Retention of Patients with Schizophrenia in Complex Intervention Trials: Patterns, Issues, and Practices

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A thesis submitted in partial fulfilment of the requirements of the degree of Doctor of Philosophy

2017

Statement of Originality

I, Paulina Szymczyńska, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below. I attest that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material. I accept that the College has the right to use plagiarism detection software to check the electronic version of the thesis. I confirm that this thesis has not been previously submitted for the award of a degree by this or any other university. The copyright of this thesis rests with the author and no quotation from it or information derived from it may be published without the prior written consent of the author.

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Details of collaboration and publications:

The findings of the systematic review and meta-analysis presented in Chapter 4 have been published in the *Journal of Psychiatric Research*. The primary supervisor Professor Stefan Priebe advised on aspects of study design, interpretation, and presentation of the findings. Dr Stephen Taylor, second supervisor, provided guidance on all chapters, in particular the qualitative studies reported in Chapter 6 and Chapter 7. Statistical advice and support with analyses was provided by Lauren Greenberg (Chapter 4) and Dr Gian Luca Di Tanna (Chapter 5). For purposes of reliability checking in Chapter 4, Sophie Walsh duplicated 20% of the abstract screening and 20% of the full paper screening. In Chapter 5, the anonymised datasets were obtained from five previous trials (Burns *et al.* 1999, 2013, Priebe *et al.* 2007, 2013, 2016). Amy Fernandez helped with transcribing a proportion of the interview data reported in Chapter 6.

Abstract

Background: Inability to retain participants in a clinical trial poses a threat to clinical research as it can lead to a number of issues ultimately affecting generalisability, validity and reliability of the study. Patients with schizophrenia have been reported as particularly difficult to engage and retain in research and psychiatric treatment. This thesis aimed to improve the current understanding of the retention of people with schizophrenia in trials evaluating complex interventions.

Methods: This thesis adopted a mixed method design. Quantitative methodology was used to identify the scale of attrition and to explore potential predictors of dropout. This included a systematic review and meta-analysis and a separate meta-analysis of individual patient data. Qualitative methodology was used in two studies to explore the perspectives of both trial staff and former trial participants on the factors important for retention and effective practices and strategies.

Results: The results of the systematic review and meta-analysis demonstrated the rates of dropout from studies to be higher than from experimental interventions. Dropout from interventions significantly increased as the number of intervention sessions increased. The individual patient data meta-analysis found retention to be higher at the final follow-up assessment than at the penultimate one. The effect of arm allocation almost reached statistical significance pointing to the possibility of participants in the active arm having higher odds of completing the final follow-up than those in the control arm. Two qualitative studies identified barriers and facilitators to retention related to factors related to participant, researcher, study, and wider context. Some of the identified barriers were specific to schizophrenia.

Conclusion: Attrition is a phenomenon that should be anticipated by trialists and prevented with the use of multiple strategies. The extent to which dropout can be minimised depends on a number of factors associated with the participant, researcher, study, and context.

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List of Abbreviations

BPRS	Brief Psychiatric Rating Scale
CANSAS	Camberwell Assessment of Need Short Appraisal Schedule
CAT	Cognitive Adaptation Therapy
CBT	Cognitive-Behavioural Therapy
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMHT	Community Mental Health Team
CONSORT	Consolidated Standards of Reporting Trials
CONSORT-SPI	Consolidated Standards of Reporting Trials for Social and Psychological Interventions
CRT	Cognitive Remediation Therapy
CSO	Clinical Studies Officer
CSQ-8	Client Satisfaction Questionnaire
DSM	Diagnostic and Statistical Manual for Mental Disorder
EBM	Evidence-Based Medicine
EBP	Evidence-Based Practice
EPOS	Effective Patient-Clinician Communication in Community Mental Health Care
GSS	General Self-Efficacy Scale
ICD	International Classification of Diseases
IPD	Individual Patient Data

IPD-MA	Individual Patient Data Meta-Analysis
ITT	Intention to Treat Analysis
JAMA	Journal of American Medical Association
MANSA	Manchester Short Assessment of Quality of Life
MRC	Medical Research Council
MeSH	Medical Subject Headings
NHS	National Health Service
NIHR	National Institute of Health Research
NRES	National Research Ethics Service
OR	Odds Ratio
PANSS	Positive and Negative Syndrome Scale
PI	Principal Investigator
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
STAR-P	Scale for Assessing Therapeutic Relationships in Community Mental Health Care
QMUL	Queen Mary University of London
UK	United Kingdom
USA	United States of America
WEMWBS	Warwick-Edinburgh Mental Well-Being Scale

Acknowledgements

I need to thank Professor Stefan Priebe for always having a challenge for me up his sleeve, for making me think on my feet and, consequently, allowing me to grow as a researcher. I will always be grateful for being welcomed into the team, although I unexpectedly "fell from the sky" onto the Unit's doorstep.

A heartfelt thank you goes to Dr Stephen Taylor who was endlessly supportive and encouraging during many hours spent discussing my research and who provided invaluable feedback on the work presented in this thesis.

I thank the patients who shared their experiences with me, despite often struggling to remember, and who made it to the interviews even when they did not feel like speaking to anyone. Thank you to the trial professionals for sharing their thoughts and experiences in interviews. I would also like to recognise the tremendous support I have received from my colleagues at the Unit for Social and Community Psychiatry. Thanks to them I learned a lot during my PhD and made many friends who helped me in the process. I must thank Lauren Hickling for proofreading my thesis. I gratefully acknowledge Life Sciences Initiative at Queen Mary University of London for funding my studentship.

I owe a special thanks to my two partners in the "PhD crime" – Sophie Walsh and Ayşegül Dirik – for their support, advice, wise words and encouragement. I thank Svitlana Kurochkina, Iwona Bisaga, Dr Aida Farreny, and Justina Kaselionyte for always spurring me on and finding the time to listen.

Finally, I want to thank my parents Dorota and Tadeusz Szymczyńscy who have always believed in me and have given me the strength to go after my dreams.

This thesis is dedicated to the memory of my grandmother Alicja Grzybowska who passed away in the final year of my doctoral research - I am sorry she cannot be here to see me complete this challenge but I know she would have been very proud.

Chapter 1
Introduction

1.1 Background and rationale for conducting the research

Inability to retain participants in a clinical trial poses a threat to clinical research as it can reduce statistical study power, compromise the composition of experimental groups, and introduce a risk of bias. These issues can in turn affect generalisability, validity and reliability of the study (Gul and Ali 2010, Brueton *et al.* 2013). Despite the availability of statistical methods to deal with missing data from the lost participants, these are often imperfect and do not eradicate the risks associated with attrition (Hollis and Campbell 1999, Xia *et al.* 2009).

Most research investigating trial conduct and methodology, however, has focused on the recruitment of participants and this has been described as the most important aspect of a successful study (Rojavin 2005, Borschmann *et al.* 2014). While recruitment issues apply to a high proportion of studies, virtually all trials experience loss to follow-up or dropout from treatment. Not all attrition is problematic and there are no clear guidelines about what level of dropout is acceptable; however losing 5% of participants may already lead to bias and attrition rates exceeding 20% of participants are considered threatening to trial validity (Polit and Hungler 1995, Sackett *et al.* 2000, Schulz and Grimes 2002). A number of studies have examined the levels of attrition or retention in trials in a single clinical area, for example depression (Warden *et al.* 2009) and chronic pediatric conditions (Karlson and Rapoff 2009). These types of studies have reported a range of factors affecting the likelihood of completing follow-up and treatment, including patient characteristics and study factors. However there have been difficulties with ascribing differences in retention to any particular cause at an individual study level (Veldhuizen *et al.* 2015).

Existing systematic reviews of retention issues have identified possible ways of preventing dropout in health care research (Robinson *et al.* 2007), community-based

trials (Davis *et al.* 2002), population-based cohort studies (Booker *et al.* 2011), and randomised controlled trials (RCTs) (Brueton *et al.* 2013). Evidence on the effectiveness of specific strategies in particular populations is scarce as this requires explicit evaluations and complex study design, for instance nested studies (Graffy *et al.* 2010, Bower *et al.* 2014).

A Cochrane review on strategies to improve retention listed mental health as one of the most challenging disease areas to promote retention in clinical trials (Brueton *et al.* 2013). This is in line with the established patterns of service and treatment utilisation in mental health with non-adherence to psychiatric treatment reported to be higher than in physical disorders (Cramer and Rosenheck 1998). Additionally, people with schizophrenia have been described as particularly difficult to engage in psychiatric services and likely to fail to adhere to medication (Lecomte *et al.* 2008, Lecomte, Leclerc, and Wykes 2012). However, while some literature suggests that a diagnosis of schizophrenia increases the risk of non-compliance with outpatient psychiatric treatment (Kissling 1994, Kemp and David 1996, Bueno Heredia *et al.* 2001), other authors contradict this notion (Berghofer *et al.* 2000, 2002, Rossi *et al.* 2002). Some of these discrepancies in findings have been ascribed to the differences in the definitions, treatment setting, study design and sample composition (Reneses *et al.* 2009). Low engagement in services increases the vulnerability of people with schizophrenia to non-adherence to treatment, which commonly comprises long-term therapeutic plans and regular contact with services aimed to reduce the risk of relapse (Nose *et al.* 2003). The attrition rates in RCTs of antipsychotic drugs in particular have been shown to reach levels threatening trial validity (Cramer and Rosenheck 1998, Wahlbeck *et al.* 2001, Nose *et al.* 2003). The issues experienced in these type of trials have been shown to cause relevant stakeholders; including psychiatrists, trial researchers, mental health service users and their carers, to mistrust results of the majority of pharmacological trials in schizophrenia (Xia *et al.* 2009).

The factors affecting non-compliance with medication have been investigated but these are likely to be different in studies involving non-pharmacological treatment, given that most of the reported factors have been found to be directly relevant to the medication received, for instance unwanted side-effects and attitude towards drugs (Kampman and Lethinen 1999). To date, there has been only one systematic study identifying factors affecting attrition rates in RCTs on psychosocial treatment for people with schizophrenia (Villeneuve *et al.* 2010). The study was limited to psychosocial

interventions, which represent only one type of non-pharmacological treatment available to people with schizophrenia. In addition, the study was concerned with a complete withdrawal from treatment (as opposed to treatment non-compliance) and considered dropout both prior to starting treatment and during treatment. Nonetheless, the study began to address the gap in research on attrition in RCTs of interventions that do not involve taking antipsychotic medication.

Completion of follow-up assessments has been argued to be specific to both trial and disease (Brueton *et al.* 2014). Moreover, it has been argued that recruitment and retention strategies need to be tailored to the target population and the study design (Newington and Metcalfe 2014). A better understanding of which individuals have more difficulty completing a trial and which studies are more likely to retain participants can help in developing effective, evidence-based recruitment and retention strategies to engage participants on a more productive level, ultimately resulting in better quality research. Thus, the aim of this thesis was to improve the current understanding of the retention of people with schizophrenia in trials evaluating complex interventions. The specific empirical objectives and research questions this thesis set out to answer will be discussed in Chapter 3 following an introduction to the relevant background literature in Chapter 2.

1.2 Research context

This thesis presents the doctoral research undertaken as part of a Life Sciences Initiative studentship awarded in 2014. The studentship involved a multidisciplinary collaboration between the Wolfson Institute of Preventive Medicine and the School of Geography and aimed to provide the candidate with the opportunity to develop broad as well as in-depth understanding of the selected topic area from a multidisciplinary viewpoint (Life Sciences Initiative 2014). The candidate undertook the research at the Unit for Social and Community Psychiatry, part of the Wolfson Institute of Preventive Medicine at Queen Mary University of London (QMUL) comprising approximately 25 researchers with backgrounds in psychology, psychiatry, and anthropology. The Unit's portfolio of work includes a range of studies, mainly trials on novel complex interventions conducted in collaboration with the registered Pragmatic Clinical Trials Unit at QMUL. The Unit is jointly operated by QMUL and East London NHS

Foundation Trust and has been a World Health Organisation Collaborating Centre for Mental Health Service Development since 2012. The work presented in this thesis has been presented to the Unit's research team at regular research seminars, providing the opportunity to discuss the process and findings in a multidisciplinary setting.

1.3 Thesis overview

This thesis is presented in eight chapters. **Chapter 1** has outlined the rationale for this doctoral research, its main aim, the context within which it was conducted, and the structure of the thesis. **Chapter 2** provides a review of the relevant background literature, including: introduction to schizophrenia, developing and testing complex interventions for schizophrenia, and retention of patients with schizophrenia in clinical trials. **Chapter 3** is a brief interim chapter, which briefly outlines the specific objectives and research questions informed by the literature discussed in the previous chapter and discusses the epistemological and methodological approaches taken to address them. **Chapter 4** deals with the attrition rates reported in publications identified in a systematic literature search and identifying factors predicting those rates in a meta-analysis. **Chapter 4** takes a closer look at the factors associated with study retention in a meta-analysis of individual patient data from a convenience sample of relevant trials and considers the pattern of retention across the duration of a trial. **Chapters 6 and 7** present findings from two qualitative studies. Experiences of trial researchers and their practices are discussed in **Chapter 6** and the perspectives of former trial participants on their participation and retention practices are explored in **Chapter 7**. Finally, **Chapter 8** revisits the research aims and summarises study findings before offering interpretation and implications for enhancing retention rates in complex intervention RCTs involving people with schizophrenia.

Chapter 2
Background literature: theory and practice of participant retention in randomised controlled trials of complex interventions for schizophrenia

2.1 Chapter overview

Participant retention in trial follow-up assessments and completion of complex interventions for schizophrenia evaluated in a trial context are the focal themes of this thesis. The focus on schizophrenia is deliberate, rather than merely an example of a research area, as there is a widely-held concern around the level of engagement of patients with a diagnosis of a psychotic disorder in both psychiatric treatment and clinical research.

The following chapter formulates the rationale for this remit by outlining relevant methodological and clinical challenges. The nature of schizophrenia and the currently available treatments will first be introduced, followed by a discussion of an RCT as a method used to develop and evaluate new treatments for schizophrenia. It then focuses on what guides the conduct of trials in a methodological and pragmatic sense and contrasts studies evaluating pharmacological and non-pharmacological interventions. The particular issues surrounding involving and retaining people with schizophrenia in trials are discussed. Retention rates and the factors they are affected by are also considered in light of the existing evidence. Finally it discusses the strategies used by trial researchers to aid retention and examines the perspectives of participants who make decisions about their involvement in trials.

2.2 Introduction to schizophrenia

2.2.1 Clinical presentation and impact of schizophrenia

Schizophrenia is a serious psychiatric disorder characterised by disrupted thinking, behaviour, communication and emotional responses. The term 'psychosis' is used to describe a set of conditions, including schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder and non-affective psychoses. Some literature includes bipolar disorder and unipolar psychotic depression in the group of psychotic disorders. This thesis will use the term 'schizophrenia' to encompass all diagnoses falling under section F2 of the International Classification of Diseases (ICD-10), namely schizophrenia, schizotypal and delusional disorders (World Health Organisation 1992).

Although each person who develops a psychotic disorder will experience a unique combination of symptoms, there are models and guidelines used for assessing and understanding cognitive and behavioural factors associated with the diagnosis. Positive symptoms include delusions, hallucinations, disorganised speech and/or behaviour, and agitation. Negative symptoms include affective flattening (i.e. limited range of emotional expression, poor eye contact, and reduced body language), alogia (i.e. poverty of speech), and avolition (i.e. inability to initiate and persist in goal-directed activities). Cognitive symptoms may include difficulties with verbal fluency, attention, and working memory. According to the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) (American Psychiatric Association 2013) at least two of those symptoms need to be present for at least six months and include at least one month of experiencing active symptoms before a formal diagnosis can be made.

Whilst the condition has been shown to affect approximately 1% of the world's population (Freedman 2003, Saha *et al.* 2005), making it a relatively low incidence, it is one of the leading causes of disability and comprises a considerable proportion of the global disease burden (Murray and Lopez 1996). In England alone, its annual cost in 2007 was estimated at £2.2 billion, with a projected increase to £3.7 billion by 2026 (Mangalore and Knapp 2007). The scale of this burden has been attributed to two particular features of schizophrenia: early onset and persistent and fluctuating symptoms (Saha *et al.* 2005). In addition, compared to the general population, people

with schizophrenia have been reported to experience shorter life expectancy (Beary *et al.* 2012) and higher rates of mortality and suicide (McGrath *et al.* 2008, Hor and Taylor 2010, Reininghaus *et al.* 2015). Physical and psychiatric co-morbid conditions are common within this population, including substance misuse (Buckley 1998), obesity, type II diabetes and coronary heart disease (Morgan *et al.* 2014). Medication typically taken by people with schizophrenia to manage psychotic symptoms often introduces additional physiological challenges such as impaired movement, cataracts, and sexual dysfunction (Marder *et al.* 2014). Individuals diagnosed with schizophrenia have been found to struggle with employment (Morgan *et al.* 2014), social functioning (Wiersma *et al.* 2000), and self-care (Liddle 1987, Holmberg and Kane 1999). Moreover, the condition can often lead to caregiver burden (McDonell *et al.* 2003), consequently adding to the overall burden of the illness.

Given its substantial impact on individuals, caregivers and society at large, schizophrenia presents an important issue requiring further research identifying the best treatment for this population.

2.2.2 The treatment of schizophrenia

Treatment of schizophrenia most commonly involves a combination of medication, on-going support and information, and therapies or rehabilitative strategies (Adams *et al.* 2000). The currently recommended approach to treatment in the UK combines antipsychotic medication with psychological interventions (National Institute for Health and Care Excellence 2014). Despite this recommendation, the pervasiveness of pharmacotherapy is discernible in the scientific inquiry into new treatments for schizophrenia. A great proportion of clinical trials testing treatment for schizophrenia, reported to be as high as 86%, have investigated the efficacy of drug treatments (Thornley and Adams 1998). One reason for this disproportion between trials evaluating pharmacological interventions and those testing non-pharmacological treatment could be the need for the pharmaceutical industry to generate efficacy evidence in order to obtain a license and introduce the drug into the marketplace (Russell 1996). However, given that the recommended approach combines both types of treatments, this imbalance points to the need for generating more evidence around new non-pharmacological interventions for schizophrenia.

Some debate exists with regards to the mechanisms of psychiatric drug actions. The 'disease centred model of psychiatric drug action' developed in the 1950s and 1960s focuses on targeting the biochemistry that produces particular symptoms of schizophrenia. An alternative, 'drug centred model of drug action' emphasises the physical and mental states induced by pharmacotherapy (Moncrieff and Cohen 2009). In contrast to these models concerned with the impact of psychiatric drugs, a non-pharmacological approach focuses on enabling patients with psychosis to cope with the illness through cognitive, behavioural, vocational, and psychosocial approaches (Eon and Durham 2009). Current evidence proposes three strategies for non-pharmacological treatment: 1) to support or educate (for instance psychoeducational programmes or family interventions); 2) to provide specific skills training (for instance life skills programmes); and 3) to focus on a problem or symptom (for instance cognitive rehabilitation or psychodynamic therapy) (Adams *et al.* 2000, NHS Centre for Reviews and Dissemination 2000). However, this typology is not exhaustive as some existing interventions would not fall under any of the above strategies, for example solution-focused therapy, which is goal-directed and focuses on solutions rather than problems (O'Connel 2005, Priebe *et al.* 2013, 2015). Interventions can be delivered either individually or in a group setting, with the latter offering an attractive option to health care providers in light of the increasing demand for inexpensive and accessible forms of psychiatric treatment (McCrone *et al.* 2008, Burlingame 2014).

Most non-pharmacological interventions have multiple interconnecting components, which interact in non-linear causal pathways, making the majority of them fall into the category of complex interventions (Grant *et al.* 2013). Craig and colleagues (2008, p.2) list five characteristics of a complex intervention: 1) multiplicity of the interacting components; 2) multiplicity and complexity of behaviours required by those delivering or receiving the intervention; 3) multiplicity of groups or organisational levels targeted by the intervention; 4) multiplicity and variability of outcomes; and 5) permitted degree of flexibility of the intervention.

Complex interventions conform to specific processes but their format depends on the context, yielding them non-standard (Hawe *et al.* 2004, Petticrew 2011). The Medical Research Council (2000) distinguishes four types of complex interventions: 1) individual patient care, for instance cognitive behavioural therapy; 2) organisational or service modification, for instance community treatment order; 3) interventions targeting health professionals, for instance educational interventions; and 4)

population level interventions, for instance health campaigns. Because of this context-dependence and multifaceted nature, testing complex interventions in trials can pose methodological challenges (Oakley *et al.* 2006, Grant *et al.* 2013) and requires sufficient preparation and training of staff to ensure consistency of treatment (Medical Research Council 2000).

2.3 Evidence-based medicine: developing and testing complex interventions for schizophrenia

2.3.1 Evidence-based medicine

The term 'evidence-based medicine' (EBM) has been in use since 1990s when it was first coined by David Sackett and his colleagues. They defined EBM as: "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research." (Sackett et al. 1996, p.1).

EBM, also referred to in the literature as 'evidence-based practice' (EBP), advocates a move in clinical practice from an 'authoritarian' attitude based on professional opinions to an 'authoritative' one drawing on evidence (Gart *et al.* 1992, Sackett *et al.* 1996, Straus and McAlister 2000, Akobeng 2005, Seshia and Young 2014). This is achieved by helping clinicians to identify and apply the best quality information, together with clinical expertise and patients' choice, in clinical decision making (Sackett *et al.* 1996). The principles of EBM have guided medical education and supported clinicians in following evidence-based practice. The process of EBM, as described by Dawes et al. (2005) involves five steps:

Translation of uncertainty to an answerable question.
Systematic retrieval of best evidence available.
Critical appraisal of evidence for validity, clinical relevance, and applicability.
Application of results in practice.
Evaluation of performance.

With the increasing amount of evidence generated in clinical trials, there was a need to consolidate the knowledge and incorporate it systematically into medical practice. One

of the most significant developments that enabled this need to be met was the creation of the Cochrane Collaboration. The group, operating since 1993, facilitates systematic reviews of best available trials across different disciplines and provides instrumental evidence in medical treatment and health services (Chalmers 1993).

2.3.2 Methodological and practical fundamentals of a randomised controlled trial

A cornerstone of EBM was establishing a hierarchy of medical literature, which provides a system of rating evidence on the effectiveness of interventions (Elamin and Montori 2012). The hierarchical classification (Figure 2.1) places RCTs near the top due to a low risk of bias and systematic errors (Burns *et al.* 2011).

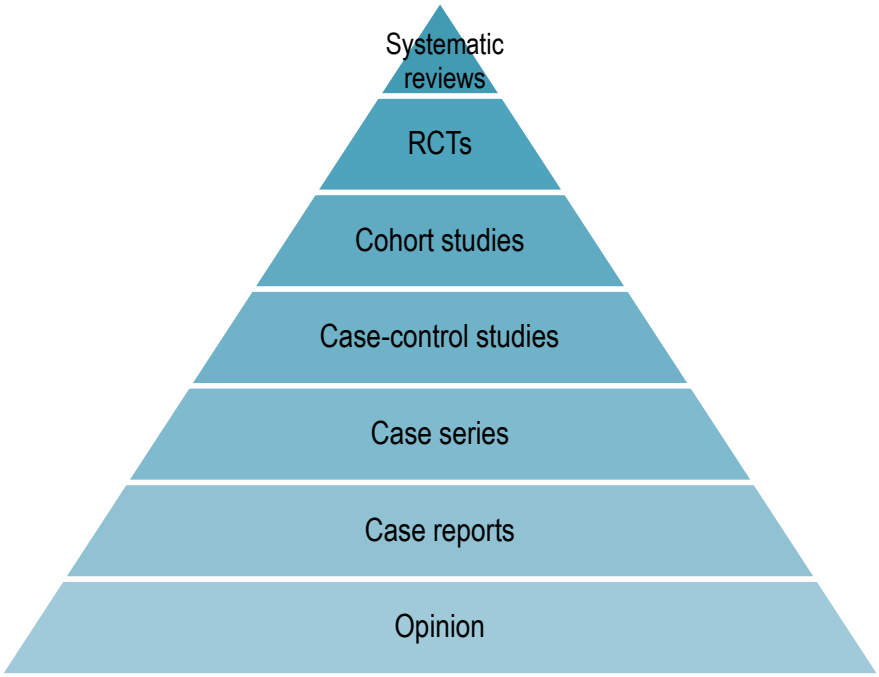


Figure 2.1 Hierarchy of evidence [adopted from (Akobeng 2005)]

A randomised controlled trial is referred to as a 'gold standard' in EBM as it offers the most scientifically rigorous method of evaluating the effectiveness of an intervention (Sackett *et al.* 1996). The need for rigorous evaluation of non-pharmacological interventions, especially psychological and behavioural ones, has resulted in the rise of trials evaluating complex interventions (Friedli and King 1998, Stephenson and Imrie 1998, Campbell *et al.* 2000).

The most commonly applied RCT design is one involving two arms delivered in parallel. One group receives a new intervention being tested ('experimental' or 'active group') and the other ('comparison' or 'control group') is given an active control condition, an inactive control (treatment as usual) or a placebo (Figure 2.2). Multiple-armed RCTs compare an active treatment with an alternative active treatment (or multiples of it) and an inactive control/placebo.

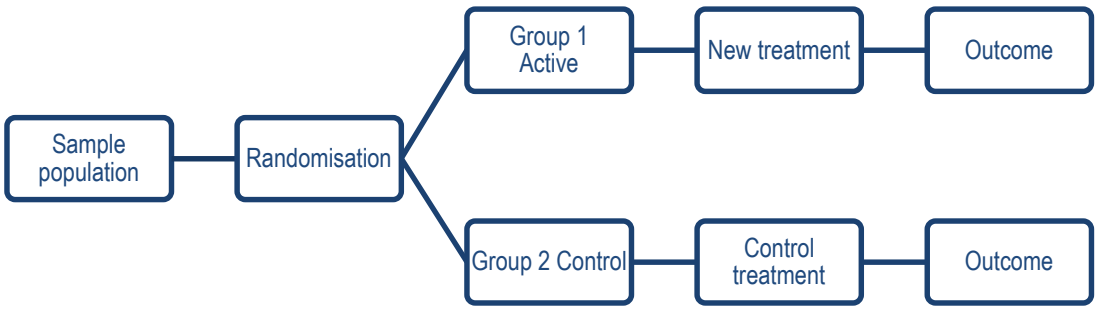


Figure 2.2 The RCT model [adopted from Kendall (2003)]

One of the key features of an RCT is random allocation to the treatment groups. Randomisation ensures that participants are assigned to either experimental or control group with no selection bias, i.e. certain characteristics affecting which intervention is given to an individual. A correctly conducted randomisation should yield treatment groups as alike as possible achieved by distributing all characteristics of patients (for instance age, sex, illness duration) randomly across the trial arms. All groups are followed up for the same period of time and subjected to the same procedures with the exception of the treatment. Since the treatment is the only factor setting the groups apart, any differences observed in outcomes can be attributed to the treatment under evaluation.

Another procedure employed to minimise bias in RCTs is 'allocation concealment'. It is an essential technique used to prevent selection bias by preventing the researcher or clinician responsible for assigning participants to treatment arms from having any influence on which patients are given which treatment. This is a different concept to 'blinding' or 'masking', which applies after participants have been allocated to treatment. The most common application of this procedure is 'double blinding', which applies to trials where both participants and researchers collecting data are unaware of

the participant's arm allocation. This practice eliminates the potential bias in measuring the outcomes and prevents the expectations of participants or researchers from influencing the possible effect. While double blinding is possible to achieve in pharmacological trials, where the study drugs can be made to look alike, it presents challenges in trials evaluating complex interventions and often requires nonstandard methods (Boutron *et al.* 2006).

The process of conducting an RCT is best illustrated by the Consolidated Standards of Reporting Trials (CONSORT) flow diagram (see Appendix 1). The diagram depicts the passage of participants through the main phases of a clinical trial. Following the selection of a representative population sample from which to recruit a required number of trial participants, each participant's eligibility is assessed and those who do not meet pre-specified inclusion criteria are excluded. Once eligibility has been checked and informed consent obtained, researchers measure relevant baseline variables. Patients who complete the baseline assessment continue on to the next stage: random allocation to treatment. Subsequently, the intervention is delivered for a specified period of time. Participants are followed-up at pre-specified time points to record outcome measures needed for the final analysis. Importantly for this thesis, given the longitudinal nature of trials and participants' right to withdraw at any point, each stage of the trial process carries the risk of losing participants. One of the ways of ensuring the internal and external validity of RCTs is to minimise the loss of participants following recruiting the required numbers.

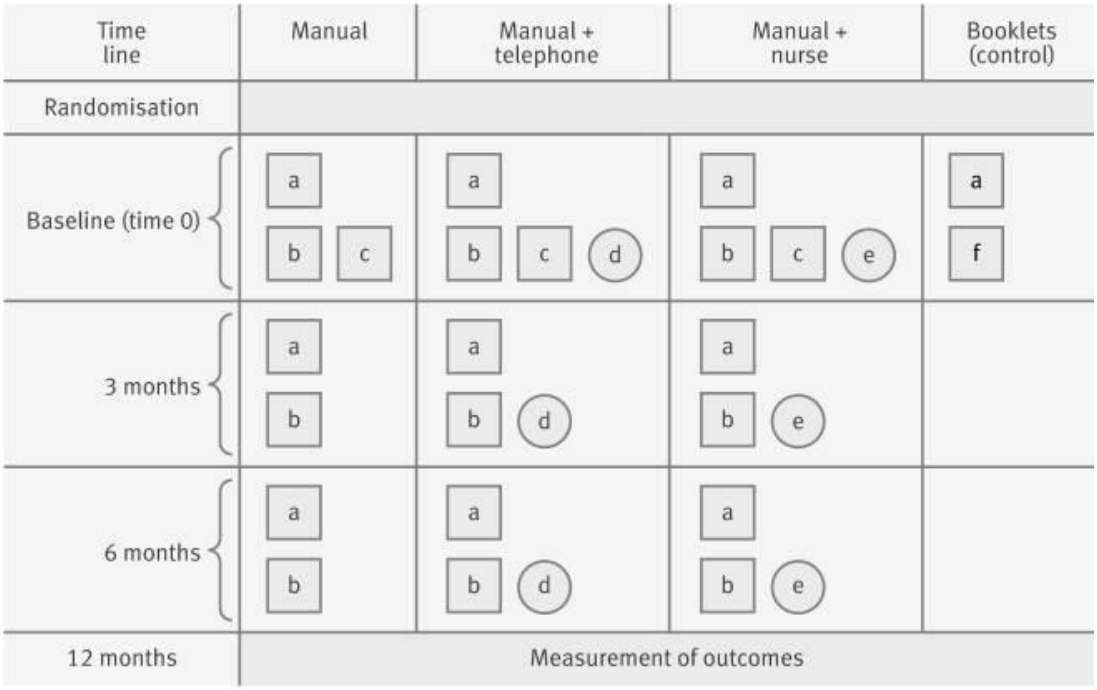
Despite the considerable development of trial processes over the past 15 years RCTs evaluating non-pharmacological interventions frequently suffer from methodological shortcomings preventing them from detecting important treatment effects (Adams *et al.* 2000, Campbell *et al.* 2000). Some of the concerns include insufficient statistical power, problems with study design, implementation failure or genuine ineffectiveness (Levati *et al.* 2016). Complex intervention trials have been argued to be particularly challenging in terms of controlling the required research conditions and reporting them adequately (Stephenson and Imrie 1998, Grant *et al.* 2013).

2.3.3 Reporting trial information

Judging the validity of trials relies on information about participant flow but the quality of reporting the details has been found to be suboptimal (Begg *et al.* 1996, Thornley and Adams 1998, Moher *et al.* 2001, Dumville *et al.* 2006). Reporting of trials evaluating complex interventions can present particular challenges given the intricacy of treatment and has been reported to be problematic (Craig *et al.* 2008, Glasziou *et al.* 2008, Michie *et al.* 2009, Pino *et al.* 2012). Problems specific to reports of this type of trials include providing incomplete descriptions of the interventions and/or materials used and a lack of definitions of intervention completion (Barnicot *et al.* 2011, Hopewell *et al.* 2011, Sohanpal *et al.* 2012, Hoffmann *et al.* 2013).

The issues with reporting across trial publications have led to the development of guidelines for transparent reporting of participant flow information. The CONSORT guidelines have been endorsed by many journals (for example *British Journal of Psychiatry*, *The Lancet, British Medical Journal*) in an attempt to encourage accurate, transparent and complete reporting of trials. This endorsement has been shown to be associated with better reporting of participant flow in RCTs (Plint *et al.* 2006, Kane *et al.* 2007, Turner *et al.* 2012), with some remaining gaps identified in a Cochrane review (Turner *et al.* 2012). Since the introduction of the original CONSORT guidelines, a further extension was developed specifically for the reporting of RCTs of Social and Psychological Interventions (SPI) and called CONSORT-SPI (Montgomery *et al.* 2013). However, so far, its uptake appears to be limited.

Other tools have been developed to aid reporting of complex interventions in addition to the CONSORT flowchart. These include the PaT plot, a graphical method for depicting the different intervention components and their sequencing (Perera *et al.* 2007)(see Figure 2.3 below) and, more recently, the cascade diagram showing the relationships between the actors delivering those components (Hooper *et al.* 2013)(see Figure 2.4 below). If used together, the three tools have been argued by their authors to form a complete description of an intervention including multiple components and levels (Hooper *et al.* 2013).



a	Questionnaire to determine stage of change, processes of change, self efficacy and decisional balance of participant using the transtheoretical model
b	"Expert system" personalised (6-8 sided) letter sent, based on participant's responses to each questionnaire. This gave feedback on the stage of change, decisional balance, self efficacy, and the process of change, with second and third letters giving progress since the previous letter
c	*Pro-change programme for a healthier lifestyle*, a 64 page colour booklet enabling participants to stage themselves. Anglicised version of booklet used in American trials. Contains exercises to help participants move from their current stage. Sent on return of questionnaire
d	Telephone call made by trained lay person (three hours training) on return of each questionnaire; based on script and non-interactive
e	Appointment with nurse made on return of each questionnaire to discuss personalised letter, participant's progress with the pro-change programme, and to encourage its implementation
f	Four standard items of self help material: *Stopping made easier*, a 24 page manual; *The quit guide to stopping smoking*, a 12 page booklet; and 2 credit card sized reminder cards (Benefits of smoking cessation, Tips for staying quit) sent on return of questionnaire

Figure 2.3 An example of a PaT diagram [adopted from Perera et al. (2007)]

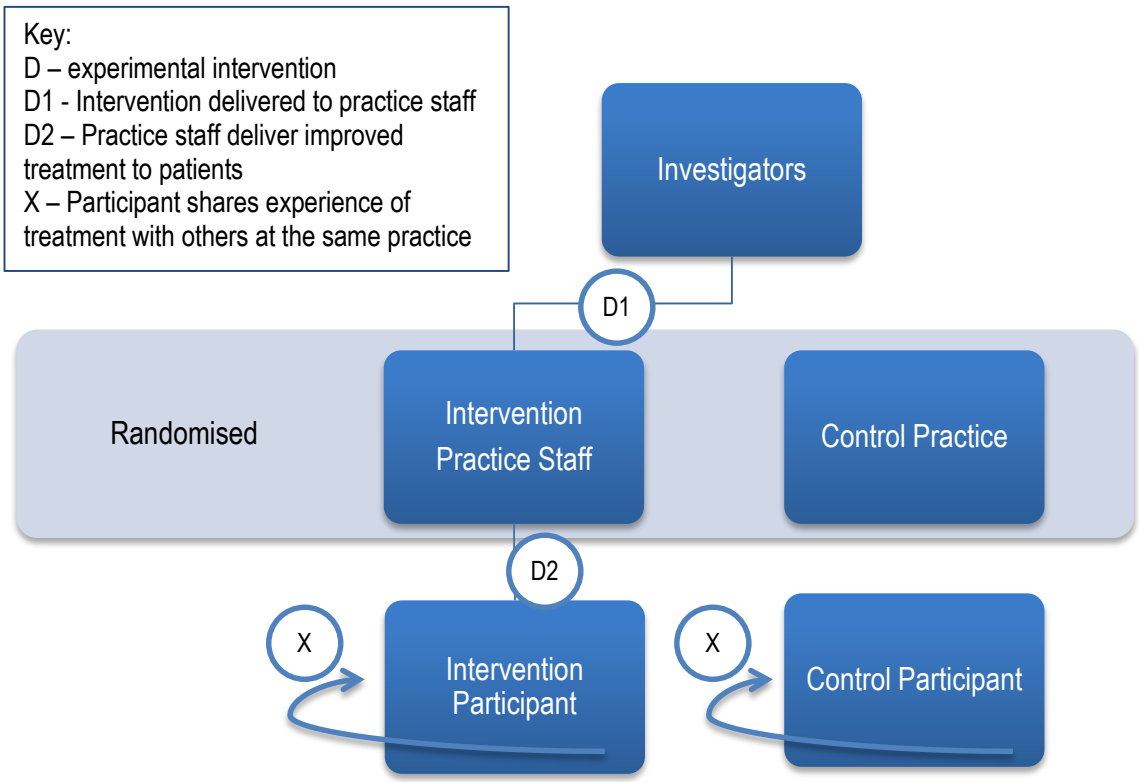


Figure 2.4 An example of a cascade diagram [adapted from Hooper et al. (2013)]

2.3.4 Patient with schizophrenia as a trial participant

In addition to the particular design and reporting standards applying to RCTs, clinical studies need to comply with a set of codes of practices and standards. All research carried out with human participants in the UK is required to obtain ethical approval of a relevant authority. Studies involving participants associated with the National Health Service (NHS) (which is the case for all RCTs of complex interventions in the UK) are subject to an ethics review by a Health Research Authority's Research Ethics Committee (REC).

Research involving people with schizophrenia needs to consider ethical concerns associated with the potential decision-making deficits experienced by some individuals with this diagnosis. A decision about participation in a trial requires every potential participant to assess the potential harms and benefits and to have some level of

understanding of particular trial attributes such as randomisation, blinding, or control condition. Trial participants need to agree to being repeatedly exposed to treatment and, in most cases, to completing multiple assessments of outcomes.

One of the most widely cited studies exploring the decision-making capacity of people with mental illness has been the MacArthur Treatment Competence Study carried out in the United States with 498 individuals with and without a diagnosis of a mental illness, including one sub-group including schizophrenia inpatients (Appelbaum and Grisso 1995, Grisso and Appelbaum 1995, Grisso *et al.* 1995). The study concluded that psychiatric inpatients had decision-making abilities similar to those without mental illness. However, approximately half of inpatients with schizophrenia showed high levels of impairment across four types of legal standards essential for decisional capacity, including the ability: 1) to understand relevant information; 2) to appreciate its implications for one's own situation; 3) to reason with information; and 4) to express a choice (Appelbaum and Grisso 1995). Furthermore, the findings suggested that these impairments could be temporary, reflecting the fluctuating nature of the severity of schizophrenia symptoms.

More recent studies present conflicting evidence on whether or not individuals with schizophrenia have sufficient capacity to provide informed consent for research participation (Carpenter *et al.* 2000, Roberts *et al.* 2002). Carpenter and colleagues (2000) proposed that impaired capacity to make decisions about taking part in research can be remediated by providing sufficient opportunities to learn the necessary information, placing emphasis on the routine procedures carried out by researchers. Other evidence has highlighted the diversity of factors affecting the ability to engage in research, including: the severity of symptoms and cognitive deficiencies (Roberts 1998); stability of lifestyle, substance misuse (Lecomte et al., 2012); sensitivity of the research subject (Jorm *et al.* 2007); specific research context, involvement of alternative decision-makers, values held by individuals, and the nature and quality of the relationship between researcher and participant (Roberts *et al.* 2000). The diversity of these factors highlights the complexity of involving people with schizophrenia in research and in psychiatric treatment (Lecomte, Leclerc, and Wykes 2012).

Although the evidence on the capacity to consent among people with schizophrenia is sizeable, it has focused mainly on the informed consent provided at the point of recruitment to a research study. Longitudinal studies require multiple assessments,

often over an extended period of time, and thus require researchers to continuously ensure that participants continue to give voluntary consent. The risk of a participant losing capacity to consent prior to the conclusion of a longitudinal study is acknowledged in the Mental Capacity Act 2005 for England and Wales (Department of Health 2005). Consequently, there is a need to consider fluctuations in mental health and their potential impact on a person's capacity to monitor their willingness to remain involved in a study. One such study by Palmer *et al.* (2013) investigated the changes in capacity to consent over time in individuals with schizophrenia and bipolar disorder taking part in a longitudinal study of the side-effects of antipsychotic medications. The results showed that any improvements in understanding of study information dissipated at each subsequent follow-up assessment. This did not affect decisional capacity in all participants but worse neuropsychological performance was associated with poorer performance. The study suggests that some patients are likely to experience fluctuations in their capacity to make decisions about research participation over the duration of study.

2.4 Retention of patients with schizophrenia in clinical trials

2.4.1 The attrition problem

Most literature concerned with trial methodology has focused on recruitment issues, presenting it as the "single most important aspect of a successful trial" (Borschmann et al. 2014, p.2) and the key to achieving a sufficiently powered sample. However, while recruitment is the first step towards achieving sufficient power and delivering a successful trial, it does not guarantee those two important aspects. In this respect, retention is required to achieve these aspects by striving to keep as many people in the trial as possible. If a high number of participants are lost following enrolment into a trial, the recruitment efforts are wasted. Retention, therefore, has a significant role in ensuring the validity and cost-effectiveness of research.

The introduction of standardised methods for reporting participant flow discussed in section 2.3.1. was an important step in enabling comparisons of retention rates across different studies as well as identifying factors predicting retention (Karlson and Rapoff 2009). However, such comparisons require a shared understanding of what retention

is and this has been found to vary across studies (Kane *et al.* 2007). The inconsistency in definitions can result in variability in the reported retention rates and may consequently complicate further analyses.

Retention has been defined as the continued involvement of research participants over the projected study duration (Davis *et al.* 2002), involving developing and maintaining relationships with participants (Patel *et al.* 2013). Failure to retain participants in a study is commonly referred to as 'attrition'. However, there is a considerable lack of clarity and consistency of terminology in trial publications and the literature discussing the different types and levels of attrition. Some of the relevant terms appearing in the literature include non-adherence (Christensen *et al.* 2009, Dodd *et al.* 2012), premature or early termination (Hatchett and Park 2003, Arnow *et al.* 2007, Ong *et al.* 2008, Swift and Greenberg 2012), non-persistence (Donkin and Glozier 2012), non-usage attrition (Eysenbach 2005), non-participation (Toerien *et al.* 2009), withdrawal (Martin *et al.* 2006, Grant *et al.* 2009, Toerien *et al.* 2009, Leucht *et al.* 2013), and discontinuation (Eysenbach 2005, Martin *et al.* 2006, Warden *et al.* 2009, Swift and Greenberg 2012).

A comprehensive typology of attrition proposes five variations, each corresponding to a different trial process outlined in the CONSORT diagram (see Figure 2.5): 1) enrolment refusal, 2) baseline attrition, 3) post-randomisation attrition during intervention, 4) post-randomisation attrition during follow-up, and 5) attrition due to missing data (Karlson and Rapoff 2009).

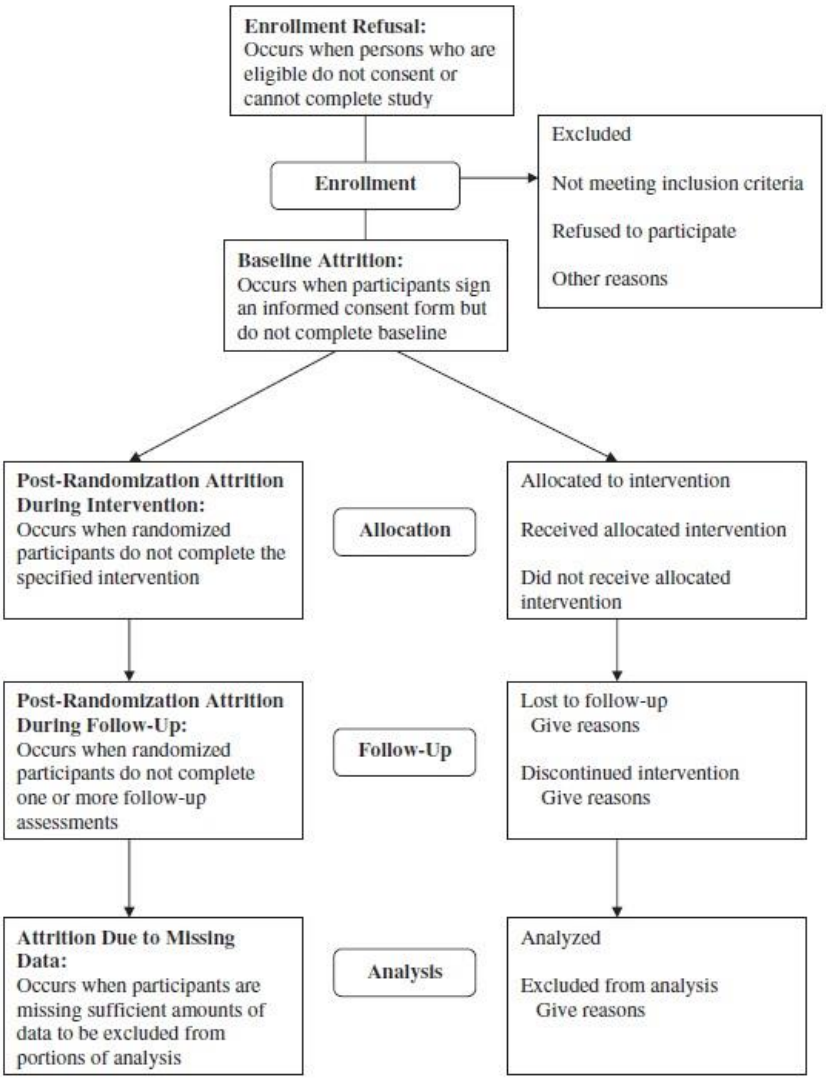


Figure 2.5 Definitions of attrition [adopted from (Karlson and Rapoff (2009)]

Marcellus (2004) proposes that participants can be considered 'non-completers' or 'dropouts' if they fail to complete the treatment protocol or if they are lost to follow-up. The former term is more commonly associated with retention at the intervention level, also referred to as 'treatment adherence' or 'treatment attendance'; the latter relates to study retention or failure to complete follow-up assessments. These definitions, however, are not consistently applied in the literature.

Treatment adherence has been defined as "the extent to which a person's behaviour in terms of taking medications, following diets or executing lifestyle changes coincides with the medical or health advice" (Haynes & Sackett 1979, p.27) and is a common

problem in psychiatry (Nose *et al.* 2003). In pharmacological trials, adherence generally relates to the extent to which patients take prescribed medication being tested. In psychiatric trials, it can be further classified into adherence to medication and adherence to scheduled appointments (Nose *et al.* 2003). In the case of trials evaluating complex interventions, adherence depends on the treatment and can be considered as entry to treatment, the amount of sessions attended, or implementation of instructions (Nose *et al.* 2003). Non-adherence to treatment has a major impact on the effectiveness of complex interventions and presents challenges in both clinical and research practice (Nose *et al.* 2003, Haynes *et al.* 2006). In addition, while in pharmacological treatment non-adherence can be an important indicator of dropout caused by problems with treatment tolerability or adverse effects (Rabinowitz *et al.* 2009), in complex interventions it may suggest issues with acceptability, willingness of participants to engage with treatment, or pragmatic issues to do with attending treatment.

The concepts of retention and attrition can be considered as two opposing ends of a spectrum of research participation. Both terms will be used throughout this thesis when referring to the phenomenon of continuous involvement of participants in a research study. Distinctions will be made between the different levels and types of retention or attrition to describe the extent to which individuals complete research procedures and/or interventions.

While retention is important for any study, it bears particular importance for clinical trials where failure to retain sufficient numbers of participants may lead to many issues, including limited statistical power, bias, lack of internal and external validity, prolonged trial duration or, in extreme cases, its premature closure (Gross and Fogg 2001, Williams *et al.* 2007, Marcantonio *et al.* 2008, Gul and Ali 2010). For example, high attrition rates have been identified as a cause of publication bias particularly in trials of Internet-based interventions, with difficulties to publish results of studies that experience a substantial loss of participants (Eysenbach 2005). Overall attrition comprises the total loss of data across all trial groups. Given that the aim of randomisation is to ensure that participants share the same characteristics at baseline, dropout can create an imbalance between the groups if the participants who have provided follow-up data are different to those who have not. In contrast, selective or differential attrition occurs when the degree of dropout differs between trial arms, resulting in groups that look different from the initial randomised groups. In this case any differences in dropout between groups can lead to researchers erroneously

attributing any changes in outcomes solely to the treatment being tested. Some evidence proposes that differential attrition can be a consequence of perceived efficacy or tolerability of treatment (Stein *et al.* 2006). In addition, Wortman, (1978) suggested that participants who receive an active intervention feel obligated to complete follow-up assessments more than those in the control arm. However, some evidence suggests that these differences are more likely to be observed in trials that cannot blind participants, thus resulting in perceived differences in treatment (Boutron *et al.* 2006). Although the risk of issues created by attrition have always been concerns for trial conduct, Gross & Fogg (2001) argue that improved access to health care information, empowerment of patients and lack of trust in research have increased the magnitude of threat posed by attrition in RCTs.

2.4.2 Reported retention and attrition rates

Attrition rates in studies across different areas of medicine and types of interventions range from 5 to 70% (Marcellus 2004), showing large variability. Some variation can be expected depending on the type of treatment (i.e. medication or therapy) and the clinical population under study. While studies investigating dropout or non-adherence in drug trials across different illnesses are abundant (for example Hugtenburg *et al.*, 2013; Gelaw *et al.*, 2014; Dauw *et al.*, 2016), such investigations in the context of trials of complex interventions are scarce and the existing ones focus mainly on mental health. This could be due to the influence of the biomedical model of illness in the physical health care, although other models that recognise the importance of psychological and social factors do exist and are in use (Wade and Halligan 2004). The number of studies investigating psychosocial interventions can be expected to directly correspond to the number of studies, especially systematic, exploring retention and adherence in this context. This in turn limits the evidence available for the purposes of making comparisons in the context of the present study to mainly mental health conditions.

Most systematic studies available on the subject of attrition in non-pharmacological interventions for mental health conditions have focused on depression as a disorder and treatment adherence as a phenomenon. The available evidence examined a range of interventions, including CBT, psychotherapy, and physical activity. For example, a meta-analysis of adherence to CBT for depression reported in 24 studies found that intervention completion was higher when the therapy was delivered face-to-face

(84.7%) than in Internet-based CBT (65.1%) (van Ballegooijen *et al.* 2014). A similar rate, although expressed as attrition, was found in a meta-analysis of 54 RCTs of psychotherapy for major depression, showing 17.5% dropout from the intervention and 19.9% at the study level (Cooper and Conklin 2015). Physical activity interventions for depression evaluated in 40 RCTs attracted an average attrition rate of 18.1% (Stubbs *et al.*, 2016, p.463). Completion of psychosocial treatment has also been systematically studied in the context of borderline personality disorder (Barnicot *et al.* 2011). While the disorder has been associated with low treatment completion rates, a meta-analysis of 41 RCTs evaluating psychotherapeutic interventions found that on average 75% of patients complete the treatment if it is shorter than 12 months. A lower completion rate of 71% was found for treatment duration longer than 12 months. Overall, the available evidence has presented adherence to complex interventions for depression and for borderline personality disorder as adequate; however, at the same time a considerable variability has been found across individual trials.

Loss of any proportion of participants creates bias, however different attrition levels lead to different levels of problems. Losing fewer than 5% of the original sample is likely to lead to little bias, however attrition levels exceeding 20% pose a serious a threat to validity (Polit and Hungler 1995, Sackett *et al.* 2000, Schulz and Grimes 2002, Gul and Ali 2010). Internal validity may be compromised if the treatment groups are non-equivalent and random composition of the groups is altered (Kazdin 1999). High attrition can also limit the generalisability of the findings to only those who remain in the study, thus compromising external validity (Karlson and Rapoff 2009).

There are multiple statistical methods to deal with missing data resulting from attrition, such as intention to treat (ITT) analysis, complete case analysis, simple imputation, and last observation carried forward. Although it is beyond the scope of this thesis to review all of these approaches, it is important to acknowledge their application. The implications of missing data need to be considered at each stage of a trial and statistical methods present one option of dealing with missing data in RCTs by increasing statistical power and reducing bias. However, a review of RCTs published in top medical journals highlighted inconsistencies in the definitions and applications of statistical methods and called for an improvement of handling missing data in RCTs (Bell *et al.* 2014). Moreover, the authors have argued that "prevention is the best way to handle missing data, so more effort needs to be put into missing data at the design and conduct stage" (p.7), underscoring the importance of maximising participant retention.

Despite the methodologically acceptable attrition rates at the study level estimated to be below 20%, as discussed above, the dropout levels judged as acceptable in published systematic reviews of antipsychotic medication were found to vary between 40% and 50% (Hutton *et al.* 2012). In addition, a survey carried out by the Cochrane Schizophrenia Group with psychiatrists, researchers and carers showed that credibility of trials can suffer if attrition exceeds 25% (Xia *et al.* 2009).

The rates of dropout from intervention vary between trials evaluating pharmacological versus non-pharmacological treatment for schizophrenia. The attrition rates from pharmacological interventions have been estimated at 33% (Wahlbeck *et al.* 2001) and 48.9% (Kemmler *et al.* 2005). In contrast, a meta-analysis of dropout from psychosocial treatment reported between 1997 and 2007, defined as "the loss of participants either prior to treatment (never showed up) or during treatment (stopped treatment before it was completed)" (p. 267), has reported the rate of 13% (Villeneuve *et al.* 2010). The authors do not report the difference between the attrition occurring prior to versus during treatment; however these two types of dropout can be expected to differ given the change of context following receiving treatment. In addition, the attrition rate obtained in the meta-analysis is discussed in the context of treatment compliance, despite the authors making a clear distinction between a complete withdrawal from treatment and a proportion of completed treatment visits. The limitations of this study highlight the need for clear definitions of attrition, especially when considering compliance with non-pharmacological treatment. Overall, the results of the meta-analyses discussed above show that compared to drug treatment, non-pharmacological interventions attract lower attrition rates, despite the treatment being on average six times longer.

In addition to attrition levels, a systematic review of adherence to either pharmacological or non-pharmacological treatment programmes by patients with psychosis in studies published since 1980 found that 25% of patients failed to adhere; a rate lower compared to previous studies (Nose *et al.* 2003). There is some evidence suggesting that high non-compliance rates in clinical trials of antipsychotic medication are not restricted to a clinical trial setting. For example, a study of the Norwegian Prescription Database showed that 43% of 9,000 patients failed to return for their second antipsychotic prescription (Kjosavik *et al.* 2011). Thus, exploring attrition in a research setting can provide some indication of the potential reasons for non-adherence to treatment in clinical practice.

2.4.3 Factors affecting participant retention in trials

In addition to estimating the levels of retention in RCTs involving people with schizophrenia, it is also important to understand the reasons for and patterns of loss to follow-up throughout the duration of a trial (Brueton *et al.* 2014). This information can affect both the interpretation of results and conduct of trials to minimise attrition and enhance the level of engagement (Davis *et al.* 2002, Thompson *et al.* 2011, Lecomte, Leclerc, and Wykes 2012). One of the most common approaches to determining the factors affecting retention involves using available data to investigate any effects of study and/or participant characteristics on retention (Karlson and Rapoff 2009).

This approach has yielded a number of studies identifying predictors of retention in clinical trials. Early research focused on patient characteristics, reflecting a belief that attrition is patient-driven, before starting to consider retention to be influenced by a range of factors, including those related to trials and to individuals (Carroll 1997). As a result, factors relevant to research staff, therapists and study design started to also be taken into account as potential predictors of retention. Studies considering the pattern of retention over time have consistently suggested that the highest proportion of dropout occurs early in a trial. Carroll (1997) explained this trend by the self-selective nature of trials, poor treatment and/or therapist fit, and inappropriate timing of treatment. On the other hand, Hewitt *et al.* (2010) posited that researchers invest more resources into retaining trial participants at the final follow-up than at earlier assessments.

There are a number of studies that have retrospectively examined the predictors of retention across trials in different disease areas, for example chronic major depression (Arnow *et al.* 2007), human immunodeficiency virus (Villaruel *et al.* 2006), and lung health (Snow *et al.* 2007). Among the factors shown to be correlated with attrition are: age (Moorman *et al.* 1999, Snow *et al.* 2007), ethnicity and gender (Senturia *et al.* 1998, Arnow *et al.* 2007), education (Hill and Humenick 1995), severity of illness (Verheggen *et al.* 1998), psychological distress (Moser *et al.* 2000), and patterns of health care utilisation (Morse *et al.* 1995). In addition, some studies have attempted to create profiles of a stereotypical participant likely to drop out, for instance: "an older, non-white male with limited education, multiple health problems, increased life stress, and a pattern of erratic health utilisation" (Davis et al. 2002, p.47) in community-based trials not limited to any specific disease and, in contrast, "young male patients with poor

insight of illness, a history of substance abuse, unemployed and with low social functioning" in a systematic review of non-adherence rates among patients with psychosis (Nosé et al. 2003, p.1155). Creating such profiles has been argued to inform judgements about the risk of the participant dropping out (Nose *et al.* 2003) and to help with adoption of appropriate retention strategies (Brueton *et al.* 2014). However, the lack of uniformity in the patient characteristics associated with dropout rates suggests that participant retention may be trial, treatment and disease specific (Carroll 1997, Brueton *et al.* 2014). Thus, factors found to be associated with dropout or retention in one group of studies cannot be reliably used to inform studies involving different populations.

Compared to other diseases schizophrenia has been argued to be particularly appropriate for the analysis of factors affecting dropout given its complexity and range of symptoms (Thompson *et al.* 2011). These types of analyses have been carried out in a small number of studies within the context of service use and participation in both pharmacological and non-pharmacological trials, with majority focusing on the former type. Results of a meta-analysis of trials evaluating antipsychotics showed an association between the study duration and higher dropout from treatment (Wahlbeck *et al.* 2001); however, the same effect was not found in trials up to three months long (Kemmler *et al.* 2005). Davis et al. (2002, p.48) argue that studies with high attrition rates tend to "have a longitudinal, repeated-measures design, complex interventions that include time-consuming contacts with unskilled or poorly trained staff, and non-relevant incentives for participation". Moreover, studies involving explicit analyses of predictors of dropout from antipsychotic trials have shown attrition to be higher amongst participants experiencing negative symptoms of schizophrenia (Thompson *et al.* 2011), those randomised to placebo arms in trials testing second-generation antipsychotics (Kemmler *et al.* 2005), and those experiencing delusions or substance abuse (Carroll 1997). Factors that did not show any significant effects on dropout are also important for considering what is and what is not associated with retention. These included patients' age, the Brief Psychiatric Rating Scale (BPRS) score at baseline, trial duration, publication year, use of multiple-dosage regiments in Kemmler *et al.*'s (2005) study and schizophrenia symptoms including positive, cognitive, excitement, and depression/anxiety as shown by Thompson *et al.* (2011).

In comparison to the literature concerned with retention in antipsychotic trials, less evidence is available on what influences retention in non-pharmacological treatment

of schizophrenia. Engagement of people with schizophrenia in services has been shown to be affected by factors such as substance abuse, rapport with their therapist, social functioning, severity of symptoms, and insight into the illness (Lecomte, Leclerc, and Wykes 2012). Similar findings were shown in a literature review of treatment compliance components among people with psychosis (Kampman and Lethinen 1999). The review included studies published between 1974 and 1997 and was therefore limited to mainly neuroleptic treatment; nevertheless the components reducing compliance included complex treatment regimens, side-effects, negative attitude towards medication, delusions, substance misuse, living alone, poor housing, and being male. Better compliance was associated with recognition of medication's benefits, support from family, family's awareness of the patient's illness, and social activity. The Villeneuve et al.'s (2010) meta-analysis of dropout from psychosocial treatment for schizophrenia discussed in the previous section also included an investigation of the moderators of treatment dropout. The study found higher treatment withdrawal to be associated with male gender, higher age, longer illness duration, longer treatment duration, and better study quality. In addition, individuals who received treatment in an inpatient setting had higher adherence rates than those in an outpatient setting. Two moderator variables that did not have an effect on the dropout rate were treatment modality (individual versus group) and severity of illness.

It has been suggested that retention is a multi-determined phenomenon affected by the interaction of sample and study characteristics (Beutler *et al.* 1997, Fenton *et al.* 1997, Stasiewicz and Stalker 1999). This was illustrated in a study of psychosocial treatment showing that providing the same intervention to a heterogeneous sample can increase the risk of drop out if participants perceive themselves to be in the wrong setting, receiving the wrong treatment from the wrong person (Carroll 1997). The finding illustrates the importance of ensuring the right fit between the trial participant and the key aspects of a trial, including researcher, intervention and context in maximising participant retention.

2.4.4 Retention from the perspective of the trial participant

An alternative approach to exploring the factors affecting retention draws on qualitative methods exploring the reasons for refusing to participate or to drop out (Karlson and Rapoff 2009). The perspectives of trial participants who make decisions

about their involvement are an imperative aspect of understanding retention and help to address some of the limitations of the analyses discussed in the previous section. There are a slowly increasing number of studies exploring the experiences of patients who take part in clinical trials but these tend to focus on the initial decision to participate during recruitment.

Research employing hypothetical scenarios to explore attitudes to trial participation has generally shown individuals to have a favourable view of research (Cassileth *et al.* 1982, Llewellyn-Thomas *et al.* 1991, Slevin *et al.* 1995). Similar results were also reported among people with schizophrenia (Roberts *et al.* 2000, 2006, Kim *et al.* 2009, Sumner *et al.* 2014). However, generalisation of findings from such studies is limited as they focus on supposed rather than actual behaviours and experiences of trial participation (Featherstone and Donovan 2002). Previous studies showed that it is possible to engage trial participants in qualitative research exploring their attitudes towards research (Verheggen *et al.* 1998, Featherstone and Donovan 2002, Hussain-Gambles 2004, Canvin and Jacoby 2006, McCann *et al.* 2010, Reynolds *et al.* 2011, Freuler *et al.* 2013, Hanley *et al.* 2013, Simmonds *et al.* 2013, Morrison *et al.* 2014), with a small number of such studies involving people with schizophrenia (for instance Roberts et al. 2004). Moreover, Featherstone & Donovan (2002) argue that non-participants report different reasons for their lack of participation than researchers, highlighting the need for gathering the views of both groups and, ideally, capturing the experiences of those who drop out or decide not to take part in the first place.

The current understanding of the decision-making process for taking part and remaining involved in clinical research is limited (Roberts et al. 2000; Trauth et al. 2000; Garety et al. 2008; Brintnall-Karabelas et al. 2011) and most available evidence comes from oncological studies. An example of such study is a systematic review and meta-analysis of patient-reported barriers to participation in trials, which analysed 12 qualitative and 21 quantitative studies addressing the attitudes and barriers of patients considering participation in cancer trials. The findings identified a number of concerns related to the trial methods, interruptions to patient lifestyle, and relationship with clinicians (Mills *et al.* 2006). These are similar to the findings of studies including other clinical populations, which have highlighted barriers such as: perceived personal disadvantage to do with receiving or not receiving treatment (McCann *et al.* 2010); health practitioners acting as gatekeepers to pragmatic RCTs (Patterson *et al.* 2011), depression trials (Mason *et al.* 2007), psychosis trials (Bucci *et al.* 2015); and poor

understanding of trial design and own participation in research (Featherstone and Donovan 2002). In addition, among the suggested reasons for participation in clinical trials in general are: altruism (McCann et al., 2010; Grant et al., 2009); willingness to contribute towards medical knowledge, an opportunity for learning about the condition, access to clinical review or monitoring, potential access to clinical treatment, personal benefit (McCann *et al.* 2010); commitment to the aims of the research, and a lack of concern about randomisation to study arms (Grant *et al.* 2009).

Attempts to explain recruitment challenges among people with a mental health problem have identified misconceptions about clinical trials, lack of equipoise, misunderstanding about trial aims, unclear eligibility criteria, and paternalism as potential factors (Howard *et al.* 2009). Brintnall-Karabelas et al. (2011) highlight the need for identifying specific factors, such as inconvenience, finances, or protocol issues, taken into account in the decision-making process that are modifiable and that could help to promote interest in research participation. Patients with schizophrenia have been shown to struggle with understanding trial-related concepts but also to be capable of improving with appropriate information-giving (Chong *et al.* 2009). The difficulties with decisional capacity of people with schizophrenia have been discussed in Section 2.3.4. The severity of schizophrenia symptoms has also been shown to affect attitudes to trial participation, with those experiencing more symptoms being, albeit modestly, less willing, less affirming and generally more negatively-inclined than those less ill (Roberts *et al.* 2006).

In contrast to recruitment, retention encompasses multiple, repeated decision-making about participation. Each time a participant who has been recruited to a study is to receive an intervention or to attend a research assessment he or she needs to make an active decision about continuing their participation. Given their right to withdraw at any point, participants are not obliged to complete their participation, thus the initial consent to take part does not guarantee their retention in a study (Harris and Dyson 2001). This is exemplified in studies showing trial participants' waning motivation over time (Wilson and Rose 1998, Lloyd-Williams *et al.* 2003, Stanford *et al.* 2003, Jancey *et al.* 2006).

There is a clear paucity of studies exploring decision-making and experiences of trial participation among people with schizophrenia, especially following enrolment into a study. It is possible that such investigations take place as part of an internal process

evaluation but their results are not subsequently published. Access to such evidence could be useful in understanding what affects the decisions of this population about remaining involved in a trial versus dropping out from treatment or study.

