i>
<i>row percentage</i>

row	col		Total
	1	2	
1	12	6	18
	12.7	5.3	18.0
	66.67	33.33	100.00
2	12	4	16
	11.3	4.7	16.0
	75.00	25.00	100.00
Total	24	10	34
	24.0	10.0	34.0
	70.59	29.41	100.00

Pearson chi2(1) = 0.2833 Pr = 0.595  
 Fisher's exact = 0.715  
 1-sided Fisher's exact = 0.440