Exploring the cost-effectiveness of psychological therapies: Analysis of a pilot Randomised Controlled Trial (RCT) of Acceptance and Commitment Therapy (ACT) for depression in the context of psychosis

and

Clinical Research Portfolio

Rosie Begbie (MA Hons)

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Institute of Health and Wellbeing
College of Medical, Veterinary and Life Sciences
University of Glasgow

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~ For mum ~

Table of Contents

Chapter One: Systematic Review

Cost-effectiveness of psychological interventions for people with psychosis: A systematic review of trial-based economic evaluations

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Abstract

Schizophrenia and related psychotic disorders pose a considerable economic burden to healthcare systems (Mangalore and Knapp, 2007) and to families, other caregivers, and wider society (Knapp, 2000; Chong et al., 2016). In the context of resource constraints, decision makers increasingly rely on economic evaluations to guide decision making processes (Garcla-Altes et al., 2004). Whilst reviews of economic evaluations of pharmacological treatments for schizophrenia have been conducted (Achilla and McCrone, 2013), there has been no review of economic evaluations of psychological interventions in this area. This review addresses this gap by examining trial-based economic evaluations of psychological interventions for psychosis. Studies were identified from a systematic search across major electronic databases in June 2017. Eight eligible studies were identified. Whilst two interventions (an intervention informed by Solution Focused Therapy and a Cognitive Behavioural Therapy intervention) were promising given their association with both reduced costs and better outcomes, small sample size and methodological limitations means that the cost-effectiveness of these interventions will need to be confirmed in larger, more robust trials. The current evidence does not support Metacognitive training, Cognitive Remediation Therapy or Adherence Therapy as being cost-effective options. The overall small study number, diversity across studies and methodological limitations mean that the conclusions of this review should be considered preliminary. Emerging results are nevertheless promising and suggest that there will be value in conducting further economic evaluations of psychological interventions for psychosis.

Keywords: schizophrenia, cost-analysis, health economics

Introduction

Despite its low lifetime prevalence (4/1,000 people; Saha et al., 2005), schizophrenia and related psychotic disorders pose a considerable economic burden to healthcare systems (Mangalore & Knapp, 2007) as well as to families, other caregivers, and wider society (Knapp, 2000; Chong et al., 2016). Schizophrenia leads to high direct and indirect costs with estimates of direct costs in Western countries ranging from 1.6% to 2.6% of total health care expenditures (Barbato et al., 1998). In light of this burden and in the context of resource constraints, it is essential that treatments for psychosis are both effective and cost-efficient.

Economic evaluation relates to the comparative analysis of alternative courses of action in terms of both their costs and consequences and is the process through which a given treatment's cost-effectiveness can be established (Drummond et al., 2015). Economic evaluation has a key role to play in informing resource allocation decisions. However, economic evaluations of psychological interventions for psychosis are rare (Patel et al., 2010). Reviews of economic evaluations in relation to the treatment of psychosis have been restricted to pharmacological studies (e.g. Achilla and McCrone, 2013) or studies which focus on considering the cost-effectiveness of early intervention services (e.g. Amos, 2012). As there has been no known systematic review of economic evaluations of psychological interventions for psychosis, the aim of this review is to address this gap.

This review will focus on the three main types of economic evaluation commonly referred to in the literature: cost-benefit analysis (CBA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) (Drummond et al., 2015). These approaches vary in the effect measure employed. In CEA, effects or benefits are expressed in natural units (e.g. changes on a symptom severity scale); in CUA a preference-based measure of health is used (such as quality-adjusted life years, QALYs); in CBA effects are measured in monetary units. Together, they are considered 'full' economic evaluations as they consider both the costs and benefits of interventions (Drummond et al., 2015). Economic evaluations tend to be undertaken using primary data collected alongside a clinical trial (trial-based analyses) or by using

secondary data and/or decision analytic modelling techniques[1] (Brettschneider et al., 2014). Given that decision analytic modeling is a specialist area which uses distinct methodology, this review focusses on trial-based economic evaluations.

Methods

Search strategy

Four electronic databases were searched for relevant published research on 23rd June 2017: MEDLINE, EMBASE, PsychINFO and National Health Service Economic Evaluation Database (NHS EED). Keywords and subject headings relating to psychosis and health economics were combined into the search strategy which was finalised following consultation with a librarian. The search was tailored to individual databases where necessary and was designed to promote sensitivity (for full search strategy see Appendix 1.2). The search did not have a start date limit.