2.4.5 Strategies for maximising retention

The efforts to understand the patterns and predictors of retention have been made in order to develop ways of maximising participation levels, which is a principal condition for a successful completion of a trial. The first step toward achieving high levels of participation is recruiting a sufficient number of participants, dictated by sample size calculations. The subsequent task for trial researchers is to retain as many as possible of those patients in the study and treatment. Both processes have been described as key to successful trial completion and as major methodological challenges.

Although often considered together, each process presents a different set of obstacles. Recruitment focuses mostly on attracting eligible participants, obtaining informed consent and offering attractive and fair incentives. The importance of recruitment is normally limited to the early stages of a trial and its success is clearly demarcated by definite targets. In contrast, successful retention is not as clearly defined but it plays an important role throughout trials, with each application of treatment and follow-up assessment. At each of these points trial researchers return to the issues dealt with in recruitment, i.e. confirming informed consent and offering incentives.

Most of the literature dealing with trial methodology has been dedicated to recruitment, which can be attributed to a high proportion of studies failing to achieve their recruitment targets (Haidich and Ioannidis 2001, McDonald *et al.* 2006). The interest in recruitment has yielded evidence on the effectiveness of different methods to enrol patients into trials, which has translated into multiple recruitment strategies at trial researchers' disposal. Some of the strategies shown to be effective in a Cochrane Review of 45 trials include: telephone reminders, use of opt-out from being contacted about participation opportunities, procedures for contracting potential participants, and open trial design (Treweek *et al.* 2011). Numerous studies have investigated factors affecting recruitment of specific populations, disease areas and trial designs (McDonald *et al.* 2006, Howard *et al.* 2009, Patterson *et al.* 2010, Borschmann *et al.* 2014, Newington and Metcalfe 2014, Hughes-Morley *et al.* 2015). Recruitment challenges identified in

studies involving patients with schizophrenia have been associated with practical barriers, conceptualisation of mental illness, protection from risk, timing of treatment and influence of other patients (Roberts *et al.* 2000, Woodall *et al.* 2010). In a survey carried out in an inpatient setting, patients diagnosed with schizophrenia were reported to be more reluctant than patients with other mental health disorders to take part in trials (Zullino *et al.* 2003). Although the study was limited to the views about participation in hypothetical studies, the differences reported by Zullino *et al.*, (2003) included being less convinced about the benefit of a new treatment (50% of patients with schizophrenia vs 71% other patients), refusing double-blind trials (42.9% vs 18.8%), being less likely to be motivated by altruistic reasons (67.9% vs 94.2%), as well as showing less reliance on their clinician to discuss participation (50% vs 71%).

Retention has received less attention in the trial methodology literature than recruitment, although studies often consider the two processes in unison, without a clear distinction made between them. The existing evidence on strategies to maximise retention comes from four main perspectives: strategies applied at different stages of a study; strategies considered in context of different stakeholders; reports of strategies utilised in individual studies; and nested trials of retention strategies.

Considering retention strategies from the perspective of the study cycle and the different stakeholders has led to development of a 'phased approach' or a 'process model'. This approach regards research participation as a phenomenon observed over time and corresponds to the Karlson and Rapoff's (2009) typology of attrition highlighting key trial mileposts where dropout can occur (see Section 2.4.1). Considering retention in the context of study processes allows for recognising how the phenomenon of retention changes over time and for considering the differences between the different types of attrition and their implications. Buben (2013) proposes considering three main phases: study design, patient consent, and patient participation. The latter can by further broken down into attrition occurring during intervention, during follow-up, or occurring due to missing data (Karlson and Rapoff, 2009).

Beginning with writing a study protocol, retention needs to be taken into account when calculating sample size and, consequently, planning recruitment efforts. This has direct cost and other resource implications as the more participants are required to identify an appropriate effect size, the more resources are likely to be required to both recruit

and retain them in a study. In addition, as argued by Buben (2013) decisions about study design should take into account the associated burden for participants. Consulting patients with similar lived experience and study site teams offers an effective way of identifying both desirable and undesirable aspects perceived as desirable and undesirable study aspects (Beresford, 2002; Sweeney and Morgan, 2009).

Once a trial has commenced participants are presented with a number of opportunities to make decisions about their participation, starting with providing consent. Refusing to participate when invited to a study can be classified as 'enrolment refusal' (Karlson and Rapoff, 2009) and is often not taken into account when considering attrition rates as it occurs pre-randomisation. Another potential reason for attrition occurring prior to randomisation may include not meeting inclusion criteria. Those participants who have consented to take part are then invited to complete a baseline assessment. This milepost presents another risk of dropout as participants may refuse to complete baseline or be unable to do so, consequently preventing them from being randomised into a study, and can be categorised as 'baseline attrition' (Karlson and Rapoff, 2009).

Post-randomisation attrition occurring during intervention is associated with the definition of completion specified in the trial protocol. Participants may either not receive the allocated intervention or discontinue the intervention before completing the treatment course. In contrast, dropout observed during follow-up (i.e. study dropout or loss to follow-up) occurs when participants fail to complete one or more follow-up assessments (Karlson and Rapoff, 2009). In addition, if large amounts of data are missing from particular participants, these individuals may be excluded from some analyses and attributed to 'attrition due to missing data'.

An alternative model of retention is the Ecological Theory of Research Participation (also referred to as the Ecological Model of Attrition) proposed by Lenora Marcellus (2004). The theory identifies four primary sources of attrition: participant, researcher, study, and environment and focuses on the relationships between them (see Figure 2.6 below).

Participant	Researcher	Study	Environment
Motivation	Motivation	Complexity of design	Philosophical
Values	Personal meaning	Perspective on subject	Disciplinary
Beliefs	Values	Participation	Organizational
Personal meaning	Beliefs	Perceived importance	Practice
Specific population characteristics	Communication style		Political
	Respect for participants		Geographical
			Funding

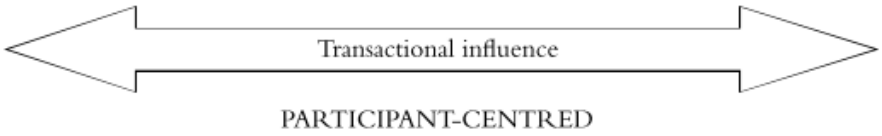


Figure 2.6 An ecological model of research participation [adopted from Marcellus (2004)]

As can be seen in Figure 2.6, Marcellus' (2004) model pictures research participation as a multi-faceted system of factors affecting attrition built on interplay between all levels: "This model consists of a series of nested layers that represent various influences on an individual's ability and desire to participate in a study. The factors within each layer are drawn from longitudinal studies of attrition." (p.87).

In addition, the model recognises two types of influences are recognised across all levels: transactional and participant-centred. The first is concerned with the direct influence of adjacent layers, which can be "transactional, reciprocal, and interactive" in nature. The second influence emphasises the importance of putting participants at the heart of efforts to increase retention, in line with the previous calls for moving away

from traditionally paternalistic research relationships (Gross and Fogg 2001). The Ecological Theory of Research Participation was developed to provide a guide to identifying factors within each level that affect attrition and to "give investigators the opportunity to address situation-specific barriers and develop strategies specific to the study and the population of interest in order to maximise participation." (Marcellus, 2004, p.89).

Strategies related to the participants focus on their personal characteristics, including values, beliefs, motivation, and demographics. Awareness of these factors can be used by researchers to develop a participant-centred approach with retention strategies tailored to the specific study population and/or an individual. For example, if a participant is in full-time employment, they may need to be offered out-of-hours appointments in order to enable them to complete follow-up assessments. In addition, the onus is on the relationship between participant and researcher. Examples of participant-level strategies identified in the Ecological Model of Attrition include: forming a participant advisory group, ensuring convenience, timeliness and accessibility of research activities, matching incentives with the needs of the population (Marcellus 2004). Strategies at the researcher level aim to minimise the logistical and personal barriers between researcher and participant, for instance plan for continuity of researchers, express appreciation, emphasise collaborative effort. Retention efforts related to the study aim "to develop interventions and procedures that take the needs and resources of participants into account" (Marcellus 2004, p.93). Marcellus proposes this to be achieved by individualising retention strategies to fit the study, tracking participants, showing respect for participants' time, etc. One of the unique contributions of the Ecological Theory of Research Participation is the consideration of environmental factors in retention related to organisational, funding, practice, political, geographical, disciplinary and philosophical issues. In terms of strategies these can translate into an assessment of transportation and monitoring organisational policies affecting research processes, for example reimbursing individuals for their participation.

Much of the existing evidence on retention strategies comes from retrospective reports of lessons learned by study authors (Robinson *et al.* 2007), with a small number of studies investigating specific strategies in a systematic way. A review of 87 community-based trials published between 1990 and 1999 identified 21 studies that discussed retention rates and retention strategies (Davis *et al.* 2002). The review found that the

trials with the highest reported retention rates employed multi-component retention strategies, supporting a previous suggestion made in relevance to psychosocial trials that a combination of strategies will be more effective than a single retention strategy (Carroll 1997). The review identified nine retention strategies utilised in studies across different disease areas. These included: 1) generating study publicity, 2) emphasising the significance of study for participants, 3) recruiting those who demonstrate compliance with key participation activities, 4) using meaningful incentives, 5) offering an appealing control group treatment, 6) maintaining contact between follow-ups, 7) training staff in interpersonal skills, 8) individualising data collection to participants' needs and preferences, and 9) keeping a database of all available personal details. Although none of the community-based trials included in the review applied all nine strategies, the studies with high retention rates used a combination of the following strategies: establishing a project identity, offering incentives, training staff, and using participant databases.

The need to assess the effectiveness of strategies to improve retention in RCTs has been identified as a result of researchers applying strategies lacking evidence supporting their use (Brueton *et al.* 2013). One of the most methodologically sound ways of testing retention strategies is embedding retention trials within larger trials evaluating a clinical intervention (Bower *et al.* 2014). This design, referred to in the literature as a 'nested trial', 'embedded trial', or 'trial within a trial', enables an evaluation of the effectiveness of a specific strategy in a sample already involved in an on-going clinical trial. Despite its methodological superiority, this type of research has limitations as it presents a number of potential challenges, such as increased complexity, incompatibility with the host trial, and potential impact on the collaboration between researchers (Graffy *et al.* 2010, Bower *et al.* 2014). Most of the retention trials identified in the small number of the existing systematic reviews focused on studies utilising questionnaires as a method of collecting follow-up data and showed monetary incentives to be the most effective in achieving retention (Edwards *et al.* 2009, Brueton *et al.* 2013, Bower *et al.* 2014). However, findings of these studies are not directly applicable to RCTs evaluating complex interventions in which face-to-face assessments are a typically utilised method of collecting outcome data.

There is a dearth of evidence on the effective ways of retaining participants with a diagnosis of schizophrenia in clinical trials. The available suggestions come from studies investigating patterns of retention in antipsychotic trials with little evidence

specific to non-pharmacological trials. For example, Thompson et al. (2011) emphasise the need to focus on retaining patients with high levels of negative schizophrenia symptoms and suggest achieving this through home visits, engaging caregivers in designing trials, and using text message reminders. In a trial evaluating non-pharmacological interventions for people with psychosis and substance misuse researchers attributed the high retention rates to home visits, flexible scheduling of appointments, and persistence of researchers (Barrowclough *et al.* 2010). This however was not subjected to a formal evaluation and stemmed from the researchers' observations of their own practice. Studies employing more systematic and in-depth approaches, ideally eliciting multiple stakeholders' perspectives, to identifying retention practices and strategies utilised in trials evaluating non-pharmacological treatment for schizophrenia are needed in order to improve the current understanding of this trial practice context and inform the efforts to make improvements.

2.5 Summary

Medical practice informed by evidence relies on RCTs in developing and evaluating new treatments. In psychiatry in particular there is a need to develop complex interventions for schizophrenia, which could complement or replace the currently offered pharmacotherapy.

The specific context of testing non-pharmacological treatment for schizophrenia presents a number of challenges. One of the issues is poor retention of patients with schizophrenia as trial participants in terms of treatment adherence and completion of follow-up assessments.

There is a need to understand the scale of this challenge and the factors contributing to the retention of this population, taking into account the perspectives of different stakeholders. Generating such evidence could help with informing strategies enabling trial researchers to encourage adherence to treatment and study retention.

Chapter 3
Research Questions and Methods

3.1 Chapter overview

The previous chapter presented the available theory and research evidence relevant to practicing evidence-based medicine informed by well-conducted RCTs. Poor retention of participants with schizophrenia from trials evaluating complex interventions was introduced as a potential problem requiring more investigation in order to inform current trial practices. The currently available evidence and the identified gaps in the literature have informed the research questions addressed in this thesis and the methods chosen to investigate them. This brief interim chapter lays the foundation for the four empirical chapters that follow by first formulating the specific research questions and then outlining the methodological approach taken to address them.

3.2 Research questions and research objectives

Based on the aim specified in the introduction (Section 1.2, p.15) and the literature discussed in Chapter 2, this thesis addresses the following four research questions:

1. What is the degree of attrition occurring in trials evaluating complex interventions for schizophrenia?
2. What is the retention of patients with schizophrenia in RCTs evaluating complex interventions influenced by?
3. How can patients with schizophrenia be retained in trials?
4. What are the experiences of patients with schizophrenia in the context of retention in trials?

The specific actions taken to answer the above research questions are expressed as the following research objectives:

Research Objective 1: To estimate the attrition rates in trials of complex interventions for schizophrenia.

Research Objective 2: To determine and explore the factors associated with retention of patients with schizophrenia in trials.

Research Objective 3: To identify and investigate the retention practices used in trials of complex interventions for schizophrenia.

Research Objective 4: To explore how people with schizophrenia experience participation in trials and to identify what factors influence their experiences.

3.3 Methodological considerations

The choice of the research design and specific research methods was dictated by the nature of the research problem expressed in the research questions, the doctoral candidate's background and experience, and resources available (Creswell 2014).

To address the overall aim and specific research questions this thesis employed a concurrent triangulation design comprising two quantitative and two qualitative parts. Each part is referred to as a 'study' throughout this thesis; however, combined, they form a single study investigating the issue of retention of participants with schizophrenia in complex intervention trials. Rationale for undertaking each part and the relevant approach is provided in corresponding chapters (4, 5, 6 and 7). This section focuses on the overall research paradigm, study design and the choice of mixed methods approach.

3.3.1 Pragmatism as a research paradigm

Research paradigms are "a basic set of beliefs that guide action" (Guba, 1990, p.17), which shape the approach to research and the choice of specific methods. Therefore, it is important to acknowledge the theoretical perspectives and assumptions made when conducting this doctoral research.

Different paradigms have been associated with either quantitative or qualitative methods. The most prominent ones in mixed methods research include: postpositivist,

constructivist, participatory, and pragmatist (Creswell and Plano Clark 2011). Their overview is presented in Table 3.1 below.

Table 3.1 Characteristics of four paradigms used in mixed method research

Postpositivist paradigm • Determination • Reductionism • Empirical observation and measurement • Theory verification	**Constructivist paradigm** • Understanding • Multiple participant meanings • Social and historical construction • Theory generation
Participatory paradigm • Political • Empowerment and issue oriented • Collaborative • Change oriented	**Pragmatist paradigm** • Consequences of actions • Problem centred • Pluralistic • Real-world practice oriented

The choice of the paradigm guiding this research was made based on the best fit with the research questions. Given the focus of this doctoral study on the problem of attrition and finding ways of optimising participant retention, a pragmatic logic of inquiry was chosen as it bases knowledge claims on practical grounds and allows for an integration of different research methods (Tashakkori and Teddlie 1998, Morgan 2013, Parvaiz *et al.* 2016). The use of both qualitative and quantitative methods has been argued to build on the strengths of each and at the same time to reduce limitations of each (Tashakkori and Teddlie 1998).

Pragmatism focuses on the problem to be addressed by research by considering relevant questions and coming up with relevant solutions (Parvaiz *et al.* 2016). Furthermore, pragmatism supports mixing inductive and deductive logic (Johnson and Onwuegbuzie 2004), typically moving back and forth between them. Deduction is appropriate for testing hypotheses and theories, especially in quantitative methods. Induction allows for discovery of patterns and suits some qualitative methods. The use of both quantitative and qualitative methods has been argued to require adopting both the subjective and the objective points of view (Tashakkori and Teddlie 1998). Adopting pragmatism forces researchers to be careful and self-conscious about their practice in

order to choose the most appropriate method for the research question at hand (Seale *et al.* 2007).

3.3.2 Mixed methods design

Adopting a mixed method design allows for approaching the same research problem from different angles or 'lenses' (Silverman 2011, 2013), which can complement each other and draw on a range of relevant disciplines (Ritchie *et al.* 2014).

Qualitative and quantitative data can be collected either sequentially or concurrently. In this study a convergent parallel mixed methods design was followed. This model was deemed most appropriate given the nature of the research questions and rationale for collecting each data set. Adopting this design allowed for converging quantitative and qualitative data to provide a comprehensive analysis and to add to the depth and scope of findings. In line with the features of concurrent triangulation design, quantitative and qualitative parts were treated with equal status.

Integration of findings was planned according to how the different parts provided distinctive answers to the research questions. As a result, findings from all four parts were integrated at the interpretation phase and brought together in the discussion section of this thesis. An outline of all four studies and the structure within which they were conducted is provided in Figure 3.1.

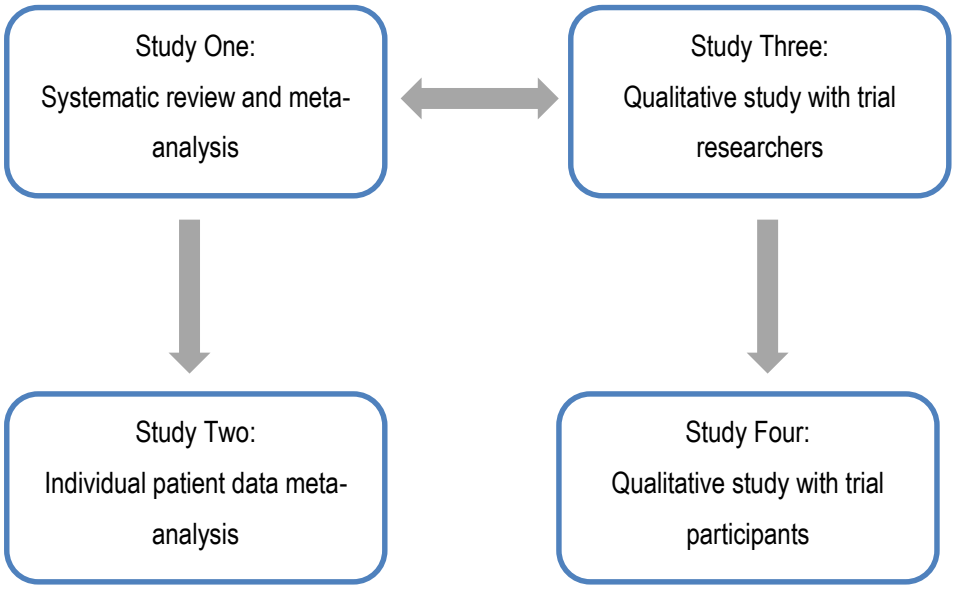


Figure 3.1 Sequence of the studies

Chapter 4
Attrition rates in randomised controlled trials of complex interventions for schizophrenia: systematic literature review and meta-analysis

4.1 Chapter overview

The aim of this chapter is to address two research questions: 1) What is the degree of attrition occurring in trials evaluating complex interventions for schizophrenia?; and 2) What is the retention of patients with schizophrenia in RCTs evaluating complex interventions influenced by? To address these questions, a systematic literature search was conducted, looking at large-scale RCTs exploring the effectiveness of complex interventions for people with schizophrenia and related disorders. Data extracted from published trial reports were pooled together using random-effect meta-analyses to establish the proportion of participants who drop out of either experimental interventions or follow-up assessments. Meta-regression analyses were conducted to identify the potential predictors of attrition, particularly patient and study characteristics.

The chapter first provides the details of the systematic literature search and its results. The subsequent sections present the findings of meta-analyses that followed the literature search. The discussion considers the main findings in the context of the wider literature and their implications for both trial and clinical practices.

Although 'retention' is the key term used throughout this thesis, the results reported in this chapter will be mainly expressed as 'attrition' or 'dropout'. This allows for making direct comparisons with the wider literature reporting attrition, rather than retention.

A version of the work presented in this chapter has been published in *the Journal of Psychiatric Research* (Szymczynska *et al.* 2017). The publication manuscript is provided in Appendix 2.

4.2 Rationale

The attrition rates in schizophrenia trials are currently known for studies evaluating antipsychotic medication (Leucht *et al.* 2013) and psychosocial interventions (Villeneuve *et al.* 2010). There is no such evidence about the dropout from non-pharmacological interventions for schizophrenia at the levels of both experimental intervention and study. In addition, efforts have been made to identify what factors affect or predict dropout but this again bore relevance to pharmacological trials (Kampman and Lethinen 1999, Nose *et al.* 2003) and a limited range of complex interventions (Villeneuve *et al.* 2010). This evidence points to the need to establish the reported attrition rates in trials evaluating a range of current complex interventions for schizophrenia and to identify factors influencing discontinuation of interventions and loss to follow-up.

The most robust method available to conduct a study that would allow for addressing this gap in the literature is a systematic review of literature followed by a meta-analysis of data extracted from trial reports identified in the literature search and/or obtained directly from authors of papers. This method has been chosen to address Research Questions 1 and 2 and the results are discussed in the present chapter.

4.3 Objectives

This study had the following objectives:

1. To identify all relevant trials of non-pharmacological interventions for people with schizophrenia.
2. To estimate the attrition rates reported at intervention- and study-level.
3. To estimate the overall attrition rate reported across relevant trials.

4. To identify factors that may influence retention in RCTs of non-pharmacological interventions for schizophrenia.

4.4 Method

4.4.1 Literature search

A methodological framework and a protocol were developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) (Moher *et al.* 2009). Five bibliographic databases, including Medline, PsycINFO, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Cochrane Central Database were searched in January 2016 for manuscripts reporting results from RCTs evaluating complex (also referred to as non-pharmacological in this chapter) interventions for adults with schizophrenia and related disorders published between January 1996 and January 2016. As the study was interested in the dropout rates reported in published trial reports, the lower time limit was set based on the publication date of the first iteration of the CONSORT statement (Begg *et al.* 1996). As discussed in the previous chapter, the introduction of the guidelines for transparent reporting of participant flow information resulted in the expectation to include the CONSORT statement in trial publications and meant that since 1996 more peer-reviewed papers would include the information required for the purposes of this review. In addition, hand searches of six key psychiatric journals: *Schizophrenia Bulletin, The British Journal of Psychiatry, The American Journal of Psychiatry, The Journal of the American Medical Association* (JAMA) *Psychiatry, Acta Psychiatrica Scandinavica,* and *Trials*; and reference lists of relevant systematic reviews were carried out to identify other eligible manuscripts.

A comprehensive Medical Subject Headings (MeSH) and text-word search strategy was defined prior to database searching. Titles and abstracts were searched using the following MeSH headings and linking operators: 'SCHIZOPHRENIA' OR 'PSYCHOSIS' OR 'PSYCHOTIC DISORDERS' AND 'CLINICAL TRIALS' OR 'RANDOMIZED CONTROLLED TRIAL/S' and text words including 'psychos*s' OR 'psychotic' OR 'schizo*' OR 'therapy' OR 'intervent*' OR 'nonpharmacological' AND 'RCT' OR

'randomi*ed controlled trial' OR 'clinical trial'. These search terms were modified to match the specific requirements of each database.

4.4.2 Study selection

The following eligibility criteria were applied:

(i) The study had an RCT design. This was decided based on whether a reference was made either to a randomisation procedure and/or the presence of a control condition.
(ii) At least 100 participants were randomised to the trial.
(iii) The experimental treatment condition was a non-pharmacological intervention delivered either individually or in a group.
(iv) Participants were adults above the age of 18 with a diagnosis of schizophrenia (including undifferentiated schizophrenia, paranoid schizophrenia, hebephrenic schizophrenia, catatonic schizophrenia, and residual schizophrenia) and/or related disorders including schizotypal disorder (i.e. delusional disorder, persistent delusional disorder, and other persistent delusional disorders), schizoaffective disorder (i.e. schizoaffective manic, depressive and unspecified subtypes), as outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) diagnostic manuals applicable at the time of trial publication.
(v) Manuscript was written in English.

Studies were excluded if they:

(i) Involved, in any of the trial arms, healthy individuals, family members and/or caregivers, participants 'at risk' of schizophrenia, or participants who did not have a diagnosis of schizophrenia or a related disorder.
(ii) Involved procedures considered to be physically invasive, for instance brain stimulation or electroconvulsive therapy.

The decision to include RCTs with a sample size of at least 100 participants was made to increase the homogeneity of the set of trials and to produce more precise estimates

of the results through obtaining narrower confidence intervals. Interventions requiring involvement of a third party (for example relatives involved in family therapy) were excluded as involvement of other individuals could potentially influence decisions about trial participation made by people with schizophrenia. Interventions considered to be invasive were also excluded as they present a different type of risk and physical discomfort to be considered by individuals and are therefore likely to affect decisions about participation.

A two-step screening process was performed. The doctoral candidate acted as the primary reviewer and screened all titles and abstracts in the first step and, subsequently, all articles at the full text review phase. To ensure study selection accuracy, a second reviewer (Sophie Walsh, SW) who was a researcher at the Unit for Social and Community Psychiatry, independently screened a random selection of 20% of the citations in both study selection phases using the agreed set of eligibility criteria.

4.4.3 Data extraction

Using a structured format, all papers that met the eligibility criteria were independently extracted by the doctoral candidate and 20% of them were subsequently checked by SW. Attrition rates were extracted either from the CONSORT diagram (if provided) or from the text of the article. Nineteen studies did not fully report these data and, consequently, their corresponding authors were contacted by the doctoral candidate with a request for information or clarification. Twelve responses were received. Papers of authors who were unable to respond were excluded from the analysis due to insufficient information.

In addition to the attrition rates, data on participant and study characteristics were extracted to enable analyses of potential predictors. The following study information was extracted: year of publication, study setting (inpatient or outpatient), intervention delivery (individual or group), type of control intervention (experimental or treatment as usual), sample size, duration of intervention period, study duration, number of intervention sessions, number of evaluations, and quality score (more details are provided in section 3.4.5). Participant socio-demographic characteristics included: age, gender, and illness duration. The choice of the factors was made based on the consistency of reporting variables across publications.

For the meta-regression of study attrition data were extracted for all randomised participants. For the analysis of dropout from experimental intervention only data for those who were randomised to the active arm were extracted.

4.4.4 Outcomes

Two primary outcomes were identified for the purposes of the planned meta-analyses. The first was 'dropout from experimental intervention', defined as the proportion of participants randomised to receive an experimental intervention and who were reported as failing to complete the intervention (study authors' definition of completion or dropout was used) after beginning it. The second outcome was 'study dropout', defined as the proportion of participants across all trial arms who failed to complete the last follow-up assessment. Participants who were lost prior to being randomised were not considered dropouts and were therefore excluded from the analysis.

The distinction between the two types of dropout, experimental intervention versus study, was drawn in order to investigate the differences between treatment adherence and completion of follow-up appointments within the duration of the study.

4.4.5 Quality assessment

Most of the existing tools for assessing risk of bias, such as the Cochrane Collaboration's Risk of Bias Tool (Cochrane Collaboration 2011), have been developed for the purposes of assessing clinical relevance and thus did not fit in with the purpose of this study, which was interested in the methodological and pragmatic aspects of retaining participants in a trial. In order to assess the methodological quality of the eligible studies a unique set of criteria was developed, including: 1) provision of the CONSORT diagram; 2) clear definition of intervention completion; and 3) information on sample size calculation. Each criterion was given a score of 0 or 1, with the total possible score ranging from 0 to 3. The total score was used in analyses as an indicator of study quality in the context of reporting information relevant to attrition.

4.4.6 Data analysis

Meta-analytical techniques were used to statistically pool together findings from the eligible trials.

The first set of meta-analyses investigated the reported attrition rates across trials. The two primary outcomes were calculated in Stata 11 software using the *metaprop* command. Calculating dropout from experimental intervention involved dividing the number of participants who discontinued any experimental intervention evaluated in the identified trials by the total number of individuals who began the intervention:

$$Intervention\ dropout\ = \frac{number\ of\ participants\ who\ discontinued\ intervention}{total\ number\ of\ participants\ who\ began\ intervention}$$

In addition, a subgroup analysis was carried out to investigate any differences across different intervention types, including practical or educational interventions, CBT, cognitive or neurocognitive interventions, adherence strategies, and any other interventions.

Study dropout was calculated by dividing the number of participants lost to follow-up by the total number randomised to all trial arms:

$$Study\ dropout\ = \frac{number\ of\ participants\ lost\ to\ follow-up}{total\ number\ of\ participants\ randomised\ to\ study}$$

The 95% confidence intervals were calculated using the Freeman-Tukey double arcsine transformation as it can be used for data restricted to the range of 0% to 100%. Without this transformation, studies with an estimated percentage near either extreme would be automatically excluded from the analysis, leading to a biased pooled estimate.

The second set of meta-analyses explored the effect of potential predictors on attrition rates. Data were pooled using a random-effects meta-analysis in Stata software. A random-effects model was used for meta-regression as it assumes that differences in the dropout rates are not just due to the sampling error but represent real differences between studies. The potential predictors used in the meta-regression of experimental intervention dropout included the following participant and study variables: age, gender, illness duration, study location, study setting, intervention delivery method, duration of the intervention period, study duration, number of intervention sessions, and study quality. For the analysis of study dropout the models included the following

variables: age, gender, illness duration, study location, study setting, type of control intervention, study duration, number of evaluations, and study quality.

First, the above predictors were tested for associations in univariable models. Second, the variables showing an association with the dropout rate (p-value <0.1) in the univariable models were included in the multivariable models.

The level of between-study heterogeneity was assessed visually and by calculating the Q-statistic and the I^2 statistic. In order to assess the evidence for publications bias Egger's test of the intercept with the Freeman-Tukey double arcsine transformation and a funnel plot of standard error against study attrition rate were computed.

4.5 Results

4.5.1 Characteristics of included studies

The systematic search identified 5,450 studies (see Figure 4.1 below for the PRISMA flow diagram). After screening, 49 papers based on 43 studies were included. Some trial results were reported in multiple papers; therefore data were extracted per study, not per paper. Table 4.1 below presents details of the 49 papers. References of the papers reporting on the same trial are provided together with the key paper from which data were extracted and indicated with square brackets; for instance [Bell et al., 2005]. Two studies were excluded from the meta-analyses due to inadequate reporting of the primary outcomes for the present study.

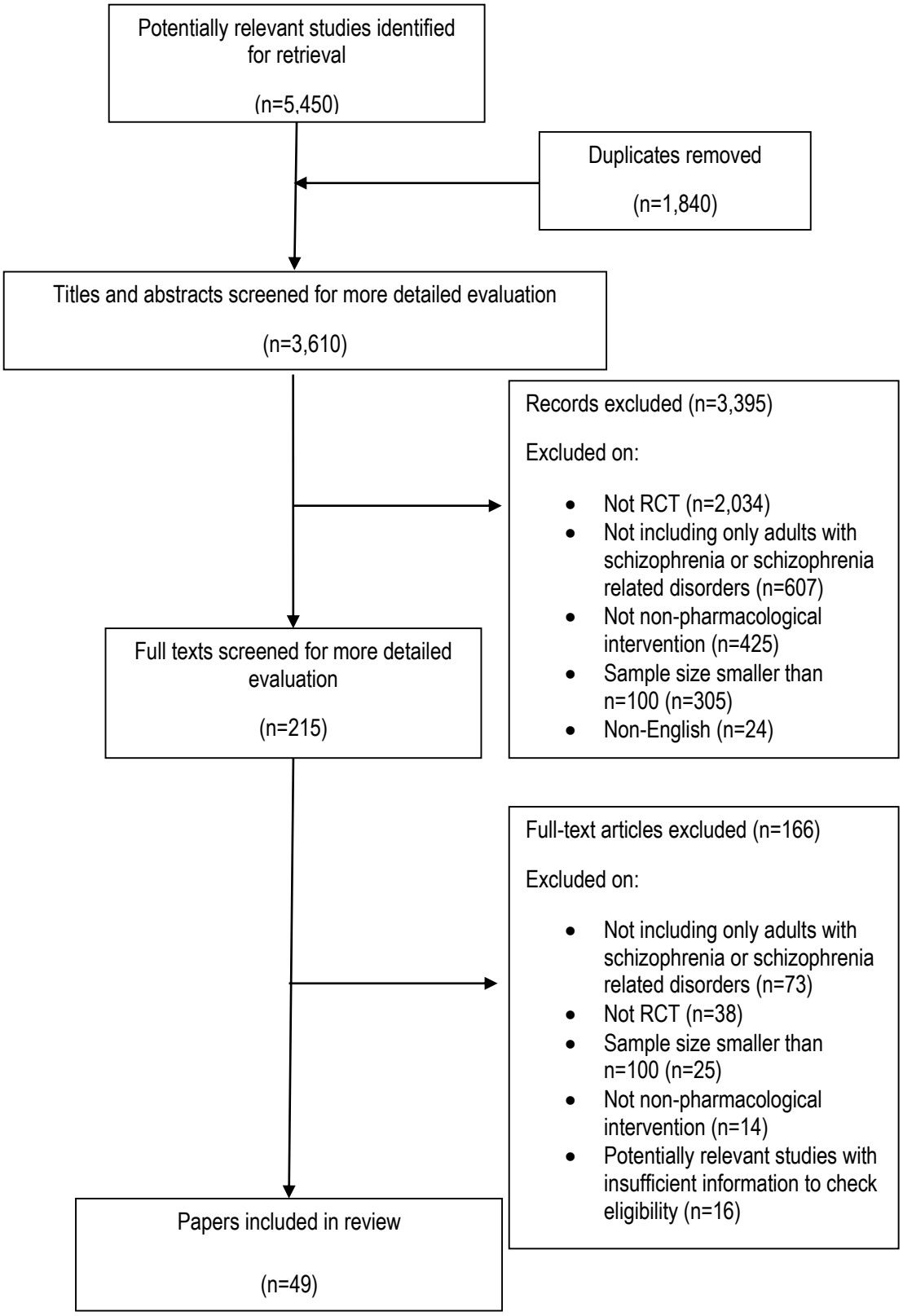


Figure 4.1 PRISMA Diagram for Paper Selection

Table 4.1 Description of studies identified in the systematic review

Study reference	Region	Experimental intervention(s)	Number of randomised participants	Intervention delivery	Study setting	Length of follow-up (months)	Intervention duration (months)	Quality score
Barkhof et al., 2013	Europe	Motivational interviewing / Health Education	114	Individual	In- and out-patient	12	6.5	3
Barrowclough et al., 2006	Europe	Cognitive Behavioral Therapy (CBT)	113	Group	Out-patient	12	6	3
Bell and Lysaker, 1997	USA	Work program	150	Individual	Out-patient	12	6	1
Bell et al., 2003 [Bell et al., 2005] [Bell et al., 2007]	USA	Neurocognitive Enhancement Therapy with Work Therapy	131	Individual	Out-patient	12	6	0
Bowie et al., 2012	USA	Cognitive remediation / Functional Adaptation Skills Training/ Combined Treatment	114	Group	Out-patient	3	6	2

Chien et al., 2015	Asia	Adherence therapy	114	Individual	Out-patient	6	4	2
Crawford et al., 2012	Europe	Group art therapy/Activity Groups	417	Group	Out-patient	24	12	2
Franck et al., 2013	Europe	Individualized therapy / Cognitive Remediation Therapy (CRT)	138	Individual	Out-patient	9	3	1
Freeman et al. 2015	Europe	CBT	150	Individual	In- and out-patient	6	2	3
Gomar et al. 2015	Europe	Computerized Cognitive Remediation	130	Group	In- and out-patient	6	6	1
Gouzoulis-Mayfrank et al. 2015	Europe	Implemented integrated treatment	100	Group	In-patient	12	Not reported	1
Granholm et al. 2014	USA	Cognitive Behavioral Social Skills Training / Active Goal-Focused Supportive Contact	149	Group	Out-patient	21	9	1
Gray et al. 2006	Europe	Adherence therapy / Health Education	409	Individual	In- and out-patient	13	18	3

Gumley et al. 2003 [Gumley et al. 2006]	Europe	CBT	144	Individual	Not reported	13	3	2
Hamann et al. 2006	Europe	Shared decision aid	113	Individual	In- and out-patient	18	0.03	1
Hansson et al. 2008	Europe	DIALOG (computer-mediated structured patient-key worker communication)	507	Individual	Out-patient	12	12	0
Hogarty et al. 2004	USA	Cognitive Enhancement Therapy / Enriched Supportive Therapy	121	Group	Out-patient	24	Not reported	0
Jahn et al. 2011	Europe	Neurocognitive training	122	Group	In-patient	9	1	1
Jones et al. 2001	Europe	Personalized computer-based information / Community Psychiatric Nurse / Combined treatment	112	Individual	Not reported	3	Not reported	3
Klingberg et al. 2010	Europe	Cognitive Behaviorally Oriented Service	169	Group	In-patient	6	2	3

Klingberg et al. 2011	Europe	CBT / CRT	198	Individual	Out-patient	12	9	3
[Klingberg et al. 2012]		CBT / CRT						
Li et al. 2015	Asia	CBT / Supportive Therapy	192	Group	In- and out-patient	21	6	2
Montes et al., 2010	Europe	Telephone-based nursing strategy to improve adherence to antipsychotic treatment	928	Individual	Out-patient	4	3	1
Montes et al. 2012	Europe	Short message service-based strategy for enhancing adherence to antipsychotic treatment	340	Individual	Out-patient	6	3	3
Moritz et al. 2013	Europe	Complementary Metacognitive Training	150	Group	In- and out-patient	6	Not reported	2
[Moritz et al. 2014]								
Mueller et al. 2015	Europe	Integrated Neurocognitive Therapy	156	Group	Out-patient	9	3.75	1

Patterson et al. 2006 [Mausbach et al. 2008]	USA	Functional Adaptation Skills Training	240	Group	Out-patient	18	6	1
Pitkanen et al. 2012	Europe	Patient education	311	Group	In-patient	12	1	1
Salyers et al. 2014	USA	Illness Management and Recovery / Problem-Solving Group	118	Group	Not reported	18	9	0
Schirmer et al. 2015	Europe	Medication training program	141	Individual	Out-patient	Not reported	1.64	
Schulz et al. 2013	Europe	Adherence therapy	161	Group	In- and out-patient	3	Not reported	3
Sibitz et al. 2007	Europe	Low intensity booster sessions of psychoeducation	103	Group	Out-patient	11.25	2.25	1
Silverstein et al. 2014	USA	Attention shaping	105	Group	In-patient	5.5	5.5	1
Staring et al. 2010	Europe	Treatment adherence therapy	109	Individual	Out-patient	12	6	1
Terzian et al. 2013	Europe	Social Network intervention	357	Not reported	Out-patient	24	24	1

Van Der Gaag et al. 2011	Europe	CBT	216	Group	Not reported	18	6	1
Van der Krieke et al. 2013	Europe	Web-based information and decision tool	250	Individual	Out-patient	12	12	2
Van Oosterhout et al. 2014	Europe	Metacognitive group training	154	Group	In- and out-patient	6	2	2
Van Os et al. 2004	Europe	Two-way Communication Checklist	134	Individual	Out-patient	2	1.5	1
Velligan et al. 2013	USA	Interventions for improving adherence to oral medications	142	Group	Out-patient	9	6	1
Velligan et al. 2015	USA	CBT / Cognitive Adaptation Training (CAT) / CBT and CAT	166	Individual	Out-patient	15	9	1
Williams et al. 2003	USA	Enhanced guideline implementation strategy	349	Individual	In- and out-patient	20	Not reported	0
Xiang et al. 2007	Asia	Community Re-Entry Module	103	Group	In-patient	24	4	2

Geographical location of studies

Twenty-nine studies were conducted in Europe, followed by eleven in North America and three in Asia.

Interventions

Fifty-nine interventions were evaluated in the 43 trials. Their details are presented in Table 4.1. Data required for the meta-analysis of intervention non-adherence or non-attendance were available for 50 interventions reported in 34 papers.

Reasons for dropout

Extracting the reasons for discontinuing participation was limited by poor reporting of this information. Twenty-nine out of 43 studies (69%) provided the CONSORT diagram. Out of these, 18 did not provide the reasons for dropout. In addition, 11 papers did not provide the CONSORT diagram at all. In total, only 14 out of 43 trials (32.5%) reported the information required for the purposes of this study.

Quality analysis

Quality scores ranged from 0 to 3. Five studies scored 0, 17 studies scored 1, 10 studies scored 2, and 9 studies scored 3. The scores for each included study are provided in Table 4.1.

Dropout from active intervention

Dropout from active intervention was estimated at 14% (95% CI: 13-15%), with a range of 0-63% and a median of 19.4%. Heterogeneity was high at I^2=93.13%.

Subgroup analysis by intervention type showed overall estimates of intervention drop-out of 25% (95% CI: 14-35%) for CBT interventions (n=8), 24% (95% CI: 16-32%) for cognitive or neurocognitive interventions (n=9), 21% (95% CI: 13-29%) for practical or educational interventions (n=8), 11% (95% CI: 6-17%) for adherence therapies (n=7), and 34% (95% CI: 23-46%) for other interventions (n=18). The results of the analysis are shown in Figure 4.2.

Dropout from study

Study dropout was estimated at 20% (95% CI: 17-24%), with a range of 4-71% and a median of 16%. Heterogeneity was high at I^2=95.69%. The results of the analysis are shown in Figure 4.3.

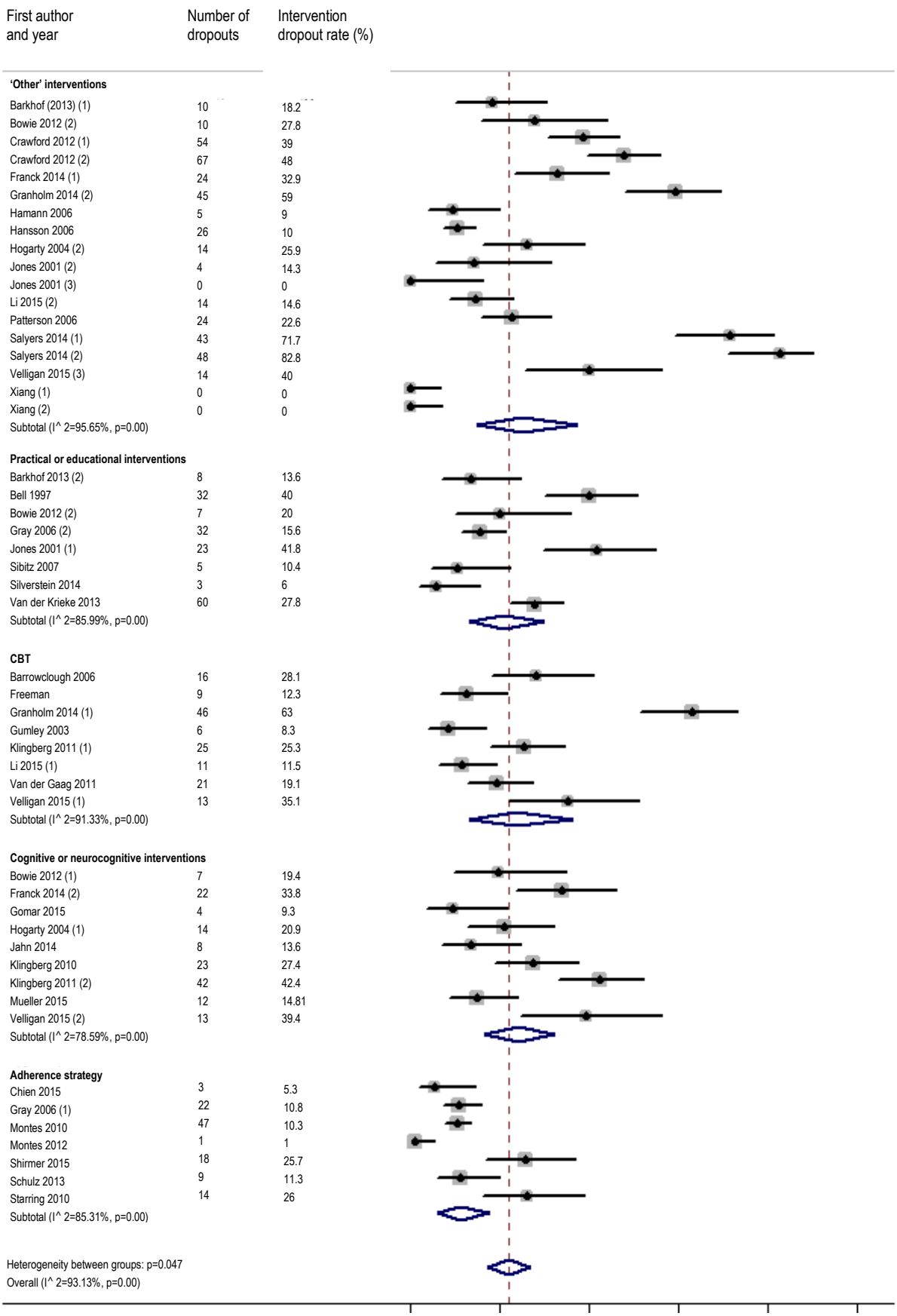


Figure 4.2 Meta-analysis of intervention non-adherence rates by subgroup

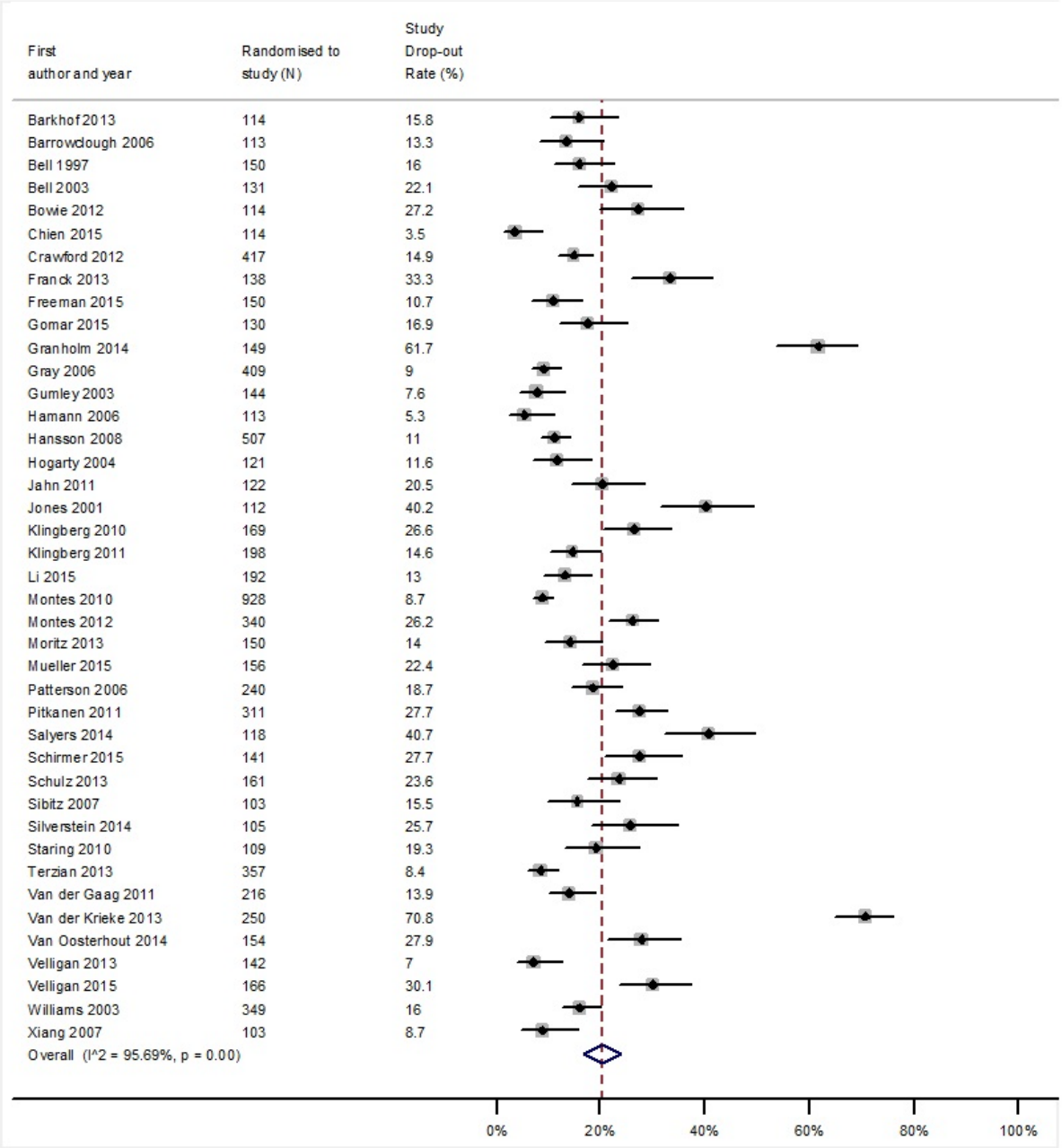


Figure 4.3 Meta-analysis of study dropout rates

4.5.2 Predictors of dropout

Dropout from experimental intervention

Findings of the random effects meta-regression showed that the dropout rates from experimental interventions significantly increased as the number of intervention sessions increased (p-value=0.011). The results are shown in Table 4.2 and Table 4.3 below.

Table 4.2 Univariable meta-regression for intervention non-adherence

Factor	Coefficient	95% Lower	95% Upper	*P*-Value
Age	0.53	-0.77	1.83	0.410
Gender	0.53	-0.03	1.11	0.065
Illness duration	1.12	-0.12	2.37	0.075
Study location	-9.93	-22.49	2.63	0.117
Study setting (inpatient vs outpatient)	-6.38	-18.30	5.54	0.284
Intervention delivery (individual vs group)	-6.37	-18.30	5.54	0.284
Duration of intervention period	2.37	0.51	4.23	0.014
Study duration	0.83	-0.11	1.77	0.082
Number of intervention sessions	0.66	0.26	1.05	0.002
Study quality	-2.27	-6.64	2.09	0.300

Table 4.3 Multivariable meta-regression for intervention dropout

Factor	Coefficient	95% Lower	95% Upper	*P*-Value
Gender	0.23	-0.53	1.00	0.235
Illness duration	0.10	-1.44	1.65	0.884
Duration of intervention period	0.09	-2.29	2.48	0.931
Number of intervention sessions	0.97	0.28	1.67	0.011
Study duration	-0.38	-1.81	1.05	0.570

Dropout from study

None of the tested variables in the study dropout models showed any significant effects. The results of the univariable meta-regression are shown in Table 4.4 below.

Table 4.4 Univariable meta-regression for study dropout

Factor	Coefficient	95% Lower	95% Upper	*P*-Value
Age	0.10	-0.70	0.90	0.803
Gender	0.09	-0.27	0.46	0.606
Illness duration	0.43	-0.37	1.23	0.279
Study location	6.62	-1.56	14.81	0.110
Study setting (inpatient vs outpatient)	1.29	-2.74	5.33	0.521
Study duration	-0.20	-0.95	0.54	0.579
Number follow-up assessments	-0.23	-3.84	3.38	0.897
Type of control (active vs treatment as usual)	1.25	-4.31	6.82	0.651
Study quality	0.05	-4.76	4.86	0.984

4.5.3 Publication bias

Egger's test of the intercept calculated for study dropout showed no presence of publication bias (p=0.10). The funnel plot is presented in Figure 4.4 overleaf and can be interpreted as showing no evidence of publication bias with a few outliers. The lack of publication bias could be explained by this review including only RCTs with a sample size ≥ 100. This finding suggests that trials of this size are likely to be published despite the reported dropout rates.

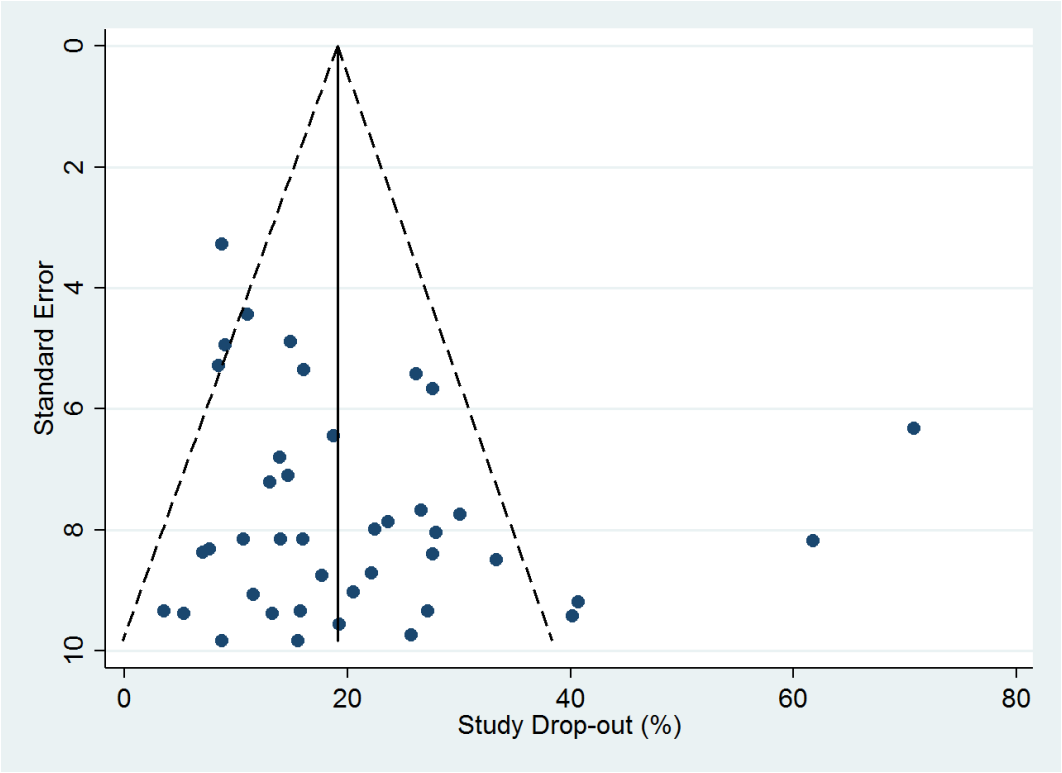


Figure 4.4 Funnel plot of standard error by study dropout rate

4.6 Discussion

4.6.1 Main findings

The objectives of this chapter were to establish the attrition rates reported in published trials of complex interventions for schizophrenia and to identify the factors that influence those rates. The overall study dropout rate of 20% obtained in this study suggests that retention in schizophrenia trials can be problematic; however the range of rates observed in individual studies suggests that good retention rates are achievable. Compared to study attrition, dropout from interventions estimated at 14% is lower; nonetheless it suggests that a proportion of patients can be expected to fail to complete experimental treatments.

In the meta-analyses of factors influencing dropout from study and from active intervention, the only significant association was found between the number of

intervention sessions and dropout from treatment, with more sessions resulting in poorer completion. This finding suggests that predictors of retention or attrition in schizophrenia research identified in previous studies may not apply to RCTs evaluating complex interventions for schizophrenia. Before discussing the findings in the context of the wider literature and their implications for practice, the next section will present the key strengths and weaknesses of the study.

4.6.2 Strengths and limitations

The data were obtained in a wide and systematic literature search involving two independent reviewers, minimising the possibility of bias or oversight. The focus of the study was on complex interventions for schizophrenia and related disorders, which allowed for inclusion of a range of non-pharmacological treatments for schizophrenia. Some of these treatments would not have been considered in the previous meta-analysis of treatment withdrawal rates solely in psychosocial treatment for schizophrenia (Villeneuve *et al.* 2010); nonetheless they are an important type of intervention available to this population. In addition, the current analyses included attrition at both intervention and study levels, a distinction that has not always been made in the literature but has critical implications for practice. A further strength is that many of the authors who were contacted with a request to clarify information or provide additional data responded to those queries and, as a result, their studies could be included in the analyses.

The key limitations of this study are associated with the poor reporting of participant flow in the published reports of trials. Despite the established practice of providing the CONSORT flow diagram (Altman 1996, Begg *et al.* 1996, Moher *et al.* 2001), a large proportion of eligible papers failed to include it. To overcome this shortcoming, where possible, information that would normally be provided in the CONSORT diagram was sought in, and extracted from, the main body of papers. Poor reporting was also found in the provision of definitions of study and intervention completion. These were either not provided or, when present, were often inconsistent across studies, which restricted the analyses. The lack of detail about study and sample characteristics also limited the scope for testing other potential predictors of dropout, for instance incentives.

The applicability of the findings of the study is limited to trials with a sample size of at least 100. The review excluded smaller studies, which may observe different levels of engagement. Attrition in the control intervention was outside of the scope of the study, but it is important to acknowledge that engaging those randomised to the control arm is an important aspect of ensuring quality of a trial.

4.6.3 Interpretation and comparison with wider literature

The number of intervention sessions was found to predict intervention dropout. In contrast, study dropout could not be predicted by any of the tested variables. Overall, there was poor reporting of information about the retention methodology and practice, as well as participant treatment adherence and assessment completion. Each one of these findings will be discussed in turn and compared with the wider literature before considering their implications for trial and clinical practices and discussing the study's strengths and limitations.

Attrition rates

Prior to the present study, there had been only one other systematic review focusing on attrition in trials evaluating non-pharmacological treatment of schizophrenia. The review focused on withdrawal from treatment and found it to be 13% (Villeneuve *et al.* 2010). This result is very similar to the 14% active intervention dropout rate found in this study; despite Villeneuve's (2010) study considering a complete withdrawal from treatment (as opposed to the current study considering treatment completion as defined by trial investigators), focusing specifically on psychosocial treatment and excluding other forms of non-pharmacological interventions, which were included in the current study.

The findings of this doctoral study suggest that retention in both study and intervention is higher in non-pharmacological RCTs than in those evaluating antipsychotic medication. A large proportion of systematic studies investigating retention or attrition of individuals with psychotic disorders have been conducted on trials testing antipsychotic drugs. These have shown varying results, with study attrition ranging from 33% of patients who were treated with antipsychotics to 33.6% of those who received placebo in trials published from 1995 to 2000 (Wahlbeck *et al.* 2001), compared to a later study reporting 48.9% dropout for those receiving

antipsychotics and 60.2% for patients in a placebo arm in studies published between 1992 and 2004 (Kemmler *et al.* 2005). It is noteworthy that those studies define dropout as "patients leaving the study preterm due to any reason" (Wahlbeck *et al.*, 2001, p.2), although they subsequently discuss the findings in the context of adherence to treatment – an issue treated separately in this thesis.

Furthermore, a systematic review of studies estimating adherence to treatment programmes for people with psychosis offered outside of trial settings revealed that 24.3% individuals did not keep appointments as scheduled compared to 29.74% failing to take drugs as prescribed (Nose *et al.* 2003). When compared with the 14% intervention dropout rate found in the current study, non-adherence to psychiatric treatment, either pharmacological or non-pharmacological, offered outside of trial settings can be higher than non-adherence to complex interventions provided in a trial context. Differences between trial and practice contexts can be expected as, despite most trials adopting a pragmatic design recreating clinical practice settings as much as possible, patients enrolled in a trial are subject to different procedures than those receiving treatment outside of a research setting. For example they are required to sign consent forms, attend follow-up appointments with researchers and complete assessment measures. In addition, some of these procedures can be expected to differ depending on the geographical location of the study, given the differences in national and local standards and norms applying to research. The additional procedures introduced by the nature of trial participation can be experienced as additional burden for the patients and can therefore lead to poorer retention. On the other hand, trial participants are often actively encouraged to remain involved in a study through various practices and strategies that aim to improve their engagement, consequently resulting in potentially higher retention rates in experimental interventions within trials than in treatment offered in routine clinical practice.

Treatment non-adherence observed in trial settings bears importance for clinical practice as it gives an indication of the acceptability of an intervention and the likely retention rates once it has been implemented in practice. Adherence to or completion of treatment is also associated with the cost of delivering health care, with better retention having the potential to achieve long-term savings for treatment providers. In contrast, interpretation of the treatment dropout rates obtained in this study is difficult as there is no guidance on the acceptable non-adherence rates. Nonetheless, compared to both pharmacological treatment and non-pharmacological treatment for

schizophrenia provided outside of research settings, dropout from complex interventions evaluated in RCTs is lower.

In contrast to treatment dropout, loss of participants from trials can be evaluated and interpreted against the evidence showing that attrition rates exceeding 20% introduce issues with bias and validity of the trials (Polit and Hungler 1995, Sackett *et al.* 2000, Schulz and Grimes 2002), as discussed in section 2.4.2 of Chapter 2. In light of the existing evidence, the overall rate obtained in the current meta-analysis can be interpreted as acceptable. In sum, the rate of 20% suggests that many non-pharmacological RCTs may be at risk of bias and threat to validity, but a large number of trials succeed in achieving much lower attrition rates. The rate is not high enough to cause major credibility concerns (Xia *et al.* 2009), but it would be qualified as low-quality evidence according to the accepted standards of EBM (Centre for Evidence-Based Medicine 2009).

Predictors of attrition

In addition to estimating attrition rates in trials, the current study aimed to identify factors associated with these rates and to add to the existing body of literature attempting to identify predictors of dropout. Previous studies have shown inconclusive results, with significant effects found for different study and/or participant characteristics. For instance, in a meta-analysis of dropout from psychosocial treatment for schizophrenia Villeneuve et al. (2010) found higher dropout to be associated with higher age, male gender, longer illness duration, and longer treatment duration. In contrast, receiving psychosocial treatment in a hospital setting was associated with better adherence. Furthermore, in a meta-analysis of schizophrenia interventions provided outside of a trial setting, Nose et al. (2003) found "young male patients with poor insight of illness, a history of substance abuse, unemployed and with low social functioning" (p.1155) to be more likely to not adhere to treatment. Dropout from outpatient psychiatric treatment provided outside of a trial setting was also studied in a non-matched retrospective case-control study by Reneses, Munoz and Jose Lopez-Ibor (2009). The factors predicting higher dropout in four community mental health centres included young age and male gender, as well as having more than one clinician involved in treatment. What these three studies have in common is the finding suggesting that male patients with schizophrenia are more likely to fail to adhere to treatment but there was no agreement on other factors. The current evidence on

adherence to treatment for patients with psychosis is difficult to compare due to the differences in definitions of dropout, methodologies and types of treatment. In addition, there have been no previous studies investigating predictors of study attrition in schizophrenia research.

This doctoral study did not find significant effects for the predictors reported in these previous studies; however, in addition to treatment duration considered in Villeneuve et al.'s (2000) meta-analysis, it also tested the number of sessions offered to patients. This particular study characteristic was the only variable to be predictive of study attrition, with the higher number of sessions leading to higher dropout. One possible interpretation of this finding is that being asked to attend many intervention sessions can be seen by participants as a serious commitment to which they initially agree at enrolment but struggle to meet the demands as the trial progresses. This could be a particular challenge for patients with schizophrenia who often lead chaotic lifestyles and deal with fluctuations in their mental health. An alternative interpretation, although not rebutting the former one, is that missing one out of many sessions may be seen by patients as less problematic than skipping one of a limited number of offered appointments. This can also depend on the intensity of the intervention, in other words the number of sessions provided over a specified period of time.

The lack of significant results for other variables tested in the current study could be due to high heterogeneity of trials identified in the systematic review and poor reporting of information about both study and sample characteristics found across a large proportion of included studies. The poor quality of details about recruitment and retention is a phenomenon also present in non-psychiatric studies and one previously reported to limit analyses of recruitment and retention rates and their predictors (Trivedi *et al.* 2013). Together with the differences in the findings from previous analyses, this doctoral study suggests that identifying predictors of retention using information reported in published trials is methodologically possible but it may be impeded by the quality of information provided in trial reports.

4.6.4 Implications of findings for trial conduct and further methodological research

Currently, estimating sample size when planning trials is often based on arbitrary assumptions regarding the expected loss of participants to follow-up (Rutterford *et al.* 2015). This has important pragmatic and cost implications as it directly influences the resources put into recruitment and retention of participants required to test new interventions. This study adds to the limited pool of evidence on retention or attrition rates in trials evaluating complex interventions for schizophrenia. Estimating an average dropout rate achieved across published trials provides insight into the practice of engaging patients with schizophrenia in RCTs and gives guidance on what level of retention is achievable in the specific type of trials. However, it is important to note that this is different to determining the acceptable rates of attrition, which was not the aim of this study.

Moreover, looking at the range of attrition rates found in the current study, there are a large number of trials suffering from problematic loss to follow-up, questioning their validity and absence of bias. This study was unable to unpick which factors may lead to such low retention rates, suggesting the need for better reporting of information and more exploration of this issue. Exploring and demonstrating relationships between trial retention or treatment adherence and characteristics of studies or samples has important implications for the design of clinical trials involving people with schizophrenia. Beyond trial context, such relationships, if found, may also bear relevance to the issue of retaining patients with schizophrenia in treatment outside of trial settings.

4.7 Conclusion

The findings discussed in this chapter addressed the objective of estimating the attrition rates in RCTs evaluating complex interventions for schizophrenia expressed as dropout at both intervention and study levels. In addition, the study identified one potential predictor of intervention completion and did not confirm factors previously found to be significantly associated with retention rates. Poor quality of reporting

information about participant flow, especially using the recommended CONSORT tool, has emerged as a barrier to studies investigating participant retention.

The following chapter will continue to explore the relationships between study and participant characteristics and retention rates drawing on a different type of data.

Chapter 5
Patterns of retention and factors predicting study completion in trials of complex interventions for schizophrenia: individual patient data meta-analysis

5.1 Chapter overview

This chapter addresses the second research question: What is the retention of patients with schizophrenia in RCTs evaluating complex interventions influenced by? The outline of this chapter is as follows. The first section presents the rationale for undertaking this study and explains how it is linked to the previous analyses presented in Chapter 4. Next, specific objectives are listed before presenting the methods and the process of the current study where individual patient data meta-analysis (IPD-MA) was applied to data from five trials involving people with schizophrenia. The results of the analysis are presented before they are discussed in the last section.