Study selection

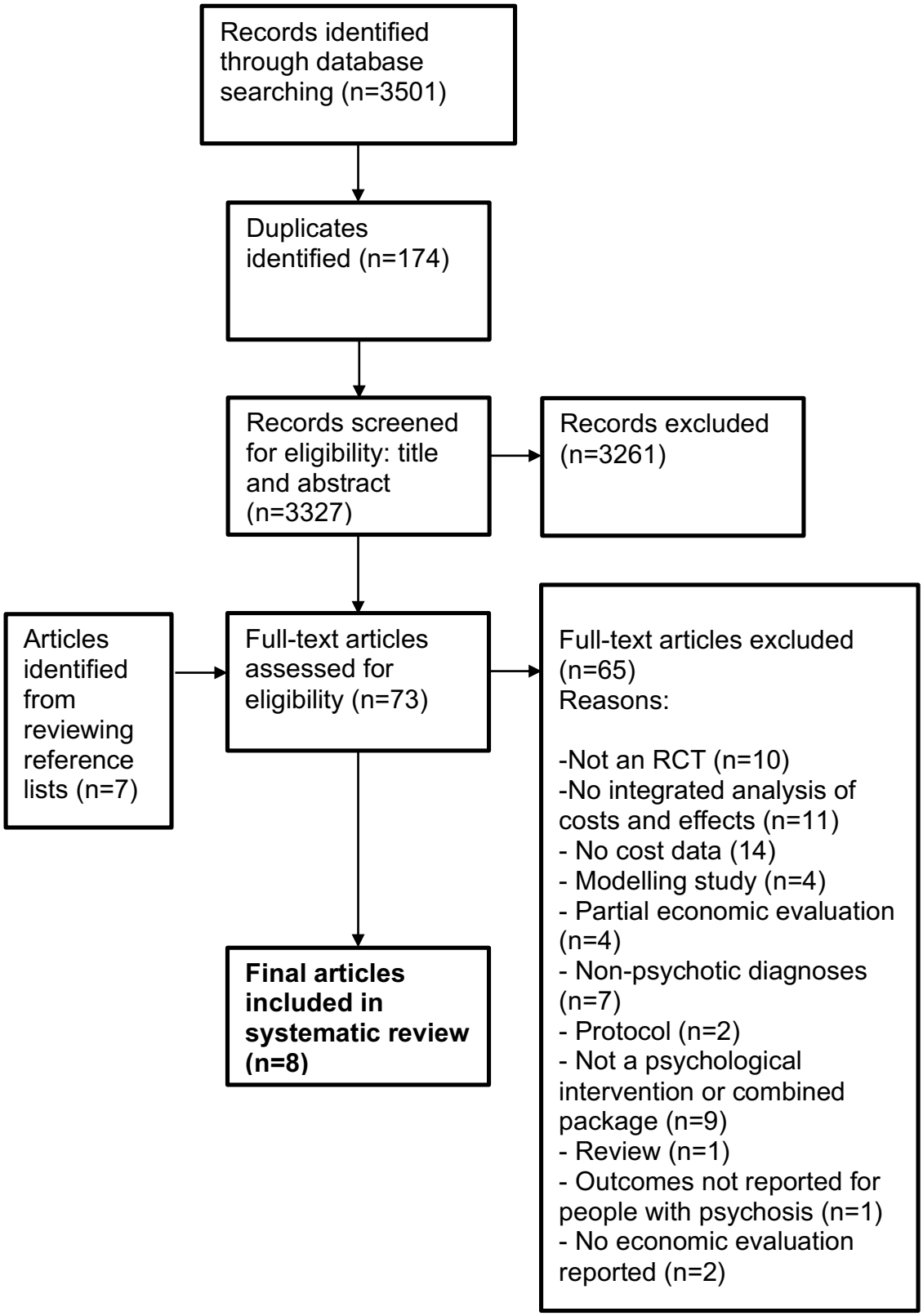
Studies were included if they reported a comparative cost-effectiveness analysis (CEA, CUA and CBA) of alternative interventions for people diagnosed with a psychotic disorder, with at least one intervention being a psychological intervention, undertaken within a randomised controlled trial (RCT). Studies were excluded if they did not integrate cost and effectiveness analyses, if they used a decision analytic model or were not in English. Book chapters, dissertations, reviews, study protocols and conference abstracts were also excluded.

The search process is summarised in Figure 1. The electronic search retrieved 3501 papers in total. Following removal of duplicates, titles and abstracts were screened, with those clearly not meeting inclusion criteria excluded. Where eligibility was unclear based on title and abstract, full-text articles were reviewed. Following review

[1] A decision analytic model defines a set of mathematical relationships characterising the possible consequences of alternative interventions using data from a range of sources (Drummond et al., 2015).

of the full-text papers, eight studies were included in the final review. A manual search of the reference lists of these eight papers identified seven further papers of interest however none were found to be eligible for inclusion. A list of the studies excluded following full-text review is available in Appendix 1.3.