5.2 Rationale

The results of the systematic review and meta-analysis presented in the previous chapter (Chapter 4) highlighted poor reporting of information relevant to the retention of participants and revealed high heterogeneity of studies. This is a recognised challenge of undertaking meta-analyses of primary studies that rely on summary data presented in published reports (Stewart and Tierney 2002, Abo-Zaid *et al.* 2012). The lack or poor presentation of data readily available in a uniform or accessible format within trial publications, or directly from study authors identified in the systematic review, provided justification for conducting a more thorough exploration of potential

predictors of participant engagement. For this type of exploration IPD-MA has been suggested as a superior and more reliable approach to a synthesis of summary statistics by medical statisticians (Stewart and Tierney 2002, Simmonds *et al.* 2005, Tudur Smith and Williamson 2007). This argument has been made based on the advantages offered by IPD-MA, including: the ability to examine data in detail, more thorough data validation and quality assessment, standardisation of outcome definitions, and testing additional hypotheses associated with individual patient socio-demographic characteristics. For these reasons this approach was applied in the study presented in this chapter, looking to gain better understanding of the factors affecting participant retention in trials on the sample of five RCTs evaluating different complex interventions for schizophrenia.

5.3 Objectives

The two objectives of this study were:

1. To identify patient and study characteristics that may influence retention in non-pharmacological RCTs involving people with schizophrenia.
2. To compare the role of these characteristics in retention at the penultimate follow-up assessment and the final assessment.

5.4 Method

5.4.1 Individual patient data meta-analysis as a method

As discussed in the previous chapters, systematic reviews sit at the top of the hierarchy of evidence, providing the most rigorous and robust method for evidence-based medicine (Elamin and Montori 2012). This method allows for identification of clinical trials evaluating similar outcomes in a methodical way and, subsequently, quantitatively synthesising data from those studies to enable relevant analyses. There are many types of meta-analyses, depending on the research question and data available, most commonly using the summary statistics reported in trial publications (Lyman and Kuderer 2005). However, using summary data, usually in a form of

weighted averages, has its limitations. For example, patient averages at the study level can suffer problems with aggregating data and confounding by trial-level covariates. Furthermore, as highlighted in the previous chapter and reported in the literature, systematic reviews are limited to mainly published reports often presenting inadequate information and suffering from publication bias (Stewart and Tierney 2002). It has been suggested that meta-analyses drawing on aggregate patient data may be used to decide whether or not it is worthwhile proceeding with a more resource intensive analysis using data recorded for individual patients (Lyman and Kuderer 2005). This type of analysis, called individual patient data meta-analysis, is relatively new and seldom used due to resource intensity, which will be discussed later in the chapter (Tudur Smith and Williamson 2007).

Most trials report aggregate data, averaged across all participants in a study, for instance the mean age or proportion of participants who spoke English as their first language. In contrast, data recorded for each participant who takes part in a clinical trial are described as 'individual patient data' (IPD). These can include demographic characteristics such as gender or age, pre- and post-treatment outcome measures, or an indicator of arm allocation.

Meta-analyses using IPD, like other meta-analyses, are applied to answer a specific question related to clinical practice by drawing on data from multiple similar trials. Traditionally, this type of analysis follows the same basic methods and philosophy as other types of systematic reviews; however the structure and the process of data collection and analysis are different (Chalmers 1993). The key premise of a conventional IPD-MA is using raw data obtained from studies previously identified in a systematic review of literature. Using raw data enables analyses that are difficult to perform on aggregate data; for example investigating whether a given treatment is more effective for patients with longer illness duration. If the distribution of illness duration is similar across studies there will be no relationship between treatment efficacy and duration of illness at the trial level. IPD-MA can be used to explore such relationships between outcomes and patient characteristics.

The process of individual patient data meta-analysis

Another difference setting IPD-MA apart from the 'conventional' aggregate data meta-analyses is the process it needs to follow. Figure 5.1 illustrates the key stages.

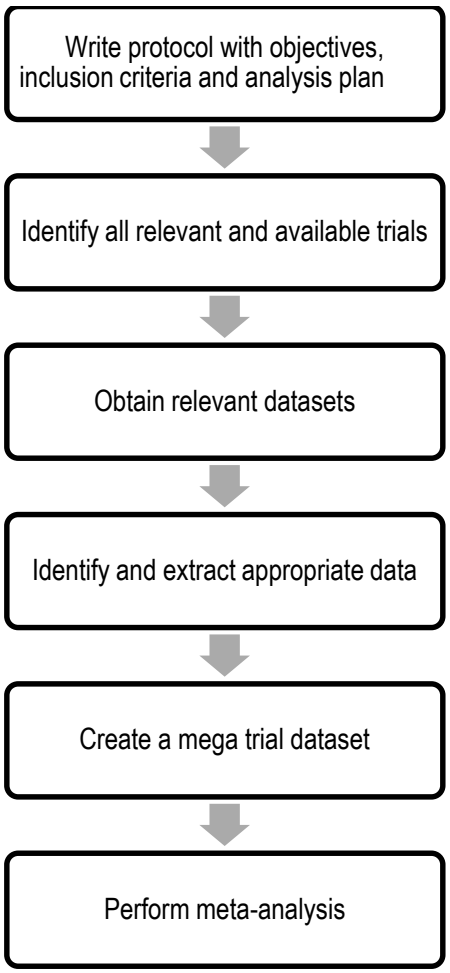


Figure 5.1 Stages of an Individual Patient Data Meta-Analysis (adapted from Stewart & Tierney 2002)

The key consideration when undertaking an IPD-MA is deciding on the scope of the analysis and the ways of obtaining the required data. The traditional and most scientifically robust way of performing an IPD-MA is a systematic review approach (Tierney *et al.* 2015). Here, literature is systematically searched to identify all relevant trials and then the authors of those studies are contacted with requests for individual patient data. Depending on the scope of the literature search, especially publication date and study location, obtaining raw data can require significant effort on behalf of

researchers undertaking IPD-MA as well as those who are asked to provide raw data. Thus, adopting the systematic review approach normally involves forming a collaborative group responsible for the process. As a consequence, IPD-MA can be the most time consuming and costly type of study, often rendering them unfeasible due to lack of resources (Stewart and Tierney 2002, Simmonds *et al.* 2005, Abo-Zaid *et al.* 2012) or lack of willingness to collaborate (Jaspers and Degraeuwe 2014). In addition, the ethical and regulatory processes involved in sharing data vary across the world, with some countries (including the Unite Kingdom) requiring a formal review by a Research Ethics Committee (Phillips *et al.* 2017). As a consequence of these barriers, the majority of IPD-MAs have been possible in the fields considered to be major public health concerns, which attract substantial funding; namely cancer and heart disease (Simmonds *et al.* 2005).

An alternative approach requiring fewer resources involves pooling resources with existing collaborators and, effectively, drawing on convenience samples (Riley *et al.* 2010). Examples of such analyses are present in the literature and include prominent studies such as the pooled analysis of 18 datasets investigating prognostic markers in breast cancer carried out by the European Organisation for Research and Treatment of Cancer (Look *et al.* 2002). However findings of such studies need to be interpreted with caution as they might not be representative of all existing trials in the area of interest and might therefore be susceptible to bias. One example of an IPD-MA conducted on a convenience sample is a study examining participant attrition in 10 trials evaluating treatment of musculoskeletal disorders (Hewitt *et al.* 2010). The study aimed to investigate the impact of attrition on the imbalance in baseline characteristics of those randomised to a trial. The authors did not provide clear rationale for drawing on a small number of easily available trials but it could be inferred that this was due to resource constraints.

Following acquisition of relevant datasets, all data need to be checked and cleaned before extracting relevant variables. Since different studies record different types of data, often in different formats, data extraction needs to be followed by checking consistency and combining different scales of measurement. Only after all covariates are reported in the same format, can all data be combined into a single 'mega-trial' dataset.

Prior to performing meta-analyses a decision needs to be made about how the analyses will be conducted. Researchers have two options at their disposal: a one-step and a two-step approach. These should provide similar results, although they cannot be expected to be due to some key differences in the assumptions they require to be made (Jones *et al.* 2009, Debray *et al.* 2013). In the one-step analysis data collated from all available studies is analysed simultaneously, based on the assumption that the true effect is fixed across studies (Jones *et al.* 2009). Depending on the type of data and assumptions of the meta-analyses (fixed or random effects), an appropriate model needs to be specified. In contrast, the two-step approach treats each study separately. The first step involves analysing data in each separate study to produce aggregate data for each one of those studies. In the second step, these aggregate data are combined across included studies (Debray *et al.* 2013). This produces a summary effect size (for example the odds ratio) for the factor-outcome relationship of interest, simultaneously accounting for differences between studies.

5.4.2 Sample

In this study, a convenience sample of five RCTs evaluating complex interventions and involving people with schizophrenia and related disorders was subjected to an IPD-MA. Three trials were undertaken at QMUL and two at the University of Oxford. The characteristics of included studies are provided in Table 5.1.

Table 5.1 Characteristics of included trials

Trial name	Reference	Total number of randomised participants	Active intervention	Control intervention	Penultimate follow-up point	Final follow-up point
EPOS	Priebe et al. 2013	n=179	DIALOG+ (iPad-mediated procedure to discuss 11 domains with patients) used with a clinician	DIALOG+ used independently, without a clinician	6 months	12 months
MECCA	Priebe et al. 2007	n=507	DIALOG (computer-mediated procedure to discuss 11 domains with patients)	Standard treatment	Not applicable	12 months
NESS	Priebe et al. 2016	n=275	Manualised group body psychotherapy	Pilates class	6 months	12 months
OCTET	Burns et al. 2013	n=336	Hospital discharge on Community Treatment Order	Hospital discharge on Section 17 leave	12 months (end of Phase I)	24 months (study extension)
UK700	Burns et al. 1999	n=708	Intensive case management	Standard case management	12 months	24 months

Conducting this analysis following completion of a systematic review of literature and meta-analysis presented in the previous chapter allows to ascertain the extent to which the results from this IPD-MA study generalise to other trials evaluating non-pharmacological interventions for people with schizophrenia. This can be achieved by comparing the characteristics of studies in the systematic review and those in the IPD-MA convenience sample. However, it should first be noted that the trials in the systematic review were identified following applying specific inclusion and exclusion criteria, thus it was not representative of all trials evaluating non-pharmacological interventions for schizophrenia.

Table 5.2 shows the comparison of key study characteristics, including average number of randomised participants, study setting (inpatient vs outpatient), type of control (active vs standard care), intervention delivery (individual vs group), and average study duration.

Table 5.2 Characteristics of trials in the IPD-MA sample and the systematic review sample

Study characteristic	IPD-MA sample (n=5) (n, %)	Systematic review sample (n=43) (n, %)
Average number of randomised participants	401	200.93
Study setting	Outpatient 5 (100)	Inpatient 6 (14) Outpatient 23 (53.5) In- and out-patient 10 (23.2) No information 4 (9.3)
Type of control	Active 2 (40) Standard care 3 (60)	Active 15 (34.9) Standard care 20 (46.5) Other 8 (18.6)
Intervention delivery	Individual 4 (80) Group 1 (20)	Individual 20 (46.5) Group 22 (51.2) No information 1 (2.3)
Average study duration (last follow-up)	16.8 months	11.92 months

Compared to trials identified in the systematic review reported in Chapter 4 the convenience sample in this study had, on average, larger sample size and longer duration. Nonetheless, these were within the ranges identified in the systematic review.

All trials subjected to IPD-MA were conducted in outpatient settings. Thus, this IPD-MA is limited to studies conducted in this context. Majority of trials in the systematic review were also conducted with outpatients (53.5%) or a combination of in- and out-patients (23.2%).

Four out of 5 evaluated interventions were delivered individually, compared to an almost even split in the systematic review sample. Thus, in the IPD-MA sample there is an underrepresentation of interventions delivered in a group format and the findings may only apply to studies evaluating individually-delivered interventions.

Similarly to the trials in the systematic review, majority of studies in IPD-MA used a standard care control. However, there is representation from studies using both active and standard care controls.

Overall, given the high heterogeneity of the studies identified in the systematic review, the characteristics of this convenience sample fall within the ranges reported in the review; however it is important to acknowledge the differences, which may limit the generalisability of the study.

5.4.3 Definitions

Retention was defined as completion of follow-up assessments at two time points for each trial. Completion was considered for both the penultimate and the final follow-up to allow for comparisons. These time points were chosen as it has been suggested that the pattern of retention varies over the duration of a trial, with the highest proportion of dropout occurring in the early stages (Carroll 1997, Hewitt *et al.* 2010).

5.4.4 Data collection

Researchers who worked on each of the identified studies were approached with a request for the data listed in Table 5.3 below. Researchers were free to provide data in

the most convenient format for them, given that the details of coding were supplied and the data were anonymised.

Table 5.3 Data requested from trial researchers

Trial level data	Individual patient level data (as recorded at baseline)
Setting (inpatient or outpatient)	Age
Population (inclusion and exclusion criteria)	Gender
Number of follow-up assessments	Ethnicity
Timing of follow-up assessments	Country of birth
Method of outcome measurement (measures used)	Marital status
	Occupation
	Employment status
	Education level
	Age of onset
	Age of first admission
	Diagnosis
	Income
	Number of children
	Living situation
	Type of residence
	Treatment group allocation (active vs. control)
	First language
	Number of psychiatric admissions
	Completion of penultimate follow-up assessment or outcome score recorded at penultimate follow-up assessment
	Completion of final follow-up assessment or outcome score for final follow-up assessment
	Reason for missing data

5.4.5 Outcome measures

The clinical outcomes of each study were not relevant to this meta-analysis but their availability was used as a proxy measure for assessment completion if the trial did not record completion as a separate variable.

5.4.6 Data synthesis

Upon acquisition of data for all included trials the candidate performed thorough checking to ensure consistency and quality of reporting. Any missing data, inconsistencies between variables, or extreme values were discussed with the researchers who worked on the trial that the results came from. Where studies used different classifications or measurements data were translated and combined to achieve consistency across studies, for instance some data sets did not record age as a numerical variable but provided date of birth and so enabled calculations of participants' age. Following checks, data were inputted into a single database to build a 'mega-trial database'.

5.4.7 Data analysis

A one-stage analysis was performed, where data are modelled simultaneously whilst accounting for the clustering of subjects within studies. Compared to a two-stage IPD-MA, the one-stage approach is more statistically exact and is recommended for analyses of data available from few studies (Debray *et al.* 2013). A one-stage IPD-MA is a multilevel logistic regression model with mixed effects.

The variables included in the analysis were selected based on the consistency of reporting across all included trials. The dependent variables (outcomes) were: 1) retention at penultimate follow-up and 2) retention at final follow-up. The covariates (potential predicting factors) included: allocation to arm, gender, age, ethnicity, education level, employment status, and marital status.

Three sets of mixed-effects logistic regression analyses were carried out relating to the two outcomes, considered separately. The first set included two univariate logistic regressions of the effect of arm allocation on retention at two follow-up points. This

began to investigate confounding as well as provided an initial and unadjusted view of the importance of each variable, by itself. The second set comprised analyses to examine the associations between retention and each covariate separately. Arm allocation was kept as a fixed effect for calculations of the effect of age, sex, education, ethnicity, employment status and marital status. Finally, two last analyses examined the associations between retention and covariates in a multivariate way. These associations were expressed as odds ratios (ORs) with 95% CIs. Odds ratios were used to compare the relative odds of the outcome (i.e. completion of follow-up assessment), given the exposure to the variable of interest (i.e. socio-demographic characteristics and arm allocation) (Szumilas 2010).

5.4.8 Ethics and governance

This study did not require a separate ethics committee approval for the following reasons. First, investigators of each of the included studies obtained appropriate approval from their local ethics committee and written informed consent from patients prior to including the cohorts in this meta-analysis, which permitted secondary analysis of the data. Second, the current study used anonymised data preventing identification of the participants recruited to the original study.

5.5 Results

5.5.1 Sample characteristics

The total sample size available for analysis achieved by combining the five trials was 2,006. Data on the penultimate follow-up assessment completion were collected in four trials, with one having before/after design and therefore not included in the analysis of retention at penultimate follow-up point. Baseline covariates of interest measured at the patient level included: age, sex, ethnicity, education level, marital status, and employment status. Table 5.4 provides an overview of the counts observed for each variable across the five studies.

Overall, the majority of the total sample was male (64.4%), 41 years old on average, with 11.6 years spent in education. Most participants were of White background (59.5%), followed by Black ethnicity (27.5%), Asian ethnicity (7.6), and 'Other' ethnicities (5.4). The majority lived alone (87.8%) and were employed (87%). In terms of trial involvement, 51.5% were randomised to the active arm and 48.9% received the control condition. Allocation to arm (active vs control) was also recorded for the purposes of the analysis.

The IPD available for analysis included a wide range of outcomes and patient socio-demographic characteristics with differences in definitions, completeness, and consistency between data sets. Some items were not reported consistently across all studies; this is because some trials did not collect specific variables, such as employment status, country of birth, or age of onset. The unrecorded data led to a reduced data set available for a multivariate analysis, with 984 patients available for the penultimate follow-up analysis and 988 for the final follow-up. For that reason only results of the univariate analyses are presented and discussed.

Table 5.4 Overview of available data by study

Trial name	Total study sample	Gender (n, %)	Age (mean)	Ethnicity (n, %)	Length of education (mean years)	Marital status (n, %)	Employment status (n, %)	Allocation to arm (n, %)
EPOS	n=180	Female 56 (31) Male 124 (69)	41.7	White 46 (25.7) Black 70 (39.1) Asian 49 (27.4) Other 14 (7.8)	11.2	Live alone 146 (81.6) Live with partner 33 (18.4)	Variable not reported	Active 94 (52.5) Control 85 (47.5)
MECCA	n=507	Female 171 (34) Male 336 (66)	42.3	White 431 (85) Black 53 (10.4) Asian 14 (2.8) Other 9 (1.8)	Variable not reported	Live alone 439 (86.7) Live with partner 67 (13.3)	Working 348 (69.6) Not working 152 (30.4)	Active 271 (53) Control 236 (47)
NESS	n=275	Female 72 (26) Male 203 (74)	42	White 142 (51.8) Black 80 (29.2) Asian 30 (1.1) Other 22 (9)	10.9	Variable not reported	Working 266 (99.2) Not working 2 (0.8)	Active 140 (51) Control 135 (49)

OCTET	n=336	Female 111 (33) Male 225 (67)	40	White 206 (61.3) Black 78 (23.2) Asian 29 (8.6) Other 23 (6.9)	12.6	Live alone 297 (91.4) Live with partner 28 (8.6)	Working 322 (98.8) Not working 4 (1.2)	Active 167 (49.7) Control 169 (50.3)
UK700	n=708	Female 304 (43) Male 404 (57)	38	White 367 (51.8) Black 270 (38.1) Asian 30 (4.3) Other 41 (5.8)	11.7	Live alone 626 (88.4) Live with partner 82 (11.6)	Working 628 (89.2) Not working 76 (10.8)	Active 353 (49.9) Control 355 (50.1)
Total	n=2,006	Female 714 (35.6) Male 1,292 (64.4)	40.8	White 1,192 (59.5) Black 551 (27.5) Asian 152 (7.6) Other 109 (5.4)	11.6	Live alone 1,508 (87.8) Live with partner 210 (12.2)	Working 1,564 (87) Not working 234 (13)	Active 1,025 (51.1) Control 980 (48.9)

5.5.2 The effect of arm allocation on retention

For the penultimate follow-up completion there were data from 1,493 participants. The number of available observations was reduced due to one trial adopting a before/after design. Out of the available data, 1,236 participants were completers and 257 did not complete the follow-up. The results are presented in Table 5.5 below.

Table 5.5 Summary data of penultimate follow-up retention by arm allocation

Penultimate follow-up completion	Arm (n, % completion)		Total (n, % completion)
	Active	Control	
Yes	631 (83.9)	605 (81.65)	1,236 (82.8)
No	121 (16.1)	136 (18.35)	257 (17.2)
Total	752	741	1,493

For the final follow-up completion there were data from 2,005 participants. Out of those, 1,671 were completers and 334 did not complete the follow-up. The results are presented in Table 5.6 below.

Table 5.6 Summary data of final follow-up retention by arm allocation

Final follow-up completion	Arm (n, % completion)		Total (n, % completion)
	Active	Control	
Yes	871 (85)	800 (81.6)	1,671 (83.3)
No	154 (15)	180 (18.4)	334 (16.7)
Total	1,025	980	2,005

Univariate logistic regression

The results of the univariate logistic regression suggest absence of substantial heterogeneity ($Tau^2 = 0.79$). There was a marginally significant result with unadjusted OR of 1.27 (p=0.051) suggesting that the odds of participants in the active treatment arm completing the last follow-up were 27% more than in the control arm. The results are presented in Table 5.7 below.

Table 5.7 Univariate models of retention by arm allocation

	Number of studies	Number of participants	p-value	OR (95% CI)
Penultimate follow-up	4	1,493	0.347	1.1, 0.89 to 1.56
Final follow-up	5	2,005	0.051	1.27, 0.99 to 1.61

5.5.3 Patient socio-demographic characteristics associated with retention

Mixed effects logistic regression with multiple variables

Possible associations between individual patient socio-demographic characteristics and retention were assessed using mixed-effects logistic regressions. Each model was adjusted for arm allocation. Age, gender, length of education, occupation status, and marital status were continuous variables and ethnicity was a categorical variable. Results for the penultimate follow-up point are reported in Table 5.7 and for the final follow-up in Table 5.8. None of the tested characteristics were found to be significantly associated with retention at either of the follow-up points. The difference between individuals with White and those with Black ethnicity approached an acceptable significance level (p=0.057), which suggests that White participants could have higher odds of completing the penultimate follow-up compared to those with Black ethnicity. However, this result does not allow for making any firm conclusions given the high p-value and wide confidence interval.

Table 5.8 Individual patient socio-demographic characteristics predicting retention at penultimate follow-up tested in multivariate models

Outcome: retention at penultimate follow-up	Number of studies	Number of participants	p-value	OR (95% CI)
Age (years)	4	1,493	0.481	0.99 (0.98 to 1.01)
Gender	4	1,493	0.701	1.06 (0.79 to 1.42)
Ethnicity:	4	1,492		
White vs Black			0.057	0.74 (0.54 to 1.01)
White vs Asian			0.287	0.76 (0.46 to 1.26)
White vs Other			0.662	1.15 (0.62 to 2.14)
Education (years)	4	1,435	0.927	1.00 (0.95 to 1.06)
Employment status (working vs not working)	3	1,293	0.469	0.79 (0.43 to 1.48)
Marital status (live alone vs live with partner)	3	1,216	0.568	1.14 (0.72 to 1.83)

Table 5.9 Socio-demographic predictors of retention at final follow-up tested in multivariate models

Outcome: retention at final follow-up	Number of studies	Number of participants	p-value	OR (95% CI)
Age (years)	5	2,005	0.501	0.99 (0.98 to 1.00)
Gender	5	2,005	0.267	0.86 (0.68 to 1.11)
Ethnicity:	5	2,004		
White vs Black			0.092	0.78 (0.59 to 1.04)
White vs Asian			0.097	0.69 (0.44 to 1.07)
White vs Other			0.832	1.06 (0.61 to 1.86)
Education (years)	4	1,439	0.772	0.99 (0.94 to 1.04)

Employment status (working vs not working)	4	1,798	0.967	1.01 (0.65 to 1.56)
Marital status (live alone vs live with partner)	4	1,727	0.699	1.08 (0.73 to 1.59)

5.6 Discussion

5.6.1 Main findings

This study analysed the potential impact of patient characteristics on study retention in a convenience sample of five randomised clinical trials of non-pharmacological interventions for schizophrenia. The average retention rates were 82.8% (17.2% attrition) and 83.3% (16.7% attrition) for the penultimate and the final follow-up assessment, respectively. Retention within the active intervention group was 83.9% (16.1% attrition) at the penultimate and 85% (15% attrition) at the final follow-up; and within the control group, it was 81.65% (18.35% attrition) at the penultimate and 81.6% (18.4% attrition) at the final follow-up.

The present study suggests that patients with schizophrenia randomised to experimental interventions evaluated in RCTs are more likely to complete the final follow-up assessment compared to those who receive control conditions. However, given that the result fell just short of the traditional definition of statistical significance, the finding should be treated with caution.

Further meta-regressions showed no evidence of a significant relationship between any of the tested patient characteristics and completion of assessment at either time point. This result is similar to the findings of the systematic review and meta-analysis presented in Chapter 3 and builds on them to widen the evidence about retention of participants with schizophrenia in non-pharmacological trials.

5.6.2 Strengths and limitations

This IPD-MA represents the first, albeit limited in scope, of its kind in the context of mental health. It has demonstrated that this type of analysis is feasible and can provide important insight into what factors predict or do not predict retention in trials involving people with schizophrenia. Conducting a full IPD-MA employing a systematic review was not feasible given the constraints of this doctoral study. However, IPD-MAs based on convenience samples have been deemed useful for gaining insight into specific issues (Hewitt *et al.* 2010, Riley *et al.* 2010) and such was the intention of this study.

The main limitation of this study is the limited number of and the crude nature of the tested characteristics. The choice of variables was limited to those present in the available trial databases, but there may be other factors affecting the completion of follow-up assessments.

5.6.3 Interpretation and comparison with the wider literature

Previous meta-analysis conducted as part of this thesis analysed trials of non-pharmacological interventions for schizophrenia reported in the literature and compared attrition at both intervention and study levels. The findings showed that a higher number of sessions led to higher intervention dropout (Chapter 3). Other patient and study characteristics did not show significant associations with either intervention or study dropout.

The IPD-MA presented in this chapter aimed to explore the patterns and predictors of study retention further. Given that study attrition is defined by the loss of participants to follow-up and most trials involve multiple assessments over an extended period of time, it was possible to explore the differences in retention across the duration of a project. This analysis was able to include patient socio-demographic characteristics and allocation to arm as potential predictors of study retention.

Impact of age and gender

Like in the preceding meta-analyses exploring predictors of dropout, no effect was found for age or gender. As discussed in the previous chapter, this lack of association

is not consistent with the findings of Nosé et al. (2003) and Villeneuve et al. (2010), which identified age and gender as predictors of dropout of people with psychotic disorders. Although it is important to note that the two studies disagreed on the direction of association for age, with the former study reporting higher dropout to be associated with lower age, and the latter reporting older participants to be more likely to withdraw from treatment.

Impact of employment status and education

Unlike Nosé et al. (2003) (although the focus of their study was on treatment adherence) this IPD-MA did not find a significant effect of employment status on retention. Similarly, while Villeneuve et al. (2010) reported living alone and having high education to lead to better adherence to psychosocial treatment for schizophrenia, the current study did not find employment status or length of education to be associated with completion of follow-up assessments.

Impact of ethnicity

The association between ethnicity and study retention approached significance level, suggesting that there might be differences between the groups included in the analysis (i.e. White, Black, Asian and Other) and that individuals of different ethnic backgrounds might not be equally likely to complete follow-up assessments. However, further analyses are required to ascertain this finding.

The presence of such association would have implications for the involvement of patients from ethnic or racial minorities in mental health research, which has been the subject of considerable debate in the literature (Brown *et al.* 2014). Individuals from ethnic minority groups have been found to be more likely to refuse participation in mental health research (Miranda 1996, Hussain-Gambles 2004, Jackson *et al.* 2004, Woodall *et al.* 2010, Williams *et al.* 2012). The same has been shown specifically for patients with psychotic disorders (Patel *et al.* 2017).

In comparison to the initial agreement to participate less evidence is available about the likelihood of completing treatment and research assessments within a trial context, especially in the area of psychotic disorders. However, retention has direct implications for the representation of minorities in clinical studies as, if they are also more likely to drop out after being recruited, the problem of unequal representation would remain throughout studies. Research conducted by Baekeland & Lundwall (1975) found

patients receiving psychotherapy to be more likely to prematurely discontinue treatment if they had ethnic minority background. It is difficult to judge the relevance of these findings in today's practice given the societal and political changes that have occurred since its publication. One the one hand, one would anticipate that people from ethnic minorities are better integrated into communities and thus not as affected by the barriers they have been reported to experience (Hussain-Gambles 2004, Yancey *et al.* 2006, Woodall *et al.* 2010, Brown *et al.* 2014, Hartlieb *et al.* 2015), resulting in less ethnic inequalities. On the other hand, research on the use of mental health services has shown that individuals from ethnic minorities are less likely to engage and to complete treatment (Alvidrez 1999, Hines-Martin *et al.* 2004, Gary 2005, Carpenter-Song *et al.* 2010). Nonetheless, it is not possible to ascertain from the evidence generated by the current study whether this phenomenon translates into non-pharmacological treatments provided within trial settings and completion of research assessments.

Impact of arm allocation

A marginally significant association was found between arm allocation and completion of the final follow-up assessment. A similar effect was found in a meta-analysis of dropout rates in trials of antipsychotic drugs, showing that participants receiving placebo were more likely to drop out than those receiving medication (Kemmler *et al.* 2005). The present study suggests that participants who receive an active intervention may be more likely to complete final assessments, which can be interpreted in different ways.

The first potential explanation is linked to the research on treatment preferences and their effect on attrition in trials. Although Sidani et al. (2015) highlight that the evidence is inconsistent, two meta-analyses (Preference Collaborative Review Group 2009, Swift *et al.* 2011) and two individual studies (Raue *et al.* 2009, Kwan *et al.* 2010) showed that patients who received treatment that matched their preference were less likely to withdraw from trials. If one assumes that most individuals want to receive the new treatment evaluated in a trial they are invited to participate in (something that will be explored in the subsequent chapter), especially when the other option is standard care, those randomised to the active arm can be considered as 'matched' to their preference and thus less likely to drop out. The current study would suggest however that this

effect is significant only for the final follow-up, indicating that a different factor might explain the difference between the penultimate and the final assessments.

The second interpretation takes into consideration potential researcher bias and the possibility that trial researchers somehow influence completion of final follow-up assessments, despite blinding. Hewitt et al. (2010) suggest that "researchers often focus increased efforts on data collection at the final time point" (p.1266), although they do not provide any empirical evidence to support this statement. If this were true, the effect on retention in trials where researchers are blinded to participants' treatment allocation would be equally observed across both arms. This was not the case in the current study. However, it is possible that the efforts are influenced, perhaps unconsciously, by unblinded researchers responsible for arranging appointments with participants. This would mean that the effort made to make sure that participants attend their final follow-up appointments is greater with those who received an intervention than those who were in the control condition.

An alternative potential explanation considers the varying levels of involvement in a trial depending on arm allocation. Participants randomised to an active arm, especially in case of non-pharmacological treatment, are expected to attend individual or group sessions, or to complete regular activities comprising an intervention. As a consequence, they often receive reminders, are in frequent contact with providers of an intervention and other patients (in case of group interventions), and are likely to discuss their experience of treatment with their clinician. A different level of involvement can be expected in some control conditions; this however will depend on the type of control offered in a given trial. In trials offering 'standard care' or 'treatment as usual' as a control intervention, the differences can be more pronounced as taking part as a control participant would not subject one to a new treatment. However, in the case of an active control (two out of five trials analysed in this study), the level of expected involvement would be more or less the same across trial arms. And, again, this would not explain the lack of effect for the penultimate follow-up completion.

5.6.4 Implications of findings for trial conduct and further methodological research

This study addresses a gap in the evidence on factors affecting retention in schizophrenia trials. Although this study did not find strong evidence for an effect of participant characteristics on retention, it shows that IPD-MA provides a reliable approach to examine the issue of study completion and can therefore be treated as an exemplar for future investigations of retention patterns and predictors. A systematic review IPD-MA could yield a larger sample and thus more powerful analysis; however given the resources it would require, it would be difficult to justify.

Whilst the previous meta-analysis (Chapter 3) was limited by poor reporting in published research, this study had to deal with lack of consistency in variables recorded across different trials. Although, it is important to note that this study was sufficiently powered to identify any effects of relevant magnitude. Difficulties with extracting data for the purposes of meta-analyses of prognostic factors have been acknowledged in the literature (Abo-Zaid *et al.* 2012). A larger study with variables more consistently reported across individual trials is needed to generate a more precise estimate of the effect. However, the issues with the consistency and quality of data recorded in trial databases encountered in this study highlight the need for a careful consideration before undertaking a systematic IPD-MA in the future.

Since none of the participant socio-demographic characteristics tested in this meta-analysis were identified as having being significantly associated with study retention, it is suggested that multiple strategies for achieving study completion are necessary, without the need to tailor the approach based on specific socio-demographic demographic characteristics.

5.7 Conclusion

This chapter discussed the findings of an analysis of predictors of retention, which aimed to extend the results from the systematic review and meta-analysis reported in Chapter 4 by drawing on individual patient data from relevant RCTs. The findings confirmed the lack of strong associations between the tested socio-demographic characteristics and retention. However, the study identified a relationship between

receiving an intervention and completing the last follow-up assessment. Consequently, this suggests that there is no need in focusing retention strategies on specific subgroups with a higher risk of dropping out, since they cannot be identified given the available data.

The following two chapters will continue to examine retention in RCTs, including potential predictors, by employing qualitative methods. Chapter 6 will investigate the perspectives of trial researchers and Chapter 7 will deal with the experiences of trial participants.

Chapter 6
Qualitative study of trial retention practices

6.1 Chapter overview

Chapter 5 addresses the second and the third research questions: 2) What is the retention of patients with schizophrenia in RCTs evaluating complex interventions influenced by?; and 3) How can patients with schizophrenia be retained in trials?

This chapter begins with an overview of the method before it describes the study sample and the recruitment strategy. The details of the materials used to recruit participants and to collect data, as well as the overall procedures followed during data collection are also provided. The findings from the qualitative study are presented and discussed in the 'Findings' section before they are interpreted in the following section.

6.2 Rationale

Chapters 4 and 5 of this thesis presented results of two quantitative studies, both conducted to identify factors affecting retention in trials of complex interventions for schizophrenia. These investigations identified some issues with analyses relying on both published data as well as individual patient data obtained directly from researchers. Nonetheless, they have provided insight into which patient socio-demographic characteristics and study characteristics may or may not have impact on retention.

Simultaneously to conducting these quantitative analyses, a qualitative study was conducted investigating the experiences and practices of trial researchers and therapists working on studies relevant to the focus of this thesis. Conducting these

studies in parallel allowed for prompting interviewees about some of the factors being tested in the meta-analyses. The primary purpose of adopting a qualitative methodology was to identify, analyse and report the patterns of retention and trial professionals' understanding about retaining participants with schizophrenia in non-pharmacological trials. The importance of qualitative research, especially in the context of medicine and clinical research, has been emphasised in a recent debate about publishing qualitative studies in the *British Medical Journal,* with 76 senior academics from 11 countries arguing that "Qualitative studies help us understand why promising clinical interventions do not always work in the real world, how patients experience care, and practitioners think" (Greenhalgh *et al.*, 2016, p.2). The purpose of the present study was to grasp the understanding of trial practices that would be beyond the quantitative approach, not least because of the reporting inconsistencies highlighted in the previous chapters. As a secondary aim, the findings from this study, together with the literature identified in Chapter 2, the results of quantitative studies presented in Chapters 4 and 5, and another qualitative study presented in the subsequent chapter will be used to inform conclusions about retention and recommendations for trial methodology and practice.

6.3 Objectives

This study had the following objectives:

1. To examine the process of recruiting patients with schizophrenia to non-pharmacological RCTs and its impact on retention of this population.
2. To identify the points in the research process where retention is considered.
3. To explore the reasons for dropping out provided to trial researchers by participants.
4. To identify retention strategies used by trial researchers and therapists.
5. To identify any specific challenges of engaging people with schizophrenia in RCTs.

6. To identify lessons to be learned about how retention in future trials of complex interventions for schizophrenia might be improved.

6.4 Method

6.4.1 Study design

This study's prime interest was individual stories and perspectives of working on trials and, more specifically, retaining people with schizophrenia in complex interventions and follow-up assessments. For this reason individual interviews were chosen as the most appropriate method of data collection. Group interviews were considered as a data collection method but it was thought that the trial researchers would be less likely to share their practices and strategies with those working in other groups or institutions, since they may wish to project a certain image or protect their practices as they often compete for the same funding.

The choice of method was dictated by the research question. The aim was to understand the experience of managing retention of people with schizophrenia in trials from the perspective of trial staff who have worked on RCTs evaluating complex interventions. Qualitative methods are uniquely positioned to collect data on experiences, allowing to explore their breadth and depth (Ritchie and Spencer 2002, Creswell 2003, Seale *et al.* 2007, Yin 2010). Particular attention was paid to the factors which affected or which could modify participant retention and strategies used to increase retention or prevent attrition.

Framework Method was chosen as a type of qualitative content analysis and thematic analysis, the choice and application of this method will be discussed in more detail below. The aim of this method is not to generate theory, but it allows for the use of constant comparative techniques [a feature of Grounded Theory (Bryant and Charmaz 2010, Charmaz 2013)] through the review of data in the matrix.

Approach to data

When developing explanations, the doctoral candidate applied retroductive logic, which aims to identify explanatory mechanisms or structures (Blaikie and Priest 2017).

This logic of inquiry was applied in order to identify key factors or processes that could explain patterns appearing in the data. As a result, alternative explanations were developed and proposed to make logical sense of the patterns. These drew on both emic and etic perspectives. The emic perspective, focusing on explicit accounts provided by participants, "attempts to capture participant's indigenous meanings of real-world events" (Yin, 2010, p.11) and "looks at things through the eyes of members of the culture being studied" (Willis, 2007, p.100), thus allowing to gain in-depth understanding of the participant's perspective. This approach has been combined in the present study with the etic perspective, which takes an external view on the studied phenomenon by applying the "structures and criteria developed outside of the culture as a framework for studying the culture" (Willis, 2007, p.100). These implicit accounts involved making inferences and applying logical sense to the participants' accounts; these drew on relevant theories or existing empirical studies where appropriate.

6.4.2 Ethics approval

Prior to data collection, approval for the study was granted by the Queen Mary Ethics of Research Committee (see Appendix 3).

6.4.3 Recruitment

Participants were sought from various academic research institutions across the UK, especially trial units known for conducting studies evaluating non-pharmacological interventions. They were identified using different strategies: Internet searches, network contacts, and snowballing. Subsequently, each potential participant was contacted directly by e-mail or by phone with an invitation to take part. Compensation was not offered for participation.

Eligible individuals needed to have experience of working on trials evaluating non-pharmacological interventions involving people with schizophrenia, in a role that involved direct contact with patients. This requirement excluded PIs who were deemed to be too removed from the direct practice of retaining patients in a trial to provide information pertinent to the study objectives.

Participant information sheets were presented together with an invitation letter, either by post or email. After one week, email reminders followed. Participants were offered the option to be interviewed either at their site or in a neutral private location.

6.4.4 Materials

An information sheet was developed to invite potential participants to the study and to provide information about the purpose of the study and the nature of participation. The document included details of the type of data collected, the likely length of the interview and the types of questions, the intended use of the findings, and the details of the funder of the study and the candidate's supervisor. The potential participants were advised about data confidentiality and given the details of the ethics approval. Contact details of the candidate were also provided. The full information sheet can be found in Appendix 4.

A consent form was provided together with the information sheet to make the data collection process transparent to potential participants. The consent form complied with the requirements of the Queen Mary Ethics of Research Committee and was designed to confirm that the participants fully understood the contents of the information sheet and agreed, in writing, to take part in the study. The form advised the participants about their right to withdraw at any point and the confidentiality of their personal information (see Appendix 5).

The interview schedule comprised four parts: participant introduction and background; experience of recruitment and retention; factors affecting retention and issues specific to trials in schizophrenia; and interview end. The purpose of the interview schedule was to first establish the relevant knowledge and experience of each participant and, subsequently, to ask questions about the experience of recruiting and retaining participants, with emphasis on the latter. This included any specific practices and strategies used and the factors observed by participants as affecting retention in trials. Prompts were used to enable participants to elaborate on points of interest further, as well as to elucidate reflections on their own experience in greater depth. Appendix 6 provides a full interview schedule.

6.4.5 Procedure

Once contacted individuals expressed their willingness to take part, the interviews were scheduled. Potential participants were given the option of being interviewed over the telephone or Skype if meeting in person was problematic. Twenty-four interviews were conducted in person, three over the telephone, and one using Skype. All interviews were conducted at a convenient time and location for the participant. All face-to-face interviews took place at the participants' workplaces, in a confidential space.

Following obtaining written informed consent and prior to the interview, participants were asked to complete a short demographic details form.

All interviews were recorded with a digital voice recorder. The duration of the interviews ranged from 28 minutes to 2 hours and 27 minutes, with an average duration of 51 minutes. The majority were between 28 minutes to 1 hour, with variations in length depending on interviewees' availability. Interview notes were taken immediately after the interview. Six interviews were transcribed by a graduate student volunteer recruited specifically for this purpose and the remaining 22 by the candidate. All transcripts were checked for accuracy by the candidate before being included in the analysis.

All questionnaire data were kept in a locked filing cabinet and digital information was kept on a secure, password-protected computer. Each set of data was allocated a code to ensure participant anonymity.

6.4.6 Data analysis

The data were analysed using the Framework Method. This type of analysis was considered to be more appropriate than traditional thematic analysis for the purpose of this study because it enables both a priori issues and emergent data to guide the development of the analytic framework (Ritchie and Spencer 1994, Parkinson *et al.* 2015). The Framework has been defined as a set of techniques or a data analysis strategy falling under the umbrella of thematic analysis (Gale *et al.* 2013). The analysis followed five stages described in the original Framework Method (Ritchie and Spencer 1994), as described below.

1) Familiarisation

The familiarisation stage involved reading and re-reading the transcripts and studying interview notes, with the aim of gaining an overview of the data gathered and starting conceptualisation. Although all data were collected by the doctoral candidate this stage was important in ensuring that the recollection of interviews was not partial. Key ideas and recurrent themes were listed during this process, using analytic memos.

2) Identifying a thematic framework

A thematic framework was developed by drawing upon a priori issues included in the interview schedule and key themes identified during the familiarisation stage, combining inductive and deductive approaches to research. This allowed for incorporation of the interview schedule, ideas from the existing literature and prominent themes identified from a preliminary review of the transcripts.

The first version of the framework was then applied to a selection of transcripts with the aim of refining the categories. The categories were developed to facilitate organising data into manageable portions, enabling subsequent mapping and interpretation. A definition for each code was developed to ensure consistency of coding. To improve the reliability of coding, the thematic framework was consulted with the candidate's second supervisor (ST). Throughout the process, the relationships of themes and interpretation of data were discussed.

3) Indexing

The final coding structure was applied to all interview transcripts by coding systematically line by line using NVivo 10 software. Based on the structure, the framework matrix was created.

4) Charting data into the framework matrix

Once appropriate categories and codes were assigned, the matrix was populated with summaries of coded data organised by both participant and theme. The summaries were carefully written to reduce the data for the ease of analysis; however effort was made to retain the original meaning.

5) Mapping and interpretation

In this stage the whole data set was reviewed to compare and contrast the accounts of interviewees, search for any patterns, and develop explanations for these within the data.

6.5 Findings

6.5.1 Study sample

Fifty-three individuals were invited to participate in an interview. Data saturation was reached after 28 interviews, when no new information was arising from the collected data. The data collection period lasted between the 17th April and 16th October 2016. Characteristics of the sample are shown in Table 6.1 below.

Table 6.1 Characteristics of the sample (n=28)

Characteristic	n (%)
Gender	
Female	23 (82)
Male	5 (18)
Mean age	34.5
Education Level	
Undergraduate	4 (14)
Postgraduate	18 (64)
Professional degree	2 (7)
Doctoral	4 (14)
Professional role	
Research Assistant	11 (39)
Trial Manager	5 (18)
Senior Researcher	5 (18)
Clinical Psychologist	4 (14)
Research Nurse	2 (7)
Clinical Study Officer	1 (4)

Experience of working on trials varied from one year to 20 years, with a median of 5 years. Twenty-three out of 28 participants were female. The greater proportion of females in this sample may be reflective of the greater proportion of women undertaking a degree in psychology (Howard *et al.* 1986). This type of degree is likely to be held by most professionals working on trials in mental health. The age of participants ranged from 24 to 57, with an average of 34.5 years. Thirty-nine percent of

the sample worked as research assistants. This reflects the traditional spread of professional roles within a trial team, usually comprising one trial manager and supporting staff responsible for recruitment and follow-up (i.e. assistants, senior researchers, and clinical study officers). The sample also included therapists delivering the interventions under evaluation who worked on trials as clinical psychologists. Professional roles and demographic characteristics of each participant are provided in Table 6.2 below.

Table 6.2 Demographic characteristics of each participant

Participant number	Participant professional role and ID applied in text	Gender	Age	Length of research experience (years)
1	Trial Manager 1	Male	34	6
2	Trial Manager 2	Female	35	8
3	Trial Manager 3	Male	28	4.5
4	Research Assistant 1	Male	29	5
5	Research Assistant 2	Male	28	1
6	Research Assistant 3	Female	28	4
7	Research Assistant 4	Female	33	4
8	Research Assistant 5	Female	24	1
9	Senior Researcher 1	Female	50	11
10	Senior Researcher 2	Female	39	11
11	Senior Researcher 3	Female	29	8
12	Research Assistant 6	Female	36	8
13	Research Assistant 7	Female	26	2
14	Senior Research Nurse 1	Female	42	20
15	Clinical Psychologist 1	Female	27	3
16	Research Assistant 8	Female	44	5
17	Trial Manager 4	Male	35	6
18	Research Assistant 9	Female	29	3
19	Senior Researcher 4	Female	57	13
20	Research Assistant 10	Female	28	3
21	Senior Researcher 5	Female	31	3
22	Trial Manager 5	Female	32	7
23	Research Nurse 1	Female	57	3

24	Clinical Psychologist 2	Female	31	5
25	Clinical Psychologist 3	Female	34	6
26	Research Assistant 11	Female	38	3.5
27	Clinical Psychologist 4	Female	29	6
28	Clinical Studies Officer 1	Female	34	3.5

6.5.2 Presentation of study findings

The findings will be presented in three parts. The first part includes two themes: the complexity of trial participation by patients with schizophrenia and mechanisms of attrition in complex intervention trials. The second part comprises four categories of factors identified as key to retention of participants with schizophrenia in complex intervention trials, including: participant, researcher, study, and context factors. Third part deals with practices and strategies reported by trial staff as important to participant retention. These are presented in three categories: minimising participant barriers, dealing with study factors, and addressing contextual challenges. All categories are divided into their component sub-themes, to allow for an in-depth discussion. Interpretations of the themes are accompanied with illustrative extracts from the transcripts where appropriate. The quotes are accompanied by the job title and order number of the interviewee to provide additional context and to distinguish between different participants.

6.5.3 The complexity of involving patients with schizophrenia in trials

The impact of schizophrenia symptoms

A typical presentation of a person with schizophrenia was described by trial researchers as characterised by disorganised thinking, apathy, suspiciousness, difficulty with opening up, anxiety and tiredness, paranoid thoughts and beliefs and chaotic lifestyle. This is similar to the symptomatology presented in medical literature, as described in Chapter 2, with most characteristics relevant to negative presentation of schizophrenia. Chaotic lifestyle was described as emerging from a combination of chronic mental health problems and 'socio-economic problems'; for instance many patients were described as struggling with money, housing, and relationships.

Experiencing paranoid thoughts was also a symptom affecting engagement. The struggle to use a phone by some patients was seen as an obvious barrier to getting in touch with them about research. Suspiciousness and paranoia were also found to directly impact how potential participants perceived research, with concerns voiced around the use of medical records and being treated as subject of experimentation, for example:

> "I find that there's a few that don't [want to take part] and there's usually valid reasons, they're pretty suspicious because of the psychosis and they just think you're using them as a guinea pig." (Senior Research Nurse 1)

> "We had some people who were paranoid about medical records, about 'Oh, where are you going to store my data? Is it going to be used by X, Y, and Z?'" (Trial Manager 5)

A distinction in terms of engagement was made based on the type of symptoms. For example, Trial Manager 1 noted that patients with negative symptoms were challenging to engage in general, but especially in group interventions:

> "[Patients with negative symptoms] are not people that will naturally engage in a social environment. So encouraging people to go regularly to an active group with people is obviously going to impact upon their attendance in a way that patients with other presentations may not." (Trial Manager 1)

This symptom-based distinction also revealed disparity in trial professionals' perceptions of the implications of symptoms for participation in research. One view was that those with negative symptoms were easier to recruit, compared to those experiencing positive symptoms, because of leading less chaotic lives and having more availability. Those with a contrasting view discussed the anxiety and lack of motivation experienced by those patients as a barrier to engagement. It is difficult to ascertain the cause of these two contrasting views but they might be caused by the differences in the understanding of schizophrenia or various experiences of working with patients.

In addition, in case of patients experiencing positive symptoms, Research Assistant 2 emphasised the importance of the research space in which follow-up assessments were carried out. It was important for the researcher to ensure that the environment provided limited amount of stimulation outside of the research assessment:

> "I think it's just being aware of things that could perpetuate their positive symptoms if there was voices in the room or something, other hallucinations going on in the room, just making sure that there was space to just sit." (Senior Research Assistant 2)

In contrast to the challenges experienced by participants, as identified by trial researchers, the symptomatology of schizophrenia was not always presented as a barrier to participation in trials and many patients were able to engage in research activities regardless; for instance:

> "Generally if people have agreed to meet with us, they do turn up and they do engage, most of the people engage quite well in the study and the dropout rate isn't that high. So I would say that diagnosis in that sense [...] isn't a huge predictor of whether or not someone's likely to engage." (Research Assistant 2)

> "I found that the people who actually took part were the ones who had the better insight about their illness in a way, so I think that's, in terms if you're looking at why someone would take part in research, especially if it's like a treatment type of research, I think that insight would probably be up there." (Research Assistant 1)

However, the second quote seems to suggest that those who decide to take part in clinical trials may differ in their presentation (for instance having insight about the illness) from those who are prevented from taking part because of the severity of the symptoms they experience.

The impact of employment status

Another distinction was made based on the trial participants' employment status. Unemployed individuals were described as having more time to participate, but also as having a more "laissez-faire attitude towards research" (Research Assistant 2). To illustrate, Research Assistant 2 described the challenge of engaging participants who had the time but lacked the structure to organise their day as "a catch-22":

> "It's kind of a catch-22, because the lack of... if somebody's in unemployment, the lack of structure they have to their day means they have more free time to do these interviews. But then at the same time I think people who've been out

> of employment for long periods of time, they're perhaps not as used to having structure to their day, and kind of agreeing to be here at this time, on this day to do this thing. And so quite often you find participants who have like a very laissez-faire attitude towards actually kind of doing the research." (Research Assistant 2)

On the other hand, those who are able to work had to be met outside of normal working hours and researchers needed to be flexible in order to schedule an appointment, with some having to offer meetings in the evening or weekends in order to complete follow-up assessments. Another challenge was contacting participants with jobs during the usual working hours, which required researchers to adjust to the participants' particular preferences as much as possible given researchers' working hours and any restrictions imposed by the employing institution.

Moreover, homelessness at the time of recruitment was recognised as an issue directly linked to the higher risk of dropping out and the lower level of engagement in clinical trials. These socio-economic issues were described as often resulting in a large proportion of patients being difficult to contact as they often lose phones and have little contact with family. Consequently, some trials excluded homeless individuals at screening.

The impact of illness duration

A distinction was made between patients who were fairly new to services, often experiencing their first episode of psychosis, and therefore more likely to be young, and those who were long-term service users. Participants who have experienced only their first psychotic episode were described as young, likely to lead chaotic lifestyle and "not being that keen on engaging with services in general" (Clinical Psychologist 3). This was in contrast to patients with longer illness duration who were more likely to be suspicious of staff and to experience delusions. However, despite the suspiciousness, these patients were described as motivated to take part in order to use their experience to make recommendations for improving care.

The impact of geographical location of the trial

Another source of diversity noted by interviewees in the context of engagement in clinical trials was geographical location of the trial. The 'type of participant' varied depending on the NHS Trust and the available services. In areas with more specialist services there were higher rates of psychosis in secondary services (through which most complex intervention trials recruit).

> "What I found in the Trust I was working in [was that it] had high levels of psychosis, it was about 60 to 65% of everyone who entered the crisis team had one of those [psychotic disorder] diagnoses. [...] From talking to colleagues it seems that the numbers of people with psychosis who use crisis teams is partly affected by what other services are in the borough for people with psychosis." (Research Assistant 4)

In areas with lower specialist capacity patients would utilise alternative services, such as third sector support, which were not always accessible by researchers for the purposes of trial recruitment. Availability of services was also described as having an impact on the threshold of severity required to access a specific type of service. Consequently, it yielded differences in the presentation of trial participants. This bore particular relevance to multi-site trials operating across different NHS Trusts with different service capacity and therefore with varying rates of patients with psychosis eligible to participate in trials.

The impact of researchers and clinicians

Researchers reported that resilience of patients with schizophrenia was not always recognised by mental health professionals. There was a feeling that staff, sometimes including trial researchers themselves, can sometimes be defensive and overprotective of patients. For example, it was felt that patients with a different diagnosis would have been "pushed a bit more" (Trial Manager 2) to complete follow-up assessments. Clinical gatekeepers were described as often hesitant to approach eligible patients because of the low likelihood of them engaging, a phenomenon widely recognised in the literature (Bartlett and Canvin 2003, Patterson *et al.* 2011, Fletcher *et al.* 2012, Bucci *et al.* 2015, Joseph *et al.* 2016). This was referred to as "diagnostic overshadowing" by one of trial managers in the example below:

> "Because of the topic of the project, a big thing that we explore is something called diagnostic overshadowing, which you are probably aware of. So when we go into GP practices and they say 'Well, this group don't engage, what's the [...] point of trying?'" (Trial Manager 2)

Diagnostic overshadowing is generally referred to in the literature as misattribution of physical symptoms to mental illness (Nash 2013, Shefer *et al.* 2014). Nash (2013) argues that this phenomenon occurs due to mental health stigma and negative attitudes of clinicians and requires education and training. In the example above Trial Manager 2 uses the term to describe instances where clinicians do not attempt to engage their patients in research as they assume their motivation is low due to the diagnosis of schizophrenia. This type of gatekeeping was described as potentially preventing some patients eligible to take part in trials from even considering this opportunity.

In the context of risk assessment, people with psychosis were presented as more likely to be screened out for risk in trials involving other diagnostic groups. However, the approach to risk varied depending on the geographical area. For example, Research Assistant 5 reported that screening out certain patients with psychosis was a measure to prevent putting strain on those delivering the intervention:

> "If someone has... say had quite unstable periods of psychosis, they [gatekeepers] feel that it's putting the [person who delivers the intervention] at risk because they can't predict what it would be like to go to their house or something like that. So they [gatekeepers] tend to screen out people with psychosis a lot more." (Research Assistant 5)

The candidate observed that the trial staff were careful when discussing their practices, making references to good practice and ethical conduct. The importance of applying the same, non-stigmatising approach across all populations was emphasised. However, a more nuanced picture emerged when specific cases were discussed. It suggested that practices could be or were in fact adapted specifically to people with psychosis. As the following sections highlight, there are specific complexities associated with dealing with people with psychosis as trial participants.

6.5.4 Mechanisms of attrition in complex intervention trials

The interviews revealed the nuances of retention and attrition in trials evaluating complex interventions, which were not unique to mental health research. Interviewees distinguished between 'dropout from study' and 'dropout from intervention'. Dropout from study was referred to as 'full withdrawal from the study' and was described as easy to define. Dropout at the intervention level was associated with missing data or poor attendance. Trial researchers highlighted the difficulty of defining dropout from a complex intervention, normally comprising numerous sessions or multiple uses of an intervention. Some trials set a specific proportion of attendance or completion required to qualify a participant as a 'completer', for example the number of attended sessions out of all offered sessions. These definitions were however described as arbitrary, given the lack of strict rules of what comprises a 'completed intervention':

> "I mean to me it's absolutely clear that there must be a difference and also that depends on what you call a completer. If you say someone who completed, a therapy completer is one who attended say 75% of the sessions, then the numbers would also be different." (Senior Researcher 2)

Another nuance of retention was the mechanism of participants communicating the decision to drop out. Where patients communicated this directly, researchers had the opportunity to explore the reasons for the decision and to offer some options, for example full withdrawal versus withdrawal from intervention only. Other mechanisms occurred when the decision could not be communicated directly. One such mechanism was the inability to contact participants. After making a number of failed attempts to get in touch with a participant randomised to the study, the researchers would make a decision to withdraw the participant and "send a letter saying that they had to be withdrawn" (Research Assistant 1). In addition, in those cases where contact could not be made, there was no opportunity to explore the reasons for ceasing involvement. In some cases, where researchers could make contact with care coordinators, some information about the status of the participant was obtained through those means.

The involvement of care coordinators also presented a challenge when the decision to drop out was communicated through them. This 'proxy dropout' was another mechanism of communicating dropping out but this was not always seen as acceptable by those trial researchers who preferred to discuss the different options available to the

participants wanting to drop out. A need for separating the trial and the relationship with care coordinators was emphasised in the following extract:

> "The patient might just have a shocking appointment with them […], it might be that the care coordinator just thinks that actually this person… they [care coordinator] make their own judgement call and that's not a true withdrawal for me." (Senior Researcher 5)

This quote illustrates Senior Researcher 5's discomfort with the decision to withdraw from the trial being seemingly made on the basis of the care coordinator's judgement and not the patient's will. In order to ensure ethical conduct, the researcher felt they needed to speak to the patient directly.

6.5.5 Influential factors in the retention of trial participants with schizophrenia

A number of factors influencing the retention of trial participants were identified by trial researchers, with "not any one particular reason that determines a high follow-up rate" (Trial Manager 1). These fell into four categories of factors: participant, researcher, study, and context.

The diagram below (Figure 6.1) provides a visual interpretation of the categories of factors affecting retention of trial participants in complex intervention trials. The four categories are arranged in nested layers that represent various influences on an outcome of trial participation. This model was developed inductively based on the findings of this qualitative study but similar paradigms appear in the literature. For example, the Ecological Theory of Research Participation (Marcellus 2004), discussed in Chapter 2, stresses the importance of the interactions between participants and researchers, study, and environment. In addition, the theory recognises the influences between each layer and how these impact on the retention strategies used in trials.

The presentation of findings will begin from the centre of the diagram representing the participant-related factors, moving outwards.

Figure 6.1 The range of factors affecting participant retention in RCTs

Category 1: Participant factors

Participant factors were defined for the purposes of the analysis as inherent characteristics, for example gender, age, and diagnosis or attributes in control of the participant, for example interest in the intervention.

Socio-demographic characteristics

People with schizophrenia were described by trial professionals as very diverse in terms of background, with details often unknown to the researcher. When some details were known, trial staff were able to comment on the possible relationship of a characteristic and engagement in research.

Age was one characteristic associated with retention. Young patients, especially males, were described as most challenging to retain in studies. Some possible explanations for this phenomenon were offered by interviewees, including not having a true interest in

the intervention, being attracted only by the initial incentive, and experiencing a first episode of psychosis, leading to the lack of engagement in services or the lack of desire to engage. This type of participant was compared to older participants who were described as "just quite lonely and stuff, and quite happy to receive a phone call" (Research Assistant 7). This finding points to the potential differences in study retention based on age of the trial participants; an association that was not found to be significant in the meta-analyses presented in Chapters 4 and 5.

Socio-economic status was another characteristic discussed in interviews. Divergent observations were made about its impact on engagement and retention in research. One argument was that patients with higher socio-economic status were more engaged and showed more interest in research compared to those with lower status. This was also echoed in the views that socio-economic status had impact on how much people are willing and able to express themselves; something that was attributed to the amount of life stressors and perceived assessment burden. It was proposed that those who experience a lot of stress might find it difficult to talk in interviews or to think about their situation to answer questionnaires and therefore experience assessments as challenging. The opposing argument centred on the role of incentives with the indication that participants living in deprived areas were more engaged and more willing to remain involved in a study if financial incentives were available. This is reflected in the following extract, describing people from deprived areas as more willing to help:

> "We have really good engagement from the actual, more deprived areas. When I think of [city anonymised] as a map, the [city part anonymised] is notoriously deprived and we've got really good engagement from people. They were willing to help. Whereas in the other areas we wouldn't get as much engagement. Areas with people with more money." (Research Assistant 11)

This "good engagement" could be linked to, but was not always directly attributable to, monetary incentives. This will be discussed further in the section titled 'Motivation to participate' on page 125.

Understanding of trial procedures

Explaining (for trial researchers) and understanding (for patients) the concept of randomisation in trials presented a challenge. The ability to understand randomisation was described as hindered by the symptoms of schizophrenia and side effects of anti-psychotic medications, for example poor retention of information. When compared to those who end up not participating in trials, trial participants were described as having better insight about their illness and wanting additional help through participating in a trial, for example:

> "I found that the people who actually took part were the ones who had the better insight about their illness in a way [...] especially if it's like a treatment type of research, I think that insight would probably be up there, you know. That's what I've experienced. If they had good insight about...something, you know, wanting something extra to help themselves, I found that they were quite keen to actually [take part] because they wanted some help. While a lot of people [might] not even [be] thinking about the possibility of being helped by the... by the research, you know, just a burden in a sense..." (Trial Manager 4)

Trial professionals' familiarity with the possible side effects of medication and the ability to judge the extent to which a patient is able to understand the information was described as necessary to having a de-stigmatising approach. Other issues not directly linked to psychosis such as illiteracy and expecting research to be complicated were also identified as barriers to understanding randomisation.

This presented a plausible dilemma for trial researchers. On the one hand, they had to make sure that potential participants receive all information about the trial, including randomisation, before they could provide informed consent. On the other hand, they also needed to make sure that the information was easy to understand, which could result in what was described as "downplaying randomisation" (Trial Manager 3) as giving all information could "freak them out" (Trial Manager 3). This weighing of good practice against the pressure to recruit and retain participants was described as a "conflict of interest" (Research Assistant 3).

In case of the trials evaluating monetary incentives (for example to adhere to treatment) it was particularly important for the participants to understand that there was an equal chance of being assigned to the intervention and the control arm as this

was directly associated with the total amount received by participants in either arm. A manager of a trial evaluating financial incentives provided an example illustrating this specific issue:

> "The point is to explain to them that there's two groups and there's a 50:50 chance of them ending up in either of the group and that if they are offered incentives, if they stick with the whole period it would be £240." (Trial Manager 4)

One possible solution used by researchers and therapists in order to ensure ethical conduct was explaining to participants that the intervention itself may or may not be helpful, for example:

> "We're always absolutely sure that there are no incentives to be in the intervention apart from the possibility of the intervention helping. And we, with that as well, we don't say 'Oh, it's great'. We sort of say 'This is helpful for some people; this is the way it works. It may be helpful for these things, it may not. And it's up to you whether you want to give it a go.'" (Clinical Psychologist 2)

Another area of difficulty in understanding the nature of RCTs observed by trial researchers was a failure to differentiate between research and treatment, a phenomenon recognised in the literature as therapeutic misconception (Henderson *et al.* 2007). This challenge occurred on two levels: staff and treatment. Patients were reported to sometimes struggle to make a distinction between research staff and clinicians external to the trial. This was exacerbated in studies where patients were introduced to a researcher by their care coordinator. On the treatment level, this conflation meant that patients did not always understand the difference between trial procedures and standard practice. Consequently, having previous negative experience of care was found to affect patients' attitude to research and the likelihood of remaining involved in a trial.

Motivation to participate

The initial appeal of participation in a trial was considered in the context of retention later in the process, connecting the motives for taking part in the first place to making decisions about continued participation in an intervention and/or follow-up assessments. Patients' motives to participate identified by trial researchers included

having an interest in the intervention, receiving monetary incentives, and altruistic reasons. Some of these factors are also described in Section 6.5.6 from the perspective of what is offered as an incentive in trials.

Having an interest in the intervention on offer was considered to be important for retention. Those who did not show initial interest in the intervention were found to be more difficult to contact after randomisation. Complex intervention trials were described as easier to attract potential participants to, compared to pharmacological studies, given that patients were assured about the non-pharmacological nature of the treatment they would receive, for example:

> "A lot of people worried about research thinking it's drugs, so [it was important] to go in and explain that we wouldn't be changing their medication and we wouldn't be getting them to do anything extra medication-wise." (Clinical Psychologist 1)

As the quote above illustrates, this attitude to trial participation was explained by the patients' hesitation to either take medication or to change current pharmacotherapy and pointed to the potential appeal of complex interventions.

An interesting aspect of motivation by treatment was the difference between the active and control conditions. While having an interest in the intervention applied to both active and control condition in the context of retention, trial researchers highlighted that the active arm could be expected to have higher retention rates compared to the control arm, especially given that most complex intervention trials offer 'treatment as usual'. This was in line with the findings of the IPD-MA presented in Chapter 5. One explanation offered for this phenomenon was more contact with staff and therapists for those in the active arm, resulting in more commitment and identification with the trial as a participant for this group. The following excerpt illustrates this explanation:

> "If someone's allocated to therapy they have potentially weekly input from someone in our team, in which case I suppose more contact with their team would be beneficial in order to kind of maintain that relationship. And that is encouraged but understood to not always be feasible considering the constraints under which we work in terms of time and areas." (Clinical Psychologist 2)

Moreover, it was implied that a lot of complex interventions focused on patients' goals, which could potentially result in better engagement and higher retention. One highlighted exception was some participants preferred to be randomised to control treatment as they were openly motivated by monetary incentives and preferred the lowest level of involvement possible; an option offered by the control condition.

Some patients were described as motivated by receiving compensation for participation. Trial researchers also described instances of patients expecting to be paid for taking part in the intervention. However, in most trials, with the exception of those evaluating monetary incentives in mental health care, participants received payment for completing assessments and not for attending or completing the intervention. Paying for attending treatment sessions was discussed as a hypothetical option to increase retention at the intervention level but this was dismissed due to two reasons: first, it was seen as unfair to the participants randomised to the control group; and second, it was argued to potentially interfere with any effect of the intervention as any changes in outcome measures could then be attributed to the effect of money.

In most trials participants were offered money or vouchers for completing an assessment. Some researchers described either themselves or clinical gatekeepers explicitly mentioning payment to entice patients to complete follow-up, although caution was applied when discussing the monetary incentives due to potential coercion and the concern around participation only because of being offered money, as illustrated in the following excerpt:

> "I think [offering monetary incentives is] so much better. I think for the person taking part. But I do think there's a big element of coercion and many people will take part simply because of the money. So the one that I'm particularly involved in is an inpatient one where quite often they have limited access to funds. And so £5 can mean a pack of cigarettes and it's quite, it's quite important to them. People will outright say, you know, 'Do I get money for this?'" (Clinical Studies Officer 1)

Money was explicitly described as a motivating factor for retention, with some exceptions involving refusal of compensation. It was also seen as an opportunity for researchers to directly and tangibly express gratitude to participants for their time and effort. The motivational aspect of money was in some cases explained by the difficult financial situation experienced by people with psychosis. Trial researchers' descriptions

suggested that this population often receives benefits, lives in deprived areas, or struggles financially and so the payment from the trial can be helpful:

> "So people get £20 for questionnaires at baseline and again at follow-up. I do think there are some people who do it just to get the 20 quid. Which I think given the client group is quite understandable. For some people 20 quid is a lot of money." (Research Assistant 4)

Some potential implications of money being the main motivation for trial participation were discussed. The implications included reliability of follow-up data, impact on therapy, and impact on retention. Trial researchers indicated that in cases where money is the main or sole motivator participation can lack meaningful engagement and there is also a risk of coercion. This echoes previous findings showing that participants motivated mainly by compensation were more likely to not adhere to treatment and to drop out (Gross *et al.* 2001). A sign of this type of motivation described by interviewees included repetitive and dismissive in tone responses to (often long) questionnaires. In addition, working with trial participants motivated by money was described as a potential therapeutic challenge as it can distract from the goals of the intervention, for instance:

> "And there's the group who just want money or… that'd… personally that'd be tricky, that'd be very tricky to find a goal to work on then." (Clinical Psychologist 3)

Despite money being identified as the main influence, altruism was another motivating factor for taking part in trials. This was especially evident in instances described by trial researchers where participants refused payment, explaining that their intrinsic motivation was to help. Altruistic motives were also presented as a potential means of encouraging participants to remain involved in a trial. Researchers appealed to the participants' sense of selflessness by emphasising how their involvement in the trial will potentially help other people, for example:

> "I always try to stress that, you know, their views now may help other people, you know, who may experience their participation to help other people, who may experience similar problems." (Research Assistant 1)

> "But some of the things I might say is that, you know, '[…] I know I'm not allowed to know whether you got the group or not, but either way I just want

> to thank you for your time because even if didn't get the group, your participation and your scores and results will help towards the… see whether this intervention's effective and it will be able to help people's lives in the future, hopefully'. So I kind of try and kind of say something like that as well, because you know, I do sometimes feel it is hard." (Research Assistant 3)

In addition to money and altruism being appealing factors when considering participation, receiving an intervention and seeing it through to the end was also described as a motivator. This view however was described as not always shared by participants, especially those expecting to receive payment for attending intervention sessions.

Some trials offered other benefits associated with being in the intervention arm, such as transport to the sessions, materials, gadgets or snacks. Trial researchers considered these as incentives. However, given the design of an RCT, not all participants receive the intervention under evaluation and some are randomised to the control group, often with treatment as usual. Not being able to offer an intervention to everyone in a study was seen as problematic for researchers wanting to offer it to everyone. This dilemma is illustrated in the following quote:

> "I find randomised control trials, I think all of us would agree that sometimes we're like 'Argh, I wish we could offer it to everybody but we can't, and there's the chances. A lot of people I know as well, just as conscious human beings, you don't want to disappoint people, and it is quite hard sometimes to kind of explain and say 'You might not get it, I know your care coordinator might have told you about this wonderful intervention, but actually there's only a 50% chance." (Research Assistant 3)

The above quote illustrates the concern of Research Assistant 3 about the satisfaction of participants with the outcome of their allocation to treatment and shows how the initial expectations need to be managed when explaining how randomisation works, especially for those motivated by the prospect of receiving an intervention.

Barriers to retention

Poor health or wellbeing was provided as a potential factor negatively affecting retention. It was not always made clear to trial researchers by trial participants whether

the issues related to physical or mental health but in a lot of instances it was due to fluctuations in mental health or negative symptoms of schizophrenia.

> "I think it could be mental illness symptoms getting worse and so they're not really in a mental state that means that they can consent to carry on with the research." (Research Assistant 2)

Another factor identified as a barrier to retention was losing interest in the intervention or in the study as a whole. Exploration of this issue, especially in regards to the differences between participants randomised to the active versus control arm, was limited in this study as majority of interviewees were blinded to the allocation. However, the following quote illustrates this type of challenge:

> "I remember there was a subset of people who were recruited to the trial and you were randomised to the intervention and you had absolutely no interest in doing the intervention whatsoever. We'd call them every week and they wouldn't pick up or they would pick up and make an excuse." (Research Assistant 7)

Lack of time was a common reason for dropping out provided by patients. This was sometimes linked to a change in circumstances and taking on new responsibilities, for instance childcare, college, and work), which prevented participants from being able to keep to their commitment to appointments, for example:

> "Some people are like 'I've gone back to work and I'm just too busy'. We do offer to do weekends and evenings so it's a bit, you know, some people when they're back in work are just like 'I just wanna get on with work now.'" (Research Assistant 5)

> "They've come up with certain excuses… well; one person says he now has to look after his child on that day when his partner goes to work, so he can't come." (Research Nurse 1)

Like with losing interest, the explanation of this factor by trial participants was vague due to blinding and prevented the trial researchers from elaborating on the matter.

The tendency to lose phones and forget appointments was presented as a barrier to retention, for example:

> "With people with psychosis [...] in general, not tied to any age, they tend to lose their phones and they tend to forget appointments even if you send them a text message right before the intervention [...]. I basically think that they change their phone numbers so often it's unbelievable." (Senior Researcher 1)

This forgetfulness and frequent changes of contact details were described as consequences of a chaotic lifestyle, discussed earlier in Section 6.5.3 , making it difficult to contact participants after they have lost their phones and were also often estranged from their families, precluding this as an alternative way of getting in touch.

<u>Category 2: Researcher factors</u>

Rapport between researcher and participant

Establishing a good rapport with trial participants, among other factors like the usefulness of an intervention and researcher's skills, was discussed as key to engagement and retention. Having a good relationship led to establishing trust and this in turn increased the chance of people completing a follow-up assessment.

> "I think [what] relates to having a good relationship with the patient, and if they generally liked you as a researcher, [is] the way you explain the information, all of that, and they have that level of trust, chance are they're happy to come back and do a second interview." (Trial Manager 3)

This was seen as a skill and something that some researchers were better at than others. The valuable skills included mirroring participants' language, creating a supportive environment where participants felt listened to, informing participants about their rights, and sharing some personal information to establish rapport and to have something to talk about at the next interview. Power dynamics were considered important and establishing an equal relationship with a shared goal was seen as desirable. This was achieved by being clear about what trial participation involved, empowering individuals by telling them about their right to withdraw or to refuse to answer a particular question, informing them about the goal of research and showing gratitude for their time and input. Work culture at the level of trial unit was presented as an external force that defined the values underpinning research, especially when it

was driven by empathy, recovery, and empowerment. However, one factor impeding rapport was the tension between a target-driven culture of trials and the importance of building relationships with participants involved in longitudinal research. For instance, researchers were under pressure to complete assessments efficiently, allow the time to listen to people and build rapport, but also to avoid assessment fatigue with prolonged and frequent meetings. The challenge of juggling these responsibilities is illustrated in the following quote:

> "It's important to sort of build the trust first and I think that (…) the amount of work that it can often take for people to, it can be quite substantial. I think it's hard to build that into a modern research project cause, you know, it's so target-driven nowadays, you're trying to get as many people as possible to justify the numbers you promised in the grant because you kind of want more and more impact, knowledge exchange and all these wonderful words on the back of the research but the practicality side of it is, there is a lot of stress on the research team to not maybe to spend the time they might want to just building the core and I think the soft skills I would say are very vital in quality research. Maybe they should focus more on quality not so much on quantity with evaluating how the study went on." (Senior Researcher 3)

Another factor affecting rapport was researcher continuity. In trials where researchers were assigned to a particular participant this practice was described as enabling building relationships and ensuring retention because participants "know the deal, they know who you are. Once they are engaged in the process, they're easy to maintain, to retain in the study" (Trial Manager 1). Maintaining continuity was found to decrease anxiety about meeting a stranger who asks personal questions. Researcher continuity across assessments was a factor that was not in the direct control of trial researchers and often depended either on the study design decided by the PI and the management team, or on the rate of trial staff turnover. There were also pragmatic reasons for maintaining the consistency of the researcher, including researchers being assigned to a specific geographical location and therefore being the default researcher to complete an assessment with patients based in that area.

Researchers' persistence

Being persistent with approaching participants for follow-up assessments was discussed as an important trait of effective researchers. The degree to which researchers felt confident in their persistence varied. One approach was to "contact people pretty relentlessly" (Research Assistant 2) and not stop until the participant has been contacted. Often different means of contact were used, such as phone calls, letters, and contact via care coordinator until all options have been exhausted. A more relaxed approach involved trying but also considering when it was appropriate to give up. This was a grey area requiring judgement calls made on an ad-hoc basis, for example:

> "But sometimes people just don't want to talk to you [laughter], so you need to give up at some point, otherwise you're stalking them [laughter]." (Clinical Psychologist 1)

> "So we have… there is this thing about so how many times should you contact someone before the interview? And then should you give up? So that's a trick question." (Senior Researcher 1)

The first quote, although expressed humorously, suggests a certain level of discomfort experienced by the therapist with putting too much pressure on nonresponsive participants. It also raises a question about the limit of pressure to be put on participants to remain in a study, as expressed in the second quote. The data show it is a matter of judgement of individual researchers, putting the responsibility for the ethical and yet effective conduct in their hands.

Category 3: Study factors

Consistency of procedures

Having clearly defined systems and procedures was identified as important for ensuring retention. This involved both externally- and internally-oriented procedures. Externally-oriented procedures included what was communicated to participants in terms of their involvement, process and their expectations, for instance provision of transport to intervention sessions, reimbursement, and number of follow-up

appointments. Making participants aware from the outset about the procedures was described as helpful in increasing the chances of them remaining in a study. Internally oriented procedures comprised maintaining efficient systems for facilitating appointments and reminders about them. This included therapists recording intervention attendance, for example:

> "We've created a database of all the sessions attended and the session adherence, tick boxes as variables. So we will know by the end of the trial how many sessions people have completed. In a sense of who's had a good dose if you like. It's probably not the best term, a good amount of sessions." (Clinical Psychologist 3)

The level of details kept in study databases varied, with some trials recording detailed notes about each participant and each contact made with them and others leaving this up to individual researchers.

Experience of assessment

The extent to which participants enjoyed assessments was described as important for retention. Factors facilitating retention included positive experience of the first assessment, and enjoyment of receiving the attention and time of a researcher. An enjoyable first meeting or assessment was described as likely to encourage trial participants to meet with the researcher again and complete follow-up assessment:

> "I think it really depends on their experience at baseline and whether they actually want to do the follow-up [...] So as long as the first one has gone fine I think the second one isn't something that people will actually worry about." (Research Assistant 5)

In contrast, what impeded retention was assessment burden caused by using numerous outcome measures. This was especially pronounced in the cases where patients struggled with literacy and consequently found questionnaires especially challenging, for instance:

> "The person who did drop out just struggled with reading and writing. So the idea of being confronted with lots of paperwork I think was quite scary for her." (Senior Researcher 5)

Having shorter follow-up appointments increased the chances of patients completing them more fully and also returning to a subsequent appointment. Another potential issue was described as interview burden, where participants were asked personal questions, increasing the intensity of the assessment. Having to answer a lot of personal questions about one's illness or quality of life made some trial participants emotional or tense, which led to them to weighing up the effort against the reimbursement on offer and, in some cases, withdrawing from the trial.

> "I do remember one or two people I did a baseline with them and then they were getting emotional throughout the interview and then they decided that they didn't want to do it there and then [...] and I think that it largely arose from questionnaires like the MANSA [Manchester Short Assessment of Quality of Life] which are really, really... it's like a stranger coming in and asking you, you know, 'Do you feel guilty about things? Do you have regrets about the past?', all of that. It's quite intensive." (Research Assistant 8)

In addition to the intensity of the follow-up interview, the nature of the questions in some questionnaires or interviews could be quite invasive and personal, although the extent to which participants and researchers could perceive this as problematic can be expected to vary depending on personal views and cultural background.

Experience of intervention

The willingness to remain involved in a trial was discussed in the context of the interventions offered to patients. The relationship between the experience of intervention and study retention spun beyond mere enjoyment. There were aspects associated with attending intervention sessions that were identified as catalysts for drop out, including inconvenient location of therapy sessions, lack of reliable transport, disliking group interventions, and anxiety associated with attending therapy. Group interventions in particular presented a challenge for participants who found them anxiety provoking. Group interventions also tend to offer less flexibility than individual sessions, which only need to consider two people's availability. A potential consequence of the lack of flexibility with rearranging times is increased non-attendance and non-adherence to treatment. The following quote illustrates the lack of flexibility with group interventions:

> "[Offering flexibility with assessments] may also explain why our treatment group attendants were so much lower than our assessment attendants, cause obviously we couldn't really be flexible with the groups because it's group intervention. The rooms are booked, everyone has to come at that time." (Trial Manager 1)

Intermittent attendance and missed appointments were presented as common issues, echoing previous trial reports and methodological literature (Barrowclough *et al.* 2009, 2010, Swift and Greenberg 2012, Fouad *et al.* 2014).

Similarly to when motivation to participation was considered (see section titled "Motivation to participate" above), interventions were experienced differently by those in the active arm and patients receiving in the control condition. Participants in the active arm are often expected to attend more appointments, especially in trials evaluating talking therapies. This naturally results in more opportunities for missing sessions or dropping out "because they're having to go to their intervention appointments as well as do the follow-ups" (Trial Manager 2). On the other hand, they have more contact with staff and have higher level of engagement, which was described as aiding retention.

Trial participants were usually still offered to complete follow-up assessments even if they disengaged from the intervention, which is in line with the ITT analysis (discussed in section 2.4.2, p.33). In trials where researchers were blinded to the allocation dropping out of the intervention would often not come up as an issue as follow-up assessments would be completed in complete separation to intervention sessions.

Category 4: Context factors

Organisational factors

The level of overall research activity in trial sites was discussed as a factor impacting on retention. Areas with a lot of research activity were described as having the grounds for running a successful trial due to staff experience and familiarity with the trial processes. Clinicians and other mental health professionals who often act as gatekeepers during recruitment were also found to be important in keeping patients involved in trials, alas

not always helpful. This emphasised the importance of researchers making an effort to build relationships at the recruitment phase that could carry on until the trial end, or even beyond. It was however highlighted that in areas with high research activity gatekeepers can be "desensitised to people coming in and being engaged in research" (Trial Manager 1). This phenomenon was referred to as 'research burden' and applied also to patients who were potential trial participants and who would be approached about research numerous times.

Organisational culture was a factor permeating trial researchers' accounts. This was identified at two levels: the internal organisational culture and the culture of other organisations involved in trials, in most cases the NHS. Successful retention was attributed to flexible and accommodating culture of trial teams, but also to good reputation built over time. There was criticism of the 'target culture' resulting in consenting and retaining patients who should not be involved in trials. When considering the cultures of other organisations, trial researchers' experiences ranged from liaising with supportive care coordinators who would remind their patients about trial appointments at one extreme, to dealing with "old-fashioned attitudes towards research" (Senior Research Nurse 1) of clinicians, discouraging patients with schizophrenia from taking part in trials in case it would destabilise them.

Geographical factors

A number of factors affecting retention related to the geographical location of the trial operations or the intervention delivery were identified.

Transport presented a challenge for patients needing to travel to sessions or appointments over long distances or experiencing issues with using public transport in terms of cost, location of stops and stations, frequency, etc. These issues were pronounced in trials involving group interventions, which required a centrally located venue. Patients experiencing negative symptoms and leading chaotic lifestyles were identified as particularly struggling with transport to interventions and appointments and therefore more likely to drop out. The mobility of patients presented an issue at a different scale depending on the type of geographical area. Trial sites located in cities were described as more likely to observe high mobility and frequent changes in circumstances, especially high turnover of patients and staff, whereas small cities and rural areas did not experience it to the same extent.

> "I know in [city anonymised] [retention is] even more problematic than maybe here in [city anonymised] and in small communities. And I remember in [city anonymised] when I was involved in observational studies, not in a trial, it was so, so difficult to follow patients because basically they were moving all [the] time, et cetera. My feeling is it's much easier kind of in small areas like small communities like [city anonymised] and also in rural areas, but it still happens." (Senior Researcher 1)

Participants moving away from the original location presented an issue, with the extent of the problem depending on the new location. It was not always possible for researchers to travel to new locations and this resulted in an automatic exclusion of those participants even if they were willing to provide follow-up data. Researchers who worked directly with participants highlighted limited resources and needing to check any decision about going to the participant with a more senior member of the team.

Another factor contributing to the geographical limitations was the need to conduct follow-up assessments in person. This was often dictated by the nature of outcome measures, for example the BPRS described by Research Assistant 2:

> "Some of the way the interview is scored is like using measures like the BPRS, which means that you have to be able to like see the person to do the interview with them. It's not really something you can do over the phone or whatever." (Research Assistant 2)

The inclusion of observational measures in the study protocol often automatically required a face-to-face appointment, even if there were other measures that could have been completed independently by the participants who moved away.

6.5.6 Practices and strategies for participant retention

The previous section presented the findings pertaining to the factors influential in retaining trial participants organised into four categories: participant, researcher, study, and context. This section will focus on the ways in which trial researchers manage participant retention and how they address some of the issues they identify as key to retention. These are organised into three categories, which correspond to the

issues presented in the previous section. Participant and researcher factors are discussed together as they are difficult to disentangle in the context of trial practice.

Category 1: Minimising participant and researcher barriers

Negotiating exit

As discussed in section 6.5.4, there are different mechanisms of participants dropping out of trials and communicating this decision. In situations where the decision to withdraw was communicated directly to researchers, it presented an opportunity to present available options to the participants. For example, for those wanting to drop out of the intervention there was the option to remain involved in the study and have data collected either directly in follow-up appointments or indirectly from medical records:

> "We train our researchers if you have a patient who doesn't want to be involved in the study anymore, accept it, absolutely, and it's up to them, they have right for that, but try to introduce this conversation with them and find out what are the reasons and because it is important for us as researchers to know that and especially for the randomised controlled trials. And it is important whether, to find out whether they don't want to be interviewed in that time point, but you can come back in the next time point; whether they don't want to be interviewed at all but you can collect data from their medical records. So all this stuff is important because you don't actually want to have missing data." (Senior Researcher 1)

The practice of discussing the reasons for the decision to drop out varied. Three main approaches were identified in trial researchers' accounts. The first was recording this information routinely, if the participant was willing to provide it. This was facilitated by a system providing space for storing these data about attrition. The second approach was not requesting the reason for withdrawal. This was explained by low rates of attrition and, as a result, lack of interest in understanding why such a small proportion of participants decided to withdraw. Third was an ad-hoc approach allowing researchers to make a judgement about whether to explore the reasons or accept the

decision without trying to understand the underlying causes. This was especially applicable in cases of participants experiencing health fluctuations. Those individuals were described as not wanting to make a decision to drop out entirely and so, if possible, researchers would offer to contact them again at a later data. This rendered the option of returning to the study or the intervention at a later point.

In scenarios where the conversation about the decision was opened, trial researchers described their careful attempts to negotiate participants' exit. Interviewees emphasised the importance of ethical conduct when trying to convince patients to remain involved in a trial and presenting them with alternatives to a complete withdrawal:

> "I may just say one last time that what the importance of that study was and what it would mean to us if they carried on and that we're really grateful that they've already given up their time and we'd make it as, least intrusive as possible by coming to their home at whatever time they like. But one… if it's still a no, then you just have to say no – I mean agree and help them." (Clinical Studies Officer 1)

This commitment to ethical conduct was also emphasised when talking about trials collecting data from medical records, often in addition to data collected in follow-up appointments. In those studies participants consented to researchers accessing their records for the duration of the study. Discontinuing an intervention or refusing follow-up did not automatically withdraw the initial consent to medical records access. However, trial researchers considered it good practice to remind participants about this fact and ask them to re-confirm if they are happy for their medical records to be accessed for the purposes of collecting data without their involvement.

The data suggest that researchers were aware of good practice, but there was an element of judgement when it came to deciding whether or not to negotiate different withdrawal options with the participant or not.

The importance of adaptability

The ad-hoc approach outlined in the previous section is one example of researchers adapting processes to suit the participant and help them to remain in the study if they are willing to do so. Trial researchers who emphasised the importance of adaptability

discussed the importance of understanding schizophrenia and its symptoms. Having an appreciation of what the patients were experiencing was described as helpful in interpreting their behaviour and responding appropriately. Examples of situations requiring adaptation of standard procedures included participants never answering the phone the first time it rang, struggling to complete a questionnaire or an interview when hearing voices, or being worried about sharing personal information. This view was however accompanied by caveats about non-stigmatising approaches to dealing with people with schizophrenia, juxtaposed to the medical model of dealing with patients:

> "I think in services so much of the time they're seen as their diagnosis; they're seen as a number, whereas [in research] you get to communicate to that person on that person to person level…" (Trial Manager 5)

When considering adaptations, trial researchers recognised three types of triggers: risks, needs, and preferences**.** Assessing participants' needs and risks at the beginning of the trial was identified as "quite important to learn a little bit about that person and how they like to be approached" (Research Assistant 10). This was done either directly with the participant, with their clinician or via medical records. Different types of needs were recognised, including logistical issues with organising time and getting participants to appointments, physical health issues, and anxiety. Risks were particularly relevant to interventions requiring physical activity (for example body psychotherapy) but also were routinely considered for the safety of both patients and researchers meeting face-to-face to complete follow-up assessments. Identifying those needs and risks allowed researchers to make necessary adjustments to enable patients to participate and remain involved in the trial, for example asking care workers to help patients living in sheltered housing with getting organised for appointments, allowing anxious patients to attend appointments with a support person, organising taxi transport to intervention sessions, and sending text reminders before each session.

Preferences presented a different type of trigger, which required an element of judgement on behalf of trial staff due to requiring additional resources. Examples of specific requests included a preference for the researcher's gender, seeing the same researcher throughout the study, receiving letters instead of phone calls or texts, meeting in specific locations, and being called from a mobile showing caller's number

(as opposed to a hidden number often imposed on researchers by their employing organisation).

Empowering the participant with information

In line with the non-stigmatising approach, trial researchers discussed the importance of equipping participants with sufficient information about the study, including their rights, to make decisions about their involvement at and beyond recruitment. Whilst all trials were subject to ethical scrutiny and consequential procedures, the extent to which these were followed through and communicated to participants was described as controlled by the researchers. This required careful judgement about the level of detail to be given to participants, especially in the context of explaining randomisation, for example:

> "Some people ask if they can be randomised again [laughter] [...] If someone isn't used to the idea of an RCT then it's kind of hard explaining how it kind of works." (Research Assistant 9)

As discussed in the section titled 'Understanding of trial procedures' on page 124, this aspect presents particular challenges for both researchers and participants. Researchers identified the following practices to overcome this challenge: investing time to explain the study, using videos to accompany written information sheets, organising an event for participants to inform them about the research, and involving service users to present the study.

Reminding participants about incentives

As already discussed in the section titled 'Motivation to participate' on page 125, trial researchers identified incentives as a motivating factor for participants as they offer something in exchange for their time and effort. Bearing this in mind, researchers admitted to mentioning money as soon as possible when contacting participants about a follow-up either by phone or text. Other incentives offered to participants included vouchers, sweets, and intervention-relevant advice.

Category 2: Dealing with study factors

Study-related barriers presented a challenge that was more in control of trial researchers compared to participant and context factors. This control was applied throughout the duration of the project and will be presented chronologically.

Study design

When designing a study, it was possible to improve retention by planning closely spaced appointments. This was argued to decrease the risk of forgetting about them. Another strategy applied at that stage of the study was planning to recruit over the required sample size. Over-recruiting was put in place "to allow for attrition" (Research Assistant 3) as trial researchers expected patients to drop out at some point. In trials evaluating group interventions these included running additional groups to help "against the possibility we may have slightly higher dropout at six months than we thought we would" (Trial Manager 1).

Recruitment; reaching beyond the low hanging fruit

Researchers described it as common practice to take consent to follow-up at baseline. Depending on the trial, this also could have given researchers access to medical records even if a patient stopped attending intervention sessions and follow-up appointments. A common recruitment strategy described by trial researchers was using multiple services to access potential participants, "with the idea that we basically get the low hanging fruit as it were, relatively easy people to recruit and then we move on" (Trial Manager 4). Selecting trial participants on the basis of their commitment was at odds with the pressure on recruiting sufficient numbers of patients and avoiding a biased sample, nonetheless trial researchers proposed it as one potential strategy to aid retention. Screening meetings were found to serve as "a good indicator if people [...] weren't really gonna turn up for the three assessments and potentially therapy" (Clinical Psychologist 1). However, this was described only as a hypothetical option requiring further investigation, rather than actual practice.

Another retention strategy linked to recruitment was particularly relevant to group interventions requiring bringing a number of patients together, namely arranging interventions as close to randomisation as possible. This was explained by preventing

loss of interest between the point of trial entry and start of intervention, so "that people are still interested, don't change their mind, don't lose contact" (Research Assistant 3). Trial researchers found this challenging but also important for minimising loss of participants prior to intervention start.

Intervention

The way participants in the active arm experienced an intervention was described as central to retention. However, researchers had little control over the extent to which patients enjoyed the interventions and therefore their focus was on offering flexible arrangements. This included, for example, always welcoming back participants who have missed sessions or even offering therapy breaks if needed:

> "In terms of study retention I think we did a really good job there actually. In terms of treatment retention, I don't think we were quite as systematic in the level of support that we provided patients to attend groups, and particularly at the beginning cause I think that was, it was a bit of a learning process as to what the logistical issues might be and then how we would help to resolve them." (Trial Manager 1)

As the above quote illustrates, the flexibility was not always a carefully planned strategy and was a result of a "learning process".

Follow-up assessments

Ensuring retention at the study level offered the most scope for control, both in terms of managing resources and conduct of assessments. Resources were managed in two ways: prioritising retention by blocking out time to focus only on arranging follow-up assessments and moving staff to sites requiring help with follow-up assessments. The main theme permeating the conduct of assessments was flexibility. Trial researchers emphasised the importance of having a person-centred approach focused on finding out the particular barriers experienced by an individual and investing effort into coming up with a suitable strategy that would enable the participant to be retained in the study.

The first assessment strategy was flexibility with the timing of the appointments, linked to adaptability discussed in the 'The importance of adaptability' section on page 140.

For researchers, this often meant meeting participants in the early mornings, evenings or weekends. As a result, this enabled those patients who were in full-time employment or had other commitments to remain involved, for example:

> "So they would, if they got a job, they couldn't see us during the hours of 9 to 5, so we had to stretch to evenings or weekends. So we would do that." (Senior Researcher 1)

Although, it is important to note that this strategy did not guarantee better retention in all cases:

> "And then some people are like 'I've gone back to work and I'm just too busy'. We do offer to do weekends and evenings so it's a bit, you know, some people when they're back in work are just like 'I just wanna get on with work now.'" (Research Assistant 5)

The second strategy involved using alternative venues for appointments. Usual practice was to either see patients in their usual community services or at home. However, some participants preferred to meet in a more neutral space, such as a park, pub, or a coffee shop. The third strategy involved selectivity when choosing outcome measures for follow-up for patients struggling with completing numerous questionnaires. Assessment burden due to the number of and/or intrusive nature of questions can have negative impact on the decisions to remain involved in a trial (Gross and Fogg 2001).

Achieving continued interest with regular contact

The main ways in which trial researchers ensured continued interest was sending reminders and staying in touch. The strategies varied across trials from a structured approach with "a little hierarchy that we tried calling at least three times, if that didn't work we'd send letters" (Trial Manager 5) to a more ad-hoc approach "reflective of their attendance as opposed to this will be something that we'll prescriptively do to everyone from the beginning" (Trial Manager 1). A participant-centred approach was taken in trials where reminders were tailored to specific preferences of a participant. This was especially important for people who did not like to use telephones but still needed to be reminded about an upcoming appointment.

Six means of reminding participants about their appointments were identified in trial researchers' accounts: phone calls, text messages, e-mails, letters, cards, and newsletters. Despite the widespread use of mobile phones and general departure from postal communication, letters with the details of the appointment were found to be effective. This was attributed to patients being used to receiving such letters from the NHS, although this was an interesting observation given the high non-attendance rates reported in mental health services in the UK (Stone *et al.* 1999, Department of Health 2003, Mitchell and Selmes 2007).

Regular reminders were also identified by interviewees as central to "personal engagement, reducing burden on people [achieved by] warm and empathetic listening stance and giving people time" (Research Assistant 10). This approach was however in contrast to sending text messages, a method preferred by participants who "couldn't quite bring up the courage or the motivation to talk" (Clinical Psychologist 1). This discrepancy in strategy highlighted the importance of participant-centred approach, putting participant needs at the core and having a repertoire of strategies to choose from when getting in touch. In addition to reminders about specific appointments, contact was also made in trials involving telephone follow-up and in between intervention sessions contact (also described as "an economic measure" by Research Assistant 11). Two purposes of these types of contacts were identified: completion of a trial procedure and keeping in touch.

> "A member of our trial steering committee who suggested that [study newsletter] is a good way of improving retention basically said it's a way of thanking people for their time and effort in the trial really does improve people's willingness to kind of engage basically." (Trial Manager 4)

Thanking participants for their involvement, mainly through newsletters and cards, like in the quote above, was described as a retention strategy within a trial but also as an engagement strategy spanning beyond a single study in a given research site.

Category 3: Addressing contextual challenges

As outlined in section 6.5.5. two types of contextual factors influencing retention in trials included organisational and geographical aspects. Ways of addressing these will be presented in turn.

Liaison with care coordinators

The extent to which trial researchers were able to affect the organisational factors was limited and involved mainly liaising with care coordinators based in the NHS. The liaison was described as key to good retention and requiring long-run effort as:

> "That sort of trust and relationship seem to build up over the years, [it] helps the study retain patients that maybe other studies may not get to if they were sort of starting afresh, building up these pathways." (Senior Researcher 3)

Liaising with care coordinators served the following functions: seeking advice about retaining particular patients, contacting patients through care coordinators, getting information about trial participants, asking care coordinators to remind patients about appointments or to encourage them to contact researchers, and receiving updates about patients.

Working against geography

As discussed in the section 'Geographical factors' on page 137, trial researchers experienced issues with participants' mobility and location. These became even more pronounced when using observational measures. Ways in which trial researchers dealt with those issues included six preventive strategies.

The first strategy was applied at the recruitment stage of the trials and involved excluding homeless individuals when screening. These patients were described as "very transient" (Trial Manager 4) and therefore at high risk of dropping out of a trial. The awareness of high mobility of patients with schizophrenia led to two strategies applied at baseline assessment: recording alternative contact details and providing researcher's details to participants. The former was a simple task but it provided researchers with "more avenues to get hold of [participants]" (Trial Manager 4). This was achieved by taking contact details of family members and friends, recording participant's date of

birth to enable medical records search, and contacting patients' care coordinators to check for any changes in circumstances. Contact information was also checked throughout the duration of the trial, to prevent losing participants who change their number or location. Frequent changes of address have been previously reported to cause low retention rates. Another simple strategy included leaving researchers' details with the participant, for example on a thank you card, "to all patients who were involved because, as usual, so they could ask, they could get in touch" (Senior Researcher 1).

Following enrolment into a trial, intervention adherence became an important consideration. This was ensured by either supporting participants with getting to sessions using public transport, for example purchasing and posting train tickets in advance of intervention sessions, or by providing door-to-door taxi transport.

Two strategies came into play once a participant had already moved away. One was travelling to the participant to complete a follow-up assessment. This was possible within the available travel budget, and therefore was subject to geographical limitations. In cases of patients who moved outside of the geographical cut-off point, a second strategy was considered: using alternative means of collecting data. This however was not always possible due to resource limitations and the protocol approved by the REC. In some cases, researchers were able to complete measures that did not require face-to-face meeting with the participant:

> "A small questionnaire you can ask people over the phone and we did collect patient data." (Senior Researcher 1)

This was contrasted by Research Assistant 4 who could not offer the option of completing follow-up assessments over the phone:

> "We can't do these [self-rated] questionnaires say over the phone or by post with people cause our research ethics says it has to be done in person and that is a barrier […]. Can we post them the questionnaire and get them to at least do most of the data? But they say we can't because of the research ethics and it would take too long to go and apply to get that amended. And I think that that's a pity. It's a shame that it does affect the potential rate of the number of follow-ups we do cause you're losing a lot. You're losing data. They would do most of it, most of it is easy, a bit of demographics, so the questionnaires are quite straightforward." (Research Assistant 4)

Research Assistant 4 explains that the need to conduct assessments in person was dictated by the protocol approved by the research ethics committee and any changes would require an amendment to the original application, which can be timely.

6.6 Discussion

6.6.1 Main findings

Failure to retain study participants in a trial was an important methodological and pragmatic concern for trial professionals. Retaining participants with schizophrenia in RCTs presented issues that are both specific to this population and those that apply to trials in any area of medicine. Trials evaluating non-pharmacological interventions provide a specific context for retention, with a different combination of issues to those reported in pharmacological trials.

Trial researchers identified two types of attrition: loss to follow-up and intervention non-attendance, which are affected by different factors and require different approaches to deal with dropout. There are a range of factors affecting trial retention that are attributable to different agents involved in the trial system, including participants, researchers, study, and wider context. These factors correspond to the actions taken to increase retention; however the actions vary from standard practices to ad-hoc or intentional strategies. The interrelations between the main influential factors and practices and strategies are depicted as a system in Figure 6.2.

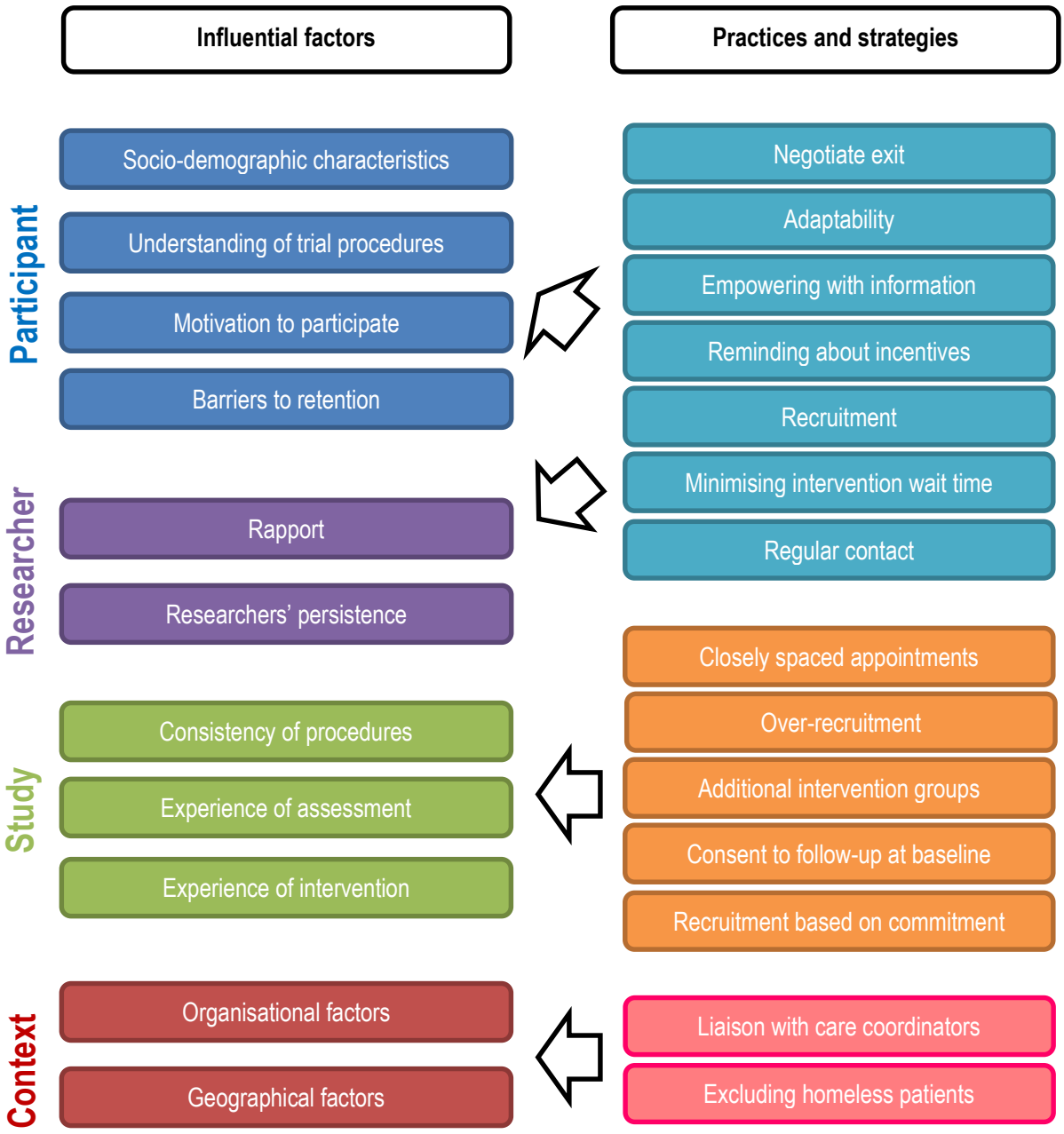


Figure 6.2 Interralations between influential factors and practices and strategies

6.6.2 Strengths and limitations

This study makes a contribution to the sparse literature on participant retention in mental health trials by exploring the factors researchers deal with and the ways in which they minimise retention. Data saturation was achieved, allowing for a thorough exploration of the emerging themes.

Collecting data in face-to-face interviews allowed for an in-depth exploration of relevant issues and additional probing following responses. However, it is possible that some responses were influenced by social desirability bias given the focus on practice and conduct.

The use of purposive sampling may have limited the representativeness of the population, however the character of the study was explorative and the final study sample reflects the characteristics reported for academic researchers.

6.6.3 Interpretation and comparison with the literature

Meta-analyses presented in the two previous chapters showed that it was difficult to identify the factors influencing retention in trials evaluating non-pharmacological interventions for schizophrenia, especially socio-demographic characteristics of participants. This qualitative study adds to the previous findings of this doctoral study by gaining in-depth insight into the practice of managing retention in trials involving people with schizophrenia.

Framework analysis of the interview transcripts uncovered four categories of factors important for retention in non-pharmacological RCTs in schizophrenia and ways in which trial researchers address some of those factors. These findings address the second and the third research questions concerned with the factors influencing retention of patients with schizophrenia in complex intervention RCTs and the current practices of retaining patients in trials. Together, they provide insight into the challenges and practices of retaining patients with psychotic disorders in trials.

The way in which the doctoral candidate structured and presented the findings corresponds closely to the Ecological Theory of Research Participation proposed by Marcellus (2004) (see Chapter 2) and provides further support for seeing attrition as a complex issue involving interactions between multiple variables, as well as between individuals and their environment. Although the ways in which factors affecting retention were categorised in the present findings are related to the Marcellus' model, they do not correspond to all types of factors identified by in the model. For instance, Marcellus lists values, beliefs, and personal meaning as participant factors; however, these were not discussed by the trial researchers in the present study. Thus, beyond the core layers, the findings of the current study reveal different sets of factors specific to

trials involving people with schizophrenia and evaluating complex interventions. However, the notion of a participant-centred approach to research in the model permeates a number of themes identified in the data presented in this chapter and provides further support for this aspect of the theory.

In addition to the four categories of factors, the study was able to identify the diversity of schizophrenia presentation and the different mechanisms of attrition. As Buckley et al. (2009, p.383) put it "The clinical heterogeneity of schizophrenia is indisputable. Virtually no 2 patients present with the same constellation of symptoms." Furthermore, symptoms such as hallucinations, antisocial behavior, anhedonia, depressive symptoms, emotional processing, and mood induction have been shown to vary across cultures (Banerjee 2012). This heterogeneity is also present in other mental disorders, where individuals with the same diagnosis can differ in the type and severity of the symptoms they experience (Goldberg 2011, Wardenaar and de Jonge 2013). In addition, fluctuations in mental health as well as psychiatric, physical and substance use comorbidities are common across severe mental illnesses, further contributing to their complexity (Buckley *et al.* 2009, de Hert *et al.* 2011, Naylor *et al.* 2012, Hartz *et al.* 2014). Many of the challenges experienced by people with schizophrenia are also present in other populations. However, there are challenges unique to people with this diagnosis such as paranoid thoughts and anhedonia, which can have impact on their retention in trials. This group is generally thought to be difficult to engage in services and research and perceived as 'high risk' to themselves and others, especially among public (Humphreys *et al.* 1992, Dickerson *et al.* 2002, Thompson *et al.* 2002, Lecomte *et al.* 2008). The researchers interviewed in the present study identified similar attitudes among staff facilitating access to potential trial participants, demonstrated in gatekeeping and risk aversion, which presented barriers to retention. This emphasised the importance of liaison between researchers and care coordinators to engage patients in an ethical and effective way throughout the duration of a trial.

Participant factors

The first of four categories, participant factors, can be compared to the results of the quantitative studies presented in chapters 4 and 5 as they tested the impact of participant characteristics on retention. The findings of this qualitative study partially support the results of the meta-analyses. Trial researchers were able to identify factors

affecting retention in schizophrenia trials, such as age and socio-economic factors, but they had diverging views on some characteristics, yielding them ambiguous in the context of predicting retention. This suggests that retention strategies applied across the whole sample should not be developed based on specific patient characteristics, for example introducing additional measures for participants with a specific socio-economic status. Thus, a more individualised approach taking into account a combination of socio-demographic factors may be needed to retain participants in a trial.

Despite none of the patient characteristics emerging as a clear predictor, the data included ideas explaining why some patients are more likely to be retained than others. These included having insight about own illness, understanding trial nature and procedures, and having an interest in the intervention. Randomisation was a particularly difficult concept to understand for patients, a challenge previously reported in other, non-psychiatric populations (Featherstone and Donovan 1998, 2002). The complexity of randomisation presents a challenge for researchers responsible for making sure patients sufficiently understand what they can expect from their participation and what is expected of them as participants. Nonetheless, the findings suggest some ways of effectively equipping participants with the required information, taking into account the potential difficulties experienced by people with schizophrenia, especially those experiencing side effects of antipsychotic medication affecting their cognitive abilities. Aside from allowing time for explanations, the focus was on the method of delivering information, including interactive and collaborative methods such as videos, events and patient-led information sessions.

Offering incentives for research participation was a major theme, which had important implications for retention. Previous attempts to understand the impact of incentives on research participant behaviour have drawn on the principles of the exchange theory in proposing that research participation is dependent on the estimate of the anticipated reward (Woolard *et al.* 2004). The exchange theory, which has been seminal in understanding power and behaviour, provides a cost-benefit formula for predicting behaviour: 'behaviour = rewards of interaction – cost of interaction' (Cook and Rice 2006). In the context of retention in trials, the behaviour can be seen as completion of intervention or follow-up assessments, the rewards are either tangible (money, vouchers, materials) or intangible (receiving an intervention, interaction with others), and the cost is the time and effort spent on attending sessions and completing outcome

measures. Considering retention through the lens of the exchange theory once again shows that there are multiple components affecting participant behaviour and the resulting retention. The interviews with trial staff allowed for identification and investigation of some of those components, which will be discussed next.

This study has identified three main motivators for retention in non-pharmacological trials or schizophrenia. First, having an interest in the intervention led to better retention, especially in the active arm. This finding corresponds to the results of the IPD-MA presented in Chapter 4 showing that those in the active arm are more likely to complete follow-up assessments. Assuming that most patients prefer to receive an active intervention, the finding also relates to the literature showing that participants who receive an intervention they prefer are half as likely to drop out than those who do not receive their preferred treatment (Swift and Callahan 2009). This qualitative study generated some potential explanations for better retention rates in the active arms, including having more contact with staff and better engagement resulting from the nature of most complex interventions. However, it is important to note that some patients preferred to be randomised to the control arm as they perceived interventions as high commitment. This should be taken into account when making predictions about the likelihood of an individual to drop out.

The findings show that monetary incentives were the most effective but also most problematic motivator. The effect of financial incentives on retention rates has been shown in a systematic review of retention strategies (Robinson *et al.* 2007). However, similarly to the findings of the present study, the impact of money has been recognised as a controversial issue (Roberts *et al.* 2004) and the respondents in the current study were wary of the risk of coercion, or perhaps revealing such practice, when discussing this type of incentive. This could have impacted on how much information they were willing to disclose. In addition, money acting as a main motivator was linked to issues with engagement, reliability of data, and benefit of treatment, mirroring the findings of Gross et al., (2001) who proposed that "monetary rewards may effectively get a participant's attention but that may not be sufficient to sustain their interest over time" (p.246). The evidence suggests that although monetary incentives can be effective in improving participation levels, their use for the purposes of retention in trials should be studied further.

The third type of motivation observed by trial researchers was altruism, which is a concept that has received a lot of attention in the literature. In the specific context of trials, two main notions have been proposed: 'weak altruism' and 'conditional altruism'. Weak altruism occurs when individuals consent because they see 'no positive net difference' between interventions and perceive no potential loss (Edwards and Braunholtz 2000). Conditional altruism proposes that although people may initially agree to participate in order to help others, they will remain engaged only if it brings some benefit to them (McCann *et al.* 2010). Although the reverse has been found; with helping others emerging as a by-product of participation in a clinical trial rather than a primary motivation (Locock and Smith 2011). The present study found that appealing to altruistic instincts was one of the strategies for recruiting and retaining participants in a trial but this was used in combination with other incentives, usually monetary.

Researcher factors

The second category was concerned with factors dependent on the researchers. The leading theme here was the relationship between the researcher and the participant. While a lot of literature has been produced on the subject of clinician-patient relationship (Street *et al.* 2009, Thompson and McCabe 2012), less is known about the researcher-patient relations, particularly in the context of trials. Some evidence is available on these relations in qualitative enquiry (Wilde 1992, Pitts and Miller-Day 2007, Eide and Kahn 2008, Guillemin and Heggen 2009) and survey research (Jacomb *et al.* 1999, Lavin and Maynard 2001, Evans *et al.* 2002) but there seems to be a gap when it comes to the specific context of trial research, which often combines the two types of methods (i.e. interviews and questionnaires) in follow-up assessments.

Some literature has emphasised the importance and the intensity of the interface between researcher and patient for the ethical conduct and the success of research (Bookman *et al.* 2013). The present study suggest that this requires skills and points to the importance of recruitment of staff who have the ability to work with people with mental health disorders and provision of training on rapport building among other important skills. Linked to the relationship was the persistence of researchers, which seemed to balance on the fine line of ethical conduct in terms of the amount of contact with participants and the methods used to do so.

Although a lot of activities were enforced by the standard operating procedures, which will be discussed in the next section, a lot of actions key for retention were down to the efforts of individual researchers. These were previously categorised by Sullivan (2004) as logistical and personal factors that have impact on the researcher-participant relationship, for example negotiating the decision to drop out could be seen as reflective of the level of researcher's personal investment in the study. The level of researcher's adaptability was also a factor dependent on personal circumstances and the work ethic of the researcher. In addition, not assigning researchers to specific patients for the duration of the trial could be reflective of an unstable research team, a logistical factor. There were also factors that hinged on both logistical and personal circumstances, for instance the way in which information was communicated to patients and reminders about incentives can be built into the trial procedures but putting it into practice and the nuances of communication are in the hands of the researchers.

Study factors

Study factors comprised the third category and dealt with the decisions that affected the operations of the whole trial. The themes revolved around key activities and procedures, which introduced the risk of losing patients' engagement, namely research assessments and interventions.

Underpinning all of trial activities were procedures and systems. The consistency of these was emphasised as important for retention. The feasibility and acceptability of interventions and procedures can be tested in pilot studies preceding full trials if similar studies do not exist (Donald *et al.* 2009, Thabane *et al.* 2010, Shanyinde *et al.* 2011, Hubbard *et al.* 2016). However, neither of these options was discussed in the interviews. This could mean either that the interviewees did not have much experience with pilot trials, or that they did not make a link between the procedures they described as important and the option of testing them before a full trial. It is also possible that it is the role of the Principal Investigators (PIs) to assess the likelihood of success of the intervention and study procedures and this group was purposefully not included in this study.

The discussion of the impact of the enjoyment of an intervention provided further insight into the finding of the IPD-MA (see Chapter 5) pointing out the differences

between retention in the active versus the control conditions. In this qualitative study trial researchers also gave emphasis to the impact of arm allocation on the nature of engagement in a trial, pointing to the intensity of engagement and increased contact with therapists.

Having a person-centred and flexible approach was identified as a strategy to deal with some of the study factors. This echoed the literature on retention advocating tailoring study procedures and interventions to individuals; for example "A retention strategy related to the study itself is to develop interventions and procedures that take the needs and resources of participants into account" (Marcellus, 2004, p. 93). The practices described by trial researchers provided evidence of a person-centred approach, especially in the context of organising follow-up assessments. It is interesting to note that, despite the widespread efforts to increase patient and public involvement in research (Staniszewska *et al.* 2011), there was no mention in the interviews of the role participant advisory groups have in advising on the conduct of research, and especially retention strategies or procedures used to maximise retention.

Context factors

Factors concerned with the external context were outside of the control of the researchers but their impact could be mediated. This required a more proactive approach utilising preventive measures compared to the reactive ones described in the previous sections. Interestingly, this category of factors attracted the most well-defined strategies, compared to the other three categories.

A number of organisational factors were determined by the research site and the clinical staff involved in recruitment and retention of their patients. Liaison with care coordinators has been described in the literature but mainly in the context of recruitment to trials (Yancey *et al.* 2006, Howard *et al.* 2009). The present study highlights the importance of a continued relationship with care coordinators throughout the duration of a trial to achieve a good retention rate.

The geographical location was another contextual factor researchers could not alter but often had to deal with given the mobility of the population, especially those living in urban areas. The trial literature has mainly focused on the travel burden for the participants needing to attend sessions (Hussain-Gambles 2004, Karlson and Rapoff

2009, Kanarek *et al.* 2012, Kaur *et al.* 2012). What the current study highlights is the efforts made by researchers to reach participants who have changed their location or contact details. This was described as a particular issue when working with people with schizophrenia who often led chaotic lifestyles. Some preventive measures helped with tracking participants and locating them after they have moved, for example recording alternative contact details at recruitment. This corresponds to the existing literature, for example Bindman (1993) found that recording details of three other people was the most useful resource in following-up. In instances when the move was far, it was up to the study resources and the researcher's flexibility to travel to the patient and collect data.

6.6.4 Conclusion

This chapter presented findings from qualitative interviews with trial researchers about their experiences with engaging people with schizophrenia in RCTs of complex interventions. It has developed themes around four categories of factors influencing retention and strategies used to address those factors. The perspectives shared by the different types of professionals seem to complement one another, presenting a picture of trial practices in the context of retaining people with schizophrenia in trials evaluating complex interventions. The findings have pragmatic implications for improving participant retention as they make links between common issues and the ways in which they can be addressed. The research and practice implications of the findings will be discussed in the final chapter.

Chapter 7
Qualitative study of trial participants' perspectives on retention: the EPOS trial

7.1 Chapter overview

The study reported in this chapter sought to provide insight into trial participants' perceptions of retention in complex intervention trials, as defined by the fourth research question: 'What are the experiences of patients with schizophrenia in the context of retention in trials?' This was achieved by examining key facets of patients' attitudes towards trial participation and their role within it: decisions about continuing or discontinuing participation, motivation for enrolling and staying engaged, and understanding of the trial procedures.

The chapter will first provide the rationale for conducting this qualitative study with its specific objectives. This will be followed by an outline of the context for this study and the methods used to collect data. Finally, the findings will be presented and then interpreted in light of the wider literature.

7.2 Rationale

The previous chapter explored the experiences of researchers working on trials involving people with psychotic disorders. When planning this study, it was important to also gain the perspective of trial participants who are the decision-makers in the context of engaging in research.

The importance of involving patients in both their care and research relevant to them has gained significant interest in the literature. The level of the involvement can vary and this has been placed on a continuum, from low to high involvement (Hanley *et al.*

2004). Other literature talks about the move from a participatory model of research, where individuals with relevant experience act as advisors on a study, to emancipatory research, which gives the individuals control over the process (Beresford 2002, Henn *et al.* 2009). This variation has resulted in multiple terms used to define the type and model of patient involvement (Sweeney and Morgan 2009). Despite the challenges surrounding the terminology, patient engagement has become an ethical mandate to democratise medical care and research in order to make their processes and results more relevant to patients' concerns and preferences (Kitchin 2000, Domecq *et al.* 2014). In addition, Kitchin (2000, p.39) proposes that "such partnership approaches seek a democracy between (non-disabled) re-searcher(s) and disabled co-researchers that is based upon recognising that both parties have expertise but from differing frames of reference." However, it has been argued that the shift towards valuing patient perspectives has been more influential in healthcare than in research (Sacristán *et al.* 2016) and it has received criticism based on the risk of tokenism and increased cost (Domecq *et al.* 2014).

Public and patient involvement in research can take on different conceptualisations and formats, depending on the research question, resources available, and overall study design (Barello *et al.* 2014). Previous efforts aimed at understanding patients' experiences of participating in trials have included retrospective questionnaire studies (for example: Tallon et al., 2011; Wendler et al., 2008), studies involving rating hypothetical research opportunities (for example: Leathem et al., 2009; Moser et al., 2002; Roberts et al., 2002), and qualitative investigations of experiences, for instance of completing questionnaires or of reasons to enrol into trials (for example: Holmberg et al., 2014; Howard et al., 2009; Kost et al., 2011). These studies have yielded important findings relevant to recruitment and retention strategies, decisional capacity, ways of supporting participants with completing assessment measures, and their motivations to participate. Out of the existing methodological options, employing qualitative methods seems to yield most in-depth data about the participation experiences, which are not easily quantified, and for exploring issues identified as pertinent by participants.

However, identifying former trial participants for the purposes of a qualitative study is challenging given the guaranteed anonymity of participation. This important ethical consideration can also create a barrier to giving participants a voice. One option would be to seek such individuals in the general population, however given the focus of this doctoral study on the complex interventions for psychosis, this approach would be

likely to yield a small number of eligible participants. An alternative would be to identify eligible patients through specific studies. This approach however requires either an existing ethics approval allowing for approaching participants to invite them to a qualitative study or an application for a new approval, which defines the study as a separate endeavour linked to the main trial. If such qualitative investigation is built into a trial from the outset, the process is made much easier (Holmberg *et al.* 2014). This can also be part of a wider study nested within a main trial, allowing for investigating the effectiveness of different recruitment and/or retention strategies (Graffy *et al.* 2010, Rick *et al.* 2014, Madurasinghe *et al.* 2016). Such trials within trials have been conducted and can be considered gold standard in research on recruitment and retention, however this model requires considerable resources and time (Graffy *et al.* 2010, Bower *et al.* 2014). The timing of this doctoral study unfortunately did not allow for embedding it within a planned or on-going trial. Thus, the best available option was to conduct this qualitative study as a follow-up to the EPOS trial, which was in its final stages when the candidate began the doctoral studies. The trial and the procedure followed will be discussed in the subsequent sections.

7.3 Objectives

The specific objectives of this study were:

1. To examine patients' reasons for continuing or discontinuing participation in the EPOS trial.

2. To explore their perceptions of EPOS and their understanding of this particular trial, and how these perceptions and understanding contributed to their decisions about participation.

3. To identify lessons to be learned about how retention in future trials similar to EPOS might be improved.

7.4 Study context: the EPOS trial

7.4.1 Trial overview

The trial titled "Effective Patient-Clinician Communication in Community Mental Health Care" (EPOS) was an exploratory pragmatic cluster RCT on the effectiveness and cost-effectiveness of the DIALOG+ intervention (Priebe *et al.* 2013, 2015). The study was funded by a National Institute of Health Research (NIHR) Programme Grant for Applied Research and the access to it was facilitated through the Unit for Social and Community Psychiatry where the candidate was based for the duration of her doctoral research. The study was conducted in seven community mental health teams (CMHTs) in East London.

The intervention was delivered using an iPad, which was shared between patient and clinician (also referred to as 'care coordinator' throughout this chapter) during the routine appointments. Each session began with patients rating their satisfaction with eight life domains: mental health, physical health, job situation, accommodation, leisure activities, friendships, relationship with family or partner, personal safety; and three treatment aspects: medication, practical help, meetings with professionals. Each item was rated on a Likert-type scale from 1 ('totally dissatisfied') to 7 ('totally satisfied') and this was followed by asking if the patient needed additional help in the given domain. A graphical summary of the ratings was produced for the benefit of both the patient and the clinician after each session, allowing for comparisons with previous ratings. Appendix 7 provides screenshots of the DIALOG+ intervention.

Following the rating exercise, the results were used to inform the discussion between the patient and the clinician. First, clinicians offered positive feedback on the domains showing improvement or attracting high scores. Second, the patient and the clinician together chose any domains they wanted to discuss in greater depth. The selected domains were addressed using a four step approach based on the principles of solution-focused therapy, which involved: 1) understanding the patient's concerns and coping strategies effective in the past; 2) identifying best-case scenarios and small steps for improvement; 3) exploring options and resources available to the patient; and 4) agreeing on actions to address the identified concerns to be reviewed at the subsequent meetings.

The control condition included treatment as usual and an assessment of the patient's satisfaction with the different life domains using a tablet without the involvement of clinicians. Clinicians involved in the trial were trained in using DIALOG+ and instructed to use it at least once per month over six months, allowing for variations due to the practical organisation of care.

7.4.2 Trial recruitment

Recruitment to the EPOS trial was through clinicians who first identified eligible patients on their caseloads and then approached the person to ask for consent to be contacted about the trial. Each assessment was conducted in one-to-one meetings between an EPOS researcher and a patient and involved an observer rated structured interview for the Positive and Negative Syndrome Scale (PANSS) as well as the following self-report measures: the Manchester Short Assessment of Quality of Life (MANSA), Camberwell Assessment of Need Short Appraisal Schedule (CANSAS), Client Satisfaction Questionnaire (CSQ-8), General Self-efficacy Scale (GSS), Warwick-Edinburgh Mental Well-Being Scale (WEMWBS), and the Scale for Assessing Therapeutic Relationships in Community Mental Health Care (STAR-P). All outcomes were measured at baseline and at three follow-up assessments at 3, 6 and 12 months. The assessments took place at the CMHTs or in patients' homes. Participants received £20 for completing each assessment.

The principal inclusion criteria for the EPOS study included: aged between 18 and 65 years; a diagnosis of schizophrenia or a related disorder; capacity to provide informed consent; treatment in a CMHT in the NHS for at least one month; and a mean score of less than 5 on the MANSA. Exclusion criteria included: insufficient command of English; a mean score of 5 or more on the MANSA; and learning difficulties.

7.4.3 Participant Flow

A total of 709 patients were assessed for eligibility. Following baseline assessments, 188 patients were randomised to the DIALOG+ or control condition. Of those patients, nine either withdrew from the study or were discharged from the clinician's caseload before randomisation, without the knowledge of the research team. This group was deemed

as 'randomised in error' due to no longer being eligible and, as a consequence, excluded from the analysis. The correctly assigned sample included 179 patients, of whom 94 were randomised to the intervention arm and 85 to the control condition. Of those, 14 participants (11 experimental, three control) did not receive the allocated intervention, for example because of clinician changes.

The primary outcome was assessed in 120 (61 experimental, 59 control) out of 179 patients at three months, representing 67% retention. At six month follow-up, 147 (73 experimental, 74 control) patients were assessed, with 82.1% retention rate. At 12 months, 129 (61 experimental, 68 control) patients completed follow-up, accounting for 72.1% retention. A full CONSORT diagram for the EPOS trial can be found in Appendix 8.

7.5 Method

7.5.1 Study design

As the main objective of the study was to explore the experiences of the EPOS trial participants, in-depth interviews were chosen as the most suitable data collection method. Given the focus on individual experiences and decision-making, it was decided to conduct individual, semi-structured, face-to-face interviews. This type of interview can be used to elicit a holistic understanding of the interviewee's point of view and provides an opportunity to further investigate interesting areas arising during an interview. The choice of a semi-structured format allowed for asking open-ended questions and probing wherever necessary to obtain relevant data.

As in the qualitative study with trial researchers presented in the previous chapter, Framework Method was used to analyse the data. The approach to data and the process were the same as in the preceding study and further details can be found in Section 6.4.1 (p.107) of Chapter 6.

7.5.2 Ethics approval

The initial plan was to obtain an ethics approval from the NHS REC to conduct this qualitative study as an extension of the EPOS trial. This was possible as the doctoral candidate's supervisor was the PI and had access to the trial data. The main advantage of submitting the qualitative study as an amendment to the EPOS trial was a much shorter review process compared to a full application and review. This was particularly important given the anticipated impact of the time lag on participants' recall of their experience of the trial, a limitation of any retrospective study (Beckett *et al.* 2001). It was important to begin interviews as soon as possible after the last follow-up assessment, which took place on the 3rd of November 2014.

Consequently, an application was made for an amendment to the main trial adding a qualitative follow-up investigation of patients' decisions about their participation throughout the duration of the trial. This amendment was submitted on the 7th of January 2015, approximately three months after the start of this doctoral study. The Committee declined the application as they perceived the qualitative study to be separate from the original trial and therefore requiring a full review by the NHS REC.

Following the rejection of the amendment, a full application was prepared by the doctoral candidate and submitted on the 13th of May 2015. This process was subject to delays caused by the local Research and Development department, which were outside of the candidate's control.

The final approval letter was granted seven months after the last EPOS follow-up assessment by the National Research Ethics Service (NRES) Committee London – Stanmore, REC on the 30th of June 2015 (reference 15/LO/0991) and can be found in Appendix 9.

7.5.3 Recruitment and sampling

Participants were recruited through the EPOS trial, with assistance from the original trial team and patients' care coordinators. Multistage stratified purposive sampling was used to identify the final sample.

In the first step, trial records were reviewed to identify the study completion status of each participant. If the patient withdrew consent and specified that he or she did not want be contacted again, they were not approached about the study. Following exclusion of those patients, the remaining participants were first stratified into those who completed all follow-up assessments (henceforth referred to as 'completers') or completed the assessments only partially ('partial completers'). Once the participants were categorised into one of the two strata, 15 participants per strata were selected on the basis of achieving maximal variation of demographic characteristics and trial arm allocation. One of the reasons for selecting stratified sampling was to minimise the amount of contact with the clinicians (and thus the potential burden on them) who potentially had more than one trial participant on their caseload. In these cases, the candidate needed to explain the purpose of the study only once for multiple patients. The doctoral candidate contacted the care coordinators of these 30 patients, providing information about the study and asking care coordinators to ask their patient for permission to be contacted by the candidate. Participant information sheets were sent to the care coordinators by email (see Appendix 10). If the patient agreed to be contacted by the candidate, their contact details were obtained from the care coordinator and they were sent an invitation to participate in an interview together with the participant information sheet. Potential participants were contacted again at an agreed time and date to discuss their decision to participate or not. All participants were offered the option to be interviewed in person in a convenient location with confidential space, such as a local community centre or a CMHT. Each participant received £20 for his or her time upon completing the interview.

Out of the initial sample of 30 patients, 12 were impossible to contact following several attempts to call, seven refused contact and 11 were interviewed (Round 1). Once all responses had been received, another sample of 30 was identified from the list of eligible participants in each strata (Round 2) and the same procedure followed for obtaining assent. Out the second sample, 18 were impossible to contact, seven refused contact and five were interviewed. Preliminary analysis of the 16 completed interviews suggested data saturation point was being approached but had not been achieved. Consequently, given a small number of interviews anticipated to be required to reach data saturation, a different strategy was adopted in Round 3, with potential participants invited to the study one by one and these interviews reviewed using the same approach. The last round yielded four interviews. Once 20 interviews had been completed the

candidate determined that data saturation was reached. This was decided, in line with the Fusch and Lawrence's (2015) guidance, on the basis of further coding being no longer feasible (Guest *et al.* 2006, O'Reilly and Parker 2012), having sufficient information to replicate the study (O'Reilly and Parker 2012), and the ability to collect additional new information has been attained (Guest *et al.* 2006). The process resulted in 20 interviews, following selection of 64 patients and contact made with their care coordinators. Figure 7.1 overleaf presents the process of recruitment with the numbers obtained at each stage.

Figure 7.1 Recruitment process

7.5.4 Materials

A participant information sheet was developed to invite potential participants to the study and to provide information about the purpose of the study and what their participation would involve. This was also used to provide information for the care coordinators acting as gatekeepers to their patients, in addition to a verbal explanation during the first contact made by the candidate.

The information sheet was written in lay language and followed guidance provided by the NRES (2009). The invited individuals were given information about the purpose of the research, the reasons for being invited, the voluntary nature of their participation, the reimbursement, the nature of their involvement, the advantages and disadvantages of taking part, the course of action in case of a problem, the confidentiality and privacy of the participation and the data, the organisation of the study and the ethical approval, the details of a complaint procedure and an explanation of how the findings will be used. In addition, contact details of the candidate were provided. The full information sheet can be found in Appendix 10.

When contacted to arrange an interview, each participant was offered the option of completing a Participant Preference Form, which recorded any preferences they had in regards to the interview. This allowed the candidate to make appropriate arrangements and also have a record of the participant's wishes in different scenarios, for example what to do if the participant does not turn up for the interview or is unwell during the interview. This form can be found in Appendix 11.

There was a separate written consent form presented to the participants before the interview. The form was also prepared in accordance with the requirements of the NRES (2009). It comprised seven statements allowing the participant to express in writing their agreement to the different aspects of taking part in the study. The form informed the participants about their right to withdraw at any point and the confidentiality of their personal information. Participants could also express their agreement to being recorded and to receive a summary of findings upon completion of the study (see Appendix 12).

Two interview schedules were developed: one for completers and one for partial completers. Both interview schedules began with an introduction to the study and

asking them to describe their involvement in the EPOS trial. Once their recollection of the trial was established, the interview moved on to the topics of being invited and making the decision to take part, expectations about the participation, involvement in the study, and experience of any retention strategies. The only section that differed between the two schedules was 'Involvement in the study'. This was done to explore specific reasons for completing assessments versus failing to complete some. Here, completers were asked questions about what motivated them to stay involved throughout the study, whether anything would have made their participation easier or more interesting, whether they considered dropping out at any point. In contrast, partial completers were asked about how long they stayed involved, what made them cease their participation, whether anything could have changed their mind, and whether they experienced any effects of their partial completion of assessments. The interview was flexible as it depended on the recall of the trial experience; however, some predetermined prompts were used to encourage participants to elaborate on points of interest further, if possible. The interview schedule also included the opportunity for the participant to add more information that they considered pertinent and to ask any questions. Appendix 13 provides the full interview schedule for those who completed all assessments and Appendix 14 for those who failed to complete some of the assessments.

7.5.5 Procedure

Once the contacted patients expressed their willingness to take part, the interviews were scheduled. All interviews were conducted at a convenient time and location for the participant. Six out of 20 interviews took part in participants' homes. The duration of the interviews ranged from 17 to 38 minutes, with an average of 23 minutes per interview.

Written informed consent was obtained prior to the interview. Participants were asked to confirm their demographic details and diagnosis obtained from the trial records. Any updates were noted. Two out of 20 participants chose not be recorded. In these cases notes were taken during the interview. The candidate transcribed the remaining 18 audio-recordings of interviews.

All data were kept in a locked filing cabinet and digital information was kept on a secure, password-protected computer. Data was coded to ensure participant anonymity.

7.5.6 Data Analysis

Interview transcripts were analysed using NVivo qualitative data analysis software version 10 using the Framework Method. The process was conducted in five steps, as per the original Framework Method (Ritchie and Spencer 1994). The details have been provided in Section 6.4.6 (p.110) of Chapter 6.

7.6 Findings

7.6.1 Study sample

Thirteen out of 20 participants were female and the average age was 42 years, ranging from 31 to 62. Out of 10 participants who received the intervention, eight completed all follow-up assessments (indicated in the findings as 'Intervention, Completer') and two missed some assessments ('Intervention, Partial completer'). In the group of 10 participants in the control arm, four completed all follow-up ('Control, Completer') assessments and six completed only some ('Control, Partial completer'). This is presented in Table 7.1 below. Demographic characteristics of the sample are provided in Table 7.2 and compared to the total trial sample. The profile of the participants is indicated in the findings section, where direct quotes are used.

Table 7.1Total sample by type of trial participant

		Trial allocation	
		Intervention	Control
Participation status	Completer	n=8	n=4
	Partial completer	n=2	n=6

Table 7.2 Characteristics of the qualitative study sample (n=20) and the total EPOS sample at baseline (n=179)

Characteristic	Qualitative study sample n (%)	EPOS sample at baseline n (%)
Gender		
Male	13 (65)	123 (69)
Female	7 (35)	56 (31)
Ethnicity		
White	5 (25)	46 (26)
Black	6 (30)	70 (39)
Asian	7 (35)	49 (27)
Mixed/other	2 (10)	14 (8)
Mean age	42	41.6
Primary diagnosis (ICD-10)		
Schizophrenia	13 (65)	141 (79)
Delusional disorder	1 (5)	2 (1)
Schizoaffective disorder	4 (20)	24 (13)
Not provided	2 (10)	N/A
Trial arm allocation		
Intervention	10 (50)	94 (52.5)
Control	10 (50)	85 (47.5)
Retention status		
Full completion	12 (60)	95 (50.5)
Partial completion	8 (40)	93 (49.5)

N/A = not applicable

The sample included in this qualitative study had similar characteristics to the total EPOS sample. The majority of participants were male, which corresponds to the median male to female risk ratio of 1.4:1 reported for the population with schizophrenia (Saha *et al.* 2005) and the gender ration of the participants in the EPOS trial. The original trial sample was ethnically diverse and this was also reflected in the profile of the interviewees, with interviewees from each of the four ethnic categories specified in the EPOS trial, the majority of whom were Asian in this study and Black in the trial. The average age of participants was 42 years, which is similar to the 41.6 reported in the

EPOS trial. The majority of patients were diagnosed with nonspecific schizophrenia, similar to the trial. The spread of arm allocation and retention status is a result of the sampling strategy.

7.6.2 The initial participation experience; invitation to take part in the EPOS trial

Assessing patients' experiences after the study is one of the possible ways of engaging them in clinical research, although more active patient participation methods are possible, for example advising on study design (Sacristán *et al.* 2016). Gathering the experiences and opinions of former research participants has been shown to have the potential to inform future studies and improve their design to achieve greater acceptance and effectiveness (Kost *et al.* 2011, Tallon *et al.* 2011) .

The interviews in the present study began with establishing how the patients' were first invited to participate in the trial. Care coordinators were identified as those who introduced the participants to either the EPOS trial or the trial researcher directly. This was in accordance with the study protocol, which specified that clinicians would ask for their patient's permission to be approached by the researcher and to be given more information. Involvement of clinicians or key workers as gatekeepers to potential research participants is considered good practice and often expected by the REC issuing necessary approvals. Gatekeeping bears particular importance in populations considered as 'vulnerable', a category which normally includes people with mental illness (Patterson *et al.* 2011, Probstfield and Frye 2011).

Participants who were completers were more likely to remember who approached them about the EPOS trial in the first instance; partial completers did not recall this very well. This could be due to the completers either being more engaged in the study or having better wellbeing in general, which would affect their memory of the trial. Nonetheless, it is interesting to note that those who had no recollection of being introduced to the trial still suspected it was their clinician, as expressed by Participant 17:

> "I see him on a regular [basis], so we talk a lot. I think he was the one because he sometimes mentions something about research." (Participant 17, Control, Completer)

This assumption of clinician's involvement could be a reflection of the care coordinators being the main source of contact and the gatekeepers to both services and research.

The data on this part of the patient experience illustrate the importance of the clinicians' role in introducing the study to patients and communicating about research. It is worth pointing out that in the case of the EPOS trial, the health professionals were recruited to the study to deliver the intervention and they had a stake in finding a number of eligible patients on their caseloads to enrol in the trial. Those who were completers recalled the researchers explaining the study to them; partial completers had trouble remembering this. However, interviewees who did recall meeting the researchers did not refer to them as 'researchers', suggesting they may have not been aware of their professional background. This is similar to one of the findings reported in the previous chapter (section titled "Understanding of trial procedures" on p.125), where trial researchers reported participants confusing care coordinators with researchers. The initial meeting with a researcher took place either in the presence of care coordinators (for example Participant 4 below) or in a separate meeting that took place either at the CMHT or in participants' homes, as described by Participant 18 below:

> "When I had my appointment with my social worker I had somebody come in and tell me that they were trying to find out something about my mental health without trying… giving me lots of different drugs… And so I said 'Why not?' and signed some papers…" (Participant 4, Intervention, Completer)

> "I said 'Okay' and they came to my house and explained everything and I… there were like some papers, forms that I had to sign […] and they explained what was going to happen." (Participant 18, Intervention, Partial completer)

Overall, the interview data were limited by the time gap between being invited to the EPOS trial and being recruited to this qualitative study, often resulting in poor memory of some events and decisions made at the time. However, the differences noted between the two types of participants indicate that those who completed all assessments remembered more than those who were partial completers. In addition, completers who could remember the initial meeting recalled signing forms (although, importantly, giving little detail on what they understood that they were signing) and had different

perceptions of being asked to do so. In the quotes below, Participant 18 and Participant 7 were not particularly wary of entering the trial:

> "It was fine, it was okay. I don't worry too much." (Participant 18, Intervention, Partial Completer)

> "Oh yeah, there were some forms or something. I did sign." (Participant 7, Intervention, Partial Completer)

In contrast, Participant 16 highlighted his or her worry over signing forms in general, which was overcome by receiving an explanation about the study:

> "I don't like signing things because you hear so much about things going wrong but I had to and they explained what was going to happen." (Participant 16, Intervention, Completer)

In the example below, Participant 4 made it clear he or she did not think a lot about what the study involved at the point of giving consent to take part in the study. The focus was more on making the initial decision and the importance of the study. The specific information was obtained later, when the patient had already enrolled in the study and was able to understand what would be involved in outcome assessments, i.e. completing the same set of questions for follow-up every couple of months.

> "I didn't think too much about what I would have to do [at first]. I was asked, I thought it was important, and I said 'yes'. It was later I found out that I had to do some questions every few months and meet with someone. [...] I probably didn't think much of it. I meet different people at the [CMHT] all the time. I listened when they were talking but then I was like 'I want to get on with my day, if they want something, they have my details now.'" (Participant 4, Intervention, Completer)

Moreover, being able to refuse to answer questions or to change one's mind later seemed to provide some reassurance to individuals and in some cases delay their curiosity about the trial until a specific procedure (for example being contacted by a researcher or completing a questionnaire) was happening. The option to refuse will also be discussed in the following section in the context of motivation to take part.

7.6.3 Facilitators of retention; motivation to enter and to remain in the trial

The second theme emerging from the data focused on the reasons for deciding to take part, both initially and at follow-up assessments. As per the EPOS trial protocol, following receiving information about the study, potential participants were asked to make a decision about their involvement and asked to confirm their consent at every follow-up assessment.

Different types of motivators emerged from participants' responses. The first motivation was the desire to help others. Participants described their appreciation of the importance of research and saw their involvement as an opportunity to help other people with mental health problems. These quotes illustrate this reasoning:

> "Oh, I wanted to help. If it's going to help other people and it's trying out something then I will do it. It's like doing something good for others, other people. And I know how it is to live with this, in this condition." (Participant 17, Control, Completer)

> "I say yes to things if I think they will help [...] I like to help if I can. I can't do much but if I can sit and think and answer and it helps someone, why not? And they give me money for every time, that doesn't hurt [laughter]. So I help others and I help myself." (Participant 2, Control, Partial completer)

Similar to the first quote above, other participants were also able to make a direct connection to mental health and the NHS, emphasising the potential usefulness of their experience and input for other people with mental health disorders:

> "It's good, people need to get involved to give more information to the NHS, or whoever is doing the research [...] then clearly it's of future benefit." (Participant 4, Intervention, Completer)

> "I wanted mental health people to become, if they wanted to, more involved. And I do it myself. For mental health service users, they've got to have a say because... [...] And any treatment, any change in life, like they've moved out, and any change in any part of their lives has to be handled and has to be based on the individual. You can't turn around and say all schizophrenics would benefit from this. You can't assume everyone is the same basically." (Participant 14, Intervention, Completer)

The last statement above from Participant 14 emphasises the importance of considering differences between people with schizophrenia and what may help them.

The second type of motivation was gaining personal benefit from the intervention. Here, completers in both active and control arms seemed able to recall the details of the intervention or being told about the potential benefits better than those who were partial completers. Participants put most emphasis on just 'getting help', which is illustrated in the quotes below:

> "I take all help they can give me, innit [*sic*]? If they offer I don't say no. So I did." (Participant 7, Intervention, Partial completer)

> "I think they said it might help. They were testing it, so there was no guarantee but there was no danger. So I thought I will give it a go and see. If it helps, it helps. It's not going to make me worse than I already am." (Participant 2, Control, Partial completer)

Perceiving trial participation as low risk seemed to be an encouraging factor, which suggests that patients considered not only the potential gains but also losses. For example, Participant 16 took into account the difficulty of the participation versus potentially benefitting from it and not experiencing any harm:

> "I don't know… I just… it was just a different thing I suppose. I was like 'It's not too hard, I can do it.' and they said it can be good for me and it can't do any harm, can it?" (Participant 16, Intervention, Completer)

Participant 14 in particular described a combination of factors that led them to take part, namely the ease of participation, no change of medication, and making a contribution for the benefit of other people:

> "It was easier to say yes to a questionnaire. I don't want more medication. I don't want to change my medication. But I want to have my say and answering questions helps other people. It was fun. I enjoyed it." (Participant 14, Intervention, Completer)

In addition, Participant 14 wanted to have their voice heard and saw participation in the trial as the opportunity to achieve this and help others at the same time.

Another aspect that encouraged the decision to take part, as already acknowledged in the previous section, was the option of refusing further participation after being recruited. This seemed to provide some reassurance to patients who were not sure about their level of commitment or about the reality of participating. For Participant 2 it was having the option of stopping an interview if they got tired:

> "I'm not sure what I thought back then, like, they ask you something and say you can change your mind, so there is no danger. You can always say you are finished if you don't like it. Like if I am tired of answering I will just stop. I don't know if they still give money but you can." (Participant 2, Control, Partial completer)

Agreeing to take part and signing the consent form was seen as making a promise to the researchers. This led to keeping one's word being provided as a reason to fully complete participation, for example:

> "I signed the documents, so I promised to do everything they asked. I keep my word." (Participant 9, Control, Partial completer)

The prospect of receiving money for completing baseline and follow-up assessments had impact on the initial decision to take part. Patients indicated weighing up whether it was worth their time by considering the amount of money versus the activities or procedures they would be subjected to:

> "I would be lying if I said I didn't do it for money. I need money, they offer money, so I go and do what I need to do. If they were sticking a needle in me then maybe I would think twice but this was just talking and ticking answers." (Participant 11, Control, Completer)

> "I don't know. I just didn't have a reason to say no. They were giving money so I was like 'Yeah, I'll do it'. It was just questions, nothing too serious." (Participant 12, Intervention, Completer)

> "This woman came and said they were doing this thing, what you have there [points to an iPad], and they asked if I wanted to make £20 and I said 'Of course, who wouldn't?' and that was it." (Participant 19, Intervention, Completer)

The quotes above show that being asked questions was not seen as invasive, especially when compared to receiving injections or changes to existing prescriptions, as

exemplified by Participant 11 above. This indicates potential differences in how patients make decisions about their participation in trials of pharmacological versus complex interventions. In addition, the impact of payment was not limited to the initial decision to participate but played a role in the decision-making at every follow-up assessment.

Money was described as an alternative to 'doing nothing' and as a reason to get out of bed, especially for those experiencing low motivation and side-effects of medications, like Participant 5:

> "But then I think about money and I go. It's worth it. I can sit at home and do nothing and get no money or I can go answer some questions and get cash in my pocket. I have days when I don't want to do nothing, like, the tablets sometimes make me so weird, like I could sleep all day and then I wake up and I'm like it's not that different to being in bed. So that makes it harder to do anything." (Participant 5, Control, Completer)

In the quote below Participant 12 compares research assessments to appointments with his or her social worker and, although humorous, points out the motivating nature of monetary incentives to see the researcher:

> "I just thought about getting money and what I would do with it. So it got me up and I don't think I missed it once. It doesn't always work like this with the social worker [laughter] but they don't pay any money for my time [laughter]. Maybe if they started paying people they would come more. It gets you up." (Participant 12, Intervention, Completer)

This outward recognition of the effect of monetary incentives confirms the findings of the previous qualitative study and evidence from other studies investigating the role of incentives in research participation (Mee 2009, Brueton *et al.* 2014). Nonetheless, being motivated by monetary incentives and wanting to make a contribution were not mutually exclusive. The ability to achieve both was seen as a 'win-win' situation, with some benefit to both the participant and the researchers.

> "And I thought it could help and they were paying money, so I was like everyone is happy, right? I give something and I get something and they are also happy because they need people doing those things, like people who go to NHS and use them." (Participant 15, Intervention, Partial completer)

On the whole, money was important to both groups but partial completers did not identify and discuss other types of motivators as much as completers did.

7.6.4 Barriers to study retention

Those who were partial completers were asked about the reasons for not being able to meet with the researcher. Completers were asked to reflect on why they think some people could not be retained in studies.

The character and intensity of a follow-up assessment presented a potential barrier, especially for those who did not expect to be asked a lot of questions and to have to complete questionnaires. This was not described as directly leading to a missed appointment but it seemed to create such risk. One factor, which seemed to help overcome this barrier was how nice the researchers were towards participants, as expressed by Participant 7 below, highlighting the rapport as the potential redeeming factor in the otherwise burdensome and repetitive assessment experience.

> "It was… I didn't know they were going to ask so many questions but it was okay. She [researcher] was nice. I have to take my time with reading. Reading questions and I have to think out loud sometimes, so she knew and it took a long time." (Participant 7, Intervention, Partial completer)

> "Sometimes the questions were too many, just too many questions. And it's the same thing all over and you just don't want to do it anymore. […] Yeah, I don't like that." (Participant 8, Control, Completer)

Conversely, for Participant 15, being subjected to more invasive procedures that involved taking medication or receiving injections would be a barrier preventing them from taking part:

> "And it wasn't like I was going to lose anything, like they were not going to make me pay or like put stuff on me. I'm not doing that. I have a friend who does that and they get money and stuff but I'm like get off me and I don't want people doing stuff to me. Like I can talk to people and stuff but don't prod me with anything, you know what I'm saying?"(Participant 15, Intervention, Partial completer)

The setting in which an intervention was delivered was also important, for example if participation required being admitted to a hospital it would present a potential barrier. However, if the intervention was embedded into the existing service or care (such as DIALOG+ in the EPOS trial), this was more acceptable.

Participant 15 discussed the difficulties people with schizophrenia experience, such as hearing voices and experiencing side effects of medication, and how these can act as barriers to regular participation, as opposed to intentional decision not to complete part of the trial. The quote below illustrates Participant 15's account of the challenges experienced by people with schizophrenia, especially hearing voices and experiencing side effects of medication. This meant that for Participant 15 the choice not to do something was often a result of not being able to do it:

> "I guess schizophrenics go… like because of the symptoms we can't always do what we want because we just don't feel up for it. […] It's not like we can't be bothered, not like that. It's more like even if you want to do something you really can't. So even if we want to, if we say yes and then people think 'Oh, they just didn't want to do it' or 'They really didn't care' or something like that. It's not like… it's more to do with the mental health and how we… like daily struggle of life and it's hard for normal people. For us it's like double as hard because we have the voices and the thoughts all the time and the medications and everything. And then life with people and family and food and bills and everything." (Participant 15, Intervention, Partial completer)

Another barrier to retention that was specific to people with psychotic disorders was experiencing paranoid thoughts, which came into play especially when researchers were visiting participants at home.

> "I mean I think if someone is paranoid maybe they don't want someone in their house? I don't know… it's just a guess. I know some people I see in my group and I know they don't leave the house but they also, they don't like when someone comes knocking because they don't want to open the door, so they pretend they are not there (…) some even when someone calls but they still have a phone, so of course it is going to ring. So but those are people who are not really well, they're really sick." (Participant 17, Control, Completer)

This presented a potential challenge, which was related to the severity of psychotic symptoms experienced by trial participants and thus would not apply to all patients involved.

7.6.5 "I just do what I'm told"; a passive approach to decision-making

One of the main themes permeating patients' accounts was their passive approach to making decisions about participation in the EPOS trial, which often seemed to mirror the level of involvement in their mental health care and could be linked to negative symptoms of schizophrenia. Negative symptoms, avolition (i.e. lack of initiative or motivation) in particular, have been argued to threaten the decisional capacity of patients with schizophrenia as it affects the ability to initiate and participate in goal-oriented tasks (Anderson and Mukherjee 2007, Foussias and Remington 2010). Thus, it is possible that some of the EPOS trial participants were experiencing these symptoms and this contributed to the passive approach to making decisions.

Overall, the answers showed varying degrees of involvement in decision-making. Based on this diversity, two main types of a participant emerged. An 'active participant' was someone who was curious about the study and their involvement in it and, as a result, asked questions to find out more or to clarify the information provided to them. Subsequently, an active participant would make an autonomous decision about their participation in a study. In contrast, a 'passive participant' was an individual who was generally obedient in following instructions, depended on directions from others and did not question anything. Similar distinctions have been previously made in the context of medical care, including shared decision-making or therapeutic alliance (Neeraj and McHorney 2000, Street and Millay 2001, Brown *et al.* 2002), observed involvement in care as an inpatient (Latvala *et al.* 2000), and perceptions of own involvement in care (Brody *et al.* 1989). In the research context, the term 'participant' replaced 'research subject' to suggest a more active and equal role (Corrigan and Tutton 2006); however, less has been written about the extent to which participants are actually involved in research participation decisions.

The accounts provided by the EPOS participants interviewed in this qualitative study show that they all exhibited a passive approach but this took on different forms. The passivity was particularly pronounced in the descriptions of participation including

statements such as "I just do what I'm told and that's it" (Participant 1, Intervention, Completer) or "I guess it's like I didn't know what to expect, so you just do it. You just do it in the moment." (Participant 2, Control, Partial completer). In addition, there was a 'wait and see' standpoint, where the participants did not fully understand the process but obliged to do what was asked of them. This suggested a certain level of dependency on someone else for making sure they were safe, most commonly care coordinator or researcher.

> "I didn't know what was going to happen, so I thought I will wait and see. Whatever they ask me to do I will have to do. This is how it works. They help me." (Participant 6, Control, Completer)

> Because, see, at first, when they talked to me, I was like 'Okay, I will do it, why not?' but I didn't… I wasn't sure what they were asking me. I just went with it. [The researcher] was nice, so why not? But then I had to see her again and I was like 'Is this going to be happening now?' and she explained how it was going to work. They answered questions, it was good." (Participant 4, Intervention, Completer)

The above quote from Participant 6 in particular makes a direct reference to being helped by the same health professional who introduced the patient to the trial. On the other hand, Participant 4's attention is on the researcher who provided an explanation both at the start, when the participant seemed to be overwhelmed with information, and at the follow-up. Participant 4 is also an example of an individual who initially had a passive approach to taking part but then asked questions when seeing the researcher again. This implies that it may be easier for trial participants to take on a more active role when dealing with a specific task and less abstract information. Good practice advises researchers, especially when working with vulnerable populations such as psychiatric patients, to check for consent at each assessment point and it seems that it also provides a good opportunity to reassess understanding of the study and encourage the participant to ask questions they may not have thought of in the beginning, when hearing about the study for the first time (Li *et al.* 2016).

Associated with the dependency on others was a sense of trust patients had in those whose role it was to support them. For example, one patient relied on the care coordinator to make their decision about trusting the researchers and agreeing to participate in the study:

Interviewer: "Did you need to ask any questions about what the information meant?"

Participant 16 (Intervention, Completer): "I don't remember but I think I was just like 'I trust them because [care coordinator] was there and I trusted her and she said it was okay."

This reliance on the clinician to make decisions could potentially be indicative of paternalism, a phenomenon widely recognised in medical literature in situations where health professionals make choices for their patients (Coulter 1999, Rodriguez-Osorio and Dominguez-Cherit 2008). However, it has also been recognised that some patients may prefer a passive role and do not want to take responsibility for their treatment (Coulter 1999). This was difficult to decipher from the interview data. The EPOS trial participants interviewed in this study seemed to be comfortable with the care coordinator acting as the final decision-maker and/or advisor about their study participation.

Nonetheless, assuming a passive stance was not without consequences for the trial and the participants. One of the consequences of not taking a more active approach to one's participation was the lack of understanding of the trial procedures, for example expecting a follow-up assessment to be conducted by a health professional, not a researcher:

"She [researcher] came and she asked me things and I didn't know what it… what it was. I didn't have much to say. I thought she came from the team to do an assessment or something but she just said it was going to be one time and she gave me £20 in the end, so that was good. So I did some ticking the boxes and that's it." (Participant 18, Intervention, Partial completer)

In some cases reliance on others was extended to involving family members in making decisions about trial participation. Patients discussed their decision to participate with their spouses in the context of receiving payment and the researcher coming to their house to complete assessments. However, these conversations happened after consenting to take part in the trial.

"I told [my spouse] they said like we were going to get money for speaking to someone and they would come here." (Participant 5, Control, Completer)

Those who did not consult with anyone other than their clinician explained this by the low risk involved in taking part in the EPOS trial. However, there was an acknowledgement of a difference between a trial evaluating a complex intervention, such as DIALOG+ in the EPOS trial, and a study testing a pharmacological treatment. In cases where the trial or the intervention was potentially invasive or intensive, participants said they would require more time and would appreciate the option of consulting with someone else. In contrast, making decisions about participation in non-pharmacological trials did not require support from people other than those already responsible for their psychiatric care.

7.6.6 Participants' needs and preferences

Participants were asked about their experiences of being contacted by the EPOS researchers. The responses revealed a number of common types of preferences and needs that the participants had.

One type of preference was concerned with how individuals wanted to be contacted. Telephone contact was the most commonly given answer, however examples of specific preferences included receiving a text or a voicemail as this was seen as allowing more time to think about the answer.

> Interviewer: "What would be your preferred way [of being contacted] now? Phone? Text? Letter?"
>
> Participant 1 (Intervention, Completer): "Phone. I have voicemail, so when I'm sleeping or I can't hear the ringing they can record and then I can go and listen to it later."
>
> "She [researcher] would text me. I prefer that. I don't like phones. I mean if I have to, answer but I prefer text. I read and I think and… it's better." (Participant 4, Intervention, Completer)
>
> "Phone I think it was. Phone. I can answer when I want and when I'm home. I have a mobile but sometimes I don't hear it… I forget it." (Participant 5, Control, Completer)

The explanations above suggest that patients appreciated having the chance to think and reflect on a message before replying to researchers. Although telephone was still seen as the most accessible method of contact, for some calls from unknown numbers were a source of anxiety. One way of dealing with this barrier was recording the number of the researcher on the patient's mobile in order to quickly identify who was calling them.

> "They call but I don't answer if the number… if number unknown." (Participant 6, Control, Completer)

> "I think she [researcher] called. Yes, because I asked her to put the number into my phone. I always ask people, so I know who's calling. I don't like those number that come up on the screen and you don't know who it is and they tell you it's like an accident or something. Like, now I know it's scamming but first time it happened I was like 'Did I do something?', so I kept on the line and then it wasn't making sense, so I don't answer anymore." (Participant 13, Intervention, Partial completer)

Compared to partial completers, those who completed all follow-up assessments put more emphasis on receiving reminders about appointments when discussing their experiences. Having researchers calling them or sending text messages prior to the meeting was described as helpful and, in some cases, necessary to ensure a meeting was attended:

> "I think they called me to see if I was going to be home. It was good. I sometimes forget. I put it in my calendar but then I don't look at it. So I was ready when she came." (Participant 2, Control, Partial completer)

> "She [researcher] did tell me before, the day before. Just to make sure. So I never missed it." (Participant 4, Intervention, Completer)

Another important preference referred to where the follow-up assessments took place. The responses showed divergent views, with some participants requesting to be seen at home (Participants 5 and 7) and others not wanting to have strangers in their home (Participant 9). The quotes below illustrate this difference in opinions:

> "I wanted him [researcher] to come here. I don't like to go out and I like when she [mother] is around when strangers are around." (Participant 5, Control, Completer)

> "Here [CMHT], I always come here. I know where it is and I don't like looking for new places. I get nervous and stuff. So I prefer here." (Participant 7, Intervention, Partial completer)

> "I don't like people here…. I mean in my flat. I come here. If I want to be on my own I stay in and I don't want to come out, see people. I have food in the flat, so it's okay. I can stay, it's okay." (Participant 9, Control, Partial completer)

Participants also reflected on the preferences of other people with schizophrenia they knew and identified those who experienced agoraphobia and those who disliked unannounced visitors as particularly struggling with having meetings in their homes.

In addition to the assessment venue, the timing of calls and appointments was also identified as important. Preferences ranged from very specific hours when a participant could be contacted, to a more flexible approach with a preferred time of the day:

> "I don't work, so it's okay. I am free in the day. Just not early and not late but I think we met at 12 or something like that." (Participant 11, Control, Completer)

> "As long as they don't call very late or very early, it's okay." (Participant 19, Intervention, Completer)

A particular need described as important to anxious participants was having a support person present during the assessment. As the quote below illustrates this was possible to arrange while ensuring confidentiality of the content of the meeting:

> "I remember it being okay. She [researcher] was nice and we sat in my mom's living room and my mom stayed in the kitchen because she wasn't supposed to be listening but I wanted her to be there." (Participant 16, Intervention, Completer)

However, having a third party present at the assessment was not a common request and in practice would require special arrangements given the confidential nature of assessments. Therefore, it may not always be possible to accommodate all patient preferences.

7.6.7 Challenges of gaining trial participants' perspective and possible alternatives; lessons learned

As described in Section 7.5.2, this study was affected by the delay in obtaining ethics approval. This directly influenced the quality and depth of data that participants were able to share in interviews. However, the study also provided an opportunity to make observations (which were recorded as field notes to supplement interview data) and learn about the challenges of conducting retrospective qualitative research.

The nature of this study with the main focus on a different research study presented a challenge to a lot of interviewees. Although effort was made to ensure participants' understanding of the purpose of this qualitative study, this 'research on research' meant that participants struggled to distinguish between the candidate and the trial team.

Many patients who were asked about the reasons for missing appointments were either unable to recall the reasons or did not elaborate and presented it as a fact that did not require explaining, despite the prompts. These issues with exploring some topics in the interviews could be attributed to a number of reasons: the time gap between recruitment to the EPOS trial and the qualitative interview, memory affected by medication, other side effects of medication, and experiencing negative symptoms. Some patients were visibly nervous or experiencing side effects of medication. As an interviewer the candidate had to observe their non-verbal behaviour and carefully judge how much they could be prompted about the same issue before moving on to the next question. Previous experience of conducting research with patients with severe mental illness that the candidate gained prior to undertaking the doctoral studies proved useful when dealing with difficult interviews.

Another observation, which mirrors the findings of the study, is the motivation to take part in the interviews. When invited to the study patients were asking directly if they were going to receive money, like in the EPOS trial. Many asked about reimbursement during the interview, especially as they were getting impatient towards the end of the meeting. This opens up a question about using incentives in an ethical and effective way, which will be considered in the final chapter.

7.7 Discussion

7.7.1 Main findings

This study has identified a number of facilitators and barriers to retention reported by former participants in the EPOS trial. Figure 7.2 below presents an overview of those factors. A proportion of those were specific to people with schizophrenia. The decision to participate involved a consideration of risk and potential benefit of participation. The involvement of health professionals in introducing prospective participants to the trial and provision of their support was an important factor influencing participants' decisions and experiences related to the trial. Researchers had an important role in addressing patients' needs and preferences, sometimes with clinicians' support, which were related to the symptoms they were experiencing.

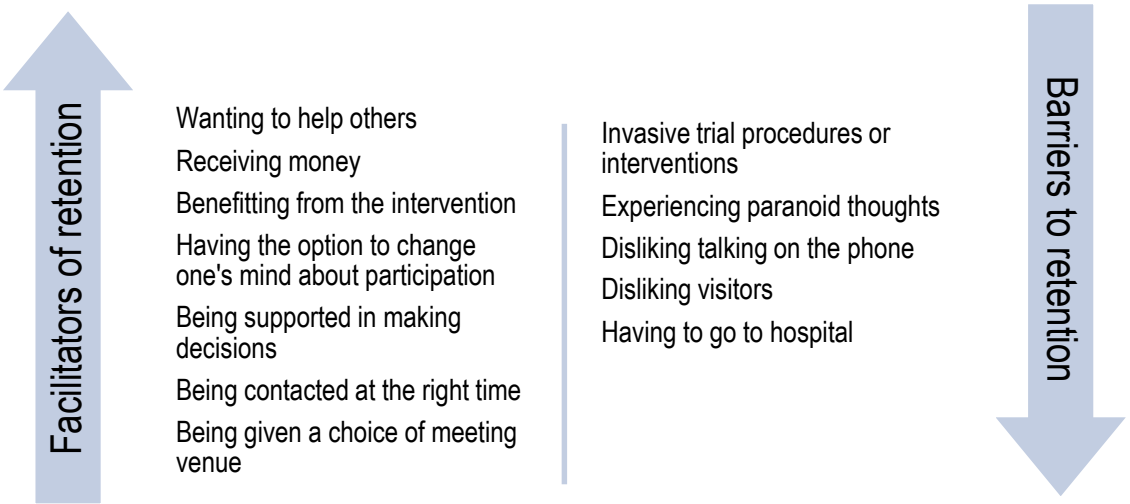


Figure 7.2 Barriers and facilitators of retention

7.7.2 Strengths and limitations

This study contributes to the limited understanding of decision-making about trial participation by people with schizophrenia. The interviews were conducted face-to-face to allow for in-depth exploration of participants' views and experiences. The sample included a mixture of participants who completed all follow-up assessments and those who missed at least one. However, the candidate was unable to approach

those who dropped out of the EPOS trial, which could have provided further understanding into the challenges of retention in clinical trials, especially around the factors directly contributing to their decision to withdraw.

The main limitation of the study stems from its positioning in time, which affected participants' recall of their experiences and the breadth of data they were able to provide. This logistical issue highlights the importance of building qualitative evaluations into trials from their outset.

In addition the study involved former participants of a single trial and one that experienced high retention rates, therefore the findings may not generalise to other trials and other disease areas. These findings are most likely to be applicable to trials involving people with psychotic disorders evaluating complex interventions.

7.7.3 Interpretation and comparison with the literature

The recognition of the important role of health professionals in recruitment to trials corresponds with the literature on facilitating research in mental health services. Gatekeeping has been shown to be particularly pronounced in practices dealing with vulnerable populations, such as patients with schizophrenia (Anderson and Mukherjee 2007, Howard *et al.* 2009, Patterson *et al.* 2010, Bucci *et al.* 2015, Hughes-Morley *et al.* 2015). As discussed in the previous chapter discussing trial researchers' perspectives, gatekeeping can be explained by the perceived need to protect patients from the research burden and to minimise any risk of harm to both the patient and the researcher. Previous studies have shown that clinical gatekeepers struggle with engaging their patients in research due to competing demands and limited resources (Beckett *et al.* 2011, Borschmann *et al.* 2014). Some suggestions on how to improve clinicians' involvement have included engagement of senior investigators and integrating referrals to research into routine practice, accounting for the additional cost of involving 'hard to reach' populations, educating health professionals about clinical trials, and streamlining regulatory processes (Probstfield and Frye 2011, Borschmann *et al.* 2014).

Less is known about clinicians' involvement in retaining participants in longitudinal research, especially trials. However, the findings of this qualitative study suggest that their role does not end at recruitment and may be particularly important for those

individuals who are less involved in making decisions about their mental health care, for example trying out a new treatment. This passivity observed in decision-making about mental health care was mirrored in the patients' approach to decisions about trial participation, with reliance on care coordinators and researchers to guide them through the process. This need for continued support is consistent with the findings discussed in the previous chapter, where trial researchers emphasised the importance of liaising with care coordinators throughout the duration of the trial and especially when participants were at risk of being lost to follow-up. Such risk has been shown to be associated with social and emotional withdrawal in patients with schizophrenia, making these individuals more likely to withdraw over the course of the trial (Thompson *et al.* 2011).

However, calling for the need for health professionals' support with research following recruitment should be issued with caution and needs to recognise the existing tension between their clinical obligations and the additional pressure created by research activity. In a professional culture construed as "not conducive to research" (Borschmann et al., 2014, p.1), adding provision of support with trial retention to the already heavy load of competing priorities and limited resources, may not be welcome without changes to the current interplay between clinical practice and research. Integration of clinical practice and research has been one of the tenets of the evidence-based practice approach to mental health care (Hershenberg *et al.* 2012, Teachman *et al.* 2012) and beyond (Tsang 2000), with recognition of room for improvement.

Research has shown that individuals with schizophrenia who participate in clinical trials are motivated by various factors, most significantly personal benefit and altruism (Roberts *et al.* 2000, Chong *et al.* 2009). However, the relative influence of these factors is unknown (Grant *et al.* 2009). Participants in the present study identified both personal benefit and altruism as motivating factors, often combined. Their importance varied across participants, emphasising the need to appeal to individual circumstances. The role of these factors at each follow-up assessment has not been studied and so it is not known whether the factors identified as important when entering a study remain the same throughout its duration. This study offers some insight into what may act as motivation following recruitment, although its retrospective nature does not allow for making any firm conclusions. Money seemed to be the most impactful incentive that encouraged retention in the EPOS trial. This may however be due to its direct and tangible nature and does not exclude altruism as a motivator to remain in a study.

Another factor directly affecting participants' willingness to complete follow-up assessments was seeing them as a meaningful activity and an alternative to not doing much. This however was also associated with receiving payment for participation.

Another set of factors directly affecting study retention was the extent to which participants' needs and preferences were met. These were often related to specific symptoms or side effects of medication, which dictated the preferred time of the day, mode of communication, the need for reminders, and the place of appointments. These findings correspond to the previous qualitative study (Chapter 6) showing the importance of trial researchers' flexibility and appreciation of the particular needs of participants. This highlights the need for researchers to understand the possible presentations of schizophrenia as well as to seek out the preferences of each individual and to try to meet them. Adopting such a participant-centred approach to retention is in line with the previously discussed (see Chapter 2) Ecological Theory of Research Participation, advocating consideration of situation-specific factors affecting participation (Marcellus 2004).

7.8 Conclusion

This chapter presented and discussed findings from a qualitative study eliciting perspectives of former trial participants regarding their decisions and experiences of being retained in a trial evaluating a complex intervention. Despite logistical challenges, which had negative impact on the breadth of data, the study identified themes around the motivations to engage in research, the barriers and facilitators of retention, the importance of meeting the participants' needs and preferences, and the level of engagement in participation decision-making. The implications of these findings will be discussed in the subsequent and final chapter.

Chapter 8
Final discussion and conclusions

8.1 Chapter overview

The purpose of this final chapter is to examine the implications of the findings presented in the previous four chapters, to consider the contribution they make to the current literature and to propose future directions for trial practice and research on participant retention.

The chapter will begin by returning to the overall aims of the thesis and the objectives of the individual chapters. Findings from the four studies will be revisited before discussing them in the context of the wider literature. Consideration will be given to the methodological strengths and limitations of the thesis, with reflection on the pragmatic challenges of conducting the research. The contribution made by research presented in this thesis will be discussed before reflecting on the implications of the findings for retention practice in RCTs and making recommendations for future trials and methodological research.

8.2 Summary of thesis objectives

The main aim of this thesis was to improve the current understanding of the retention of people with schizophrenia in trials evaluating complex interventions. This included identifying the reported attrition rates and examining the factors affecting them. The doctoral candidate also explored both the issues created by poor retention and the ways in which retention is managed in trial settings from the perspective of both trial researchers and patients with schizophrenia.

In the first empirical part of this thesis (Chapters 4 and 5) the objective was to explore the rates of engaging patients with schizophrenia in RCTs and to identify patient and

study characteristics that could predict the decision to remain involved or to drop out from a trial. As identified in the literature, engaging patients with schizophrenia in both long-term psychiatric treatment and clinical research can be problematic (Cramer and Rosenheck 1998, Wahlbeck *et al.* 2001, Nose *et al.* 2003, Lecomte *et al.* 2008, Lecomte, Leclerc, and Wykes 2012). This phenomenon has been reported mainly in trials evaluating pharmacological treatments (Cramer and Rosenheck 1998, Wahlbeck *et al.* 2001, Martin *et al.* 2006, Ghio *et al.* 2011), with very little literature exploring this issue in trials testing non-pharmacological interventions for psychotic disorders (Villeneuve *et al.* 2010). Two quantitative studies were conducted as part of this doctoral research to achieve these objectives. In a systematic review and meta-analysis reported in Chapter 4, the reported dropout rates from both study and intervention were calculated as well as patient- and study-level variables were examined as potential predictors of attrition. In Chapter 5, the objective was to further explore the impact of patient characteristics on study retention. This analysis drew on individual patient data from a sample of relevant trials and allowed for establishing the feasibility of employing the IPD-MA method in a systematic way and on a larger scale.

The second part of the thesis drew on qualitative methodology to explore the perspectives of both trial staff and former trial participants on the continued involvement throughout the RCT process. The objective of Chapter 6 was to investigate the trial practices and strategies concerned with maximising retention of people with schizophrenia in follow-up assessments and complex interventions. A number of effective retention strategies have been identified in the literature (Robinson *et al.* 2007, Leathem *et al.* 2009, Zweben *et al.* 2009, Brueton *et al.* 2013, Buben 2013, Hartlieb *et al.* 2015) but it has not previously been established whether those strategies are effective when working with patients with schizophrenia or if any specific actions are required to facilitate better retention of this population in RCTs. In Chapter 7 the focus was on exploring the perspectives of former trial participants in the context of their experience of being involved in the EPOS trial, including making decisions about their continued involvement in the and their experience of the trial researchers' efforts to prevent them from dropping out from the trial. While studies exploring trial participant perspectives on their involvement in trials have been conducted in other populations, such as individuals infected with the Human Immunodeficiency Virus, the elderly population with chronic neck pain, or ethnic minority participants (Hussain-Gambles 2004, Wendler *et al.* 2008, Holmberg *et al.* 2014); psychotic disorders presented a fairly

uncharted area and one that has been identified as particularly challenging to promote retention in (Brueton *et al.* 2013).

8.3 Summary of findings and comparison to the literature

Chapters 4, 5, 6 and 7 presented and discussed the findings of each individual study within the context of the wider literature. This section provides a summary of findings organised according to the four research questions the thesis aimed to address and compares the overall findings to the wider literature.

Research Question 1: What is the degree of attrition occurring in trials evaluating complex interventions for schizophrenia?

The background literature reviewed in Chapter 2 discussed the importance of developing new treatments for schizophrenia and merging the gap between the rich evidence generated for pharmacological treatments and the currently less developed evidence-base for complex interventions. The most substantial progress in minimising this gap has come from a number of RCTs testing new non-pharmacological interventions for schizophrenia. However, the success and quality of these studies depends on the effectiveness of two key processes: recruitment and retention of participants. While recruitment has received considerable attention in the literature, retention is a lesser-explored issue out of the two.

At the same time, some evidence suggests that retention of patients with schizophrenia is particularly difficult and challenges have been observed in both clinical practice and research context (Cramer and Rosenheck 1998, Lecomte *et al.* 2008, Lecomte, Leclerc, Wykes, *et al.* 2012, Brueton *et al.* 2013). However, this argument has been built largely on evidence from trials of antipsychotic medication which have attracted attrition ranging from 33% to 48.9% (Wahlbeck *et al.* 2001, Kemmler *et al.* 2005). Furthermore, a systematic review of studies estimating adherence to treatment programmes for people with psychosis offered outside of trial settings revealed that 24.3% individuals did not keep appointments as scheduled, compared to 29.74% failing to take drugs as prescribed (Nose *et al.* 2003). This evidence, together with the 14% intervention dropout rate found in the current study, non-adherence to psychiatric treatment, either

pharmacological or non-pharmacological, offered outside of trial settings can be higher than non-adherence to complex interventions provided in a trial context.

Nonetheless, only one attempt has been previously made to estimate the actual rates of attrition in interventions evaluated in RCTs that did not involve taking medication and this was limited to psychosocial treatment only (Villeneuve *et al.* 2010). Given the existing body of evidence, it was not clear what the retention rates were in trials evaluating all types of complex interventions for schizophrenia, ranging from talking therapies to technology-based interventions and new service models. Estimating retention rates in such trials was needed in order to decide if low retention was in fact a pertinent issue and if it needed to be addressed in practice.

The most robust way of answering this research question was by conducting a systematic review of the existing literature and, as the consecutive step, conducting a meta-analysis drawing on the data extracted from trial publications. This study made a noteworthy distinction between retention observed at the study and the intervention level; the importance of which was further emphasised by trial researchers in the subsequent qualitative study discussed in Chapter 6.

The meta-analysis of proportions showed that the rates of dropout from study are higher than from experimental intervention; 20% and 14% respectively. Overall study dropout was on the cusp of approaching the level previously defined as causing risk of bias and potential threat to validity (Polit and Hungler 1995, Sackett *et al.* 2000, Schulz and Grimes 2002). However, most trials identified in the systematic review achieved rates lower than the 20% and thus were not at high risk. In addition dropout from intervention was fairly low, with levels corresponding to the ones previously reported in psychosocial interventions for schizophrenia by Villeneuve *et al.* (2010).

As expected, the attrition rates were lower than those reported in pharmacological trials of antipsychotics (Wahlbeck *et al.* 2001, Martin *et al.* 2006, Rabinowitz *et al.* 2009) and of those found in outpatient psychiatric services (Nose *et al.* 2003). Some of the possible reasons for the difference in attrition rates between pharmacological and non-pharmacological trials may be fewer side effects associated with receiving complex interventions or embedding this type of treatment within psychiatric services. On the other hand, attending therapy sessions often requires additional effort on behalf of patients, such as travelling to sessions and being in a group setting, and could potentially increase the risk of dropout.

When compared to treatment dropout rates found in systematic studies of trials of non-pharmacological interventions for depression, which have ranged from 15.3% to 34.9%

(van Ballegooijen *et al.* 2014, Cooper and Conklin 2015, Stubbs *et al.* 2016), dropout from complex interventions for schizophrenia is similar. Similarly, study attrition is no higher than that reported for RCTs of non-pharmacological interventions for depression and for borderline personality disorder, reported as 19.9% and 25% respectively (Barnicot *et al.* 2011, Cooper and Conklin 2015).

Furthermore, when considering dropout from complex interventions evaluated in trials with psychiatric treatment provided in the community, it is important to note that it is not possible to control and standardise the latter as much as it can be achieved in a trial context, nor should this be the intention. As a result, researchers have struggled to estimate global attrition rates in outpatient psychiatric services, with reports varying from 20 to 60% (Bueno Heredia *et al.* 2001). When compared to these reports, the findings of the systematic review and meta-analysis suggest that retention of patients with schizophrenia in experimental non-pharmacological treatment is better than in community mental health services. Exploring the reasons for this difference was outside of the scope of this thesis.

Overall, the retention rates reported for trials evaluating complex interventions for schizophrenia do not cause immediate concern about the ability to retain participants with psychosis in RCTs and the consequential validity and success of such studies; however they indicate some room for improvement, especially in ensuring completion of follow-up assessments.

Research Question 2: What is the retention of patients with schizophrenia in complex intervention RCTs influenced by?

Following on from calculating the attrition rates in RCTs evaluating non-pharmacological interventions for schizophrenia, this thesis set out to investigate what the differences in the reported rates could be attributed to (i.e. why did some studies have problematic attrition rates while others managed to retain majority of participants). This question was addressed in all four studies reported in Chapters 4, 5, 6 and 7 by adopting both quantitative and qualitative methods, thus allowing for an in-depth investigation of the issue.

The first analysis presented in Chapter 4 followed on directly from the systematic review and meta-analysis of attrition rates, and drew on data reported at study-level for

43 trials. A random-effects meta-regression explored the effect of both sample characteristics (i.e. age, gender, illness duration) and study features (i.e. location, setting, intervention delivery method, duration of the intervention, study duration, number of intervention sessions, study quality). The results showed that dropout from experimental interventions significantly increased as the number of intervention sessions increased. This could be interpreted as a high number of sessions presenting a challenge to trial participants, who may be overwhelmed by the commitment they made when recruited to the study. Given the typical presentation of schizophrenia described in the literature (Roberts 1998, Lecomte *et al.* 2008, Lecomte, Leclerc, Wykes, *et al.* 2012) and the challenges reported by both trial researcher and participants in Chapters 6 and 7, trial participants with this diagnosis may particularly struggle with completing treatment if they are expected to attend a high number of appointments. Alternatively, being offered many sessions may affect participants' perception of the detrimental effect of missing individual sessions. An additional aspect that should be taken into account when interpreting this finding is the intensity of the treatment, i.e. the number of sessions provided over a specified amount of time. This was not tested in the analysis but could also have influence on completion rates.

None of the other sample characteristics that could be extracted from the publications had a significant effect on the dropout rates at either study- or intervention-level. This result was at odds with the previous studies agreeing on two common factors - age and gender – predicting adherence to treatment for schizophrenia (Nose *et al.* 2003, Reneses *et al.* 2009, Villeneuve *et al.* 2010). However, the reported direction of effect in case of age differed depending on the study setting, with older participants more likely to drop out of treatment provided within a trial setting (Villeneuve *et al.* 2010) and younger ones out of treatment in a community setting (Nose *et al.* 2003, Reneses *et al.* 2009).

In addition, the lack of more significant associations may be attributed to the absence of clear predictors of attrition or to the inconsistent and sometimes poor reporting of information about the study and the sample. An example of the type of data that could not be extracted from publications was information about the incentives offered to participants for most of the identified trials. Thus, it is possible that incentives are among the factors that have an effect on attrition but could not be included in the analysis because of inconsistent or poor reporting in trial publications. This obstacle identified in the systematic review and meta-analysis provides further support for the efforts to improve reporting quality in trial publications, especially those evaluating

social and psychological interventions (Dumville *et al.* 2006, Grant *et al.* 2013).

The second study (Chapter 5) addressing this research question was able to draw on individual patient level data in examining the effect of participant socio-demographic characteristics on study retention in an IPD-MA. For this purpose a meta-regression of patient and study characteristics was conducted on a sample of five trials with data from 2,006 patients. This analysis tested the association between specific factors and dropout. Finding a significant relationship would suggest that studies or participants sharing that particular characteristic were more prone to experiencing attrition. In practical terms, identifying such characteristics could allow for either making changes to the study procedures or tailoring the retention efforts to minimise the chances of losing patients at a high risk of dropping out, as long as the strategies would not affect or interfere with the study outcome. Such a move from a paternalistic relationship with participants towards a participant-centred approach has been recommended in the literature (Gross and Fogg 2001, Marcellus 2004).

This study revisited the issue of inconsistent definitions of retention and attrition. While the systematic review distinguished between the study and the intervention retention, the IPD-MA was able to extract data on study retention, a lesser-studied phenomenon, and to explore the definitions within this level of enquiry. Given the multiple follow-up assessments in RCTs, dropout could be reported for any of those time points. The most common choices in trial reports, especially those missing a CONSORT diagram, are either the final follow-up assessment or the pre-defined point of assessment of the primary outcome. However, Hewitt *et al.* (2010) argued for looking into the penultimate follow-up as a reference point for the final follow-up. For the purposes of this thesis, the IPD-MA analysed both the penultimate and the final follow-up completion to see if the same participants were likely to be retained at different stages of the trial. The results showed that retention was higher at the final follow-up assessment, in line with Hewitt *et al.'s* (2010) argument. In addition, out of all tested variables, the arm allocation almost reached statistical significance, pointing to a higher likelihood of those in the experimental intervention to complete the final follow-up compared to those in the control arm. Potential explanations include satisfaction with allocation to the active arm and thus higher likelihood of completing the final follow-up, increased efforts of researchers at the final follow-up, and participants in the active arm being more engaged in trial activities than those in the control arm resulting affecting completion of the final assessment. However, none of these suggested interpretations (even the researcher bias given blinding in most trials) explains the

presence of the effect only in the final assessment and not the penultimate one.

These findings confirm the challenge of predicting retention based on patient characteristics previously identified in the systematic review in Chapter 4. The doctoral candidate was not able to ascertain whether the lack of significant effects is due to a true lack of effect, as the power of the study was limited and not all variables of interest could be extracted. At the same time, this lack of clear predictors points to the importance of making maximal effort to retain participants despite their socio-demographic profile or a specific characteristic that is known to put them at risk of dropping out. However, in line with Newington and Metcalfe's (2014, p.2) argument, "recruitment and retention strategies need to be relevant to the target population and the research methodology used, and therefore the optimum strategy is likely to vary." Thus, a balance needs to be struck between making retention strategies relevant to the clinical population and tailoring them to individuals. This however is at odds with the argument made by and requires more investigation.

Employing a qualitative approach to address the second research question enabled exploration of the possible factors affecting dropout in more depth, including those difficult to quantify and report in trial publications. In line with the findings from the two quantitative studies, the findings discussed in Chapter 6 showed a lack of consensus on the factors predicting dropout. Age and socio-economic status especially evoked opposing opinions in terms of their effect on retention in trials, a pattern similar to that found in quantitative studies conducted prior to this doctoral research (Davis *et al.* 2002, Nose *et al.* 2003). The factors identified in this thesis as having a positive effect on retention included insight about own illness, understanding of trial procedures, and having an interest in the intervention being evaluated. These were similar to the previously reported predictors of non-adherence to community treatment for schizophrenia, such as poor insight of illness and low social functioning reported by Nose *et al.* (2003).

Interviews with the former EPOS trial participants in Chapter 7 allowed for an exploration of factors that affected their decisions to first enroll and later to attend intervention sessions and follow-up assessments. The key facilitators of retention that emerged from the data included the desire to help others, benefitting from the intervention, receiving money for participation, being supported by a care coordinator throughout the process, as well as being offered some flexibility in terms of completing research assessments. Moreover, the study also identified a number of factors having potentially negative effect on retention, including: interventions involving invasive or

inpatient procedures, being expected to use the phone or to receive visitors, and experiencing paranoid thoughts.

Thus, in summary, the second research question can be answered as follows: no single participant characteristic can determine the likelihood of being retained or dropping out, but the more intervention sessions that are offered to the participants randomised to the active arm, the higher the likelihood of premature termination of the experimental intervention. There are a number of factors that can influence participants' decisions about their involvement at each stage of the trial, either as barriers or facilitators. Some of the barriers are specific to individuals with schizophrenia as they are associated with the psychotic symptoms, others are likely to be observed in any population. Supporting participants with overcoming barriers they experience and remaining involved in trials may require a mixture of general and individualised strategies applied by trial professionals.

Research Question 3: How can patients with schizophrenia be retained in trials?

Chapters 4 and 5 employed quantitative methods to calculate the rates of retention and to investigate *what* factors were associated with those rates. The objective of this thesis was also to explore *how* these retention rates are achieved in trial practice. Qualitative methods were thus chosen to explore trial practices that aim to maximise retention as well as to identify the particular challenges of engaging people with schizophrenia in RCTs.

In-depth interviews with trial researchers from across the UK allowed for identifying a number of factors influencing retention and the ways in which trial researchers dealt with some of these factors. The findings from this study link in with the wider trial methodology literature, in particular the Ecological Model of Research Participation proposed by Marcellus (2004). The categories of factors identified in the study matched these in the ecological model and pointed to the multiple layers within which different 'agents' made key decisions or took actions and where interactions took place, all of which affected retention. These categories of factors included: 1) participant factors; 2) researcher factors; 3) study factors; and 4) context factors. Depicting the trial as a multilevel system allowed for identifying barriers and facilitators occurring at each level and associating them with a particular agent, the relationship between them, and the specific trial process or procedure.

In addition to identifying a system of factors influencing engagement in a trial, the findings explored issues common to all RCTs of non-pharmacological interventions and those specific to schizophrenia research. In the theme 'The complexity of involving patients with schizophrenia in trial' (Section 6.5.3, p. 114) trial researchers recognised the impact of psychosis symptoms and life circumstances often resulting from those symptoms on the participants' level of engagement in both interventions and research assessments. This mirrored the literature on the presentation of psychotic disorders introduced in Chapter 2 (Liddle 1987, Holmberg and Kane 1999, Wiersma *et al.* 2000, Saha *et al.* 2005, Morgan *et al.* 2014) and emphasised the importance of trial researchers' awareness of the challenges experienced by patients with schizophrenia as well as the need for appropriate training of researchers working with this population. The different levels of dropout described in the theme 'Mechanisms of attrition in complex intervention trials' (Section 6.5.4, p. 120) provided further support for exploring this issue in the context of treatment adherence and completion of follow-up assessments, an approach taken in the systematic review and meta-analysis (Chapter 4). The practices and strategies identified in section 6.5.6 illustrated a range of actions at trial researchers' disposal that could be taken to address some of the influential factors discussed in section 6.5.5. Figure 6.2 on page 150 has provided an overview of both categories, organised by the category of factors (i.e. participant, researcher, study, and context). Although researchers were the key link between the participant and the trial, they operated within the bounds of ethical conduct, study procedures and resources, and the wider organisational and geographical context.

The findings showed that when it comes to dealing with barriers to retention, the systems and procedures put in place need to allow for a balance between maintaining ethical, logistical and pragmatic standards and allowing for flexibility in order to enable participants to remain involved over the course of a trial. Some practices, such as ensuring access to medical records, that could enable tracking participants at risk of being lost to follow-up were put in place prior to the trial, while others required ad-hoc decisions about the use of resources, for example to travel to a participant or to allow patients to come back to an intervention after a break. Adaptability was a catalyst for a participant-centred approach, in which meeting the needs and preferences of the participant were central to retaining them in a study. The key building block for adaptability was a good researcher-participant relationship achieved through rapport building, continuity of the researcher, an understanding of participants' needs and

preferences, and study resources enabling researcher flexibility. The findings of the qualitative study with trial participants provided further support for the impact of good rapport on their experience of the trial and the likelihood of remaining involved. In Chapter 7 patients discussed the impact of personality characteristics of the EPOS trial researchers on their overall enjoyment and satisfaction with trial participation. Liaison between the researcher and the clinician was another type of a relationship important for achieving good retention. This finding echoes the wider literature, where involving clinicians in research and achieving their support has been described as an important factor, especially for recruitment (Bartlett and Canvin 2003, Patterson *et al.* 2011, Fletcher *et al.* 2012, Joseph *et al.* 2016). The present study adds weight to the importance of the continued liaison between clinicians and researchers beyond the recruitment phase.

The findings of the two qualitative studies combined with the findings of the two quantitative studies suggest that no single strategy will guarantee high retention rates and emphasised the importance of tailoring approaches to individuals, with awareness of the barriers to retention experienced by some people with schizophrenia, such as experiencing paranoid thoughts and disliking talking on the phone. In addition, there is no 'profile' of a stereotypical participant at risk of dropping out, contrary to what has been previously suggested in the literature (Davis *et al.* 2002, Nose *et al.* 2003, Brueton *et al.* 2014). This could be due to the diversity of the study population, despite them sharing a diagnosis falling under the same umbrella of psychotic disorders. Thus, the argument for tailoring strategies seems to apply at both study population and individual participant level, with consideration of specific and general barriers and facilitators to retention (Marcellus 2004, Newington and Metcalfe 2014).

Research Question 4: What are the experiences of patients with schizophrenia in the context of retention in trials?

Involvement of trial participants in order to investigate their experiences and perspectives and to give them a voice as decision-makers was a key consideration and also the biggest challenge in the context of this doctoral research. In the last study semi-structured qualitative interviews were conducted with 20 patients who had taken part in the EPOS trial.

Findings indicated that patients depended on the support from their clinicians, especially in making decisions about their involvement in the EPOS trial, with few also involving their family members. The data revealed that most participants had a passive approach to both their mental health care and participation in the trial, a finding which emphasised the importance of support from clinicians and researchers for those enrolling into RCTs.

The identified motivations for taking part and remaining involved in trials echo the evidence discussing the importance of both personal benefit and altruism in research participation (Roberts *et al.* 2000, Chong *et al.* 2009). Money in particular was discussed as a preferred incentive, with helping others and benefitting from the intervention identified as secondary motivators. There are a number of things to consider, however, when making decisions about the types of incentives for trial participants. Some researchers have expressed concerns about using monetary incentives and key among those concerns is that such efforts might be coercive or be an undue inducement for patients (Grady 2005). Although ethics committees and funders may have a preference for a specific reimbursement strategy, the use of incentives remain a grey area (Grant *et al.* 2010) and it is ultimately the patients and researchers who should define what is appropriate, and involving individuals with relevant lived experience in making decisions about incentives can provide relevant guidance.

The finding that emerged from both qualitative studies was the importance of having one's needs and preferences understood and met. For participants this made their participation easier and less burdensome, and thus prevented them from dropping out. The onus of supporting patients with participating in trials is on both the researchers and clinicians involved in the process. This finding emphasises the importance of liaison between those two professional groups and corresponds to the qualitative study with trial researchers discussed in Chapter 6.

8.4 Key strengths and limitations

This section will examine the methodological, practical and conceptual strengths and limitations of the thesis as a whole. These should be considered when interpreting the findings of this doctoral research. This is in addition to the critical assessment of strengths and limitations included in each chapter discussing findings from the four studies.

8.4.1 Study design

One of the strengths of this thesis is the use of mixed methods to estimate the rates of retention and to explore the patterns and predictors of this phenomenon. The strengths and limitations of mixed methods research have been discussed in Chapter 3. This approach to research allows for gaining both depth and breadth of understanding by exploring the issues from relevant vantage points and by using the most appropriate method or technique for the research question under study (Teddlie and Tashakkori 2009). In case of this thesis, it was important to first estimate the magnitude of the attrition in non-pharmacological trials for schizophrenia in a numerical manner before identifying factors influencing this phenomenon and the possible ways of moderating them in a combination of numerical and qualitative approaches.

Strengths of the quantitative work presented in Chapters 3 and 4 included the systematic literature search in the former and the use of individual patient data in the latter. Systematic literature reviews with meta-analyses represent one of the most rigorous analyses of current evidence (Elamin and Montori 2012). Traditionally, such analyses focus on outcome data from RCTs to answer questions about the effectiveness of treatments. This study took a novel angle on this method by studying the non-clinical outcome of involvement in trials. The IPD-MA comprised another novel element of the thesis as this type of analysis is only gaining popularity and has not been applied much in the mental health context. This was the first study to examine the relationship between study and participant factors on the retention at both intervention- and study-level. In addition, the use of two time points in the IPD-MA enabled the comparison between retention at the penultimate follow-up assessment

and the final one. This adds to the understanding of the patterns of retention in non-pharmacological trials for schizophrenia.

In addition to the use of systematic and novel quantitative methodologies, this thesis employed a qualitative approach to explore the perspectives of both trial researchers and patients on retention. A number of measures were taken to ensure the reliability and validity of the qualitative analyses. Attention was paid to representing participants who completed all research assessments and those whose involvement was more erratic. In the study involving trial researchers, care was taken to represent different roles within a traditional trial team and to interview staff from different research institutions.

8.4.2 Interdisciplinary approach

This doctoral study was funded by the Life Sciences Initiative with the aim of tackling a research question from multidisciplinary viewpoints (Life Sciences Initiative 2014). Consequently, in addition to methodological and data sources triangulation, this thesis also involved triangulation of disciplinary perspectives (Denzin 1978, Patton 1999). Combining multiple theories and epistemological perspectives in examining and interpreting data allowed for gaining a better understanding of retention as a phenomenon. This was enabled by the multidisciplinary makeup of the candidate's supervisory team and colleagues at the Unit for Social and Community Psychiatry combining social psychiatry, psychology and human geography perspectives.

Both the methods and the emerging findings were presented throughout the duration of the research process to a multidisciplinary team of researchers at the Unit for Social and Community Psychiatry and at relevant seminars and conferences. This yielded valuable feedback and advice on the research plan and analysis; for example, conducting a subgroup analysis in the meta-analysis following the systematic review.

One way in which the interdisciplinary approach of this thesis could have been strengthened would be by involving people with relevant lived experience in the study design and interpretation of findings. While it is important to acknowledge this as a weakness, this doctoral study did not have access to sufficient resources to engage in meaningful public and patient involvement activities. The involvement of patients with schizophrenia, especially those with experience of participating in research, could have

helped with planning the study, designing materials and analysing the findings. Any future research endeavours in this subject would benefit from patient involvement.

8.4.3 Scope of the systematic review

The systematic review needed to be defined by a specific research question and resources available. Given the number of trial publications that could be identified in a systematic literature search, it was important to minimise the heterogeneity of the results. One way of achieving this was to include trials of a specific size. Consequently, a decision was made to include only trials with a sample size of at least 100 participants. In addition, it was thought that trials of interventions involving a family member or a support person would involve a different decision-making process about patient's involvement in an RCT and such studies were therefore excluded. This limited the scope of the review and reduced its generalisability to trials with a similar profile. As a consequence, the findings may not translate to trials excluded from the systematic review, for example RCTs of family interventions for people with schizophrenia.

8.4.4 Quantitative analyses

All quantitative analyses drew on data from existing studies and pooled them in meta-analyses. As a consequence, the scope of the analyses was limited by the quality and type of the data available in publications or supplied directly by study authors. For example, information about non-adherence to interventions required for a meta-analysis in Chapter 4 was reported in 34 out of 49 papers identified in the systematic literature search.

In addition, the IPD-MA from Chapter 5 relied on the datasets available to the candidate, resulting in a convenience sample. While conducting a full IPD-MA of trials identified in a systematic literature search would have improved the power of the analysis and the generalisability of the findings, the process would have required resources in excess of what was available in this doctoral study.

8.4.5 Recall bias and data quality

The main limitation of the qualitative study with trial participants discussed in Chapter 6 is linked to its dependence on the EPOS trial and the associated requirement to gain a separate ethics approval to recruit its former participants. The delay in receiving the approval inevitably affected the quality of data collected in interviews with patients. The majority of interviewees struggled to recall details about their participation and the candidate had to ensure, as much as possible, they were reporting their actual experiences rather than discussing their decisions about participation hypothetically.

8.4.6 Reporter bias

It is possible that the qualitative data collected from trial researchers were subject to reporter bias, where the interviewees may have been inclined to share practices that were more acceptable and to conceal those which would cause controversy. All participants were reminded about the confidentiality of the data and were encouraged to be honest. Given that some potentially controversial issues were discussed, such as coercing patients to participate or excluding homeless individuals, this bias is likely to be minimal.

8.4.7 Diversity of participants

The geographical location of participants involved in both qualitative studies may have played a role in the limited diversity of their accounts and the generalisability of the findings. Almost all trial researchers and therapists who took part in the study reported in Chapter 6 were employed at academic institutions based in urban settings in the UK. There was little representation from researchers working in rural and remote areas, which could be expected to deal with different issues affecting retention and to employ different strategies. Similarly, all patients interviewed in the study discussed in Chapter 7 were recruited through a single study conducted in East London. Although this area is known for its ethnic diversity reflected in the sample characteristics, the experiences of patients from this area may be specific to this context.

8.4.8 Conceptualising retention

A key conceptual consideration was the definition of the phenomenon under study. The inconsistency in the definitions used to describe the continuous involvement of participants in a study or completion of key research activities has been highlighted in the literature (Kane *et al.* 2007) and further confirmed in this thesis. An additional complexity has been introduced in this thesis by the recognition of the multiple levels at which retention can occur: study and intervention. This was an important distinction considered in this thesis, although it was not possible to investigate both levels across all studies; for example, the IPD-MA discussed in Chapter 5 was able to investigate only post-randomisation retention during follow-up due to the lack of data on retention at the intervention level.

As discussed in Section 2.4.5, there are two main models of retention: one focused on the research process (process model) and one built around the factors affecting retention (ecological model). This thesis adopted mainly the ecological model, which enabled identification of the potential sources of attrition and the factors affecting engagement in research. The advantages of applying this model include approaching trial retention as a system comprising multiple levels (participant, research, study, and environment) and exploring the interactions between those levels. As a result, the source of problems with retention can be identified and this can guide developing strategies to address challenges identified at the specific level of the model. However, this approach does not take into account the different phases of a research process and their impact on participants' decisions about their participation. For example, different factors may influence decisions to drop out after being randomised compared to when a participant has completed their first follow-up assessment.

Adopting the process model would have required a different approach to the methods applied in this thesis. The systematic review and meta-analysis (Chapter 4) could have explored the changes in retention rates over time, making comparisons between different time points. This was addressed in the IPD-MA (Chapter 5), which explored the differences in retention rates between the final and the penultimate follow-up assessments. The two qualitative studies (Chapters 6 and 7) were designed to explore the factors affecting retention and the strategies used to minimise dropout. Introducing the process-based model would have involved exploring how trial staff adapt their retention practices depending on the stage of the study and how trial participants make

their decisions throughout the duration of a trial. While this was explored to an extent in the study involving trial staff (Chapter 6), for example by identifying the points in the research process where retention was considered, the main focus of the analysis was on the categories of factors affecting retention. In addition, investigating the impact of the different stages of the research processes on decision-making with former trial participants (Chapter 7) could have presented a number of challenges given the issues with recall observed during the study.

8.5 Contribution to the existing literature

To the candidate's knowledge this thesis was the first study to systematically look into the retention rates in non-pharmacological schizophrenia RCTs using mixed-methods. Previous attempts to study retention of patients with schizophrenia have been limited to pharmacological trials (Wahlbeck *et al.* 2001, Martin *et al.* 2006, Rabinowitz *et al.* 2009), a specific sub-type of non-pharmacological trials (Villeneuve *et al.* 2010) or employed a single method to investigate the dropout rates or their predictors (Nose *et al.* 2003, Thompson *et al.* 2011).

The results obtained in the systematic review and meta-analysis (Chapter 3) demonstrate the attrition rates reported in RCTs evaluating complex interventions for schizophrenia, both overall and for specific types of interventions and single studies. This evidence has been published and can be used by trialists to guide sample size planning in similar studies.

The lack of support for specific prognostic factors, especially those based on participant socio-demographic characteristics, negates the previous evidence proposing profiles of participants who are more likely to drop out of trials (Nose *et al.* 2003, Reneses *et al.* 2009, Villeneuve *et al.* 2010). The lack of clear predictors of retention or attrition suggests the importance of adopting a participant-centred approach, combining scientific rigour with knowledge of the specific study population (i.e. symptomatology, commonly experienced challenges in a trial context) and the needs and preferences of each individual (Gross and Fogg 2001, Marcellus 2004, Gul and Ali 2010).

The methodological challenges encountered in the process of conducting this doctoral research and discussed in this thesis provide further support to the calls for improved

and more consistent reporting of information about participant flow in RCTs using the available tools developed specifically for this purpose (Altman 1996, Moher *et al.* 2001, Dumville *et al.* 2006, Perera *et al.* 2007, Turner *et al.* 2012, Hooper *et al.* 2013, Montgomery *et al.* 2013).

Prior to this thesis there was an absence of evidence about good practice in retaining patients with schizophrenia. This study incorporates the perspectives of trial researchers, therapists and participants to gain insight into trial management practice and decision-making of patients. Gaining multiple viewpoints was instrumental for creating a fuller picture of retention practices as previous literature has shown the differences in reports regarding participation decisions provided by patients and by researchers (Featherstone and Donovan 2002).

Although this thesis did not empirically evaluate the effectiveness of different practices, it provides evidence about the possible strategies to maximise retention in non-pharmacological RCTs involving patients with schizophrenia and other populations and highlights the importance of future research in this area together with the existing gaps and potential challenges.

8.6 Implications

The findings presented in this thesis point to a number of implications for trial design, trial management practice, and provide evidence for further research. The following sections will discuss key implications from the thesis overall and offer recommendations for these areas. Priorities for research questions and the methods best suited to answer those are presented in Box 8.1.

8.6.1 Use of relevant evidence to estimate realistic sample sizes

Evidence about the dropout rates reported in previous studies involving the same population is pivotal in estimations of the required sample size (Noordzij *et al.* 2010), especially as the calculations have been found to be based on arbitrary assumptions (Rutterford *et al.* 2015). Oversampling has been used to account for the expected attrition (Ribisl *et al.* 1996); however this strategy can lead to increased costs and raises

ethical concerns in terms of involving unnecessarily large numbers of patients. To increase the accuracy of the calculations trialists should use evidence from relevant trial publications and available systematic reviews. The systematic review and meta-analysis presented in Chapter 4 has provided such evidence relevant to trials of non-pharmacological interventions for schizophrenia. This thesis showed that trialists working in this context can realistically aim to achieve dropout rates lower than 20% at both the intervention and study level. Participants with schizophrenia should not be associated with a high risk of dropping out of studies or non-pharmacological treatments. This finding could help with achieving more accurate estimations and planning resources adequately in future trials.

8.6.2 Considering the intensity of new interventions

The findings of the meta-analysis discussed in Chapter 4 suggest that completion of experimental interventions can be put at risk by a high number of sessions participants are expected to attend in order to complete a course of treatment. Although the analysis did not estimate the point at which the number of sessions can become problematic, it is an implication to be considered by investigators designing new interventions.

When conceiving new non-pharmacological treatments, trialists should take into account the required number of sessions and the intensity of interventions. The number of sessions required to show a desired effect will be dependent on the type of intervention to be offered; however trialists are advised to consider the risk of dropout in designing new complex interventions and to plan accordingly. If a high number of sessions is required for the success of experimental treatment, a trial may require specific retention strategies to prevent or at least minimise the expected dropout from intervention.

8.6.3 Adopting a flexible and participant-centred approach to retention

This thesis has demonstrated the importance of considering retention at the planning stage of a trial. There is a need for establishing procedures, which will allow for flexibility and adaptability to maximise the retention of participants while complying with ethical standards. The qualitative study discussed in Chapter 6 has provided some

examples of the areas needing flexibility from researchers, such as where follow-up assessments take place and whether patients are allowed to return to an interrupted course of treatment.

Linked to the importance of flexibility and adaptability is adopting an approach that puts the needs and preferences of each participant at the heart of trial researchers' efforts to maximise retention. Such a participant-centred approach, advocated in previous studies (Gross and Fogg 2001, Marcellus 2004), should be built on the foundation of a good understanding of the disease or health condition that can be achieved with appropriate training for researchers and experience of working with the population under study. Researchers need to be educated about the diversity of patients with schizophrenia as well as a typical presentation of the disorder. This can enable them to make appropriate arrangements in order to support participants in an ethical and considerate manner with the aim of maximising their retention in trials.

8.6.4 Use of retention strategies

The thesis has identified retention strategies used in RCTs involving patients with schizophrenia. This evidence suggests that most RCTs use multiple retention enhancing practices, and this is in line with the recommendations in the literature (Davis *et al.* 2002, Robinson *et al.* 2007, Polit and Gillespie 2010). The choice of strategies should be dictated by the sample population and the activities participants are expected to partake in, although this thesis did not find support for tailoring the approach based on specific socio-demographic characteristics. Adjusting retention practices should occur on a case-by-case basis and take into account the needs and preferences of each participant as much as possible. Different types of motivation should also be considered when planning and applying incentives to encourage patients to remain in the study, since this thesis found variability in what participants considered important. Although using personalised enticement may not be possible given ethical and moral constraints, incentives should appeal to a range of individuals with different reasons to take part in a trial.

8.6.5 Strengthening liaison with care coordinators

The findings of this thesis provide further support for the importance of care-coordinators in engaging patients in research reported in previous research (Bartlett and Canvin 2003, Mason *et al.* 2007, Patterson *et al.* 2011). Both qualitative studies have shown that establishing good rapport between researchers and clinical gatekeepers is important for ensuring an ethical and sensitive approach to each participant, as clinicians can facilitate the introduction the study, provide researchers with information about the patient's needs and preferences, help with the efforts to retain individuals in a study, and provide support with participation decision-making for their patients. The two groups of professionals should liaise to identify the needs and preferences of each participant, come up with best ways of supporting them with trial activities, and problem-solve if issues with participation arise. However, relying on clinical staff should be carefully considered as this has implications for their clinical capacity. Changes to the interplay between mental health practice and research are needed to enable the involvement of clinicians in research (Tsang 2000, Hershenberg *et al.* 2012, Teachman *et al.* 2012). This would have direct implications for the engagement of patients in research, facilitating participant retention and improving quality and reliability of studies, which is central to evidence-based medicine.

8.6.6 Need for evaluations of retention strategies

This study has provided evidence about the retention strategies currently utilised in RCTs of complex interventions for schizophrenia, and offers potential ideas for similar future studies. However, testing the effectiveness of these strategies was outside of the scope of this doctoral research and this type of evidence is needed to improve retention practices. One of the most methodologically sound methods, although not without its logistical, ethical and scientific challenges (Fletcher *et al.* 2012), used to develop and/or test specific recruitment and retention interventions is embedding them within a full trial conducted in routine settings (Graffy *et al.* 2010, Treweek *et al.* 2013, Bower *et al.* 2014, Rick *et al.* 2014, Madurasinghe *et al.* 2016). Although the existing literature is limited mainly to embedded recruitment trials, adopting this design to test interventions aimed to improve retention offers a new and exciting area. Examples of such studies, especially testing recruitment interventions, are available in the literature

(for instance Brueton *et al.* 2014, Rick *et al.* 2014) and can serve as models for future research on retention together with evidence from the existing studies on the strategies used in practice, including the current thesis.

8.6.7 Improvements to reporting of trial information

This doctoral study highlighted reporting information relevant to participant flow throughout a trial as a weakness of the current evidence base. The quality of this information bears implications for the possible research investigating retention as it relies on the primary data recorded within individual trials.

Future studies should comply with the current standards of reporting attrition rates outlined in the CONSORT (Altman 1996, Moher *et al.* 2001, Plint *et al.* 2006, Montgomery *et al.* 2013), including making a distinction between dropout from follow-up and treatment non-attendance for complex interventions. In addition, information about factors that may have affected retention rates should be offered, considering the key levels at which influences occur, namely participant, researcher, study, and context.

Standardising the data recorded at the trial level could be problematic; however such efforts have been suggested for outcome measures reported across clinical trials (Clarke 2007). Key steps would involve deciding on the core baseline variables and reporting them consistently across studies. Improved reporting of this information would enable accurate interpretation of the reported attrition rates, could facilitate systematic reviews of evidence, and could lead to further studies of effective retention efforts.

Box 8.1 Priorities for future practice and research on retention

Priority 1: Evaluation of effective retention strategies in specific populations.

Method: Quantify the effects of specific retention strategies and ascertain the applicability to the real world by conducting sufficiently powered trials embedded in host RCTs.

Priority 2: Further research exploring participant-centred trial practices to aid retention.

Method: Qualitative and/or quantitative exploration of the current and potential participant-centred approaches to maximising retention in trials, for example a narrative synthesis of literature, a survey of trial practices, or a qualitative study involving various stakeholders.

Priority 3: Improvements to the quality of reporting recruitment and retention information in trial publications.

Method: Adequate reporting is the responsibility of researchers undertaking trials and appropriate tools are available for the purpose of reporting participant flow and design of interventions. Introducing this as a requirement across all peer-reviewed journals could improve the current quality of information related to recruitment and retention of trial participants.

Priority 4: Improving liaison between researchers and care coordinators.

Method: Training research and clinical staff in ethical and effective retention strategies, with particular focus on the two groups working together to maximise participant retention while monitoring risk.

8.7 Concluding statement

In conclusion, this thesis improved the understanding of current practice regarding retaining participants in trials of non-pharmacological interventions for schizophrenia, including strategies used to enhance retention. This was achieved by establishing the degree of attrition in non-pharmacological RCTs involving patients with schizophrenia, identifying factors influencing the continued engagement in an intervention and study

follow-up assessments, and exploring the ways in which trial professionals maximise retention.

The thesis showed that attrition is a phenomenon that should be anticipated and prevented with the use of appropriate practices and strategies. The study found that the extent to which dropout can be minimised will depend on a number of factors specific to the participant, researcher, study and wider organisational and geographical context. A diagnosis of schizophrenia should not be automatically associated with a high dropout from treatment or study as it is realistic to lose less than 20% in RCTs of complex interventions for schizophrenia.

Although the quantitative analyses did not find support for patient socio-demographic characteristics being associated with retention in this population; the qualitative component of this thesis identified a number of patient- and researcher-reported barriers and facilitators to retention. These factors consist of those specific to schizophrenia as well as those previously reported in other clinical trial populations. Moreover, the study highlighted the importance of using multiple strategies and applying participant-centred approach to retention efforts.

The practices used by trial professionals identified in this thesis show the potential for enhancing retention of patients with schizophrenia in trials through addressing specific barriers and emphasising the factors encouraging continuous engagement.

Further research could employ methods such as nested trials to test the effectiveness of specific retention strategies in the population of patients with schizophrenia and should aim to involve individuals with relevant lived experience in all aspects of the research. More accurate and systematic reporting of the observed loss of participants throughout the duration of trials would enable future research on retention and raise awareness about the issue of attrition.

Development of effective retention strategies should be informed by the factors affecting participants' decision-making and the reasons for attrition observed in practice. This study suggests that these influential aspects are likely to be both general and condition specific.

List of references

Abo-Zaid, G., Sauerbrei, W., and Riley, R.D., 2012. Individual participant data meta-analysis of prognostic factor studies : state of the art? *BMC Medical Research Methodology*, 12 (56), 1–16.

Adams, C., Wilson, P., and Bagnall, A., 2000. Psychosocial interventions for schizophrenia. *Quality in Health Care*, 9, 251–256.

Akobeng, A., 2005. Principles of Evidence Based Medicine. *Archives of Disease in Childhood*, 90 (8), 837–840.

Altman, D.G., 1996. Better reporting of randomised controlled trials: the CONSORT statement. *British Medical Journal*, 313 (7057), 570–1.

Alvidrez, J., 1999. Ethnic variations in mental health attitudes and service use among low-income African American, Latina, and European American young women. *Community Mental Health Journal*, 35 (6), 515–530.

American Psychiatric Association, 2013. *Diagnostic and statistical manual of mental disorders (5th ed.)*. Washington, DC.

Anderson, K.K. and Mukherjee, S.D., 2007. The need for additional safeguards in the informed consent process in schizophrenia research. *Journal of Medical Ethics*, 33 (11), 647–650.

Appelbaum, P. and Grisso, T., 1995. The MacArthur Treatment Competence Study. I: Mental Illness and Competence to Consent to Treatment. *Law and Human Behavior*, 19 (2), 105–126.

Arnow, B.A., Blasey, C., Manber, R., Constantino, M.J., Markowitz, J.C., Klein, D.N., Thase, M.E., Kocsis, J.H., and Rush, A.J., 2007. Dropouts versus completers among chronically depressed outpatients. *Journal of Affective Disorders*, 97 (1–3), 197–202.

Baekeland, F. and Lundwall, L., 1975. Dropping out of treatment: a critical review. *Psychological Bulletin*, 82 (5), 738–783.

van Ballegooijen, W., Cuijpers, P., Van Straten, A., Karyotaki, E., Andersson, G., Smit, J.H., and Riper, H., 2014. Adherence to internet-based and face-to-face cognitive behavioural therapy for depression: A meta-analysis. *PLoS ONE*, 9 (7).

Banerjee, A., 2012. Cross-Cultural Variance of Schizophrenia in Symptoms , Diagnosis and Treatment. *The Georgetown Undergraduate Journal of Health Sciences*, 6 (2), 18–24.

Barello, S., Graffigna, G., Vegni, E., and Bosio, A., 2014. The challenges of conceptualizing patient engagement in health care: a lexicographic literature review. *Journal of Participatory Medicine*, 11 (6), e9.

Barkhof, E., Meijer, C.J., De Sonneville, L.M.J., Linszen, D.H., and De Haan, L., 2013. The effect of motivational interviewing on medication adherence and hospitalization rates in nonadherent patients with multi-episode schizophrenia. *Schizophrenia Bulletin*, 39 (6), 1242–1251.

Barnicot, K., Katsakou, C., Marougka, S., and Priebe, S., 2011. Treatment completion in psychotherapy for borderline personality disorder: a systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, 123 (5), 327–338.

Barrowclough, C., Haddock, G., Beardmore, R., Conrod, P., Craig, T., Davies, L., Dunn, G., Lewis, S., Moring, J., Tarrier, N., and Wykes, T., 2009. Evaluating integrated MI and CBT for people with psychosis and substance misuse: recruitment, retention and sample characteristics of the MIDAS trial. *Addictive Behaviors*, 34 (10), 859–66.

Barrowclough, C., Haddock, G., Lobban, F., Jones, S., Siddle, R., Roberts, C., and Gregg, L., 2006. Group cognitive – behavioural therapy for schizophrenia. *British Journal of Psychiatry*, 189, 527–532.

Barrowclough, C., Haddock, G., Wykes, T., Beardmore, R., Conrod, P., Craig, T., Davies, L., Dunn, G., Eisner, E., Lewis, S., Moring, J., Steel, C., and Tarrier, N., 2010. Integrated motivational interviewing and cognitive behavioural therapy for people with psychosis and comorbid substance misuse: randomised controlled trial. *British Medical Journal*, 341, c6325.

Bartlett, A. and Canvin, K., 2003. User Views and Ethical Issues in Qualitative Methods. *In*: G. Adshead and C. Brown, eds. *Ethical Issues in Forensic Mental Health*

Research. London: Jessica Kingsley Publishers, 58–72.

Beary, M., Hodgson, R., and Wildgust, H., 2012. A critical review of major mortality risk factors for all-cause mortality in first-episode schizophrenia: clinical and research implications. *Journal of Psychopharmacology*, 26, 52–61.

Beckett, M., DaVanzo, J., Sastry, N., Panis, C., and Peterson, C., 2001. The Quality of Retrospective Data: An Examination of Long-Term Recall in a Developing Country. *The Journal of Human Resources*, 36 (3), 593–625.

Beckett, M., Quiter, E., Ryan, G., Berrebi, C., Taylor, S., Cho, M., Pincus, H., and Kahn, K., 2011. Bridging the gap between basic science and clinical practice : The role of organizations in addressing clinician barriers. *Implementation Science*, 6 (35), 1–10.

Begg, C., Cho, M., Eastwood, S., Horton, R., Moher, D., Olkin, I., Pitkin, R., Rennie, D., Schulz, K.F., Simel, D., and Stroup, D.F., 1996. Improving the Quality of Reporting of Randomized Controlled Trials. *JAMA*, 276 (8), 637–639.

Bell, M., Bryson, G., and Wexler, B.E., 2003. Cognitive remediation of working memory deficits: durability of training effects in severely impaired and less severely impaired schizophrenia. *Acta Psychiatrica Scandinavica*, 108 (2), 101–109.

Bell, M., Fiszdon, J., Greig, T., Wexler, B., and Bryson, G., 2007. Neurocognitive enhancement therapy with work therapy in schizophrenia: 6-month follow-up of neuropsychological performance. *Journal of Rehabilitation Research and Development*, 44 (5), 761–770.

Bell, M. and Lysaker, P., 1997. Clinical Benefits of Paid Work Activity in Schizophrenia: 1-Year Followup. *Schizophrenia Bulletin*, 23 (2), 317–328.

Bell, M.D., Bryson, G.J., Greig, T.C., Fiszdon, J.M., and Wexler, B.E., 2005. Neurocognitive enhancement therapy with work therapy: Productivity outcomes at 6- and 12-month follow-ups. *Journal of Rehabilitation Research and Development*, 42 (6), 829–838.

Bell, M.L., Fiero, M., Horton, N.J., and Hsu, C.-H., 2014. Handling missing data in RCTs; a review of the top medical journals. *BMC Medical Research Methodology*, 14 (118), 1–8.

Beresford, P., 2002. User Involvement in Research and Evaluation: Liberation or Regulation. *Social Policy & Society*, 1 (2), 95–105.

Berghofer, G., Schmidl, F., Rudas, S., and Schmitz, M., 2000. Utilization of psychiatric treatment. Who drops out, who comes back and who stays? *Psychiatrische Praxis*, 27 (8), 372–377.

Berghofer, G., Schmidl, F., Rudas, S., Steiner, E., and Schmitz, M., 2002. Predictors of treatment discontinuity in outpatient mental health care. *Social Psychiatry and Psychiatric Epidemiology*, 37 (6), 276–282.

Beutler, L., Zetzer, H., and Yost, E., 1997. Tailoring interventions to clients: effects on engagement and retention. *NIDA Research Monographs*, 165, 85–109.

Blaikie, N. and Priest, J., 2017. *Social Research. Paradigms in Action.* Cambridge: Polity Press.

Booker, C.L., Harding, S., and Benzeval, M., 2011. A systematic review of the effect of retention methods in population-based cohort studies. *BMC Public Health*, 11, 249.

Bookman, E.B., Din-Lovinescu, C., Worrall, B.B., Manolio, T.A., Bennett, S.N., Laurie, C., Mirel, D.B., Doheny, K.F., Anderson, G.L., Wehr, K., Weinshilboum, R., and Chen, D.T., 2013. Incidental genetic findings in randomized clinical trials: recommendations from the Genomics and Randomized Trials Network (GARNET). *Genome Medicine*, 5 (1), 7.

Borschmann, R., Patterson, S., Poovendran, D., Wilson, D., and Weaver, T., 2014. Influences on recruitment to randomised controlled trials in mental health settings in England: a national cross-sectional survey of researchers working for the Mental Health Research Network. *BMC Medical Resesarch Methodology*, 14, 23.

Boutron, I., Guittet, L., Estellat, C., Moher, D., Hrobjartsson, A., and Ravaud, P., 2006. Reporting methods of blinding in randomized trials assessing nonpharmacological treatments. *PLoS Medicine*, 4.

Bower, P., Brueton, V., Gamble, C., Treweek, S., Smith, C.T., Young, B., and Williamson, P., 2014. Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities. *Trials*, 15

(399), 1–9.

Bowie, C.R., McGurk, S.R., Mausbach, B., Patterson, T.L., and Harvey, P.D., 2012. Combined cognitive remediation and functional skills training for schizophrenia: Effects on cognition, functional competence, and real-world behavior. *American Journal of Psychiatry*, 169 (7), 710–718.

Brintnall-Karabelas, J., Sung, S., Cadman, M.E., and Squires, C., 2011. Improving Recruitment in Clinical Trials: Why Eligible Participants Decline. *Journal of Empirical Research on Human Research Ethics*, 6 (1), 69–74.

Brody, D., Miller, S., Lerman, C., Smith, D., and Caputo, C., 1989. Patient Perception of Involvement in Medical Care. *Journal of General Internal Medicine*, 4 (6), 506–511.

Brown, G., Marshall, M., Bower, P., Woodham, A., and Waheed, W., 2014. Barriers to recruiting ethnic minorities to mental health research: a systematic review. *International Journal of Methods in Psychiatric Research*, 23 (1), 36–48.

Brown, R., Butow, P., Henman, M., Dunn, S., Boyle, F., and Tattersall, M., 2002. Responding to the active and passive patient: flexibility is the key. *Health Expectations*, 5 (3), 236–245.

Brueton, V., Tierney, J., Stenning, S., Harding, S., Meredith, S., Nazareth, I., and Rait, G., 2013. Strategies to improve retention in randomised trials. *Cochrane Database of Systematic Reviews*, 12, 1–126.

Brueton, V.C., Tierney, J.F., Stenning, S., Meredith, S., Harding, S., Nazareth, I., and Rait, G., 2014. Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis. *BMJ Open*, 4 (2), e003821.

Bryant, A. and Charmaz, K., 2010. *The SAGE Handbook of Grounded Theory*. London: Sage Publications.

Buben, C.E., 2013. Integrating Patient Retention Strategies. *Applied Clinical Trials*, 22 (6).

Bucci, S., Butcher, I., Hartley, S., Neil, S.T., Mulligan, J., and Haddock, G., 2015. Barriers and facilitators to recruitment in mental health services: Care coordinators' expectations and experience of referring to a psychosis research trial. *Psychology and Psychotherapy: Theory, Research and Practice*, 88 (3), 335–350.

Buckley, P., 1998. Substance abuse in schizophrenia: a review. *Journal of Clinical Psychiatry*, 59, 26–30.

Buckley, P.F., Miller, B.J., Lehrer, D.S., and Castle, D.J., 2009. Psychiatric comorbidities and schizophrenia. *Schizophrenia Bulletin*, 35 (2), 383–402.

Bueno Heredia, A., Cordoba Dona, J., and Escolar Pujolar, A., 2001. El abandono terapeutico. *Actas Españolas de Psiquiatría*, 29 (1), 33–40.

Burlingame, G., 2014. Some Observations on How the Practice of Small Group Treatments Can Be Built Upon the Foundation of Research: A 30+ Year Perspective. *International Journal of Group Psychotherapy*, 64 (4), 567–583.

Burns, P.B., Rohrich, R.J., and Chung, K.C., 2011. The levels of evidence and their role in evidence-based medicine. *Plastic and Reconstructive Surgery*, 128 (1), 305–10.

Burns, T., Creed, F., Fahy, T., Thompson, S., and Tyrer, P., 1999. Intensive versus standard case management for severe psychotic illness: a randomised trial. *The Lancet*, 353 (9171), 2185–2189.

Burns, T., Rugkasa, J., Molodynski, A., Dawson, J., Yeeles, K., Vazquez-Montes, M., Voysey, M., Sinclair, J., Priebe, S., Rugkåsa, J., Molodynski, A., Dawson, J., Yeeles, K., Vazquez-Montes, M., Voysey, M., Sinclair, J., and Priebe, S., 2013. Community treatment orders for patients with psychosis (OCTET): A randomised controlled trial. *The Lancet*, 381 (9878), 1627–1633.

Campbell, M., Fitzpatrick, R., Haines, A., Kinmonth, A.L., Sandercock, P., Spiegelhalter, D., and Tyrer, P., 2000. Framework for design and evaluation of complex interventions to improve health. *British Medical Journal*, 321 (7262), 694–696.

Canvin, K. and Jacoby, A., 2006. Duty, desire or indifference? A qualitative study of patient decisions about recruitment to an epilepsy treatment trial. *Trials*, 7 (32), 1–13.

Carpenter-Song, E., Chu, E., Drake, R.E., Ritsema, M., Smith, B., and Alverson, H., 2010. Ethno-Cultural Variations in the Experience and Meaning of Mental Illness and Treatment: Implications for Access and Utilization. *Transcultural Psychiatry*, 47 (2), 224–251.

Carpenter, W.W.T., Gold, J.M.J., Lahti, A.C.A., Queern, C.A., Conley, R.R., Bartko, J.J.,

Kovnick, J., and Appelbaum, P.P.S., 2000. Decisional capacity for informed consent in schizophrenia research. *Archives of General Psychiatry Psychiatry*, 57 (6), 533–538.

Carroll, K., 1997. Enhancing retention in clinical trials of psychosocial treatments: practical strategies. *NIDA Research Monographs*, 165, 4–24.

Cassileth, B., Lusk, E., Miller, D., and Hurwitz, S., 1982. Attitudes toward clinical trials among patients and the public. *JAMA*, 248, 968–970.

Centre for Evidence-Based Medicine, 2009. Oxford Centre for Evidence-based Medicine – Levels of Evidence [online]. Available from: http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/ [Accessed 15 May 2017].

Chalmers, I., 1993. The Cochrane collaboration: preparing, maintaining, and disseminating systematic reviews of the effects of health care. *Annals of the New York Academy of Sciences*, 703, 156-63–5.

Charmaz, K., 2013. *Constructing Grounded Theory*. London: Sage Publications.

Chien, W., Mui, J., Cheung, E., and Gray, R., 2015. Effects of motivational interviewing-based adherence therapy for schizophrenia spectrum disorders: a randomized controlled trial. *Trials*, 16 (1), 270–284.

Chong, S.-A., Ong, Y.Y., Subramaniam, M., Abdin, E., Marx, C.E., and Campbell, A.V., 2009. An assessment of the understanding and motivations of patients with schizophrenia about participating in a clinical trial. *Contemporary Clinical Trials*, 30 (5), 446–50.

Christensen, H., Griffiths, K., and Farrer, L., 2009. Adherence in internet interventions for anxiety and depression. *Journal of Medical Internet Research*, 14 (e152).

Clarke, M., 2007. Standardising outcomes for clinical trials and systematic reviews. *Trials*, 8 (39), 1–3.

Cochrane Collaboration, 2011. *Cochrane Handbook for Systematic Reviews of Interventions*. 5.1.0. The Cochrane Collaboration.

Cook, K. and Rice, E., 2006. Social exchange theory. *In*: J. Delamater, ed. *Handbook of*

Social Psychology. New York: Springer, 52–76.

Cooper, A. and Conklin, L., 2015. Dropout from individual psychotherapy for major depression: A meta-analysis of randomized controlled trials. *Clinical Psychology Review*, 40, 57–65.

Corrigan, O. and Tutton, R., 2006. What's in a name? Subjects, volunteers, participants and activists in clinical research. *Empirical Ethics*, 1, 101–104.

Coulter, A., 1999. Paternalism or partnership. *British Medical Journal*, 319 (719).

Craig, P., Dieppe, P., Macintyre, S., and Michie, S., 2008. Developing and evaluating complex interventions: the new Medical Research Council guidance. *British Medical Journal*, 337, 1–6.

Cramer, J.A. and Rosenheck, R.A., 1998. Compliance with medication regimens for mental and physical disorders. *Psychiatric Services*.

Crawford, M.J., Killaspy, H., Barnes, T.R.E., Barrett, B., Byford, S., Clayton, K., Dinsmore, J., Floyd, S., Hoadley, A., Johnson, T., Kalaitzaki, E., King, M., Leurent, B., Maratos, A., O'Neill, F.A., Osborn, D.P., Patterson, S., Soteriou, T., Tyrer, P., and Waller, D., 2012. Group art therapy as an adjunctive treatment for people with schizophrenia: multicentre pragmatic randomised trial. *British Medical Journal*, 344, e846.

Creswell, J., 2003. *Research Design: Qualitative, Quantitative and Mixed Methods Approaches*. Thousand Oaks, California: Sage Publications.

Creswell, J., 2014. *Research Design. Qualitative, Quantitative, & Mixed Methods Approaches*. Thousand Oaks, California: Sage Publications.

Creswell, J. and Plano Clark, V., 2011. *Designing and condcuting mixed methods research*. 2nd ed. Thousand Oaks, California: Sage Publications.

Dauw, C., Yooni, Y., Bierlein, M., Yan, P., Alruwaily, A., Ghani, K., Wolf, J., Hollenbeck, B., and Hollingsworth, J., 2016. Medication Nonadherence and Effectiveness of Preventive Pharmacological Therapy for Kidney Stones. *The Journal of Urology*, 195 (3), 648–652.

Davis, L.L., Broome, M.E., and Cox, R.P., 2002. Maximizing Retention in Community-

based Clinical Trials. *Journal of Nursing Scholarship*, 34 (1), 47–53.

Dawes, M., Summerskill, W., Glasziou, P., Cartabellotta, A., Martin, J., Hopayian, K., Porzsolt, F., Burls, A., and Osborne, J., 2005. Sicily statement on evidence-based practice. *BMC Medical Education*, 5 (1), 1–7.

Debray, T.P.A., Moons, K.G.M., Abo-zaid, G.M.A., Koffijberg, H., and Riley, R.D., 2013. Individual Participant Data Meta-Analysis for a Binary Outcome: One-Stage or Two-Stage ? *PLoS ONE*, 8 (4), 1–10.

Denzin, N., 1978. *Sociological Methods*. New York: McGraw-Hill.

Department of Health, 2003. *Hospital Activity Statistics*. London.

Department of Health, 2005. *Mental Capacity Act*. London.

Dickerson, F., Sommerville, J., Origoni, A., Ringel, N., and Parente, F., 2002. Experiences of Stigma Among Outpatients With Schizophrenia. *Schizophrenia Bulletin*, 28 (1), 143–155.

Dodd, S., White, I.R., and Williamson, P., 2012. Nonadherence to treatment protocol in published randomised controlled trials: a review. *Trials*, 13 (1), 1.

Domecq, J.P., Prutsky, G., Elraiyah, T., Wang, Z., Nabhan, M., Shippee, N., Brito, J.P., Boehmer, K., Hasan, R., Firwana, B., Erwin, P., Eton, D., Sloan, J., Montori, V., Asi, N., Abu Dabrh, A.M., Murad, M.H., Moain, A., and Dabrh, A., 2014. Patient engagement in research: a systematic review. *BMC Health Services Research*, 14 (89), 1–9.

Donald, A., Burns, K., Adhikari, N., Kho, M., Meade, M., and Cook, D., 2009. The design and interpretation of pilot trials in clinical research in critical care. *Critical Care Medicine*, 37 (1), S69–S74.

Donkin, L. and Glozier, N., 2012. Motivators and motivations to persist with online psychological interventions: a qualitative study of treatment completers. *Journal of Medical Internet Research*, 14 (e91).

Dumville, J.C., Torgerson, D.J., and Hewitt, C.E., 2006. Reporting attrition in randomised controlled trials. *British Medical Journal*, 332 (7547), 969–971.

Edwards, P.J., Roberts, I., Clarke, M.J., DiGuiseppi, C., Wentz, R., Kwan, I., Cooper, R.,

Felix, L.M., and Pratap, S., 2009. Methods to increase response to postal and electronic questionnaires. *In*: P.J. Edwards, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd.

Edwards, S. and Braunholtz, D., 2000. Can unequal be more fair? A responds to Andrew Avins. *Journal of Medical Ethics*, 26, 179–182.

Eide, P. and Kahn, D., 2008. Ethical Issues in the Qualitative Researcher-Participant Relationship. *Nursing Ethics*, 15 (2), 199–207.

Elamin, M. and Montori, V., 2012. The hierarchy of evidence: From unsystematic clinical observations to systematic reviews. *In*: J. Burneo, B. Demaerschalk, and M. Jenkins, eds. *Neurology: An evidence-based approach.* New York: Springer, 11–24.

Eon, S. and Durham, J., 2009. Schizophrenia: A Review of Pharmacologic and Nonpharmacalogic Treatments. *US Pharmacist*, 34 (11), HS2-HS9.

Evans, M., Robling, M., Maggs Rapport, F., Houston, H., Kinnersley, P., and Wilkinson, C., 2002. It doesn't cost anything just to ask, does it? The ethics of questionnaire-based research. *Journal of Medical Ethics*, 28 (1), 41–44.

Eysenbach, G., 2005. The law of attrition. *Journal of Medical Internet Research*, 7 (e11).

Featherstone, K. and Donovan, J.L., 1998. Random allocation or allocation at random? Patients' perspectives of participation in a randomised controlled trial. *British Medical Journal*, 317 (7167), 1177–80.

Featherstone, K. and Donovan, J.L., 2002. 'Why don't they just tell me straight, why allocate it?' The struggle to make sense of participating in a randomised controlled trial. *Social Science & Medicine*, 55 (5), 709–719.

Fenton, S., Blyler, C., and Heinssen, R., 1997. Determinants of medication compliance in schizophrenia: empirical and clinical findings. *Schizophrenia Bulletin*, 23, 637–651.

Fletcher, B., Gheorghe, A., Moore, D., Wilson, S., and Damery, S., 2012. Improving the recruitment activity of clinicians in randomised controlled trials: a systematic review. *BMJ Open*, 2 (1), e000496.

Fouad, M.N., Johnson, R.E., Nagy, M.C., Person, S.D., and Partridge, E.E., 2014.

Adherence and Retention in Clinical Trials: A Community- Based Approach. *Cancer*, 1106–1112.

Foussias, G. and Remington, G., 2010. Negative symptoms in schizophrenia: Avolition and occam's razor. *Schizophrenia Bulletin*, 36 (2), 359–369.

Franck, N., Duboc, C., Sundby, C., Amado, I., Wykes, T., Demily, C., Launay, C., Le Roy, V., Bloch, P., Willard, D., Todd, A., Petitjean, F., Foullu, S., Briant, P., Grillon, M.L., Deppen, P., Verdoux, H., Bralet, M.C., Januel, D., Riche, B., Roy, P., and Vianin, P., 2013. Specific vs general cognitive remediation for executive functioning in schizophrenia: A multicenter randomized trial. *Schizophrenia Research*, 147 (1), 68–74.

Freedman, R., 2003. Schizophrenia. *The New England Journal of Medicine*, 349, 1738–1749.

Freeman, D., Dunn, G., Startup, H., Pugh, K., Cordwell, J., Mander, H., Cernis, E., Wingham, G., Shirvell, K., and Kingdon, D., 2015. Effects of cognitive behaviour therapy for worry on persecutory delusions in patients with psychosis. *The Lancet Psychiatry*, 2, 305–313.

Freuler, A.C., Baranek, G.T., Tashjian, C., Watson, L.R., Crais, E.R., and Turner-Brown, L.M., 2013. Parent reflections of experiences of participating in a randomized controlled trial of a behavioral intervention for infants at risk of autism spectrum disorders. *Autism*, 18 (5), 519–528.

Friedli, K. and King, M.B., 1998. Psychological treatments and their evaluation. *International Review of Psychiatry*, 10 (2), 123–126.

Fusch, P. and Lawrence, R., 2015. Are We There Yet? Data Saturation in Qualitative Research. *The Qualitative Report*, 20 (9), 1408–1416.

Van Der Gaag, M., Stant, A.D., Wolters, K.J.K., Buskens, E., and Wiersma, D., 2011. Cognitive-behavioural therapy for persistent and recurrent psychosis in people with schizophrenia-spectrum disorder: Cost-effectiveness analysis. *British Journal of Psychiatry*, 198 (1), 59–65.

Gale, N.K., Heath, G., Cameron, E., Rashid, S., and Redwood, S., 2013. Using the framework method for the analysis of qualitative data in multi-disciplinary health

research. *BMC Medical Research Methodology*, 13 (1), 117.

Garety, P. a, Fowler, D.G., Freeman, D., Bebbington, P., Dunn, G., and Kuipers, E., 2008. Cognitive-behavioural therapy and family intervention for relapse prevention and symptom reduction in psychosis: randomised controlled trial. *British Journal of Psychiatry*, 192 (6), 412–23.

Gart, M.S., Gosain, A.K., and Evidence-Based Medicine Working Group, 1992. Evidence-Based Medicine. A New Approach to Teaching the Practice of Medicine. *JAMA*, 268 (17), 2420–2425.

Gary, F.A., 2005. Stigma: Barrier to Mental Health Care Among Ethnic Minorities. *Issues in Mental Health Nursing*, 26 (10), 979–999.

Gelaw, B., Mohammed, A., Temesgen, G., Tegegne, T., Defersha, D., Fromsa, M., Tadesse, E., Thrumurgan, G., and Ahmed, M., 2014. Nonadherence and Contributing Factors among Ambulatory Patients with Antidiabetic Medications in Adam Referral Hospital. *Journal of Diabetes Research*, 1–9.

Ghio, L., Natta, W., Barbato, A., Mercenaro, M., Gotelli, S., Jones, P.B., and Parabiaghi, A., 2011. Schizophrenia trial participation: Perceived inclusion barriers and beliefs about antipsychotics. *Pharmacopsychiatry*, 44 (4), 123–128.

Glasziou, P., Meats, E., Heneghan, C., and Shepperd, S., 2008. What is missing from descriptions of treatment in trials and reviews? *British Medical Journal*, 336, 1472–1474.

Goldberg, D., 2011. The heterogeneity of 'major depression'. *World Psychiatry*, 10 (3), 226–228.

Gomar, J.J., Valls, E., Radua, J., Mareca, C., Tristany, J., Del Olmo, F., Rebolleda-Gil, C., Janez-Alvarez, M., De Alvaro, F., Ovejero, M.R., Llorente, A., Teixido, C., Donaire, A.M., Garcia-Laredo, E., Lazcanoiturburu, A., Granell, L., Mozo, C.D.P., Perez-Hernandez, M., Moreno-Alcazar, A., Pomarol-Clotet, E., and McKenna, P.J., 2015. A Multisite, Randomized Controlled Clinical Trial of Computerized Cognitive Remediation Therapy for Schizophrenia. *Schizophrenia Bulletin*, 41 (6), 1387–1396.

Gouzoulis-Mayfrank, E., König, S., Koebke, S., Schnell, T., Schmitz-buhl, M., and Daumann, J., 2015. Trans-Sector Integrated Treatment in Psychosis and Addiction.

Deutsches Arzteblatt International, 112, 683–691.

Grady, C., 2005. Science and society Payment of clinical research subjects. *the Journal of Clinical Investigation*, 115 (7), 1681–1687.

Graffy, J., Bower, P., Ward, E., Wallace, P., Delaney, B., Kinmonth, A., Collier, D., and Miller, J., 2010. Trials within trials? Researcher, funder and ethical perspectives on the practicality and acceptability of nesting trials of recruitment methods in existing primary care trials. *BMC Medical Research Methodology*, 10 (38), 1–10.

Granholm, E., Holden, J., Link, P.C., and McQuaid, J.R., 2014. Randomized Clinical Trial of Cognitive Behavioral Social Skills Training for Schizophrenia: Improvement in Functioning and Experiential Negative Symptoms. *Journal of Consulting and Clinical Psychology*, 82 (6), 1173–1185.

Grant, J.B., Mackinnon, a J., Christensen, H., and Walker, J., 2009. Participants' perceptions of motivation, randomisation and withdrawal in a randomised controlled trial of interventions for prevention of depression. *Journal of Medical Ethics*, 35 (12), 768–73.

Grant, R.W., Sugarman, J., and Grady, C., 2010. Ethics in Human Subjects Research: Do Incentives Matter? *Journal of Medicine and Philosophy*, 29 (6), 717–738.

Grant, S.P., Mayo-Wilson, E., Montgomery, P., Melendez-Torres, G.J., and Montgomery, P., 2013. Reporting Quality of Social and Psychological Intervention Trials: A Systematic Review of Reporting Guidelines and Trial Publications. *PLoS ONE*, 8 (5).

Gray, R., Leese, M., Bindman, J., Becker, T., Burti, L., David, A., Gournay, K., Kikkert, M., Koeter, M., Puschner, B., Schene, A., Thornicroft, G., and Tansella, M., 2006. Adherence therapy for people with schizophrenia. European multicentre randomised controlled trial. *British Journal of Psychiatry*, 189, 508–14.

Greenhalgh, T., Annandale, E., Ashcroft, R., Barlow, J., Black, N., Bleakley, A., Boaden, R., Braithwaite, J., Britten, N., Carnevale, F., Checkland, K., Cheek, J., Clark, A., Cohn, S., Coulehan, J., Crabtree, B., Cummins, S., Davidoff, F., Davies, H., Dingwall, R., Dixon-Woods, M., Elwyn, G., Engebretsen, E., Ferlie, E., Fulop, N., Gabbay, J., Gagnon, M.-P., Galasinski, D., Garside, R., Gilson, L., Griffiths, P., Hawe, P., Helderman, J.-K., Hodges, B., Hunter, D., Kearney, M., Kitzinger, C.,

Kitzinger, J., Kuper, A., Kushner, S., Le May, A., Legare, F., Lingard, L., Locock, L., Maben, J., Macdonald, M.E., Mair, F., Mannion, R., Marshall, M., May, C., Mays, N., McKee, L., Miraldo, M., Morgan, D., Morse, J., Nettleton, S., Oliver, S., Pearce, W., Pluye, P., Pope, C., Robert, G., Roberts, C., Rodella, S., Rycroft-Malone, J., Sandelowski, M., Shekelle, P., Stevenson, F., Straus, S., Swinglehurst, D., Thorne, S., Tomson, G., Westert, G., Wilkinson, S., Williams, B., Young, T., and Ziebland, S., 2016. An open letter to The BMJ editors on qualitative research. *BMJ*, 352 (7473), i1563.

Grisso, T., Appelbaum, P.P.S., Mulvey, E.E.P., and Fletcher, K., 1995. The Macarthur Treatment Competence Study II: Measures of Abilities Related to Competence to Consent to Treatment. *Law and Human Behavior*, 19 (2), 127–148.

Grisso, T. and Appelbaum, P.S., 1995. The MacArthur treatment competence study III: Abilities of patients to consent to psychiatric and medical treatments. *Law and Human Behavior*, 19 (2), 149–174.

Gross, D. and Fogg, L., 2001. Focus on Research Methods Clinical Trials in the 21st Century: The Case for Participant-Centered Research. *Research in Nursing & Health*, 24, 530–539.

Gross, D., Julion, W., and Fogg, L., 2001. What motivates participation and dropout among low-income urban families of color in a prevention intervention? *Family Relations*, 50 (3), 246–254.

Guba, E., 1990. *The Paradigm Dialog*. Newbury Park, California: Sage Publications.

Guest, G., Bunce, A., and Johnson, L., 2006. How many interviews are enough? An experiment with data saturation and variability. *Field Methods*, 18 (1), 59–82.

Guillemin, M. and Heggen, K., 2009. Rapport and respect: Negotiating ethical relations between researcher and participant. *Medicine, Health Care and Philosophy*, 12 (3), 291–299.

Gul, R.B. and Ali, P.A., 2010. Clinical trials: the challenge of recruitment and retention of participants. *Journal of Cinical Nursing*, 19 (1–2), 227–33.

Gumley, A., Karatzias, A., Power, K., Reilly, J., McNay, L., and O'Grady, M., 2006. Early intervention for relapse in schizophrenia: impact of cognitive behavioural therapy

on negative beliefs about psychosis and self-esteem. *British Journal of Clinical Psychology*, 45 (Pt 2), 247–260.

Gumley, A., O'Grady, M., McNay, L., Reilly, J., Power, K., and Norrie, J., 2003. Early intervention for relapse in schizophrenia: results of a 12-month randomized controlled trial of cognitive behavioural therapy. *Psychological Medicine*, 33 (3), 419–431.

Haidich, A. and Ioannidis, J., 2001. Patterns of patient enrolment in randomized controlled trials. *Clinical Epidemiology*, 54, 877–883.

Hamann, J., Langer, B., Winkler, V., Busch, R., Cohen, R., Leucht, S., and Kissling, W., 2006. Shared decision making for in-patients with schizophrenia. *Acta Psychiatrica Scandinavica*, 114 (4), 265–273.

Hanley, B., Bradburn, J., Barnes, M., Evans, C., Goodare, H., Kelson, M., Kent, A., Sandy, O., Thomas, S., and Wallcraft, J., 2004. *Involving the Public in NHS Public Health and Social Care Research: Briefing Notes for Researchers*. Eastleigh.

Hanley, J., Ure, J., Pagliari, C., Sheikh, A., and McKinstry, B., 2013. Experiences of patients and professionals participating in the HITS home blood pressure telemonitoring trial: a qualitative study. *BMJ Open*, 3 (e002671).

Hansson, L., Svensson, B., Bjorkman, T., Bullenkamp, J., Lauber, C., Martinez-Leal, R., McCabe, R., Rossler, W., Salize, H., Torres-Gonzales, F., Van Den Brink, R., Wiersma, D., and Priebe, S., 2008. What works for whom in a computer-mediated communication intervention in community psychiatry? Moderators of outcome in a cluster randomized trial. *Acta Psychiatrica Scandinavica*, 118, 404–409.

Harris, R. and Dyson, E., 2001. Recruitment of frail older people to research: lessons learnt through experience. *Journal of Advanced Nursing*, 36 (643–651).

Hartlieb, K.B., Jacques-Tiura, A.J., Naar-King, S., Ellis, D.A., Jen, K.-L.C., and Marshall, S., 2015. Recruitment strategies and the retention of obese urban racial/ethnic minority adolescents in clinical trials: the FIT families project, Michigan, 2010-2014. *Preventing Chronic Disease*, 12, E22.

Hartz, S.M., Pato, C.N., Medeiros, H., Cavazos-Rehg, P., Sobell, J.L., Knowles, J.A., Bierut, L.J., and Pato, M.T., 2014. Comorbidity of Severe Psychotic Disorders With

Measures of Substance Use. *JAMA Psychiatry*, 71 (3), 248.

Hatchett, G. and Park, H., 2003. Comparison of four operational definitions of premature termination. *Psychotherapy*, 40, 226–231.

Hawe, P., Shiell, A., and Riley, T., 2004. Complex interventions: how 'out of control' can a randomised controlled trial be? *British Medical Journal*, 328 (7455), 1561–1563.

Haynes, R., Yao, X., Degani, A., Kripalani, S., Garg, A., and McDonald, H., 2006. Interventions for enhancing medication adherence (Review). *The Cochrane Library*, (4).

Haynes, R.B. and Sackett, D.L., 1979. *Compliance in Health Care*. Johns Hopkins University Press.

Henderson, G.E., Churchill, L.R., Davis, A.M., Easter, M.M., Grady, C., Joffe, S., Kass, N., King, N.M.P., Lidz, C.W., Miller, F.G., Nelson, D.K., Peppercorn, J., Rothschild, B.B., Sankar, P., Wilfond, B.S., and Zimmer, C.R., 2007. Clinical trials and medical care: Defining the therapeutic misconception. *PLoS Medicine*, 4 (11), 1735–1738.

Henn, M., Weinstein, M., and Foard, N., 2009. *A Critical Introduction to Social Research*. 2nd ed. London: Sage.

Hershenberg, R., Drabick, D.A., and Vivian, D., 2012. An Opportunity to Bridge the Gap Between Clinical Research and Clinical Practice: Implications for Clinical Training. *Psychotherapy*, 49 (2), 123–134.

de Hert, M., Correll, C.U., Bobes, J., Cetkovich-Bakmas, M., Cohen, D., Asai, I., Detraux, J., Gautam, S., Möller, H.-J., Ndetei, D.M., Newcomer, J.W., Uwakwe, R., and Leucht, S., 2011. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry*, 10 (1), 52–77.

Hewitt, C.E., Kumaravel, B., Dumville, J.C., and Torgerson, D.J., 2010. Assessing the impact of attrition in randomized controlled trials. *Journal of Clinical Epidemiology*, 63 (11), 1264–1270.

Hill, P. and Humenick, S., 1995. Comparison of subjects who fully versus minimally participated in a breast-feeding study. *Western Journal of Nursing Research*, 17 (3), 328–334.

Hines-Martin, V., Usui, W., Kim, S., and Furr, A., 2004. Ethnic variations in mental health attitudes and service use among low-income African American, Latina, and European American young women. *Journal of National Black Nurses' Association*, 15 (2), 17–22.

Hoffmann, T.C., Erueti, C., and Glasziou, P.P., 2013. Poor description of non-pharmacological interventions: analysis of consecutive sample of randomised trials. *British Medical Journal*, 347 (7659), 1–10.

Hogarty, G.E., Flesher, S., Ulrich, R., Carter, M., Greenwald, D., Pogue-Geile, M., Kechavan, M., Colley, S., DiBarry, A.L., Garrett, A., Parepally, H., and Zoretich, R., 2004. Cognitive enhancement therapy for schizophrenia. *Archives*, 61, 866–876.

Hollis, S. and Campbell, F., 1999. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *British Medical Journal*, 319 (7211), 670–674.

Holmberg, C., Karner, J.J., Rappenecker, J., and Witt, C.M., 2014. Clinical trial participants' experiences of completing questionnaires: a qualitative study. *BMJ Open*, 4 (3), 1–8.

Holmberg, S.K. and Kane, C., 1999. Health and self-care practices of persons with schizophrenia. *Psychiatric Services*, 50, 827–829.

Hooper, R., Froud, R.J., Bremner, S.A., Perera, R., and Eldridge, S., 2013. Cascade diagrams for depicting complex interventions in randomised trials. *British Medical Journal*, 347, 1–6.

Hopewell, S., Hirst, A., Collins, G.S., Mallett, S., Yu, L.-M., and Altman, D.G., 2011. Reporting of participant flow diagrams in published reports of randomized trials. *Trials*, 12 (1), 253.

Hor, K. and Taylor, M., 2010. Suicide and schizophrenia: a systematic review of rates and risk factors. *Journal of Psychopharmacology*, 24 (4 Suppl), 81–90.

Howard, A., Pion, G.M., Gottfredson, G.D., Flattau, P.E., Oskamp, S., Pfaffin, S.M., Bray, D.W., and Burstein, A.G., 1986. The changing face of American psychology: A report from the Committee on Employment and Human Resources. *American Psychologist*, 41 (2), 1311–1327.

Howard, L., de Salis, I., Tomlin, Z., Thornicroft, G., and Donovan, J., 2009. Why is recruitment to trials difficult? An investigation into recruitment difficulties in an RCT of supported employment in patients with severe mental illness. *Contemporary Clinical Trials*, 30 (1), 40–6.

Hubbard, G., O'Carroll, R., Munro, J., Mutrie, N., Haw, S., Mason, H., and Treweek, S., 2016. The feasibility and acceptability of trial procedures for a pragmatic randomised controlled trial of a structured physical activity intervention for people diagnosed with colorectal cancer: findings from a pilot trial of cardiac rehabilitation versus usua. *Pilot and Feasibility Studies*, 2 (51), 1–15.

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

Hugtenburg, J.G., Timmers, L., Elders, P.J.M., Vervloet, M., and van Dijk, L., 2013. Definitions, variants, and causes of nonadherence with medication: A challenge for tailored interventions. *Patient Preference and Adherence*, 7, 675–682.

Humphreys, M., Johnstone, E., MacMillan, J., and Taylor, P., 1992. Dangerous behaviour preceeding first admissions for schizophrenia. *British Journal of Psychiatry*, 161 (4), 501–505.

Hussain-Gambles, M., 2004. South Asian patients' views and experiences of clinical trial participation. *Family Practice*, 21 (6), 636–42.

Hutton, P., Morrison, A.P., Yung, A.R., Taylor, P.J., French, P., and Dunn, G., 2012. Effects of drop-out on efficacy estimates in five Cochrane reviews of popular antipsychotics for schizophrenia. *Acta Psychiatrica Scandinavica*, 126 (1), 1–11.

Jackson, J., Torres, M., Caldwell, C., Neighbors, H., Nesse, R., Taylor, R., and Al., E., 2004. The National Survey of American Life: a study of racial, ethnic and cultural influences on mental disorders and mental health. *International Journal of Methods in Psychiatric Research*, 13, 196–207.

Jacomb, P., Jorm, A., Rodgers, B., Korten, A., Henderson, A., and Christensen, H., 1999. Emotional response of participants to a mental health survey. *Social Psychiatry and Psychiatric Epidemiology*, 34 (2), 80–84.

Jahn, T., Pitschel-Walz, G., Gsottschneider, A., Froböse, T., Kraemer, S., and Bäuml, J., 2011. Neurocognitive prediction of illness knowledge after psychoeducation in schizophrenia: results from the Munich COGPIP study. *Psychological Medicine*, 41 (3), 533–44.

Jancey, J., Howatt, P., Lee, A., Clarke, A., Shilton, T., Fisher, J., and Iredell, H., 2006. Effective Recruitment and Retention of Older Adults in Physical Activity Research: PALS Study. *American Journal of Health Behavior*, 30, 626–635.

Jaspers, G.J. and Degraeuwe, P.L.J., 2014. A failed attempt to conduct an individual patient data meta-analysis. *Systematic Reviews*, 3 (1), 97.

Johnson, R. and Onwuegbuzie, A., 2004. Mixed methods research: A research paradigm whose time has come. *Educational Research*, 33 (7), 14–26.

Jones, A.P., Riley, R.D., Williamson, P.R., and Whitehead, A., 2009. Meta-analysis of individual patient data versus aggregate data from longitudinal clinical trials. *Clinical Trials*, 6 (1), 16–27.

Jones, R.B., Atkinson, J.M., Coia, D.A., Paterson, L., Morton, A.R., McKenna, K., Craig, N., Morrison, J., and Gilmour, W.H., 2001. Randomised trial of personalised computer based information for patients with schizophrenia. *British Medical Journal*, 322, 835–840.

Jorm, A., Kelly, C., and Morgan, A., 2007. Participant distress in psychiatric research: a systematic review. *Psychological Medicine*, 37, 917–926.

Joseph, R.P., Keller, C., and Ainsworth, B.E., 2016. Researchers with Shoestring Budgets. *Californian Journal of Health Promotion*, 14 (2), 81–89.

Kampman, O. and Lethinen, K., 1999. Compliance in psychoses. *Acta Psychiatrica Scandinavica*, 100, 167–175.

Kanarek, N.F., Kanarek, M.S., Olatoye, D., and Carducci, M.A., 2012. Removing barriers to participation in clinical trials, a conceptual framework and retrospective chart review study. *Trials*, 13 (1), 237.

Kane, R.L., Wang, J., and Garrard, J., 2007. Reporting in randomized clinical trials improved after adoption of the CONSORT statement. *Journal of Clinical Epidemiology*, 60 (3), 241–249.

Karlson, C. and Rapoff, M., 2009. Attrition in randomized controlled trials for pediatric chronic conditions. *Journal of Pediatric Psychology*, 34 (7), 782–793.

Kaur, G., Smyth, R.L., and Williamson, P., 2012. Developing a survey of barriers and facilitators to recruitment in randomized controlled trials. *Trials*, 13 (218), 1–12.

Kazdin, A.E., 1999. The meanings and measurement of clinical significance. *Journal of Consulting and Clinical Psychology*, 67, 332–339.

Kemmler, G., Hummer, M., Widschwendter, C., and Fleischhacker, W.W., 2005. Dropout Rates in Placebo-Controlled and Active-Control Clinical Trials of Antipsychotic Drugs. *Archives of General Psychiatry*, 62, 1305–1312.

Kemp, R. and David, A., 1996. Psychological Predictors of Insight and Compliance in Psychotic Patients. *British Journal of Psychiatry*, 169, 444–450.

Kim, J.H., Kim, D.D., Park, S.-H., and Nam, J., 2009. Accept or refuse? A pilot study of patients' perspective on participating as imaginary research subjects in schizophrenia. *Psychiatry Investigation*, 6 (2), 66–71.

Kissling, W., 1994. Compliance, quality assurance and standards for relapse prevention in schizophrenia. *Acta Psychiatrica Scandinavica*, 382, 16–24.

Kitchin, R., 2000. The Researched Opinions on Research: Disabled people and disability research. *Disability & Society*, 15 (1), 25–47.

Kjosavik, S., Hunskaar, S., Aarsland, D., and Ruths, S., 2011. Initial prescription of antipsychotics and antidepressants in gen- eral practice and specialist care in Norway. *Acta Psychiatrica Scandinavica*, 123, 459–465.

Klingberg, S., Herrlich, J., Wiedemann, G., Wolwer, W., Meisner, C., Engel, C., Jakobi-Malterre, U.E., Buchkremer, G., and Wittorf, A., 2012. Adverse effects of cognitive behavioral therapy and cognitive remediation in schizophrenia: results of the treatment. *The Journal of Nervous and Mental Disease*, 200 (7), 569–576.

Klingberg, S., Wittorf, A., Fischer, A., Jakob-Deters, K., Buchkremer, G., and Wiedemann, G., 2010. Evaluation of a cognitive behaviourally oriented service for relapse prevention in schizophrenia. *Acta Psychiatrica Scandinavica*, 121 (5), 340–350.

Klingberg, S., Wölwer, W., Engel, C., Wittorf, A., Herrlich, J., Meisner, C., Buchkremer, G., and Wiedemann, G., 2011. Negative symptoms of schizophrenia as primary target of cognitive behavioral therapy: Results of the randomized clinical TONES study. *Schizophrenia Bulletin*, 37 (SUPPL. 2), S98–S110.

Kost, R.G., Lee, L.M., Yessis, J., Coller, B.S., Henderson, D.K., Needler, N., Dozier, A., Larson, J., Britt, S., Alfano, S., D'Agostino, G., Hahn, C., Tracey, K., Saltzman, A., Cagliero, E., Jenckes, M., Ford, D., and Margatic, S., 2011. Assessing research participants' perceptions of their clinical research experiences. *Clinical and Translational Science*, 4 (6), 403–413.

van der Krieke, L., Emerencia, A.C., Boonstra, N., Wunderink, L., de Jonge, P., and Sytema, S., 2013. A Web-Based Tool to Support Shared Decision Making for People With a Psychotic Disorder: Randomized Controlled Trial and Process Evaluation. *Journal of Medical Internet Research*, 15 (10), e216.

Kwan, B., Dimidjian, S., and Rizvi, S., 2010. Treatment preferences, engagement, and clinical improvement in pharmacotherapy versus psychotherapy for depression. *Behaviour Research and Therapy*, 48, 799–804.

Latvala, E., Janhonen, S., and Moring, J., 2000. Passive Patients: A Challenge to Psychiatric Nurses. *Perspectives in Psychiatric Care*, 36 (1), 24–32.

Lavin, D. and Maynard, D., 2001. Standardization vs. Rapport: Respondent Laughter and Interviewer Reaction during Telephone Surveys. *American Sociological Review*, 66 (3), 453–479.

Leathem, C.S., Cupples, M.E., Byrne, M.C., Malley, M.O., Houlihan, A., Murphy, A.W., Smith, S.M., O'Malley, M., Houlihan, A., Murphy, A.W., and Smith, S.M., 2009. Identifying strategies to maximise recruitment and retention of practices and patients in a multicentre randomised controlled trial of an intervention to optimise secondary prevention for coronary heart disease in primary care. *BMC Medical Research Methodology*, 9, 40.

Lecomte, T., Leclerc, C., and Wykes, T., 2012. Group CBT for Early Psychosis - Are There Still Benefits One Year Later? *International Journal of Group Psychotherapy*, 62 (2), 309–321.

Lecomte, T., Leclerc, C., Wykes, T., Ph, D., Leclerc, C., Ph, D., and Wykes, T., 2012.

Group CBT for Early Psychosis - Are There Still Benefits One Year Later? *International Journal of Group Psychotherapy*, 62 (2), 309–321.

Lecomte, T., Spidel, A., Leclerc, C., MacEwan, G.W., Greaves, C., and Bentall, R.P., 2008. Predictors and profiles of treatment non-adherence and engagement in services problems in early psychosis. *Schizophrenia Research*, 102, 295–302.

Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Örey, D., Richter, F., Samara, M., Barbui, C., Engel, R.R., Geddes, J.R., Kissling, W., Stapf, M.P., Lässig, B., Salanti, G., and Davis, J.M., 2013. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. *Lancet*, 382 (9896), 951–962.

Levati, S., Campbell, P., Frost, R., Dougall, N., Wells, M., Donaldson, C., and Hagen, S., 2016. Optimisation of complex health interventions prior to a randomised controlled trial: a scoping review of strategies used. *Pilot and Feasibility Studies*, 2 (1), 1–17.

Li, C., Stellman, J., Patel, N., and Dalton, F., 2016. Improving capacity and consent to treatment recording in psychiatric inpatient wards: A multi-centre quality improvement project. *BMJ Quality Improvement Reports*, 5 (1), 1–5.

Li, Z., Guo, Z., Wang, N., Xu, Z., Qu, Y., Wang, X., Sun, J., Yan, L., Ng, R., Turkington, D., and Kingdon, D., 2015. Cognitive-behavioural therapy for patients with schizophrenia: a multicentre randomized controlled trial in Beijing, China. *Psychological Medicine*, 45 (9), 1893–1905.

Liddle, P.F., 1987. The Symptoms of Chronic Schizophrenia. *British Journal of Psychiatry*, 151, 145–151.

Life Sciences Initiative, 2014. Life sciences PhD studentships [online]. Available from: http://www.qmul.ac.uk/lifesciences/phd/index.html.

Llewellyn-Thomas, H., McGreal, M., Thiel, E., Fine, S., and Erlichman, C., 1991. Patients' willingness to enter clinical trials: Measuring the association with perceived benefits and preference for decision participation. *Social Science & Medicine*, 32 (1), 35–42.

Lloyd-Williams, F., Mair, F., Shiels, C., Hanratty, B., Goldstein, P., Beaton, S., Capewell,

S., Lye, M., McDonald, R., Roberts, C., and Connelly, D., 2003. Why are patients in clinical trials of heart failure not like those we see in every day practice? *Journal of Clinical Epidemiology*, 56, 1157–1162.

Locock, L. and Smith, L., 2011. Personal benefit, or benefiting others ? Deciding whether to take part in clinical trials. *Clinical Trials*, 8, 85–93.

Look, M.P., van Putten, W.L.J., Duffy, M.J., Harbeck, N., Christensen, I.J., Thomssen, C., Kates, R., Spyratos, F., Ferno, M., Eppenberger-Castori, S., Sweep, C.G.J.F., Ulm, K., Peyrat, J.-P., Martin, P.-M., Magdelenat, H., Brunner, N., Duggan, C., Lisboa, B.W., Bendahl, P.-O., Quillien, V., Daver, A., Ricolleau, G., Meijer-van Gelder, M.E., Manders, P., Fiets, W.E., Blankenstein, M.A., Broet, P., Romain, S., Daxenbichler, G., Windbichler, G., Cufer, T., Borstnar, S., Kueng, W., Beex, L.V.A.M., Klijn, J.G.M., O'Higgins, N., Eppenberger, U., Janicke, F., Schmitt, M., and Foekens, J.A., 2002. Pooled Analysis of Prognostic Impact of Urokinase-Type Plasminogen Activator and Its Inhibitor PAI-1 in 8377 Breast Cancer Patients. *Journal of the National Cancer Institute*, 94 (2), 116–128.

Lyman, G.H. and Kuderer, N.M., 2005. The strengths and limitations of meta-analyses based on aggregate data. *BMC Medical Research Methodology*, 5 (14), 1–7.

Madurasinghe, V.W., Sandra Eldridge on behalf of MRC START Group and Gordon Forbes on behalf of the START Expert Consensus Group, and Eldridge, S., 2016. Guidelines for reporting embedded recruitment trials. *Trials*, 17 (27), 1–25.

Mangalore, R. and Knapp, M., 2007. Cost of schizophrenia in England. *Journal of Mental Health Policy and Economics*, 10 (1), 23.

Marcantonio, E.R., Aneja, J., Jones, R.N., Alsop, D.C., Fong, T.G., Crosby, G.J., Culley, D.J., Cupples, L.A., and Inouye, S.K., 2008. Maximizing clinical research participation in vulnerable older persons: identification of barriers and motivators. *Journal of the American Geriatrics Society*, 56 (8), 1522–7.

Marcellus, L., 2004. Are We Missing Anything? Pursuing Research on Attrition. *Canadian Journal of Nursing Research*, 36, 82–98.

Marder, S., Essock, S., Miller, A., Buchanan, R., Casey, D., Davis, J., Kane, J., Lieberman, J., Schooler, N., and Covell, N., 2014. Physical health monitoring of patients with schizophrenia. *American Journal of Psychiatry*, 161, 1334–1339.

Martin, J.L.R., Pérez, V., Sacristán, M., Rodríguez-Artalejo, F., Martínez, C., and Alvarez, E., 2006. Meta-analysis of drop-out rates in randomised clinical trials, comparing typical and atypical antipsychotics in the treatment of schizophrenia. *European Psychiatry*, 21, 11–20.

Mason, V.L., Shaw, A., Wiles, N.J., Mulligan, J., Peters, T.J., Sharp, D., and Lewis, G., 2007. GPs' experiences of primary care mental health research: a qualitative study of the barriers to recruitment. *Family Practice*, 24 (5), 518–25.

Mausbach, B.T., Cardenas, V., McKibbin, C.L., Jeste, D. V., and Patterson, T.L., 2008. Reducing Emergency Medical Service Use in Patients with Chronic Psychotic Disorders: Results from the FAST Intervention Study. *Behavioura Research and Therapy*, 46 (1), 145–153.

McCann, S.K., Campbell, M.K., and Entwistle, V.A., 2010. Reasons for participating in randomised controlled trials: conditional altruism and considerations for self. *Trials*, 11, 31.

McCrone, P., Dhanasiri, S., Patel, A., Knapp, M., and Lawton-Smith, S., 2008. *Paying the Price. The cost of mental health care in England to 2026*. London.

McDonald, A., Knight, R., Campbell, M., Entwistle, V., Grant, A.M., Cook, J., Elbourne, D.R., Francis, D., Garcia, J., Roberts, I., and Snowdon, C., 2006. What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. *Trials*, 7 (9), 1–8.

McDonell, M., Short, R., Berry, C., and Dyck, D., 2003. Burden in schizophrenia caregivers: impact of family psychoeducation and awareness of patient suicidality. *Family Process*, 42, 91–103.

McGrath, J., Saha, S., Chant, D., and Welham, J., 2008. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiology*, 30, 67–76.

Medical Research Council, 2000. *A Framework for Development and Evaluation of RCTs for Complex Interventions to Improve Health*.

Mee, D., 2009. Retention in Randomised Trials Project. *Durham Anthropology Journal*, 16 (1), 63–70.

Michie, S., Fixsen, D., Grimshaw, J., and Eccles, M., 2009. Specifying and reporting

complex behaviour change interventions: the need for a scientific method. *Implementation Science*, 4 (40).

Mills, E.J., Seely, D., Rachlis, B., Griffith, L., Wu, P., Wilson, K., Ellis, P., and Wright, J.R., 2006. Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors. *Lancet Ocology*, 7, 141–148.

Miranda, J., 1996. Introduction to the special section on recruiting and retaning minorities in psychotherapy research. *Journal of Consulting and Clinical Psychology*, 64 (5), 848–850.

Mitchell, A. and Selmes, T., 2007. Why don't patients attend their appointments? Maintaining engagement with psychiatric services. *Advances in Psychiatric Treatment*, 13, 423–434.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., and the PRISMA Group, 2009. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Annals of Internal Medicines of Internal Medicine*, 151 (4), 264–269.

Moher, D., Schulz, K.F., and Altman, D.G., 2001. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet*, 357, 1191–1194.

Moncrieff, J. and Cohen, D., 2009. How do psychiatric drugs work? *BMJ*, 338.

Montes, J., Maurino, J., Diez, T., and Saiz-Ruiz, J., 2010. Telephone-based nursing strategy to improve adherence to antipsychotic treatment in schizophrenia: A controlled trial. *International Journal of Psychiatry in Clinical Practice*, 14 (4), 274–281.

Montes, J.M., Medina, E., Gomez-Beneyto, M., and Maurino, J., 2012. A short message service (SMS)-based strategy for enhancing adherence to antipsychotic medication in schizophrenia. *Psychiatry Research*, 200 (2–3), 89–95.

Montgomery, P., Grant, S.S., Hopewell, S., Macdonald, G., Moher, D., Michie, S., and Mayo-Wilson, E., 2013. Protocol for CONSORT-SPI: an extension for social and psychological interventions. *Implementation Science*, 8 (1), 99.

Moorman, P.G., Newman, B., Millikan, R.C., Tse, C.K., and Sandler, D.P., 1999.

Participation rates in a case-control study: the impact of age, race, and race of interviewer. *Annals of Epidemiology*, 9 (3), 188–195.

Morgan, C., Lappin, J., Heslin, M., Donoghue, K., Lomas, B., Reininghaus, U., Onyejiaka, A., Croudace, T., Jones, P., and RM, M., 2014. Reappraising the long-term course and outcome of psychotic disorders: the AESOP-10 study. *Psychological Medicine*, 44, 2713–2726.

Morgan, D., 2013. Pragmatism as a Paradigm for Social Research. *Qualitative Inquiry*, 20 (8), 1045–1053.

Moritz, S., Veckenstedt, R., Andreou, C., Bohn, F., Hottenrott, B., Leighton, L., Kother, U., Woodward, T.S., Treszl, A., Menon, M., Schneider, B.C., Pfueller, U., and Roesch-Ely, D., 2014. Sustained and 'sleeper' effects of group metacognitive training for schizophrenia: A randomized clinical trial. *JAMA Psychiatry*, 71 (10), 1103–1111.

Moritz, S., Veckenstedt, R., Bohn, F., Hottenrott, B., Scheu, F., Randjbar, S., Aghotor, J., Kother, U., Woodward, T.S., Treszl, A., Andreou, C., Pfueller, U., and Roesch-Ely, D., 2013. Complementary group Metacognitive Training (MCT) reduces delusional ideation in schizophrenia. *Schizophrenia Research*, 151 (1–3), 61–69.

Morrison, Z., Douglas, A., Bhopal, R., and Sheikh, A., 2014. Understanding experiences of participating in a weight loss lifestyle intervention trial: a qualitative evaluation of South Asians at high risk of diabetes. *BMJ Open*, 4 (6).

Morse, E., Simon, P., Besch, C., and Walker, J., 1995. Issues of recruitment, retention and compliance in community-based clinical trials with underserved populations. *Applied Nursing Research*, 8 (1), 8–14.

Moser, D., Dracup, K., and Doering, L., 2000. Factors differentiating droputs from completers in a longitudinal, multicenter clinical trial. *Nursing Research*, 49 (2), 9–116.

Moser, D.J., Schultz, S.K., Arndt, S., Benjamin, M.L., Fleming, F.W., Brems, C.S., Paulsen, J.S., Appelbaum, P.S., and Andreasen, N.C., 2002. Capacity to provide informed consent for participation in schizophrenia and HIV research. *American Journal of Psychiatry*, 159 (7), 1201–1207.

Mueller, D.R., Schmidt, S.J., and Roder, V., 2015. One-Year Randomized Controlled Trial and Follow-Up of Integrated Neurocognitive Therapy for Schizophrenia Outpatients. *Schizophrenia Bulletin*, 41 (3), 604–616.

Murray, C. and Lopez, A., 1996. *The global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*. Boston.

Nash, M., 2013. Diagnostic overshadowing: a potential barrier to physical health care for mental health service users. *Mental Health Practice*, 17 (4), 22–26.

National Institute for Health and Care Excellence, 2014. Psychosis and schizophrenia in adults: prevention and management.

National Research Ethics Service, 2009. *Information Sheet and Consent Forms: Guidance for Researchers and Reviewers*. London.

Naylor, C., Parsonage, M., McDaid, D., Knapp, M., Fossey, M., and Galea, A., 2012. Long-term conditions and mental health: The cost of co-morbidities. *The King's Fund and Centre for Mental Health*, 1–32.

Neeraj, A. and McHorney, C., 2000. Patient Preferences for Medical Decision Making: Who Really Wants to Participate? *Medical Care*, 38 (3), 335–341.

Newington, L. and Metcalfe, A., 2014. Factors influencing recruitment to research: qualitative study of the experiences and perceptions of research teams. *BMC Medical Research Methodology*, 14, 10.

NHS Centre for Reviews and Dissemination, 2000. Psychosocial interventions for schizophrenia. *Effective Health Care*, 6 (3).

Noordzij, M., Tripepi, G., Dekker, F., Zoccali, C., Tanck, M., and Jager, K., 2010. Sample size calculations: basic principles and common pitfalls. *Nephrology Dialysis Transplantation*, 25 (5), 1388–1393.

Nose, M., Barbui, C., and Tansella, M., 2003. How often do patients with psychosis fail to adhere to treatment programmes? A systematic review. *Psychological Medicine*, 33 (7), 1149–1160.

O'Connel, B., 2005. *Solution-Focused Therapy*. 2nd ed. London: Sage Publications.

O'Reilly, M. and Parker, N., 2012. Unsatisfactory saturation: A critical exploration of the notion of saturated sample sizes in qualitative research. *Qualitative Research Journal*, May, 1–8.

Oakley, A., Strange, V., Bonell, C., Allen, E., Stephenson, J., RIPPLE Study Team, and Team, R.S., 2006. Process evaluation in randomised controlled trials of complex interventions. *British Medical Journal*, 332 (7538), 413–6.

Ong, J.C., Kuo, T.F., and Manber, R., 2008. Who is at risk for dropout from group cognitive-behavior therapy for insomnia? *Journal of Psychosomatic Research*, 64 (4), 419–425.

van Oosterhout, B., Krabbendam, L., de Boer, K., Ferwerda, J., van der Helm, M., Stant, A., and van der Gaag, M., 2014. Metacognitive group training for schizophrenia spectrum patients with delusions: a randomized controlled trial. *Psychological Medicine*, 44 (14), 3025–3035.

Van Os, J., Altamura, A.C., Bobes, J., Gerlach, J.E.S., Hellewell, J.S.E., Kasper, S., Naber, D., Robert, P., and Well, J.S.E.H., 2004. Evaluation of the Two-Way Communication Checklist as a clinical intervention. *British Journal of Psychiatry*, 184, 79–83.

Palmer, B., Savla, G., Roesch, S., and Jeste, D., 2013. Changes in capacity to consent over time in patients involved in psychiatric research. *The British Journal of Psychiatry*, 202 (6), 454–458.

Parkinson, S., Midgley, N., Holmes, J., Stapley, E., and Eatough, V., 2015. Framework Analysis: A worked example of a study exploring young people's experiences of depression. *Qualitative Research in Psychology*, 13 (2), 109–129.

Parvaiz, G., Mufti, O., and Wahab, M., 2016. Pragmatism for Mixed Method Research at Higher Education Level. *Business & Economic Review*, 8 (2), 67–79.

Patel, A., McCrone, P., Leese, M., Amaddeo, F., Tansella, M., Kilian, R., Angermeyer, M., Kikkert, M., Schene, A., and Knapp, M., 2013. Cost-effectiveness of adherence therapy versus health education for people with schizophrenia: randomised controlled trial in four European countries. *Cost Effectiveness and Resource Allocation*, 11 (1), 12.

Patel, R., Oduola, S., Callard, F., Wykes, T., Broadbent, M., Stewart, R., Craig, T.K.J., and McGuire, P., 2017. What proportion of patients with psychosis is willing to take part in research? A mental health electronic case register analysis. *BMJ Open*, 7 (3), e013113.

Patterson, S., Kramo, K., Soteriou, T., and Crawford, M.J., 2010. The great divide: a qualitative investigation of factors influencing researcher access to potential randomised controlled trial participants in mental health settings. *Journal of Mental Health*, 19 (6), 532–41.

Patterson, S., Mairs, H., and Borschmann, R., 2011. Successful recruitment to trials: a phased approach to opening gates and building bridges. *BMC Medical Research Methodology*, 11 (1), 73.

Patterson, T.L., Mausbach, B.T., McKibbin, C., Goldman, S., Bucardo, J., and Jeste, D. V., 2006. Functional Adaptation Skills Training (FAST): A randomized trial of a psychosocial intervention for middle-aged and older patients with chronic psychotic disorders. *Schizophrenia Research*, 86 (1–3), 291–299.

Patton, M., 1999. Enhancing the quality and credibiliy of qualitative analysis. *Health Services Research*, 34 (5), 1189–1208.

Perera, R., Heneghan, C., Yudkin, P., Medicine, E.B., and Yudkin, P., 2007. A graphical method for depicting randomised trials of complex interventions Making the what, when, and who of non-drug treatments easier to understand would benefit. *British Medical Journal*, 334, 127–129.

Petticrew, M., 2011. When are complex interventions 'complex'? When are simple interventions 'simple'? *European Journal of Public Health*, 21 (4), 397–398.

Phillips, B., Ranasinghe, N., and Stewart, L.A., 2017. Ethical Implications of Sharing Individual Patient Data for Prognostic Meta-analysis [poster presentation] [online]. Available from: https://www.york.ac.uk/inst//crd/Posters/Ethical Implications of Sharing Individual Patient Data for Prognostic Meta-analysis.pdf [Accessed 25 Aug 2017].

Pino, C., Boutron, I., and Ravaud, P., 2012. Inadequate description of educational interventions in ongoing randomized controlled trials. *Trials*, 13 (63).

Pitkanen, A., Valimaki, M., Kuosmanen, L., Katajisto, J., Koivunen, M., Hatonen, H., Patel, A., and Knapp, M., 2012. Patient education methods to support quality of life and functional ability among patients with schizophrenia: A randomised clinical trial. *Quality of Life Research*, 21 (2), 247–256.

Pitts, M. and Miller-Day, M., 2007. Upward turning points and positive rapport-development across time in researcher-participant relationships. *Qualitative Research*, 7 (2), 177–201.

Plint, A.C., Moher, D., Morrison, A., Schulz, K., Altman, D.G., Hill, C., and Gaboury, I., 2006. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. *Medical Journal of Australia*, 185 (5), 263–267.

Polit, D. and Hungler, B., 1995. *Nursing Research: Principles and Methods*. 5th ed. Philadelphia: Lippincott.

Polit, D.F. and Gillespie, B.M., 2010. Intention-to-treat in randomized controlled trials: recommendations for a total trial strategy. *Research in Nursing & Health*, 33 (4), 355–368.

Preference Collaborative Review Group, 2009. Patients' preferences within randomized trials: systematic review and patient level meta-analysis. *British Medical Journal*, 338 (a1864).

Priebe, S., Kelley, L., Golden, E., Mccrone, P., Kingdon, D., Rutterford, C., and McCabe, R., 2013. Effectiveness of structured patient-clinician communication with a solution focused approach (DIALOG+) in community treatment of patients with psychosis – a cluster randomised controlled trial. *BMC Psychiatry*, 13 (173), 1–7.

Priebe, S., Kelley, L., Omer, S., Golden, E., Wash, S., Khanom, H., Kingdon, D., Rutterford, C., McCrone, P., and McCabe, R., 2015. The Effectiveness of a Patient-Centred Assessment with a Solution-Focused Approach (DIALOG+) for Patients with Psychosis: A Pragmatic Cluster-Randomised Controlled Trial in Community Care. *Psychotherapy and Psychosomatics*, 84 (5), 304–313.

Priebe, S., McCabe, R., Bullenkamp, J., Hansson, L., Lauber, C., Martinez-Leal, R., Rössler, W., Salize, H., Svensson, B., Torres-Gonzales, F., Van Den Brink, R., Wiersma, D., and Wright, D.J., 2007. Structured patient-clinician communication

and 1-year outcome in community mental healthcare: cluster randomised controlled trial. *British Journal of Psychiatry*, 191 (5), 420–6.

Priebe, S., Savill, M., Wykes, T., Bentall, R., Lauber, C., Reininghaus, U., McCrone, P., Mosweu, I., Bremner, S., Eldridge, S., and Röhricht, F., 2016. Clinical effectiveness and cost-effectiveness of body psychotherapy in the treatment of negative symptoms of schizophrenia: a multicentre randomised controlled trial. *Health Technology Assessment*, 20 (11), vii–xxiii, 1-100.

Probstfield, J.L. and Frye, R.L., 2011. Strategies for Recruitment and Retention of Participants in Clinical Trials. *JAMA*, 306 (16), 1798.

Rabinowitz, J., Levine, S.Z., Barkai, O., and Davidov, O., 2009. Dropout rates in randomized clinical trials of antipsychotics: a meta-analysis comparing first- and second-generation drugs and an examination of the role of trial design features. *Schizophrenia Bulletin*, 35 (4), 775–88.

Raue, P., Schulberg, H., Heo, M., Klimstra, S., and Bruce, M., 2009. Patients' depression treatment preferences and initiation, adherence, and outcome: a randomized primary care study. *Psychiatric Services*, 6, 337–343.

Reininghaus, U., Dutta, R., Dazzan, P., Doody, G., Fearon, P., Lappin, J., Heslin, M., Onyejiaka, A., Donoghue, K., and Lomas, B., 2015. Mortality in Schizophrenia and Other Psychoses: A 10-Year Follow-up of the AESOP First-Episode Cohort. *Schizophrenia Bulletin*, 41 (3), 664–673.

Reneses, B., Munoz, E., and Jose Lopez-Ibor, J., 2009. Factors predicting drop-out in community mental health centres. *World Psychiatry*, 8, 173–177.

Reynolds, J., Mangesho, P., Vestergaard, L.S., and Chandler, C., 2011. Exploring meaning of participation in a clinical trial in a developing country setting: implications for recruitment. *Trials*, 12 (Suppl 1), A114.

Ribisl, K.M., Walton, M.A., Mowbray, C.T., Luke, D.A., Davidson, W.S., and Bootsmiller, B.J., 1996. Minimizing participant attrition in panel studies through the use of effective retention and tracking strategies: Review and recommendations. *Evaluation and Program Planning*, 19 (1), 1–25.

Rick, J., Graffy, J., Knapp, P., Small, N., Collier, D.J., Eldridge, S., Kennedy, A., Salisbury,

C., Treweek, S., Torgerson, D., Wallace, P., Madurasinghe, V., Hughes-Morley, A., and Bower, P., 2014. Systematic techniques for assisting recruitment to trials (START): study protocol for embedded, randomized controlled trials. *Trials*, 15 (1), 407.

Riley, R.D., Lambert, P.C., and Abo-Zaid, G., 2010. Meta-analysis of individual participant data: rationale, conduct, and reporting. *British Medical Journal*, 340, c221.

Ritchie, J., Lewis, J., McNaughton Nicholls, C., and Ormston, R., 2014. *Qualitative Research Practice*. London: Sage.

Ritchie, J. and Spencer, L., 1994. Qualitative data analysis for applied policy research. *In*: B. Bryman and R. Burgess, eds. *Analyzing qualitative data*. London and New York: Routledge, 173–194.

Ritchie, J. and Spencer, L., 2002. Qualitative Data Analysis for Applied Policy Research. *In*: M. Huberman and M. Miles, eds. *The Qualitative Researcher's Companion*. Thousand Oaks, CA: Sage, 305–330.

Roberts, L., 1998. Ethics of psychiatric research: conceptual issues and empirical findings. *Comprehensive Psychiatry*, 39, 99–110.

Roberts, L.W., Warner, T.D., Anderson, C.T., Smithpeter, M. V, and Rogers, M.K., 2004. Schizophrenia research participants' responses to protocol safeguards: recruitment, consent, and debriefing. *Schizophrenia research*, 67 (2–3), 283–91.

Roberts, L.W., Warner, T.D., and Brody, J.L., 2000. Perspectives of Patients With Schizophrenia and Psychiatrists Regarding Ethically Important Aspects of Research Participation. *American Journal of Psychiatry*, 157, 67–74.

Roberts, L.W., Warner, T.D., Brody, J.L., Roberts, B., Lauriello, J., and Lyketsos, C., 2002. Patient and psychiatrist ratings of hypothetical schizophrenia research protocols: assessment of harm potential and factors influencing participation decisions. *American Journal of Psychiatry*, 159 (4), 573–84.

Roberts, L.W., Warner, T.D., Hammond, K.G., and Hoop, J.G., 2006. Views of people with schizophrenia regarding aspects of research: study size and funding sources. *Schizophrenia Bulletin*, 32 (1), 107–15.

Robinson, K.A., Dennison, C.R., Wayman, D.M., Pronovost, P.J., and Needham, D.M., 2007. Systematic review identifies number of strategies important for retaining study participants. *Journal of Clinical Epidemiology*, 60 (8), 757–65.

Rodriguez-Osorio, C.A. and Dominguez-Cherit, G., 2008. Medical decision making: paternalism versus patient-centered (autonomous) care. *Current Opinion in Critical Care*, 14 (6), 708–713.

Rojavin, M.A., 2005. Recruitment index as a measure of patient recruitment activity in clinical trials. *Contemporary Clinical Trials*, 26 (5), 552–556.

Rossi, A., Amaddeo, F., Bisoffi, G., Ruggeri, M., Thornicroft, G., and Tansella, M., 2002. Dropping out of care: inappropriate terminations of contact with community-based psychiatric services. *The British Journal of Psychiatry*, 181 (4), 331–338.

Russell, I., 1996. Towards effective prescribing, appropriate research and development methods. *In*: K. Bloor and N. Freemantle, eds. *Promoting cost effective prescribing in the UK National Health Service*. York, UK, UK: University of York, 30–57.

Rutterford, C., Taljaard, M., Dixon, S., Copas, A., and Eldridge, S., 2015. Reporting and methodological quality of sample size calculations in cluster randomized trials could be improved: a review. *Journal of Clinical Epidemiology*, 68 (6), 716–723.

Sackett, D.L., Rosemberg, W.M.C., Muir Gray, J.A., Haynes, R.B., and Scott Richardson, W., 1996. Evidence based medicine: what it is and what it isn' t. *British Medical Journal*, 312 (71), 1–3.

Sackett, D.L., Strauss, S., Richardson, S., Rosenberg, W., and Haynes, R., 2000. *Evidence-Based Medicine. How to Practice and Teach EBM*. 2nd ed. Edinburgh and London: Churchill Livingstone.

Sacristán, J., Aguarón, A., Avendaño-Solá, C., Garrido, P., Carrion, J., Gutierrez, A., Kroes, R., and Flores, A., 2016. Patient involvement in clinical research: why, when, and how. *Patient Preference and Adherence*, 10, 631–640.

Saha, S., Chant, D., Welham, J., and McGrath, J., 2005. A Systematic Review of the Prevalence of Schizophrenia. *PLoS Medicine*, 2 (5), 413–433.

Salyers, M.P., McGuire, A.B., Kukla, M., Fukui, S., Lysaker, P.H., and Mueser, K.T., 2014. A randomized controlled trial of illness management and recovery with an active

control group. *Psychiatric Services*, 65 (8), 1–7.

Schirmer, U.B., Steinert, T., Flammer, E., and Borbé, R., 2015. Skills-based medication training program for patients with schizophrenic disorders: a rater-blind randomized controlled trial. *Patient Preference and Adherence*, 9, 541–9.

Schulz, K.F. and Grimes, D.A., 2002. Sample size slippages in randomised trials: Exclusions and the lost and wayward. *Lancet*, 359 (9308), 781–785.

Schulz, M., Gray, R., Spiekermann, A., Abderhalden, C., Behrens, J., and Driessen, M., 2013. Adherence therapy following an acute episode of schizophrenia: A multi-centre randomised controlled trial. *Schizophrenia Research*, 146 (1–3), 59–63.

Seale, C., Gobo, G., Gubrium, J., and Silverman, D., 2007. *Qualitative Research Practice*. London: Sage.

Senturia, Y., Mortimer, K., Baker, D., Gergen, P., Mitchell, H., and Joseph, C., 1998. Successful techniques for study participation in an inner-city population. *Controlled Clinical Trials*, 19, 544–554.

Seshia, S.S. and Young, G.B., 2014. The Evidence-based Medicine Paradigm: Where are We 20 Years Later? Part 2. *Canadian Journal of Neurological Sciences*, 40 (4), 475–481.

Shanyinde, M., Pickering, R.M., and Weatherall, M., 2011. Questions asked and answered in pilot and feasibility randomized controlled trials. *BMC Medical Research Methodology*, 11 (1), 117.

Shefer, G., Henderson, C., Howard, L.M., Murray, J., and Thornicroft, G., 2014. Diagnostic Overshadowing and Other Challenges Involved in the Diagnostic Process of Patients with Mental Illness Who Present in Emergency Departments with Physical Symptoms - A Qualitative Study. *PLoS ONE*, 9 (11).

Sibitz, I., Amering, M., Gossler, R., Unger, A., and Katschnig, H., 2007. One-year outcome of low-intensity booster sessions versus care as usual in psychosis patients after a short-term psychoeducational intervention. *European Psychiatry*, 22 (4), 203–210.

Sidani, S., Fox, M., Streiner, D.L., Miranda, J., Fredericks, S., and Epstein, D.R., 2015. Examining the influence of treatment preferences on attrition, adherence and

outcomes: a protocol for a two-stage partially randomized trial. *BMC Nursing*, 14 (1), 57.

Silverman, D., 2011. *Interpreting qualitative data*. London: Sage Publications.

Silverman, D., 2013. *Doing Qualitative Research*. 4th ed. London: SAGE.

Silverstein, S.M., Roché, M.W., Khan, Z., Carson, S.J., Malinovsky, I., Newbill, W.A., Menditto, A.A., and Wilkniss, S.M., 2014. Enhancing and promoting recovery in attentionally impaired people diagnosed with schizophrenia: Results from a randomized controlled trial of attention shaping in a partial hospital program. *American Journal of Psychiatric Rehabilitation*, 17 (3), 272–305.

Simmonds, B., Turner, N., Thomas, L., Campbell, J., Lewis, G., Wiles, N., and Turner, K., 2013. Patients' experiences of participating in a large-scale trial of cognitive behavioural therapy for depression: a mixed methods study. *Family Practice*, 30 (6), 705–11.

Simmonds, M.C., Higgins, J.P., Stewart, L. a, Tierney, J.F., Clarke, M.J., and Thompson, S.G., 2005. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clinical Trials*, 2 (3), 209–217.

Slevin, M., Mossman, J., Bowling, A., Leonard, R., Steward, W., Harper, P., McIllmurray, M., and Thatcher, N., 1995. Volunteers or victims: Patients' views of randomised cancer clinical trials. *British Journal of Cancer*, 71 (6), 1270–1274.

Snow, W., Connett, J., Sharma, S., and Murray, R., 2007. Predictors of attendance and dropout at the Lung Health Study 11-year follow-up. *Contemporary Clinical Trials*, 28 (1), 25–32.

Sohanpal, R., Hooper, R., Hames, R., Priebe, S., and Taylor, S., 2012. Reporting participation rates in studies of non-pharmacological interventions for patients with chronic obstructive pulmonary disease: a systematic review. *Systematic Reviews*, 1 (1), 66.

Stanford, P., Monte, D., Briggs, F., Flynn, P., Tanney, M., Ellenberg, J., Clingan, K., and Rodgers, A., 2003. Recruitment and retention of Adoles- cent participants in HIV Research: Findings from the REACH Project. *Journal of Adolescent Health*, 32, 192–203.

Staniszewska, S., Adebajo, A., Barber, R., Beresford, P., Brady, L., Brett, J., Elliott, J., Evans, D., Haywood, K., Jones, D., Mockford, C., Nettle, M., Rose, D., and Williamson, T., 2011. Developing the evidence base of patient and public involvement in health and social care research: the case for measuring impact. *International Journal of Consumer Studies*, 35 (6), 628–632.

Staring, A.B.P., Van Der Gaag, M., Koopmans, G.T., Selten, J.P., Van Beveren, J.M., Hengeveld, M.W., Loonen, A.J.M., and Mulder, C.L., 2010. Treatment adherence therapy in people with psychotic disorders: Randomised controlled trial. *British Journal of Psychiatry*, 197 (6), 448–455.

Stasiewicz, P.R.P. and Stalker, R., 1999. A comparison of three 'interventions' on pretreatment dropout rates in an outpatient substance abuse clinic. *Addictive Behaviors*, 24 (4), 579–582.

Stein, D., Ipser, J., and Seedat, S., 2006. Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews*.

Stephenson, J. and Imrie, J., 1998. Why do we need randomised controlled trials to assess behavioural interventions? *BMJ*, 316 (7131), 611–613.

Stewart, L.A. and Tierney, J.F., 2002. To IPD or not to IPD? *Evaluation & The Health Professions*, 25 (1), 76–97.

Stone, C., Palmer, J., Saxby, P., and Devaraj, V., 1999. Reducing nonattendance at outpatient clinics. *Journal of the Royal Society of Medicine*, 92 (3), 114.

Straus, S.E. and McAlister, F.A., 2000. Evidence-based medicine: A commentary on common criticisms. *Canadian Medical Association or its licensors*, 163 (7), 837–841.

Street, R., Makoul, G., Arora, N., and Epstein, R., 2009. How does communication heal? Pathways linking clinician-patient communication to health outcomes. *Patient Education and Counseling*, 74 (3), 295–301.

Street, R. and Millay, B., 2001. Analyzing Patient Participation in Medical Encounters. *Health Communication*, 13 (1), 61–73.

Stubbs, B., Vancampfort, D., Rosenbaum, S., Ward, P.B., Richards, J., Soundy, A., Veronese, N., Solmi, M., and Schuch, F.B., 2016. Dropout from exercise randomized controlled trials among people with depression: A meta-analysis and

meta regression. *Journal of Affective Disorders*, 190, 457–466.

Sullivan, J., 2004. Subject Recruitment and Retention: Barriers to Success. *Applied Clinical Trials*, 13 (4), 50–54.

Sumner, K., Haddock, G., Hartley, S., Kilbride, M., McCusker, M., Pitt, L., Woodward, S., and Barrowclough, C., 2014. Preferences for psychological therapy in psychosis: trial participation, mode of treatment, and willingness to be randomised. *Journal of Mental Health*, 23 (2), 67–71.

Sweeney, A. and Morgan, L., 2009. The Levels and Stages of Service User/Survivor Involvement in Research. *In*: J. Wallcraft, B. Schrank, and M. Amering, eds. *Handbook of Service User Involvement in Mental Health Research*. London: Wiley-Blackwell, 25–35.

Swift, J. and Callahan, J., 2009. The impact of client treatment preferences on outcome: a meta-analysis. *Journal of Clinical Psychology*, 65 (4), 1–14.

Swift, J., Callahan, J., and Vollmer, B., 2011. Preferences. *Journal of Clinical Psychology*, 67 (2), 155–165.

Swift, J.K. and Greenberg, R.P., 2012. Premature discontinuation in adult psychotherapy: A meta-analysis. *Journal of Consulting and Clinical Psychology*, 80 (4), 547–559.

Szumilas, M., 2010. Explaining odds ratios. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, 19 (3), 227–229.

Szymczynska, P., Walsh, S., Greenberg, L., and Priebe, S., 2017. Attrition in trials evaluating complex interventions for schizophrenia: Systematic review and meta-analysis. *Journal of Psychiatric Research*, 90, 67–77.

Tallon, D., Mulligan, J., Wiles, N., Thomas, L., Peters, T.J., Elgie, R., Sharp, D., and Lewis, G., 2011. Involving patients with depression in research: survey of patients' attitudes to participation. *British Journal of General Practice*, 61 (585), 134–41.

Tashakkori, A. and Teddlie, C., 1998. *Mixed methodology; Combining qualitative and quantitative approaches.* Applied So. Sage Publications.

Teachman, B.A., Drabick, D.A.G., Hershenberg, R., Vivian, D., Barry, E., Goldfried,

M.R., Wolfe, B.E., and Goldfried, M.R., 2012. Bridging the Gap Between Clinical Research and Clinical Practice: Introduction to the Special Section. *Psychotherapy*, 49 (2), 97–100.

Teddlie, C. and Tashakkori, A., 2009. *Foundations of mixed methods research*. Thousand Oaks, CA: SAGE.

Terzian, E., Tognoni, G., Bracco, R., De Ruggieri, E., Ficociello, R. A., Mezzina, R., & Pillo, G., 2013. Social Network Intervention in Patients With Schizophrenia and Marked … *Canadian Journal of Psychiatry*, 58 (11), 622–631.

Thabane, L., Ma, J., Chu, R., Cheng, J., Ismaila, A., Rios, L.P., Robson, R., Thabane, M., Giangregorio, L., and Goldsmith, C.H., 2010. A tutorial on pilot studies: the what, why and how. *BMC Medical Research Methodology*, 10 (1), 1.

Thompson, A., Stuart, H., Bland, R., Arboleda-Florez, J., Warner, R., and Dickson, R., 2002. Attitudes about schizophrenia from the pilot site of the WPA worldwide campaign against the stigma of schizophrenia. *Social Psychiatry and Psychiatric Epidemiology*, 37 (10), 475–482.

Thompson, J., Berk, M., Dean, O., Kohlmann, K., Jeavons, S., Bush, A., and Copolov, D., 2011. Who's left? Symptoms of schizophrenia that predict clinical trial dropout. *Human Psychopharmacology*, 26 (8), 609–13.

Thompson, L. and McCabe, R., 2012. The effect of clinician-patient allicance and communication on treatment adherence in mental health care: a systematic review. *BMC Psychiatry*, 12 (87).

Thornley, B. and Adams, C., 1998. Content and quality of 2000 controlled trials in schizophrenia over 50 years. *British Medical Journal*, 317 (7167), 1181–1184.

Tierney, J.F., Vale, C., Riley, R., Smith, C.T., Stewart, L., Clarke, M., and Rovers, M., 2015. Individual Participant Data (IPD) Meta-analyses of Randomised Controlled Trials: Guidance on Their Use. *PLoS Medicine*, 12 (7).

Toerien, M., Brookes, S.T., Metcalfe, C., de Salis, I., Tomlin, Z., Peters, T.J., Sterne, J., and Donovan, J.L., 2009. A review of reporting of participant recruitment and retention in RCTs in six major journals. *Trials*, 10, 52.

Trauth, J., Musa, M., Siminoff, L., Jewell, I., and Ricci, E., 2000. Public Attitudes

regarding willingness to participate in medical research studies. *Journal of Health & Social Policy*, 12 (2), 23–43.

Treweek, S., Lockhart, P., Pitkethly, M., Cook, J.A., Kjeldstrøm, M., Johansen, M., Taskila, T.K., Sullivan, F.M., Wilson, S., Jackson, C., Jones, R., and Mitchell, E.D., 2013. Methods to improve recruitment to randomised controlled trials : Cochrane systematic review and meta-analysis. *BMJ Open*, 3.

Treweek, S., Pitkethly, M., Cook, J., Kjeldstrom, M., Taskila, T., Johansen, M., Sullivan, F., Wilson, S., Jackson, C., Jones, R., and Mitchell, E., 2011. Strategies to improve recruitment to randomised controlled trials. *Cochrane Database of Systematic Reviews*, 10.

Trivedi, R.B., Szarka, J.G., Beaver, K., Brousseau, K., Nevins, E., Yancy, W.S., Slade, A., and Voils, C.I., 2013. Recruitment and retention rates in behavioral trials involving patients and a support person: a systematic review. *Contemporary Clinical Trials*, 36 (1), 307–18.

Tsang, A.K.T., 2000. Bridging the Gap Between Clinical Practice and Research: An Integrated Practice-Oriented Model. *Journal of Social Service Research*, 26 (4), 69–90.

Tudur Smith, C. and Williamson, P.R., 2007. A comparison of methods for fixed effects meta-analysis of individual patient data with time to event outcomes. *Clinical Trials*, 4 (6), 621–30.

Turner, L., Shamseer, L., Altman, D.G., Schulz, K.F., and Moher, D., 2012. Does use of the CONSORT Statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane review. *Systematic Reviews*, 1 (1), 60.

Veldhuizen, S., Adair, C.E., Methot, C., Kopp, B.C., O'Campo, P., Bourque, J., Streiner, D.L., and Goering, P.N., 2015. Patterns and predictors of attrition in a trial of a housing intervention for homeless people with mental illness. *Social psychiatry and psychiatric epidemiology*, 50 (2), 195–202.

Velligan, D., Mintz, J., Maples, N., Li, X., Gajewski, S., Carr, H., and Sierra, C., 2013. A randomized trial comparing in person and electronic interventions for improving adherence to oral medications in schizophrenia. *Schizophrenia Bulletin*, 39 (5),

999–1007.

Velligan, D.I., Tai, S., Roberts, D.L., Maples-Aguilar, N., Brown, M., Mintz, J., and Turkington, D., 2015. A Randomized Controlled Trial Comparing Cognitive Behavior Therapy, Cognitive Adaptation Training, Their Combination and Treatment as Usual in Chronic Schizophrenia. *Schizophrenia Bulletin*, 41 (3), 597–603.

Verheggen, F., Nieman, F., Reerink, E., and Kok, G., 1998. Patient satisfaction with clinical trial participation. *International Journal for Quality in Health Care*, 10 (4), 319–330.

Villaruel, A., Jemmott, J., and Jemmot, L., 2006. A Randomized Controlled Trial Testing an HIV Prevention Intervention for Latino youth. *Archives of Pediatric and Adolescent Medicine*, 160 (8), 772–777.

Villeneuve, K., Potvin, S., Lesage, a., and Nicole, L., 2010. Meta-analysis of rates of drop-out from psychosocial treatment among persons with schizophrenia spectrum disorder. *Schizophrenia Research*, 121 (1–3), 266–270.

Wade, D. and Halligan, P., 2004. Do biomedical models of illness make for good healthcare systems? *British Medical Journal*, 329 (7479), 1398–1491.

Wahlbeck, K., Tuunainen, A., Ahokas, A., and Leucht, S., 2001. Dropout rates in randomised antipsychotic drug trials. *Psychopharmacology*, 155 (3), 230–233.

Warden, D., Trivedi, M.H., Wisniewski, S.R., Lesser, I.M., Mitchell, J., Balasubramani, G.K., Fava, M., Shores-Wilson, K., Stegman, D., and Rush, A.J., 2009. Identifying risk for attrition during treatment for depression. *Psychotherapy and Psychosomatics*, 78 (6), 372–379.

Wardenaar, K. and de Jonge, P., 2013. Diagnostic heterogeneity in psychiatry: towards an empirical solution. *BMC Medicine*, 11 (201).

Wendler, D., Krohmal, B., Emanuel, E., and Grady, C., 2008. Why Patients Continue to Participate in Clinical Research. *Archives of Internal Medicine*, 168 (12), 1294–1299.

Wiersma, D., Wanderling, J., Dragomirecka, E., Ganev, K., Harrison, G., An Der Heiden, W., Nienhuis, F., and Walsh, D., 2000. Social disability in schizophrenia: its development and prediction over 15 years in incidence cohorts in six European

centres. *Psychological Medicine*, 30, 1155–1167.

Wilde, V., 1992. Controversial hypotheses on the relationship between researcher and informant in qualitative research. *Journal of Advanced Nursing*, 17 (2), 234–242.

Williams, B., Irvine, L., McGinnis, A.R., McMurdo, M.E.T., and Crombie, I.K., 2007. 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 Services Research*, 7, 59.

Williams, D.K., Thrush, C.R., Armitage, T.L., Owen, R.R., Hudson, T.J., and Thapa, P., 2003. The Effect of Guideline Implementation Strategies on Akathisia Outcomes in Schizophrenia. *Journal of Applied Research*, 3 (4), 470–482.

Williams, M.T., Domanlco, J., Marques, L., Leblanc, N.J., and Turkhelmer, E., 2012. Barriers to Treatment Among African Americans with Obsessive-Compulsive Disorder. *Journal of Anxiety Disorders*, 26 (4), 555–563.

Willis, J., 2007. *Foundations of qualitative research: Interpretive and critical approaches.* Thousand Oaks, CA: Sage.

Wilson, K. and Rose, K., 1998. Patient recruitment and retention strate- gies in randomised controlled trials. *Nurse Researcher*, 6, 35–46.

Woodall, A., Morgan, C., Sloan, C., and Howard, L., 2010. Barriers to participation in mental health research: are there specific gender, ethnicity and age related barriers? *BMC Psychiatry*, 10 (1), 103.

Woolard, R.H., Carty, K., Wirtz, P., Longabaugh, R., Nirenberg, T.D., Minugh, P.A., Becker, B., and Clifford, P.R., 2004. Research fundamentals: Follow-up of subjects in clinical trials: Addressing subject attrition. *Academic Emergency Medicine*, 11 (8), 859–866.

World Health Organisation, 1992. *ICD-10 Classifications of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic Guidelines*. Geneva.

Wortman, P., 1978. Differential attrition: Another hazard of follow-up research. *American Psychologist*, 33, 1145–1146.

Xia, J., Adams, C., Bhagat, N., Bhagat, V., Bhoopathi, P., El-Sayeh, H., Pinfold, V., and

Takriti, Y., 2009. Losing participants before the trial ends erodes credibility of findings. *Psychiatric Bulletin*, 33 (7), 254–257.

Xiang, Y.T., Weng, Y.Z., Li, W.Y., Gao, L., Chen, G.L., Xie, L., Chang, Y.L., Tang, W.K., and Ungvari, G.S., 2007. Efficacy of the community re-entry module for patients with schizophrenia in Beijing, China: Outcome at 2-year follow-up. *British Journal of Psychiatry*, 190 (JAN.), 49–56.

Yancey, A.K., Ortega, A.N., and Kumanyika, S.K., 2006. Effective recruitment and retention of minority research participants. *Annual Review of Public Health*, 27, 1–28.

Yin, R., 2010. *Qualitative research from start to finish.* New York: The Guildford Press.

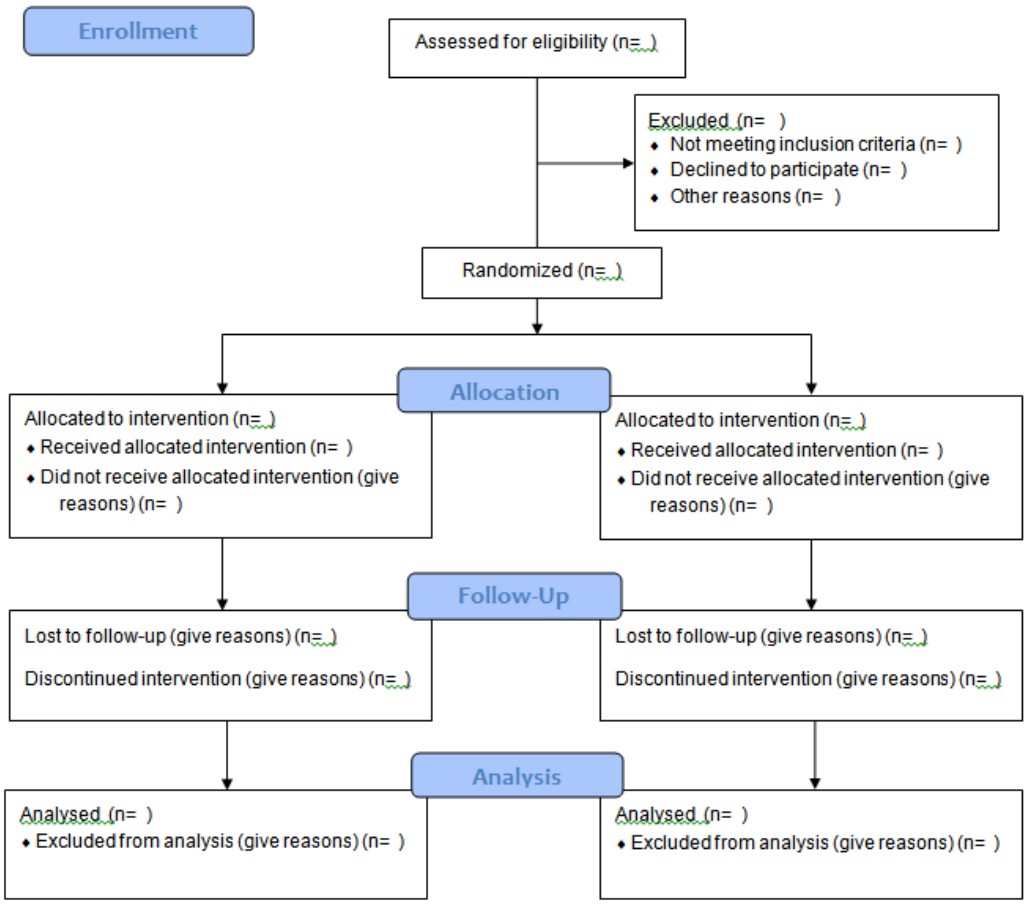
Zullino, D., Conus, P., Borgeat, F., and Bonsack, C., 2003. Readiness to participate in psychiatric research. *Canadian Journal of Psychiatry*, 48 (7), 480–484.

Zweben, A., Fucito, L., and O'Malley, S.., 2009. Effective Strategies for Maintaining Research Participation in Clinical Trials. *International Journal of Drug Policy*, 43 (4), 1–11.

Appendices

Appendix 1 CONSORT 2010 Flow Diagram

CONSORT 2010 Flow Diagram



Appendix 2 Systematic review manuscript

Journal of Psychiatric Research 90 (2017) 67–77

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Attrition in trials evaluating complex interventions for schizophrenia: Systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 17 October 2016
Received in revised form
27 January 2017
Accepted 8 February 2017

Keywords:
Psychosis
Schizophrenia
Treatment
Attrition
Retention
Review

ABSTRACT

Essential criteria for the methodological quality and validity of randomized controlled trials are the drop-out rates from both the experimental intervention and the study as a whole. This systematic review and meta-analysis assessed these drop-out rates in non-pharmacological schizophrenia trials. A systematic literature search was used to identify relevant trials with ≥100 sample size and to extract the drop-out data. The rates of drop-out from the experimental intervention and study were calculated with meta-analysis of proportions. Meta-regression was applied to explore the association between the study and sample characteristics and the drop-out rates. 43 RCTs were found, with drop-out from intervention ranging from 0% to 63% and study drop-out ranging from 4% to 71%. Meta-analyses of proportions showed an overall drop-out rate of 14% (95% CI: 13–15%) at the experimental intervention level and 20% (95% CI: 17–24%) at the study level. Meta-regression showed that the active intervention drop-out rates were predicted by the number of intervention sessions. In non-pharmacological schizophrenia trials, drop-out rates of less than 20% can be achieved for both the study and the experimental intervention. A high heterogeneity of drop-out rates across studies shows that even lower rates are achievable.

Contents

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http://dx.doi.org/10.1016/j.jpsychires.2017.02.009
0022-3956/

1. Introduction

Two major challenges in randomized controlled trials (RCTs) include treatment noncompliance and missing outcome data. These complications are caused by participants not receiving or discontinuing the allocated intervention and loss to follow-up. Although some attrition can be expected in clinical trials, ensuring retention of participants is crucial to achieve sufficient statistical power to detect the effect of treatment. There is no standard for acceptable drop-out rates but some evidence suggests that attrition levels as low as 5% may introduce risk of bias and the rate exceeding 20% can threaten trial validity (Polit and Hungler, 1995; Schulz and Grimes, 2002). The credibility of a trial also depends on the attrition rates. A survey involving patients, caregivers, statisticians and clinicians found drop-out out rates exceeding 25–30% can affect whether pharmacological trials in schizophrenia are judged as credible (Xia et al., 2009).

Loss of data can occur at different levels within a trial. Treatment noncompliance refers to issues with following the recommendations for prescribed treatments. In non-pharmacological trials it can be the failure to attend a required number of appointments or sessions (Nosé et al., 2003). Patients can also choose to completely discontinue an intervention. Treatment drop-out been estimated to be 13% in RCTs testing psychosocial treatments for people with schizophrenia (Villeneuve et al., 2010). In contrast to pharmacological trials, discontinuing a non-pharmacological intervention usually does not automatically exclude the participant from the follow-up, so outcome data can be collected if the participant is willing to provide them. Drop-out at the study level is defined as a failure to complete follow-up assessments, usually due to withdrawal from the study, and can occur following completing an intervention. Most research investigating drop-out of people with schizophrenia at a study level have focused on pharmacological trials, reporting 35% study drop-out in a meta-analysis of RCTs of antipsychotic drugs (Leucht et al., 2013). This contrast in the drop-out rates between pharmacological and non-pharmacological trials can be expected due to the differences in procedures (e.g. single-vs. double-blinding) (Huhn et al., 2014) and non-pharmacological trials not usually prohibiting taking already prescribed medication. Receiving pharmacotherapy on top of the experimental trial intervention might reduce the likelihood of dropping out even in case of the intervention not being efficacious for the patient.

To our knowledge there have been no systematic studies establishing the scale of drop-out from RCTs evaluating non-pharmacological interventions for schizophrenia at both the experimental intervention and the study level.

Complete outcome data from all randomized participants is necessary for a full application of the intention-to-treat (ITT) approach (Gupta, 2011), which is the 'gold standard' for analyzing the results from trials evaluating the effectiveness of a treatment in a pragmatic setting (Altman, 1996; Begg et al., 1996). ITT analysis includes all randomized participants, regardless of whether they adhered to or received the allocated intervention. The purpose of the ITT approach is to reflect a real-life effect of an intervention in clinical practice, taking into account the deviations from protocol that would occur in routine practice. Thus, every effort should be made to obtain complete outcome data for all randomized participants, including those who did not complete the intervention but continued to complete follow-up assessments.

Developing effective and efficient retention strategies for RCTs requires an understanding of what factors affect the likelihood of premature discontinuation of intervention or loss to follow-up. The vast majority of the literature on the determinants of attrition in psychiatric treatment has focused on pharmacological trials and identified factors negatively correlated with treatment adherence, such as substance misuse (Kampman and Lethinen, 1999; Nosé et al., 2003), unemployment (Nosé et al., 2003), unpleasant side effects of medication (Kampman and Lethinen, 1999), negative attitude towards medication (Kampman and Lethinen, 1999). In one available study analyzing drop-out from psychosocial treatment for schizophrenia the following variables were found to be associated with higher drop-out rates: being male, higher age, longer illness duration, longer treatment duration (Villeneuve et al., 2010). Lower drop-out rates were associated with study quality and inpatient setting (Villeneuve et al., 2010). These findings suggest that both study and sample characteristics can affect drop-out from clinical trials. Understanding what factors influence discontinuation of intervention and loss to follow-up can guide the development of strategies to limit these. Investigating relationships between specific study and sample characteristics and drop-out rates allows for examining if the data missing from those who dropped out is missing at random or whether individuals dropping out have any characteristics in common that make them more likely to prematurely discontinue participation in trials.

The aims of this study were first: to systematically identify relevant large-scale RCTs evaluating non-pharmacological interventions for individuals with schizophrenia; second: to perform meta-analyses to establish the proportion of participants who drop-out of a) experimental intervention and b) study; and thirdly to perform a meta-regression to examine the predictors of drop-out rates.

2. Materials and methods

2.1. Literature search

A protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) (Moher et al., 2009). Five bibliographic databases (Medline, PsycINFO, Embase, CINAHL, Cochrane Central Database) were searched in January 2016 for papers reporting results from RCTs evaluating non-pharmacological interventions for adults with schizophrenia published between January 1996 and January 2016. As this review was interested in the reported drop-out rates, the lower time limit was set based on the publication date of the first Consolidated Standards of Reporting Trials (CONSORT) statement (Begg et al., 1996). Additional hand searches of six key journals (Schizophrenia Bulletin, The British Journal of Psychiatry, The American Journal of Psychiatry, JAMA Psychiatry, Acta Psychiatrica Scandinavica, and Trials) and reference lists of relevant systematic reviews were carried out to identify other eligible papers.

A comprehensive search strategy of titles and abstracts used MeSH headings including 'SCHIZOPHRENIA' OR 'PSYCHOSIS' OR 'PSYCHOTIC DISORDERS' AND 'CLINICAL TRIALS' OR 'RANDOMIZED CONTROLLED TRIAL/S' and text words including 'psychos*s' OR 'psychotic' OR 'schizo*' OR 'therapy' OR 'intervent*' OR 'non-pharmacological' AND 'RCT' OR 'randomi*ed controlled trial' OR 'clinical trial'. Search terms were modified for each database.

A two-step screening process was performed. The first screening of all titles and abstract was performed by the primary reviewer (PS) followed by the second reviewer (SW) independently screening a random selection of 20% of the citations. The same process was followed for the second screening including full texts. Any discrepancies were resolved through discussion between the reviewers.

2.2. Study selection

The following eligibility criteria had to be met for papers to be included in the review: 1) RCT design, 2) the sample size of at least

100, 3) evaluated a non-pharmacological intervention delivered either individually or in a group, 4) the sample comprised only adults above the age of 18 with a diagnosis of schizophrenia, schizophreniform, schizoaffective or delusional disorder, 5) written in English.

The decision to include RCTs with a sample size of at least 100 was made as larger sample sizes provide narrower confidence intervals and therefore more precise estimates of the value. This increased the precision of the summary measure of the drop-out rates produced in the meta-analyses. Interventions requiring involvement of a support person (e.g. family therapy) were excluded as they were thought to potentially influence decisions about participation made by people receiving the intervention. Interventions considered to be invasive (e.g. brain stimulation) were also excluded as they present a different type of risk to be considered by participants and are therefore likely to affect attrition rates. Details of the excluded studies and reasons for exclusions are available the authors on request.

2.3. Definition of drop-out

The primary outcomes for two meta-analyses were a) drop-out from experimental intervention and b) drop-out from study. Intervention drop-out rate was defined as the proportion of participants reported as not completing the intervention (according to authors' definition) who were randomized to an arm involving a non-pharmacological intervention for schizophrenia and who began the intervention. Study drop-out rate was defined for the purposes of this study as the proportion of participants who did not complete the last follow-up assessment in all study arms. Participants who were lost prior to randomization were not considered dropouts and were not included in the calculations. The distinction between the two types of drop-out (intervention vs study) was drawn in order to investigate the differences in the proportions of participants adhering to treatment and completing follow-up appointments.

2.4. Data extraction

Drop-out rates were extracted either from the CONSORT diagrams (if provided) or from the text of the article. The authors of 19 studies were contacted with a request for clarification or for information not available in the paper. Twelve responses were received.

Data on study- and sample-level characteristics used as potential predictors of drop-out rates in the meta-regression were extracted on: year of publication, study setting (inpatient vs. outpatient), intervention delivery (individual vs. group), type of control intervention (active vs. treatment as usual), sample size, duration of intervention period, study duration, number of intervention sessions, number of evaluations, and quality score (see below). Sample-level variables included: age, gender, and illness duration. These included all randomized participants for the meta-regression of study drop-out and only the participants who were allocated to intervention for the meta-regression of intervention drop-out.

2.5. Quality assessment

A unique set of criteria was developed specifically for the purposes of this study as the data were different from those for clinical effectiveness and did not fit in with the existing tools of assessing risk of bias. The methodological quality of the studies was appraised by giving a score from 0 to 3 using the following criteria: i) CONSORT diagram provided (1 point), ii) Clear definition of intervention completion (1 point), iii) Clear information on sample size calculation (1 point). The score was also used in the meta-analyses as a measure of study quality in the context of reporting information relevant to study drop-out.

2.6. Statistical analysis

The primary outcome was the proportion of participants who dropped out of a) experimental intervention and b) study. This was calculated in Stata using *metaprop* command as the number of individuals who discontinued intervention across all active interventions in each study (a) or were lost to follow-up (b) divided by the total number of individuals who began intervention (a) or were randomized to study (b). The Freeman-Tukey double arcsine transformation was used to calculate the 95% confidence interval as it can be used for data restricted to the range of 0 and 100%. Otherwise, studies with an estimated percentage near either extreme would be automatically excluded from the analysis leading to a biased pooled estimate.

For meta-regression a random-effects model was used as it assumes that differences in the drop-out rates are not just attributed to the sampling error but represent real differences between studies. The potential predictors used in meta-regressions included both study-level and sample-level variables. Variables which were associated with drop-out (p-value <0.1) in the univariable models were included in a multivariable model.

The level of between-study heterogeneity was assessed by calculating the Q-statistic and the I^2 statistic. Egger's test of the intercept with the Freeman-Tukey double arcsine transformation and a funnel plot of standard error against study drop-out rate were computed to assess the evidence for publication bias.

3. Results

3.1. Study characteristics

The database search identified 5450 studies (see Fig. 1 for the PRISMA flow diagram). After screening, 49 papers based on 43 studies were included in this review. Because studies were reported in multiple papers data was extracted per study, not per paper. Details of the 49 papers can be found in Table 1. Two out of the 43 studies did not adequately report study drop-out information to be included in the analysis; therefore they were excluded from the meta-analysis of study drop-out rates. The majority of studies were from European countries (n = 29), followed by North America (n = 11) and Asian countries (n = 3).

The 43 studies evaluated 59 non-pharmacological interventions (Table 1), but only 34 studies reported intervention completion for 50 interventions and these were included in the meta-analysis of intervention drop-out.

Information about the reasons for study discontinuation was extracted but this was limited by the lack of reporting with absence of CONSORT (n = 11), presence of CONSORT but lack of or unclear information about the reasons for discontinuation (n = 18). Only 14 out of 43 papers reported the reasons for discontinuation of study.

3.2. Quality analysis

Study quality ranged from 0 to 3, with 5 studies scoring 0, 17 studies scoring 1, 10 studies scoring 2 and 9 studies scoring 3. Twenty-nine out of 43 studies (69%) provided a CONSORT diagram.

3.3. Drop-out rates

The overall estimate of the proportion of participants who

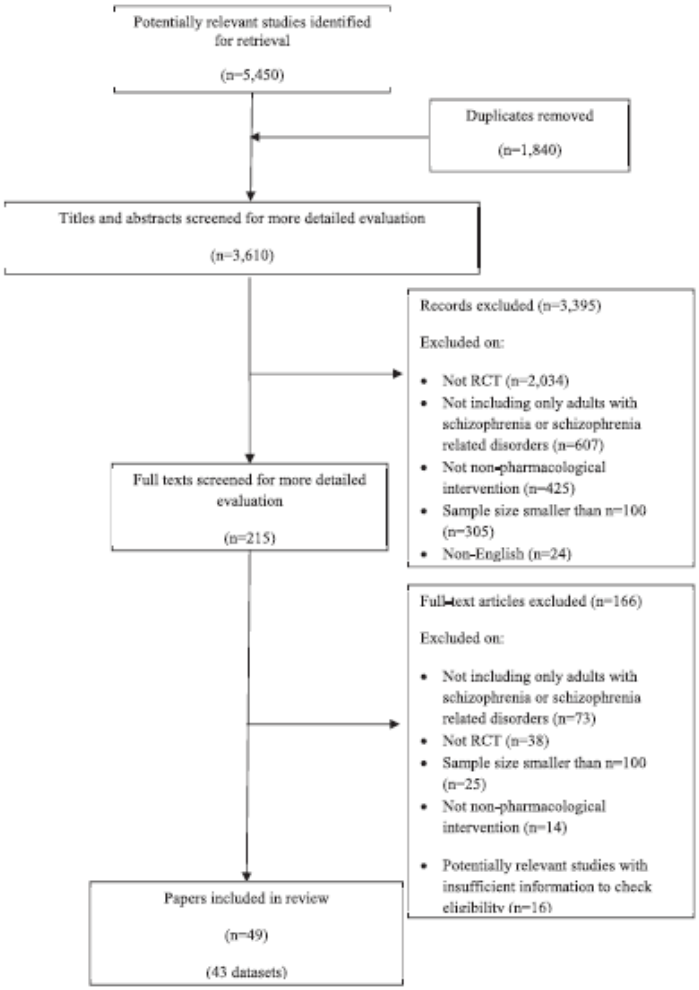


Fig. 1. PRISMA diagram for paper.

dropped out of intervention was 14% (95% CI: 13–15%), with a range of 0–63% and a median of 19.4%. Heterogeneity was high at $I^2 = 93.13\%$. Subgroup analysis by intervention type showed overall estimates of intervention drop-out of 25% (95% CI: 14–35%) for CBT interventions (n = 8), 24% (95% CI: 16–32%) for cognitive or neurocognitive interventions (n = 9), 21% (95% CI: 13–29%) for practical or educational interventions (n = 8), 11% (95% CI: 6–17%) for adherence therapies (n = 7), and 34% (95% CI: 23–46%) for other interventions (n = 18).

The overall estimate of the proportion of participants who dropped out of studies was 20% (95% CI: 17–24%), with a range of 4–71% and a median of 16%. Heterogeneity was high at $I^2 = 95.69\%$.

The results of the analyses are shown in Tables 2 and 3.

3.4. Predictors of drop-out

A random effects meta-regression using both univariable and multivariable models was used. At the intervention level, the univariable models included age, gender, illness duration, study location, study setting, intervention delivery, duration of the intervention period, study duration, number of intervention sessions, and study quality. Findings show that the proportion of drop-out from experimental interventions significantly increased as the number of intervention sessions increased (P-value = 0.011). At the study-level, the models included the following variables: age, gender, illness duration, study location, study setting, type of control intervention, study duration, number of evaluations, and study quality. Findings show that none of these variables have an effect on the drop-out from study.

Table 1
Description of studies.

Study reference	Region	Intervention(s) evaluated	Participants randomized to study (n)	Intervention delivery	Setting	Length of follow-up (m)	Intervention duration (m)	Quality score
Barkhof 2013 (14)	Europe	Motivational interviewing/Health Education	114	Individual	In- and out-patient	12	6.5	3
Barrowclough 2006 (15)	Europe	Cognitive Behavioral Therapy (CBT)	113	Group	Out-patient	12	6	3
Bell 1997 (16)	USA	Work program	150	Individual	Out-patient	12	6	1
Bell 2003(17)	USA	Neurocognitive Enhancement Therapy (NET) with Work Therapy (WT)	131	Individual	Out-patient	12	6	0
[Bell 2005] (18)								
[Bell 2007] (19)								
Bowie 2012 (20)	USA	Cognitive remediation/Functional Adaptation Skills Training/Combined Treatment	114	Group	Out-patient	3	6	2
Chien 2015 (21)	Asia	Adherence therapy	114	Individual	Out-patient	6	4	2
Crawford 2012 (22)	Europe	Group art therapy/Activity Groups	417	Group	Out-patient	24	12	2
Franck 2013 (23)	Europe	Individualized therapy/Cognitive Remediation Therapy (CRT)	138	Individual	Out-patient	9	3	1
Freeman 2015 (24)	Europe	CBT	150	Individual	In- and out-patient	6	2	3
Gomar 2015 (25)	Europe	Computerized Cognitive Remediation	130	Group	In- and out-patient	6	6	1
Gouzoulis-Mayfrank 2015 (26)	Europe	Implemented integrated treatment	100	Group	In-patient	12	NR	1
Granholm 2014 (27)	USA	Cognitive Behavioral Social Skills Training (CBSST)/Active Goal-Focused Supportive Contact (GFSC)	149	Group	Out-patient	21	9	1
Gray 2006 (28)	Europe	Adherence therapy/Health Education	409	Individual	In- and out-patient	13	18	3
Gumley 2003 (29)	Europe	CBT	144	Individual	NR	13	3	2
[Gumley 2006] (30)								
Hamann 2006 (31)	Europe	Shared decision aid	113	Individual	In- and out-patient	18	0.03	1
Hansson 2008 (32)	Europe	DIALOG (computer-mediated structured patient- – key worker communication)	507	Individual	Out-patient	12	12	0
Hogarty 2004 (33)	USA	Cognitive Enhancement Therapy (CET)/Enriched Supportive Therapy	121	Group	Out-patient	24	NR	0
Jahn 2011 (34)	Europe	Neurocognitive training (COGPIP trial)	122	Group	In-patient	9	1	1
Jones 2001 (35)	Europe	Personalized computer-based information/ Community Psychiatric Nurse/Combined treatment	112	Individual	NR	3	NR	3
Klingberg 2010 (36)	Europe	CBOS (cognitive behaviorally oriented service)	169	Group	In-patient	6	2	3
Klingberg 2011 (37)	Europe	CBT/CR	198	Individual	Out-patient	12	9	3
[Klingberg 2012] (38)		CBT/CR						
Li 2015 (39)	Asia	CBT/Supportive Therapy	192	Group	In- and out-patient	21	6	2
Montes 2010 (40)	Europe	Telephone-based nursing strategy to improve adherence to antipsychotic treatment	928	Individual	Out-patient	4	3	1
Montes 2012 (41)	Europe	Short message service (SMS)-based strategy for enhancing adherence to antipsychotic treatment	340	Individual	Out-patient	6	3	3
Moritz 2013 (42)	Europe	Complementary Metacognitive Training (MCT)	150	Group	In- and out-patient	6	NR	2
[Moritz 2014] (43)								
Mueller 2015 (44)	Europe	Integrated Neurocognitive Therapy	156	Group	Out-patient	9	3.75	1
Patterson 2006 (45)	USA	Functional Adaptation Skills Training (FAST)	240	Group	Out-patient	18	6	1
[Mausbach 2008] (46)								
Pitkanen 2012 (47)	Europe	Patient education	311	Group	In-patient	12	1	1
Salyers 2014 (48)	USA	Illness Management and Recovery (IMR)/ Problem-Solving Group	118	Group	NR	18	9	0
Schirmer 2015 (49)	Europe	Medication training program	141	Individual	Out-patient	NR	1.64	
Schulz 2013 (50)	Europe	Adherence therapy	161	Group	In- and out-patient	3	NR	3
Sibitz 2007 (51)	Europe	Low intensity booster sessions of psychoeducation	103	Group	Out-patient	11.25	2.25	1
Silverstein 2014 (52)	USA	Attention shaping	105	Group	In-patient	5.5	5.5	1
Staring 2010 (53)	Europe	Treatment adherence therapy (TAT)	109	Individual	Out-patient	12	6	1
Terzian 2013 (54)	Europe	Social Network intervention	357	NR	Out-patient	24	24	1
Van der Gaag 2011 (55)	Europe	CBT	216	Group	NR	18	6	1
Van der Krieke 2013 (56)	Europe	Web-based information and decision tool	250	Individual	Out-patient	12	12	2
Van Oosterhout 2014 (57)	Europe	Metacognitive group training (MCT)	154	Group	In- and out-patient	6	2	2
Van Os 2004 (58)	Europe	Two-way Communication Checklist (2-COM)	134	Individual	Out-patient	2	1.5	1
Velligan 2013 (59)	USA	Interventions for improving adherence to oral medications	142	Group	Out-patient	9	6	1
Velligan 2015 (60)	USA	CBT/Cognitive Adaptation Training (CAT)/CBT and CAT	166	Individual	Out-patient	15	9	1
Williams 2003 (61)	USA	Enhanced guideline implementation strategy	349	Individual	In- and out-patient	20	NR	0
Xiang 2007 (62)	Asia	Community Re-Entry Module (CRM)	103	Group	In-patient	24	4	2

Note: n – number, m – months, NR – not reported.

Table 2
Meta-analysis of intervention drop-out Rates.

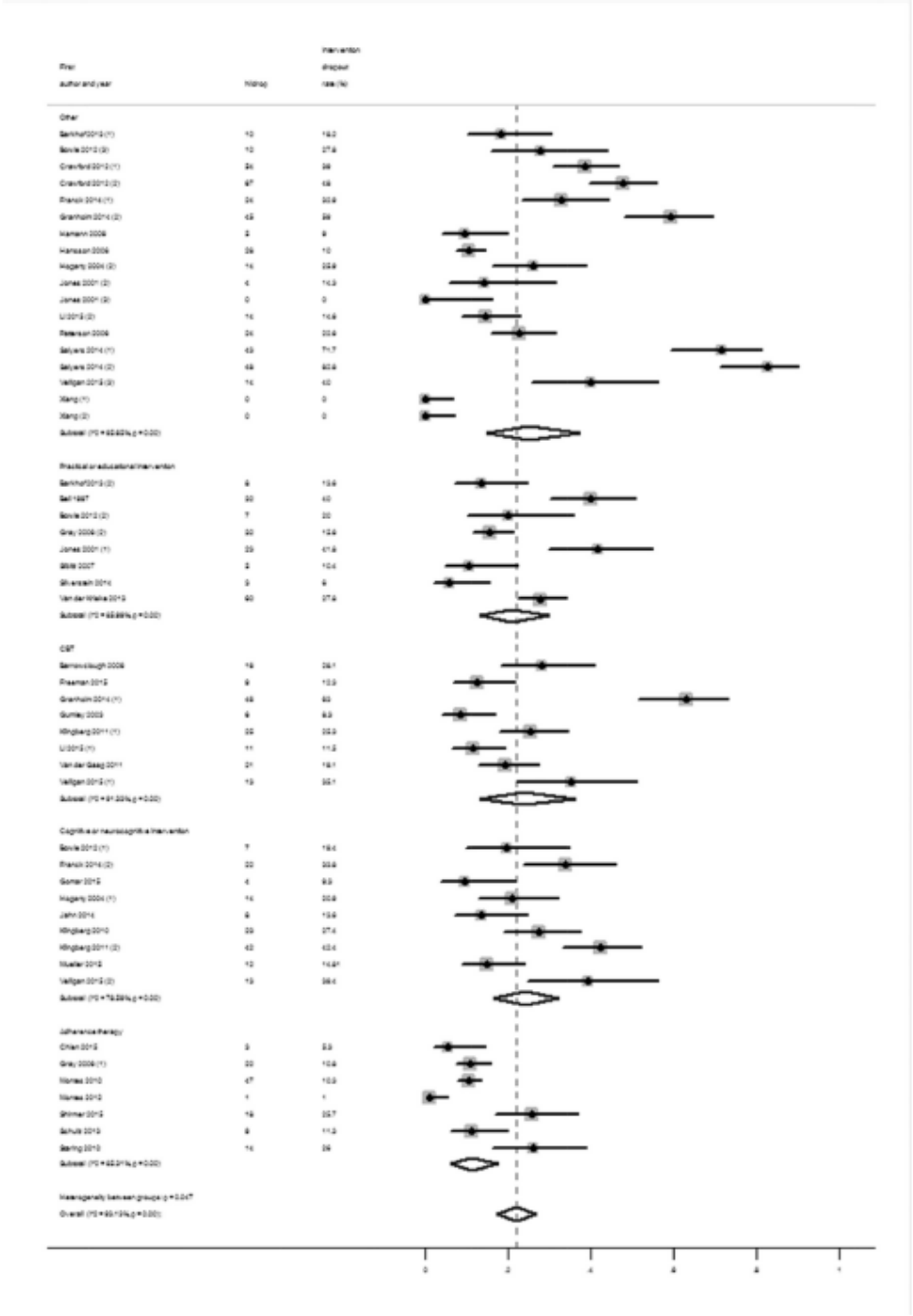
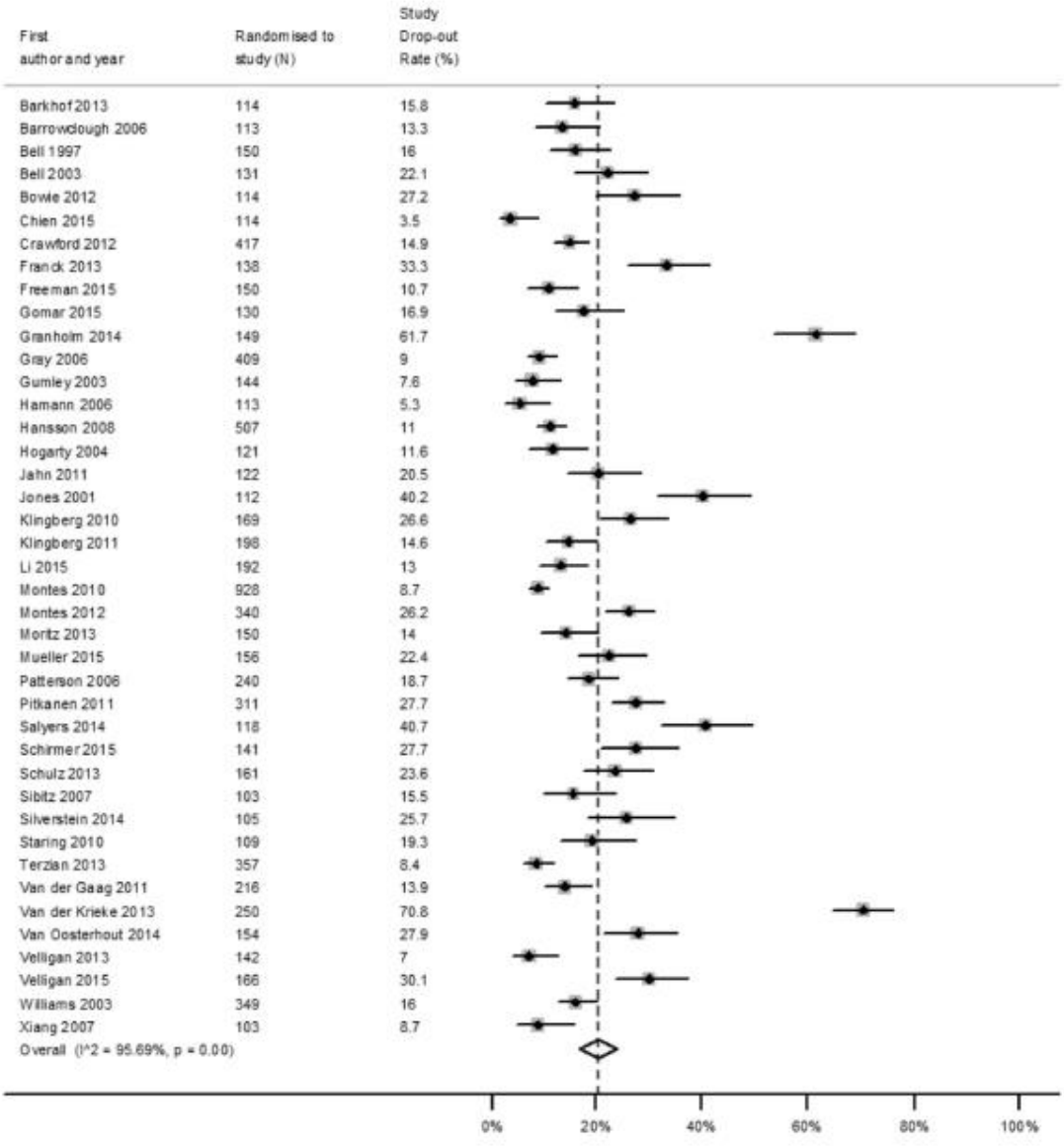


Table 3
Meta-analysis of Study Drop-out Rates.



The results of the analyses are shown in Tables 4–6.

3.5. Publication bias

Egger's test of the intercept showed no presence of publication bias (P = 0.10) for study drop-out.

The funnel plot is presented in Fig. 2 and could be interpreted as showing no evidence of publication bias with a few outliers. The lack of publication bias could be explained by this review considering only large RCTs with a sample size ≥ 100. This finding suggests that large studies are likely to be published despite how high the drop-out rate was.

Table 4
Univariable meta-regression for intervention dropout.

Factor	Coefficient	95% Lower	95% Upper	P-Value
Age	0.53	−0.77	1.83	0.410
Gender	0.53	−0.03	1.11	**0.065**
Illness duration	1.12	−0.12	2.37	**0.075**
Study location	−9.93	−22.49	2.63	0.117
Study setting (inpatient vs outpatient)	−6.38	−18.30	5.54	0.284
Intervention delivery (individual vs group)	−6.37	−18.30	5.54	0.284
Duration of intervention period	2.37	0.51	4.23	**0.014**
Study duration	0.83	−0.11	1.77	**0.082**
Number of intervention sessions	0.66	0.26	1.05	**0.002**
Study quality	−2.27	−6.64	2.09	0.300

P= 0.10.

Table 5
Multivariable meta-regression for intervention dropout.

Factor	Coefficient	95% Lower	95% Upper	P-Value
Gender	0.23	−0.53	1.00	0.235
Illness duration	0.10	−1.44	1.65	0.884
Duration of intervention period	0.09	−2.29	2.48	0.931
Number of intervention sessions	0.97	0.28	1.67	**0.011**
Study duration	−0.38	−1.81	1.05	0.570

P= 0.10.

Table 6
Univariable meta-regression for study dropout.

Factor	Coefficient	95% Lower	95% Upper	P-Value
Age	0.10	−0.70	0.90	0.803
Gender	0.09	−0.27	0.46	0.606
Illness duration	0.43	−0.37	1.23	0.279
Study location	6.62	−1.56	14.81	0.110
Study setting (inpatient vs outpatient)	1.29	−2.74	5.33	0.521
Study duration	−0.20	−0.95	0.54	0.579
Number follow-up assessments	−0.23	−3.84	3.38	0.897
Type of control (active vs treatment as usual)	1.25	−4.31	6.82	0.651
Study quality	0.05	−4.76	4.86	0.984

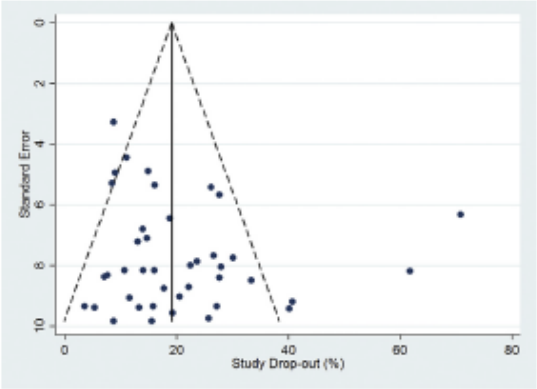


Fig. 2. Funnel plot of standard error by study drop-out rate.

4. Discussion

This study used a systematic literature search and meta-analysis to provide estimates for the proportion of individuals with schizophrenia who participate in non-pharmacological RCTs who discontinue intervention and who are lost to follow up.

Previous meta-analysis of rates of drop-out from psychosocial treatment among people with schizophrenia found that 13% of participants dropped out prior to or during treatment (Villeneuve et al., 2010). The study has also identified an association between specific study and sample characteristics and drop-out rates (Villeneuve et al., 2010). In contrast to this previous study, this systematic review included any non-pharmacological intervention for schizophrenia and considers the drop-out rates at both experimental intervention and study levels.

Two separate meta-analyses showed the drop-out rates of 14% at the experimental intervention level and 20% at the study level. Meta-regressions of study and sample characteristics as predictors of drop-out showed only one significant association between the number of intervention sessions and drop-out from the experimental intervention.

Estimating study drop-out rates is an important element of planning a clinical trial as it affects the time and cost of the study. Deciding on a statistically appropriate sample size requires information about the expected participation rates. If there is a reason to assume that a proportion of participants will fail to provide data, the sample size should be proportionately increased. Traditionally information about the expected number of participants to drop out is obtained either from a pilot study or previous studies in the same population. Results obtained in this systematic review and meta-

analysis provide evidence about the reported drop-out rates in large non-pharmacological RCTs involving people with schizophrenia, at both study and intervention level. This can guide sample size planning in studies falling into this category. This review also provides details about the included studies, including the specific intervention, how it was delivered and in what setting, as well as the length of follow-up and intervention. These context details together with the reported drop-out rates may provide useful information for sample size calculations.

This study has a number of strengths. To our knowledge, this is the first systematic review and meta-analysis to establish the experimental intervention and study drop-out rates in non-pharmacological RCTs involving people with schizophrenia. We followed a rigorous process and a comprehensive search strategy encompassing a broad range of non-pharmacological interventions for schizophrenia. Many of the authors were contacted to clarify ambiguities and to obtain information not provided in the papers.

Several limitations should be considered when interpreting findings from this study. First, almost a third of the studies did not provide information about participant flow in the form of the CONSORT flow diagram, which reflects the quality of reporting data essential for this type of meta-analysis. However, some of the papers missing the CONSORT reported relevant information in the body of the paper and were therefore included in the analysis. Second, the interpretation of intervention drop-out was based on the definitions developed by authors of each reviewed study, which differed across the sample and thus limited the comparability. The lack of a universal threshold for intervention completion can also mean that the rates of participants who completed interventions can be under- or over-estimated by authors. Third, there was a high level of heterogeneity. However this could be explained by the inherent differences in individual studies, especially the wide range of drop-out rates observed across the included trials. The fourth limitation is the restricted scope for extracting and testing other potential predictors of drop-out such as incentives or assessment mode due to the lack of these details in many reviewed publications. Finally, it is possible that relevant studies may have been omitted, particularly as studies published not in English were excluded for resource reasons. However, this study adds to the thus far limited literature on drop-out rates in schizophrenia trials and provides suggestions for future studies.

The findings of this study suggest that drop-out rates below 20% in non-pharmacological RCTs involving people with schizophrenia are possible to achieve as shown by majority of the studies included in the meta-analysis. Achieving as little drop-out as possible is important in avoiding a risk of bias, which appears at the attrition level of 5% (Schulz and Grimes, 2002). Losing more than 20% of participants with schizophrenia can and should be avoided as it can compromise validity (Gul and Ali, 2010; Polit and Hungler, 1995).

Drop-out rates lower than 20% are achievable although the available evidence is limited in showing which study or sample characteristics can help with achieving this. Only one of the tested study and sample variables that were available for extraction for the purposes of meta-analysis had an effect on the intervention drop-out rates: number of intervention sessions. This finding suggests that interventions involving a large number of sessions have an increased risk of people dropping out. No other participant or study characteristic has shown an effect on the drop-out rates. However, extracting variables was impeded by inconsistent reporting of information about study procedures, e.g. incentives, outcome collection method (i.e. remote or in person), and place of assessment. The findings suggest that different factors may need to be taken into account, such as research processes, researcher characteristics, specific recruitment and retention strategies, psychological processes. Some literature suggests that assertive engagement strategies employed by the research team, involving home visits, flexibility in scheduling appointments, persistence in following up and collaborating with mental health services can have positive impact on retention rates (Barrowclough et al., 2009) but this has not been systematically tested.

Furthermore, the study shows that more trial participants with schizophrenia drop out of studies than out of active interventions. This finding has potential implications for planning study procedures, especially follow-up assessments, in the context of minimizing attrition.

Future research could focus on building in-depth understanding of how individuals with schizophrenia make decisions about participating in RCTs, especially about discontinuing their participation, as well as the challenges and barriers researchers experience in engaging this population in clinical trials. This evidence could inform development and implementation of effective retention strategies in trials.

References

Altman, D.G., 1996. Better reporting of randomised controlled trials: the CONSORT statement. BMJ 313, 570–571.

Barkhof, E., Meijer, C.J., De Sonneville, L.M.J., Linszen, D.H., De Haan, L., 2013. The effect of motivational interviewing on medication adherence and hospitalization rates in nonadherent patients with multi-episode schizophrenia. Schizophr. Bull. 39, 1242–1251. http://dx.doi.org/10.1093/schbul/sbt138.

Barrowclough, C., Haddock, G., Beardmore, R., Conrod, P., Craig, T., Davies, L., Dunn, G., Lewis, S., Moring, J., Tarrier, N., Wykes, T., 2009. Evaluating integrated MI and CBT for people with psychosis and substance misuse: recruitment, retention and sample characteristics of the MIDAS trial. Addict. Behav. 34, 859–866. http://dx.doi.org/10.1016/j.addbeh.2009.03.007.

Barrowclough, C., Haddock, G., Lobban, F., Jones, S., Siddle, R., Roberts, C., Gregg, L., 2006. Group cognitive – behavioural therapy for schizophrenia : Randomised controlled trial. Br. J. Psychiatry 189, 527–532. http://dx.doi.org/10.1192/bjp.bp.106.021386.

Begg, C., Cho, M., Eastwood, S., Els, D., Horton, R., Moher, D., Olkin, I., Pitkin, R., Rennie, D., Schulz, K.F., Simel, D., Stroup, D.F., 1996. Improving the Quality of Randomized Controlled Trials the CONSORT Statement, vol. 8, pp. 637–639.

Bell, M., Bryson, G., Wexler, B.E., 2003. Cognitive remediation of working memory deficits : durability of training effects in severely impaired and less severely impaired schizophrenia. Acta Psychiatr Scand 108, 101–109. http://dx.doi.org/10.1034/j.1600-0447.2003.00090.x.

Bell, M., Fiszdon, J., Greig, T., Wexler, B., Bryson, G., 2007. Neurocognitive enhancement therapy with work therapy in schizophrenia: 6-month follow-up of neuropsychological performance. J. Rehabil. Res. Dev. 44, 761–770. http://dx.doi.org/10.1682/JRRD.2007.02.0032.

Bell, M., Lysaker, P., 1997. Clinical Benefits of Paid Work Activity in Schizophrenia: 1-Year Followup. Schizophr. bull. 23, 317–328.

Bell, M.D., Bryson, G.J., Greig, T.C., Fiszdon, J.M., Wexler, B.E., 2005. Neurocognitive enhancement therapy with work therapy: Productivity outcomes at 6- and 12-month follow-ups. J. Rehabil. Res. Dev. 42, 829–838. http://dx.doi.org/10.1682/JRRD.2005.03.0061.

Bowie, C.R., McGurk, S.R., Mausbach, B., Patterson, T.L., Harvey, P.D., 2012. Combined cognitive remediation and functional skills training for schizophrenia: Effects on cognition, functional competence, and real-world behavior. Am. J. Psychiatry 169, 710–718. http://dx.doi.org/10.1176/appi.ajp.2012.11091337.

Chien, W., Mui, J., Cheung, E., Gray, R., 2015. Effects of motivational interviewing-based adherence therapy for schizophrenia spectrum disorders: a randomized controlled trial. Trials 16, 270–284. http://dx.doi.org/10.1186/s13063-015-0785-z.

Crawford, M.J., Killaspy, H., Barnes, T.R.E., Barrett, B., Byford, S., Clayton, K., Dinsmore, J., Floyd, S., Hoadley, A., Johnson, T., Kalaitzaki, E., King, M., Leurent, B., Maratos, A., O'Neill, F.A., Osborn, D.P., Patterson, S., Soteriou, T., Tyrer, P., Waller, D., 2012. Group art therapy as an adjunctive treatment for people with schizophrenia: multicentre pragmatic randomised trial. BMJ 344, e846. http://dx.doi.org/10.1136/bmj.e846.

Franck, N., Duboc, C., Sundby, C., Amado, I., Wykes, T., Demily, C., Launay, C., Le Roy, V., Bloch, P., Willard, D., Todd, A., Petitjean, F., Foullu, S., Briant, P., Grillon, M.L., Deppen, P., Verdoux, H., Bralet, M.C., Januel, D., Riche, B., Roy, P., Vianin, P., 2013. Specific vs general cognitive remediation for executive functioning in schizophrenia: A multicenter randomized trial. Schizophr. Res. 147, 68–74. http://dx.doi.org/10.1016/j.schres.2013.03.009.

Freeman, D., Dunn, G., Startup, H., Pugh, K., Cordwell, J., Mander, H., Cernis, E., Wingham, G., Shirvell, K., K., D., 2015. Effects of cognitive behaviour therapy for worry on persecutory delusions in patients with psychosis. Lancet Psychiatry 2, 305–313.

Gomar, J.J., Valls, E., Radua, J., Mareca, C., Tristany, J., Del Olmo, F., Rebolleda-Gil, C., Janez-Alvarez, M., De Alvaro, F., Ovejero, M.R., Llorente, A., Teixido, C., Donaire, A.M., Garcia-Laredo, E., Lazcanoiturburu, A., Granell, L., Mozo, C.D.P., Perez-Hernandez, M., Moreno-Alcazar, A., Pomarol-Clotet, E., McKenna, P.J.,

2015. A multisite, randomized controlled clinical trial of computerized cognitive remediation therapy for Schizophrenia. Schizophr. Bull. 41, 1387–1396. http://dx.doi.org/10.1093/schbul/sbv059.
Gouzoulis-Mayfrank, E., König, S., Koehke, S., Schnell, T., Schmitz-buhl, M., Daumann, J., 2015. Trans-sector integrated treatment in Psychosis and addiction. Dtsch. Arztebl. Int 112, 683–691. http://dx.doi.org/10.3238/arztebl.2015.0683.
Granholm, E., Holden, J., Link, P.C., McQuaid, J.R., 2014. Randomized clinical trial of cognitive behavioral social skills training for Schizophrenia: Improvement in functioning and experiential negative symptoms. J. Consult. Clin. Psychol 82, 1173–1185. http://dx.doi.org/10.1037/a0037098.
Gray, R., Leese, M., Bindman, J., Becker, T., Burti, L., David, A., Gournay, K., Kikkert, M., Koeter, M., Puschner, B., Schene, A., Thornicroft, G., Tansella, M., 2006. Adherence therapy for people with schizophrenia. European multicentre randomised controlled trial. Br. J. Psychiatry 189, 508–514. http://dx.doi.org/10.1192/bjp.bp.105.019489.
Gul, R.B., Ali, P.a., 2010. Clinical trials: the challenge of recruitment and retention of participants. J. Clinical Nurs. 19, 227–233. http://dx.doi.org/10.1111/j.1365-2702.2009.03041.x.
Gumley, A., Karatzias, A., Power, K., Reilly, J., McNay, L., O'Grady, M., 2006. Early intervention for relapse in schizophrenia: impact of cognitive behavioural therapy on negative beliefs about psychosis and self-esteem. Br. J. Clin. Psychol. 45, 247–260. http://dx.doi.org/10.1348/014466505X49925.
Gumley, A., O'Grady, M., McNay, L., Reilly, J., Power, K., Norrie, J., 2003. Early intervention for relapse in schizophrenia: results of a 12-month randomized controlled trial of cognitive behavioural therapy. Psychol. Med. 33, 419–431. http://dx.doi.org/10.1017/S0033291703007323.
Gupta, S.K., 2011. Intention-to-treat concept: a review. Perspect. Clin. Res. 2, 109–112.
Hamann, J., Langer, B., Winkler, V., Busch, R., Cohen, R., Leucht, S., Kissling, W., 2006. Shared decision making for in-patients with schizophrenia. Acta Psychiatr. Scand. 114, 265–273. http://dx.doi.org/10.1111/j.1600-0447.2006.00798.x.
Hansson, L., Svensson, B., Bjorkman, T., Bullenkamp, J., Lauber, C., Martinez-Leal, R., McCabe, R., Rossler, W., Salize, H., Torres-Gonzales, F., Van Den Brink, R., Wiersma, D., Priebe, S., 2008. What works for whom in a computer-mediated communication intervention in community psychiatry? Moderators of outcome in a cluster randomized trial. Acta Psychiatr. Scand. 118, 404–409. http://dx.doi.org/10.1111/j.1600-0447.2008.01258.x.
Hogarty, G.E., Flesher, S., Ulrich, R., Carter, M., Greenwald, D., Pogue-Geile, M., Kechavan, M., Colley, S., DiBarry, A.L., Garrett, A., Parepally, H., Zoretich, R., 2004. Cognitive enhancement therapy for schizophrenia. Archives 61, 866–876.
Huhn, M., Tardy, M., Spineli, L.M., Kissling, W., Förstl, H., Pitschel-Walz, G., Leucht, C., Samara, M., Dold, M., Davis, J.M., Leucht, S., 2014. Efficacy of pharmacotherapy and psychotherapy for adult psychiatric disorders: a systematic overview of meta-analyses. JAMA psychiatry 71, 706–715. http://dx.doi.org/10.1001/jamapsychiatry.2014.112.
Jahn, T., Pitschel-Walz, G., Gsottschneider, A., Froböse, T., Kraemer, S., Bäuml, J., 2011. Neurocognitive prediction of illness knowledge after psychoeducation in schizophrenia: results from the Munich CGCPIP study. Psychol. Med. 41, 533–544. http://dx.doi.org/10.1017/S0033291710001029.
Jones, R.B., Atkinson, J.M., Coia, D.A., Paterson, L., Morton, A.R., McKenna, K., Craig, N., Morrison, J., Gilmour, W.H., 2001. Randomised trial of personalised computer based information for patients with schizophrenia. BMJ 322, 835–840.
Kampman, O., Lethinen, K., 1999. Compliance in psychoses. Acta Psychiatr. Scand. 100, 167–175.
Klingberg, S., Herrlich, J., Wiedemann, G., Wolwer, W., Meisner, C., Engel, C., Jakobi-Malterre, U.E., Buchkremer, G., Wittorf, A., 2012. Adverse effects of cognitive behavioral therapy and cognitive remediation in schizophrenia: results of the treatment. J. Nerv. Ment. Dis. 200, 569–576. http://dx.doi.org/10.1097/NMD.0b013e31825bfa1d.
Klingberg, S., Wittorf, A., Fischer, A., Jakob-Deters, K., Buchkremer, G., Wiedemann, G., 2010. Evaluation of a cognitive behaviourally oriented service for relapse prevention in schizophrenia. Acta Psychiatr. Scand. 121, 340–350. http://dx.doi.org/10.1111/j.1600-0447.2009.01479.x.
Klingberg, S., Wölwer, W., Engel, C., Wittorf, A., Herrlich, J., Meisner, C., Buchkremer, G., Wiedemann, G., 2011. Negative symptoms of schizophrenia as primary target of cognitive behavioral therapy: Results of the randomized clinical TONES study. Schizophr. Bull. 37 http://dx.doi.org/10.1093/schbul/sbr073.
Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Örey, D., Richter, F., Samara, M., Barbui, C., Engel, R.R., Geddes, J.R., Kissling, W., Stapf, M.P., Lässig, B., Salanti, G., Davis, J.M., 2013. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 382, 951–962. http://dx.doi.org/10.1016/S0140-6736(13)60733-3.
Li, Z., Guo, Z., Wang, N., Xu, Z., Qu, Y., Wang, X., Sun, J., Yan, L., Ng, R., Turkington, D., Kingdon, D., 2015. Cognitive-behavioural therapy for patients with schizophrenia: a multicentre randomized controlled trial in Beijing, China. Psychol. Med. 45, 1893–1905. http://dx.doi.org/10.1017/S0033291714002992.
Mausbach, B.T., Cardenas, V., McKibbin, C.L., Jeste, D.V., Patterson, T.L., 2008. Reducing emergency medical service use in patients with chronic psychotic disorders: Results from the FAST intervention study. Behav. Res. Ther. 46, 145–153.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., the PRISMA Group, 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann. Intern. Med. Intern. Med. 151, 264–269. http://dx.doi.org/10.1371/journal.pmed1000097.
Montes, J.M., Medina, E., Gomez-Beneyto, M., Maurino, J., 2012. A short message service (SMS)-based strategy for enhancing adherence to antipsychotic medication in schizophrenia. Psychiatry Res. 200, 89–95. http://dx.doi.org/10.1016/j.psychres.2012.07.034.
Montes, J.M., Maurino, J., Diez, T., S.-R., J., 2010. Telephone-based nursing strategy to improve adherence to antipsychotic treatment in schizophrenia: A controlled trial. Int. J. Psychiatry Clin. Pract. 14, 274–281. http://dx.doi.org/10.3109/13651501.2010.505343.
Moritz, S., Veckenstedt, R., Andreou, C., Bohn, F., Hottenrott, B., Leighton, L., Kother, U., Woodward, T.S., Treszl, A., Menon, M., Schneider, B.C., Pfueller, U., Roesch-Ely, D., 2014. Sustained and "sleeper" effects of group metacognitive training for schizophrenia: A randomized clinical trial. JAMA Psychiatry 71, 1103–1111. http://dx.doi.org/10.1001/jamapsychiatry.2014.1038.
Moritz, S., Veckenstedt, R., Bohn, F., Hottenrott, B., Scheu, F., Randjbar, S., Aghotor, J., Kother, U., Woodward, T.S., Treszl, A., Andreou, C., Pfueller, U., Roesch-Ely, D., 2013. Complementary group Metacognitive Training (MCT) reduces delusional ideation in schizophrenia. Schizophr. Res. 151, 61–69. http://dx.doi.org/10.1016/j.schres.2013.10.007.
Mueller, D.R., Schmidt, S.J., Roder, V., 2015. One-year randomized controlled trial and follow-up of integrated neurocognitive therapy for schizophrenia outpatients. Schizophr. Bull. 41, 604–616. http://dx.doi.org/10.1093/schbul/sbu223.
Nosé, M., Barbui, C., Tansella, M., 2003. How often do patients with psychosis fail to adhere to treatment programmes? A systematic review. Psychol. Med. 33, 1149–1160. http://dx.doi.org/10.1017/S0033291703008328.
Patterson, T.L., Mausbach, B.T., McKibbin, C., Goldman, S., Bucardo, J., Jeste, D.V., 2006. Functional adaptation skills training (FAST): A randomized trial of a psychosocial intervention for middle-aged and older patients with chronic psychotic disorders. Schizophr. Res. 86, 291–299. http://dx.doi.org/10.1016/j.schres.2006.05.017.
Pitkanen, A., Valimaki, M., Kuosmanen, L., Katajisto, J., Koivunen, M., Hatonen, H., Patel, A., Knapp, M., 2012. Patient education methods to support quality of life and functional ability among patients with schizophrenia: A randomised clinical trial. Qual. Life Res. 21, 247–256. http://dx.doi.org/10.1007/s11136-011-9944-1.
Polit, D., Hungler, B., 1995. Nursing Research: Principles and Methods, fifth ed. Lippincott, Philadelphia.
Schulz, K.F., Grimes, D.A., 2002. Sample size slippages in randomised trials: exclusions and the lost and wayward. Lancet 359, 781–785. http://dx.doi.org/10.1016/S0140-6736(02)07882-0.
Silyers, M.P., McGuire, A.B., Kukla, M., Fukui, S., Lysaker, P.H., Mueser, K.T., 2014. A randomized controlled trial of illness management and recovery with an active control group. Psychiatr. Serv. 65, 1–7. http://dx.doi.org/10.1176/appi.ps.201300354.
Schirmer, U.B., Steinert, T., Flammer, E., Borbé, R., 2015. Skills-based medication training program for patients with schizophrenic disorders: a rater-blind randomized controlled trial. Patient Prefer. Adherence 9, 541–549. http://dx.doi.org/10.2147/PPA.S75616.
Schulz, M., Gray, R., Spiekermann, A., Abderhalden, C., Behrens, J., Driessen, M., 2013. Adherence therapy following an acute episode of schizophrenia: A multicentre randomised controlled trial. Schizophr. Res. 146, 59–63. http://dx.doi.org/10.1016/j.schres.2013.01.028.
Sibitz, I., Amering, M., Gössler, R., Unger, A., Katschnig, H., 2007. One-year outcome of low-intensity booster sessions versus care as usual in psychosis patients after a short-term psychoeducational intervention. Eur. Psychiatry 22, 203–210. http://dx.doi.org/10.1016/j.eurpsy.2006.09.008.
Silverstein, S.M., Roché, M.W., Khan, Z., Carson, S.J., Malinovsky, I., Newbill, W.A., Menditto, A.A., Wilkniss, S.M., 2014. Enhancing and promoting recovery in attentionally impaired people diagnosed with schizophrenia: Results from a randomized controlled trial of attention shaping in a partial hospital program. Am. J. Psychiatr. Rehabil. 17, 272–305. http://dx.doi.org/10.1080/15487768.2014.935681.
Staring, A.B.P., Van Der Gaag, M., Koopmans, G.T., Selten, J.P., Van Beveren, J.M., Hengeveld, M.W., Ioonen, A.J.M., Mulder, C.L., 2010. Treatment adherence therapy in people with psychotic disorders: Randomised controlled trial. Br. J. Psychiatry 197, 448–455. http://dx.doi.org/10.1192/bjp.bp.110.077289.
Terzian, E., Tognoni, G., Bracco, R., De Ruggieri, E., Ficociello, R.A., Mezzina, R., Pillo, C., 2013. Social Network Intervention in Patients With Schizophrenia and Marked, vol. 58, pp. 622–631.
Van Der Gaag, M., Stant, A.D., Wolters, K.J.K., Buskens, E., Wiersma, D., 2011. Cognitive-behavioural therapy for persistent and recurrent psychosis in people with schizophrenia-spectrum disorder: Cost-effectiveness analysis. Br. J. Psychiatry 198, 59–65. http://dx.doi.org/10.1192/bjp.bp.109.071522.
van der Krieke, L., Emerencia, A.C., Boonstra, N., Wunderink, L., de Jonge, P., Sytema, S., 2013. A Web-Based Tool to Support Shared Decision Making for People With a Psychotic Disorder: Randomized Controlled Trial and Process Evaluationq. J. Med. Interent Res. 15, e216.
van Oosterhout, B., Krabbendam, L., de Boer, K., Ferwerda, J., van der Helm, M., Stant, a. D., van der Gaag, M., 2014. Metacognitive group training for schizophrenia spectrum patients with delusions: a randomized controlled trial. Psychol. Med. 44, 3025–3035. http://dx.doi.org/10.1017/S0033291714000555.
Van Os, J., Altamura, A.C., Bobes, J., Gerlach, J.E.S., Hellewell, J.S.E., Kasper, S., Naber, D., Robert, P., Well, J.S.E.H., 2004. Evaluation of the Two-Way Communication Checklist as a clinical intervention: Results of a multinational,

randomised controlled trial Evaluation of theTwo-Way Communication Checklist as a clinical intervention Results of a multinational, Randomised con, vol. 184, pp. 79–83. http://dx.doi.org/10.1192/bjp.184.1.79.
Velligan, D., Mintz, J., Maples, N., Li, X., Gajewski, S., Carr, H., Sierra, C., 2013. A randomized trial comparing in person and electronic interventions for improving adherence to oral medications in schizophrenia. Schizophr. Bull. 39, 999–1007. http://dx.doi.org/10.1093/schbul/sbs116.
Velligan, D.I., Tai, S., Roberts, D.L., Maples-Aguilar, N., Brown, M., Mintz, J., Turkington, D., 2015. A Randomized Controlled Trial Comparing Cognitive Behavior Therapy, Cognitive Adaptation Training, Their Combination and Treatment as Usual in Chronic Schizophrenia. Schizophr. Bull. 41, 597–603. http://dx.doi.org/10.1093/schbul/sbu127.
Villeneuve, K., Potvin, S., Lesage, a., Nicole, L., 2010. Meta-analysis of rates of drop-out from psychosocial treatment among persons with schizophrenia spectrum disorder. Schizophr. Res. 121, 266–270. http://dx.doi.org/10.1016/j.schres.2010.04.003.
Williams, D.K., Thrush, C.R., Armitage, T.L., Owen, R.R., Hudson, T.J., Thapa, P., 2003. The Effect of Guideline Implementation Strategies on Akathisia Outcomes in Schizophrenia. J. Appl. Res. 3, 470–482.
Xiang, Y.T., Weng, Y.Z., Li, W.Y., Gao, L., Chen, G.L., Xie, L., Chang, Y.L., Tang, W.K., Ungvari, G.S., 2007. Efficacy of the community re-entry module for patients with schizophrenia in Beijing, China: Outcome at 2-year follow-up. Br. J. Psychiatry 190, 49–56. http://dx.doi.org/10.1192/bjp.bp.106.023697.
Xia, J., Adams, C., Bhagat, N., Bhagat, V., Bhoopathi, P., El-Sayeh, H., Pinfold, V., Takriti, Y., 2009. Losing participants before the trial ends erodes credibility of findings. Psychiatr. Bull. 33, 254–257. http://dx.doi.org/10.1192/pb.bp.108.021949.

Appendix 3 QMUL ethics approval for qualitative study with trial professionals

Queen Mary
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Queen Mary Ethics of Research Committee
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c/o Dr Stefan Priebe
Social and Community Psychiatry
Newham Centre for Mental Health
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31st March 2015

To Whom It May Concern:

Re: QMERC1396 – Factors affecting the retention of patients with mental health problems in non-pharmacological controlled clinical trials.

I can confirm that Ms Paulina Szymczynska has completed a Research Ethics Questionnaire with regard to the above research.

The result of which was the conclusion that her proposed work does not present any ethical concerns: is extremely low risk; and thus does not require the scrutiny of the full Research Ethics Committee.

Yours faithfully

Ms Hazel Covill – QMERC Administrator

Appendix 4 Information sheet for trial professionals

Queen Mary University of London

Retention of participants in clinical trials

Information for participants

Invitation to participate

You are invited to take part in this research study to find out about the factors affecting the retention of patients with psychosis in non-pharmacological clinical trials.

You should only agree to take part if you want to. If you choose not to take part there won't be any disadvantages for you and you will not be asked to take part again.

Please read this leaflet carefully before you decide to take part; this will tell you why the research is being done and what you will be asked to do if you take part. Please ask if there is anything that is not clear or if you would like more information.

If you decide to take part you will be asked to sign the attached form to say that you agree.

You are still free to withdraw at any time and without giving a reason.

What is the purpose of this study?

The purpose of this study is to find out what retention strategies are used in non-pharmacological trials involving people with psychosis, how issues with attrition are addressed at different stages of the research process, and what trial researchers perceive to affect participants' decisions about participation.

We are interested in speaking to researchers who have experience of working on trials involving people with psychosis.

What kind of information will be collected about me?

Your name or any personal details will be treated with confidentiality. Data will be handled, stored and destroyed in accordance with the Data Protection Act.

You will be asked to describe your professional role in the interview but the place where you work will be kept confidential.

What would taking part in the study involve?

- Your participation will involve taking part in an interview that should last between 45 minutes to one hour.
- You will be asked about your experience of working on trials in the context of retention of participants. You will not be asked questions about individual patient experiences of trials.

Queen Mary
University of London

What will happen to the results of the study?

The results of this research will be used in a doctoral thesis submitted to the Queen Mary University of London. We also want to publish results in scientific journals. Please be assured that you will not be identified in any report or publication.

Who is funding and organising the research?

The research is funded by the Life Sciences Initiative at the Queen Mary University of London. The researcher is Paulina Szymczynska supervised by Professor Stefan Priebe from the Unit for Social and Community Psychiatry, Wolfson Institute of Preventative Medicine.

Who has reviewed the study?

The study has been reviewed and approved by the Research Ethics Committee at the Queen Mary University of London.

If you have any questions or concerns about the manner in which the study was conducted please, in the first instance, contact the researcher responsible for the study. If this is unsuccessful, or not appropriate, please contact the Secretary at the Queen Mary Ethics of Research Committee, Room W117, Queen's Building, Mile End Campus, Mile End Road, London or research-ethics@qmul.ac.uk.

Do you have any questions?

To find out more or if you have any questions you can contact:

Paulina Szymczynska
Email: paulina.szymczynska@qmul.ac.uk
Tel.: 020 7540 6755 Extn: 2344

Thank you for taking the time to read this Information Sheet!

Appendix 5 Consent form for trial professionals

Queen Mary University of London

Retention of participants in clinical trials

Consent form

Queen Mary Ethics of Research Committee Ref: QMERC1396

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

- Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part.
- If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

- *I understand that if I decide at any other time during the research that I no longer wish to participate in this project, I can notify the researchers involved and be withdrawn from it immediately.*
- *I consent to the processing of my personal information for the purposes of this research study. I understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.*

Participant's Statement:

I _____ agree that the research project named above has been explained to me to my satisfaction and I agree to take part in the study. I have read both the notes written above and the Information Sheet about the project, and understand what the research study involves.

Signed: _____ Date: _____

Researcher's Statement:

I _____ confirm that I have carefully explained the nature, demands and any foreseeable risks (where applicable) of the proposed research to the participant.

Appendix 6 Interview schedule for trial professionals

INTERVIEW GUIDE

Project: Retention of patients with psychosis in non-pharmacological controlled clinical trials

Before the interview/Introduction

- *Thank the participants for taking the time to be interviewed*
- *Recap the purpose of the study*
- *If participant is familiar with the interviewer and the project, ask them to assume that the interviewer does not know anything about the trial the interviewee is working on, for the purposes of the recording.*
- *Remind the participant that everything that is said in the interview will be confidential*
- *Remind the participant about the likely length of the interview (45 minutes-1 hour)*
- *Remind that the interview can be stopped at any point without giving a reason*
- *Remind they don't have to answer all questions and it's OK if they don't remember*
- *Obtain consent to audio-record interview*

1. Respondent introduction
   (Aim: understand the role of the interviewee and the trial/s they have worked on. This will help to identify topics to discuss later during the interview.)

   Can you tell me about your experience of working on trials?

   - Can you please describe the most recent study you have worked on? *[Ask to describe the patient group, setting, interventions in all arms, geographical location, duration, number of follow-up contacts]*
   - Have you worked on other trials?

   Thinking about the trial/s you have worked on, can you describe the process of recruiting people to the trial?

   - Who approached participants and explained the trial to them?
   - What incentives were used to recruit potential participants?
   - Was the recruitment target met?
   - Do you think this could have been improved?

   Thinking about the trial/s you have worked on, can you talk about the situation with the retention of participants?

   - At what points in the research process was retention considered?
   - What was the drop-out rate?
   - Who was in charge of follow-up contact?
   - Were reasons for dropping out recorded? How was this done?
   - What retention strategies were used? [Ask to compare if the interviewee has worked on more than one study.]

Looking back at the trial, is there anything that you would have done differently?

- Is there anything that can be done differently to make it easier or more interesting for people to participate and to remain in the trial?
- Explore: recruitment methods, retention strategies, blinding/masking, incentives, follow-up methods, staying in touch, study updates

2. Factors affecting retention and issues specific to trials in mental health
   (Aim: discuss the interviewee's views on participants' characteristics that make it more or less likely for them to drop out; explore what trial characteristics (design, intervention, people involved) can affect participant retention); explore issues that may be specific to involving people with mental health issues in trials.)

   In your experience, are some people difficult to engage in clinical trials?

   What can make it difficult to keep people with mental health issues in clinical trials?

   Is there anything in terms of the design of the trial that can affect drop-out?

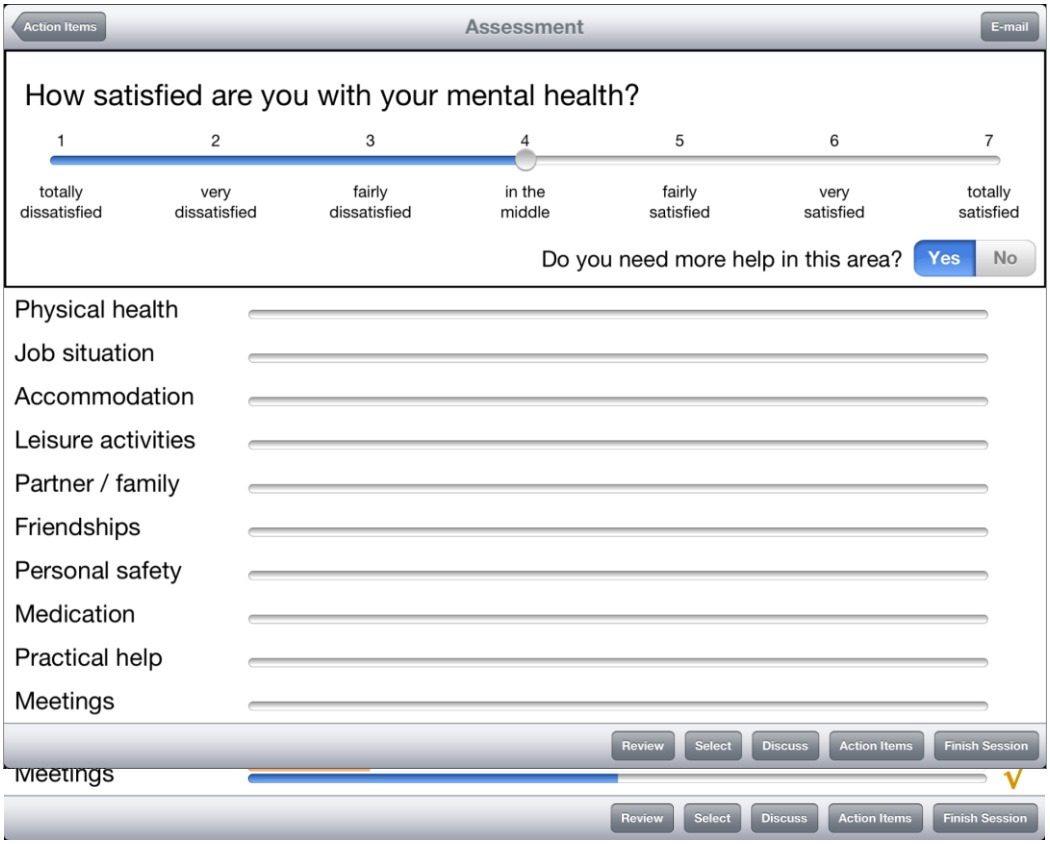
3. End
   (Aim: summarise conversation and give the participant an opportunity to add anything else)

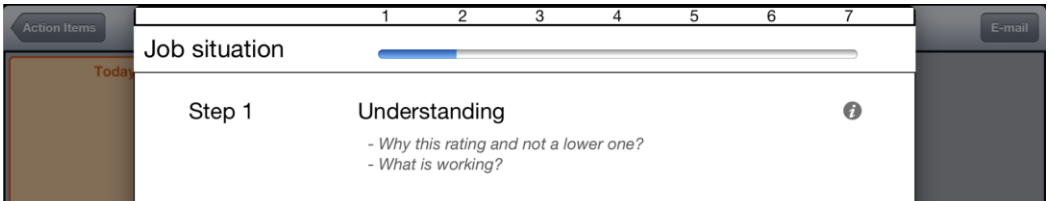
   Is there anything else that you'd like to tell me?

   Do you have any questions for me?

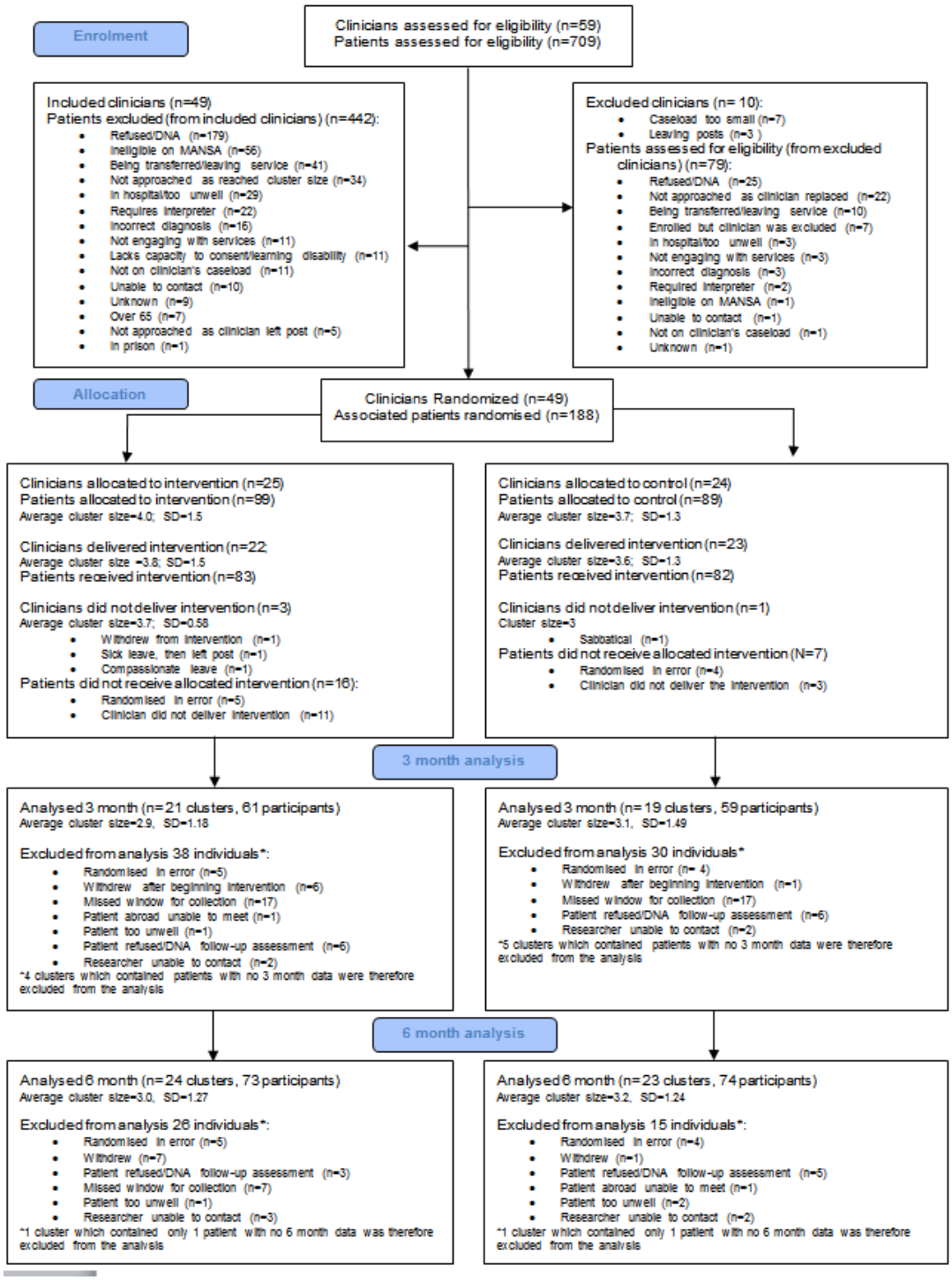
   Thank and close

Appendix 7 Screenshots of the DIALOG+ intervention





Appendix 8 CONSORT diagram for the EPOS trial



Appendix 9 Confirmation of REC ethical approval for interviews with the EPOS trial participants

NHS
Health Research Authority

NRES Committee London - Stanmore
Ground Floor
NRES/HRA
80 London Road
London
SE1 6LH

Telephone: 020 7972 2554

30 June 2015

Ms Paulina Szymczynska
Unit for Social and Community Psychiatry
Newham Centre for Mental Health
Glen Road, London
E13 8SP

Dear Ms Szymczynska

Study title:	**Factors affecting retention of people with psychosis in the EPOS trial**
REC reference:	**15/LO/0991**
Protocol number:	**1**
IRAS project ID:	**166717**

Thank you for your letter of 26th June 2015 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.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Ms Julie Kidd, nrescommittee.london-stanmore@nhs.net . Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

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 as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

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

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

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).

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

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Interview schedules or topic guides for participants [Interview guide Version A]	1	16 February 2015
IRAS Checklist XML [Checklist_18062015]		18 June 2015
IRAS Checklist XML [Checklist_26062015]		26 June 2015
Letter from sponsor [Letter from sponsor]		12 May 2015
Other [Interview guide version B]	1	16 February 2015
Other [Participant preference form]	1	16 February 2015
Other [Consent form]	2	15 June 2015
Other [Participant Information Sheet]	2	15 June 2015
Other [Response letter]		15 June 2015
Other [Verification of insurance certificate]		29 July 2014
Other [Research protocol Version 2 150615]	2	15 June 2015
REC Application Form [REC_Form_18062015]		18 June 2015
REC Application Form [REC_Form_26062015]		26 June 2015
Research protocol or project proposal [Research protocol]	1	16 February 2015
Summary CV for Chief Investigator (CI) [CV for Chief Investigator]	1	17 February 2015
Summary CV for supervisor (student research) [CV for academic supervisor]	1	16 February 2015

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.

After ethical review

Reporting requirements

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
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

15/LO/0991	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Mrs Rosemary Hill
Chair

Email:nrescommittee.london-stanmore@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Professor Stefan Priebe*
Mr Gerry Leonard, Joint Research Management Office

Appendix 10 Participant information sheet for the EPOS trial participants

Unit for Social and Community Psychiatry
Barts & the London School of Medicine
Queen Mary University of London

INFORMATION SHEET

Study title: Factors affecting retention of people with psychosis in the EPOS trial

We would like to invite you to take part in this follow up research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. A researcher will go through the information sheet with you and answer any questions you have. You may want to read the information more than once and take time to decide whether or not you want to take part. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

Why are we doing this research?

The aim of this follow up study is to find out about what makes people with psychosis stay involved in or stop participating in studies that test interventions that do not involve medications. We are interested in speaking to people who have taken part in the EPOS trial and also to those who changed their mind and left the study. This study is undertaken by a researcher (Paulina Szymczynska) pursuing doctoral studies at the Queen Mary University of London.

We think that information about how people make decisions about taking part in trials will help researchers understand what support and information people need to make decisions that are right for them. It is also important that enough people take part in research, so we hope to make some recommendations to researchers about what people with psychosis need and expect to take part in a study.

Why have I been invited to take part?

You have been invited to take part in this study because you have previously taken part in the EPOS trial and had to make a decision about whether or not you wanted to stay involved as a participant. We would like to speak to about 60 people about their experiences.

Do I have to take part?

You do not have to take part in the study and the decision is entirely yours. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a form to express your agreement. You are free to stop taking part at any time during the research without giving a reason. If you decide to stop, this will not affect the care you receive.

Will taking part in the research cost me anything?

No. The research will only require your time. In order to compensate you for this you will receive a payment of £20 when you complete an interview. If it costs you anything to get to the interview you will receive the money back if you keep a ticket or a receipt.

Participant Information Sheet: Version 2
Date: 15/06/2015

What will I have to do if I take part?

You will be asked to sign a form to express your agreement to taking part before the research begins. You will be given a signed copy to keep. Then you will meet with a researcher in a place that is convenient for you and offers safe and confidential space to talk. Or, if you prefer, you can speak to her over the phone. You will take part in an interview that will last between 30 and 45 minutes. The researcher will ask you some questions about the time when you had to decide whether or not you wanted to stay involved in the trial. You will also be asked to complete a short questionnaire asking about your background information like age, gender, and ethnicity. You will not have to answer all questions or provide a reason for not answering them. With your permission, we would like to audio record the interview. If you want to, you can later see the interview transcription and let us know if you are happy for it to be used for analysis.

What are the possible advantages and disadvantages and risks of taking part?

There is a very small risk that talking about some issues may be upsetting. You will be able to talk about any concerns you have with the researcher and you are free to withdraw from the research. This decision will not affect any care you may receive now or in the future.

The information we get from this study may help us in the future to support people with mental health problems taking part in clinical trials and those who do research.

What if there is a problem?

The researcher will support you if there is a problem completing the interview. Queen Mary University of London has agreed that if your safety is compromised as a result of your participation in the study, you will be compensated, provided that, on the balance of probabilities, an injury was caused as a direct result of the intervention you received during the course of the study. These special compensation arrangements apply where an injury is caused to you that would not have occurred if you were not in the trial. These arrangements do not affect your right to pursue a claim through legal action.

Will my taking part in the study be kept confidential?

Yes. All the information we collect will be kept strictly confidential and private. Your name, address and date of birth will be kept in a locked filing cabinet in a locked private office at an NHS site for 20 years, after which they will be destroyed. All of your information will be coded using a number instead of your name. Only the researcher will have access to the information.

The information that you provide will not be shared with other people unless you say it is OK to do so. However, if you tell us something that makes us concerned about your safety or that there is a risk to other people we may have to break your confidence and share this information with your clinician, and sometimes the police. However, we would always aim to discuss this with you first before taking action. We would only break your confidence in order to secure the best possible care for you and the public and to ensure we keep everyone safe.

Who is organising the research?

The research is funded by the Queen Mary University of London. The researcher is Paulina Szymczynska from the Queen Mary University of London, Unit for Social and Community Psychiatry. She is supervised by a Professor of Social and Community Psychiatry, Stefan Priebe.

Who has reviewed the study?

All research involving NHS patients is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the National Research Ethics Service (NRES) Committee London - Stanmore.

What do I do if I wish to make a complaint?

If you have a concern about any aspect of this study, you should speak to the researcher who will do her best to answer your questions. If she is unable to resolve your concern or you wish to make a complaint, you can contact Professor Stefan Priebe who can be reached at 020 7540 4210. If you remain unhappy, you can complain formally through the NHS Complaints Procedure. Details can be obtained from the Newham Centre for Mental Health, Cherry Tree Way, Glen Road, London E13 8SP. Tel: 020 7540 4380. You can also contact The Patient Advice and Liaison Service (PALS) who offer confidential advice, support with making complaints, and information on health-related matters. You can call NHS 111 for details of your nearest PALS.

What will happen to the results of the research study?

The results of this research will be used in a doctoral thesis submitted to the Queen Mary University of London. We also want to publish results in scientific journals. Please be assured that you will not be identified in any report or publication. If you want a summary of the findings you can tick a box on the consent form and you will receive a copy when the study is finished.

If you want to discuss this research any further please contact:

Paulina Szymczynska: 020 7540 4380 extn: 2344 or paulina.szymczynska@qmul.ac.uk

Thank you for reading this information sheet

Participant Information Sheet: Version 2
Date: 15/06/2015

Appendix 11 Participant preference form – interviews with the

PARTICIPANT PREFERENCE FORM

Title of Project: Factors affecting retention of people with psychosis in the EPOS trial

Participant's ID: ☐

This form is to be completed by the researcher when scheduling an interview and to be kept as a record of participant's preferences.

1. **When are you available to meet with me to do the interview?**

2. **What time works best for you?**

3. **Where would you like the interview to take place?**

4. **How would you like to be reminded about the interview?**
   - ☐ Phone call a few days before
   - ☐ Email a few days before
   - ☐ Other

5. **Sometimes participants do not turn up or are not home when we come to do an interview. In case this happens, what would you like me to do?**
   - ☐ Assume you changed your mind and do not want to take part
   - ☐ Call you and check if everything is OK. Keep trying until you answer.
   - ☐ Call someone else – contact details

     Name:

     Phone number:

Participant preference form Version 1
Date: 16/02/2015

EPOS trial participants

6. **In case you do not feel well during the interview or I am worried about your wellbeing, what would you like me to do?**

   ☐ Make sure you're safe before the interview ends and let you to take care of it yourself

   ☐ Let someone else know you're unwell – contact details

Name: Phone number:

7. **Do you have any special requirements I should be aware of? (e.g. access issues, speech difficulties, etc.)**

Appendix 12 Consent form for the EPOS trial participants

Queen Mary University of London

Unit for Social and Community Psychiatry
Barts & the London School of Medicine
Queen Mary University of London

Participant identification number:

CONSENT FORM

Title of Project: Factors affecting retention of people with psychosis in the EPOS trial

Name of Researcher: Paulina Szymczynska

Please initial box

1. I have read and understand the information sheet dated 16/02/2015 (version 1) for the above study. I have had the opportunity to consider the information, ask questions and I am satisfied with the answers. ☐
2. I understand that my participation is voluntary and that I can stop taking part at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that my personal information is strictly confidential. I know the only person who may see this information is the researcher. ☐
4. I agree to the interview being audio recorded. ☐
5. I agree to the use of anonymised quotes in publications. ☐
6. I agree to participate in the above research. ☐
7. I would like to receive a summary of findings. ☐

Name of participant	Date	Signature
Name of researcher	Date	Signature

Consent form Version 1
Date: 16/02/2015

Appendix 13 Interview guide for interviews with the EPOS trial participants - Version A: Participants who completed all assessments

INTERVIEW GUIDE

Title of Project: Factors affecting retention of people with psychosis in the EPOS trial

Version A – Participants who completed participation

1. Introduction
   (Aim: to make sure the participant understands purpose of the project, remind about the likely length of the interview, remind they don't have to answer all questions and it's OK if they don't remember)

2. Respondent introduction
   (Aim: to explore respondent's experience of participating in the trial and to help identify topics to discuss later during the interview)

   Q: Can you tell me about your experience of participating in the EPOS trial?

3. Research topics
   (Aim: to explore relevant aspects of interviewee's experiences of participating in EPOS)

   Invitation and decision to take part:

   Q: How were you invited to take part in the study?

   - Who told you about the study?
   - What information were you given?

   Q: What made you decide to take part in the first place?

   Q: Was there anything you were unsure of?

   Q: Did you speak to anyone else about the study before you made the decision?

   Expectations:

   Q: What did you expect in terms of your involvement?

   - How long did you think the study would last?
   - Did you expect anything to change in terms of your mental health?

   Involvement in the study:

   Q: Can you tell me what your participation involved?

   - Where did you have to go?
   - How often did you receive the intervention?
   - Who did you see when you attended the appointments?

   Q: Was there anything that could have been done differently to make it easier or more interesting for you to participate?

Q: Was there anything specific that made you stay involved until the end of the study?

Q: Did you at any point think about stopping your involvement in the study?

- If yes, why? What were the circumstances?

Q: Did participating in the trial have any effects on you?

Retention strategies:

Q: Were you sent any reminders about appointments/interviews?

- What form did they take? (phone, text, email)
- What did you think about them?
- Who contacted you?

4. End

(Aim: summarise conversation and give the participant an opportunity to add anything else)

Q: Is there anything else that you'd like to discuss?

Q: Do you have any questions for me?

Thank and close

Appendix 14 Interview guide for interviews with the EPOS trial participants - Version B: Participants who did not complete all assessments

INTERVIEW GUIDE

Title of Project: Factors affecting retention of people with psychosis in the EPOS trial

Version B – Participants who dropped out

1. Introduction
   (Aim: to make sure the participant understands purpose of the project, remind about likely length of the interview, remind they don't have to answer all questions and it's OK if they don't remember)

2. Respondent introduction
   (Aim: to explore respondent's experience of participating in the trial and to help identify topics to discuss later during the interview)

   Q: Can you tell me about your experience of participating in the EPOS trial?

3. Research topics
   (Aim: to explore relevant aspects of interviewee's experiences of participating in EPOS)

   Invitation and decision to take part:

   Q: How were you invited to take part in the study?

   - Who told you about the study?
   - What information were you given?

   Q: What made you decide to take part in the first place?

   Q: Was there anything you were unsure of?

   Q: Did you speak to anyone else about the study before you made the decision?

   Expectations:

   Q: What did you expect in terms of your involvement?

   - How long did you think the study would last?
   - Did you expect anything to change in terms of your mental health?

   Involvement in the study:

   Q: Can you tell me what your participation involved?

   - Where did you have to go?
   - How often did you receive the intervention?
   - Who did you see when you attended the appointments?

   Q: How long did you stay involved in the study?

Q: What made you want to stop participating?

Q: Was there anything that could have changed your mind about your decision to stop your participation?

Q: Did stopping your participation have any effects on you?

Retention strategies:

Q: Were you sent any reminders about appointments?

- What form did they take? (phone, text, email)
- What did you think about them?
- Who contacted you?

4. End
(Aim: summarise conversation and give the participant an opportunity to add anything else)

Q: Is there anything else that you'd like to discuss?

Q: Do you have any questions for me?

Thank and close