Figure 1: Flow diagram showing details of the systematic search process



Data extraction, interpretation and synthesis

As well as demographic data, type of analysis (CEA, CUA, CBA) and details relating to the comparators within each study, details relating to the time horizon and cost perspective were extracted from papers. Time horizons are the time-periods over which costs and benefits are likely to differ between the alternatives under comparison and in trial-based economic evaluations are usually determined by the study follow-up period (Sculpher et al., 2006). With regards to cost perspective, in health economics, different perspectives can be adopted which guide the costs that are collected and included in analyses. The perspective taken is usually one of two, either 'societal' or 'health and social care'. When an evaluation is conducted from a health and social care perspective, only costs that are incurred by the payer, i.e. the health service, are included (Drummond et al., 2015). In this instance, all direct medical and other health-related costs are measured. In addition to these costs, the societal perspective also includes indirect costs such as those relating to loss of productivity.

In cost-effectiveness analysis, an intervention is considered to be more cost-effective than its comparator if it is associated with better outcomes (i.e. increased health benefits) but at a lower cost compared to the alternative. In this instance, the intervention can be said to *dominate* the comparator. If the intervention is associated with additional health care costs and is also less effective, it can be said to be *dominated*, it is not cost-effective. If an intervention offers increased health benefits but at some additional cost it can still be considered cost-effective, in this situation, the question of whether it should be regarded as cost-effective will depend on whether decision makers consider the additional cost per extra unit of health benefit worth paying for (Drummond et al., 2015). The most common approach to analysing cost-effectiveness and selecting the preferred intervention in this situation is to calculate an incremental cost-effectiveness ratio (ICER), i.e. the additional cost per unit of effect.

In deciding whether an intervention offers 'good' value for money, the reported ICER must be compared to a specified monetary threshold which represents the maximum amount that the decision maker is willing to pay for the associated health effect (Fenwick et al., 2006). Within the UK, the preferred measure of health effect is the quality-adjusted life year (QALY): a preference-based measure of health

outcome that weights the life expectancy of a patient with an estimate of their health-related quality of life (NICE, 2012). NICE (2012) adopt an assumed threshold value of £20,000 per QALY gained. If the ICER for an intervention falls below this assumed value then it is considered cost-effective (NICE, 2012). ICERs and cost-effectiveness thresholds will be extracted from each study, where reported.

As ICERs are point-estimates, they do not capture uncertainty in the sample data on which they are based (Miller et al., 2003). The cost-effectiveness acceptability curve (CEAC) is a graphical method used to summarise the uncertainty in estimates of cost-effectiveness (Fenwick et al., 2006). The CEAC indicates the probability of a treatment being more cost-effective compared with an alternative for a range of hypothetical monetary values (λ): potential maximum amounts (celling ratios) that a decision maker may be willing to pay for an additional unit increase in the specified health outcome (Fenwick et al., 2006). The probabilities reported in relation to these graphs indicate the probability that the data are consistent with a true cost-effectiveness ratio falling below these given ceiling amounts (Haddock et al., 2003). Where CEACs are used, conclusions on cost-effectiveness can be given greater weight (Fenwick et al., 2006). The information provided by a CEAC and any statements made regarding them should be restricted to comments on the uncertainty of the estimate of cost-effectiveness rather than used to make any statements about whether an intervention should be implemented, as this will depend on the true willingness to pay and cost-effectiveness threshold values of the decision maker (Fenwick et al., 2006). Where available, findings from CEACs will be reported.

Finally, meta-analysis was not deemed appropriate for this review due to diversity between studies in terms of outcome measures used, the nature of interventions, and overall methodology. Instead, a narrative approach to synthesising the results is used.

Quality assessment

The quality of the studies was appraised using the Consensus on Health Economic Criteria (CHEC) list (Evers et al., 2005). The CHEC-list was prepared using a Delphi method (three Delphi rounds; 23 international experts) and is intended for use when

undertaking systematic review of trial-based evaluations (Langer, 2012). There are 19 “yes” or “no” questions. A sample of papers (50%) was assessed by an independent researcher. Any rating discrepancies were discussed and consensus reached.

Results

Study characteristics

Across the eight included RCTs, participants were primarily recruited from outpatient/community mental health services (Priebe et al., 2015; Patel et al., 2010; Haddock et al., 2003; Zhang et al., 2014; Barton et al., 2009). Two studies recruited participants from both community and inpatient services (Patel et al., 2013; van der Gaag et al., 2011) and another recruited from an inpatient setting alone (van Oosterhout et al., 2014). The included studies were conducted across several countries: four in the United Kingdom (UK, Priebe et al., 2015; Patel et al., 2010; Haddock et al., 2003; Barton et al., 2009), two in the Netherlands (van Oosterhout et al., 2014; van der Gaag et al., 2011), one in China (Zhang et al., 2014) and a further study was conducted across sites in the UK, Germany, Italy and the Netherlands (Patel et al., 2013). Four studies adopted a societal perspective to measuring costs (van Oosterhout et al., 2014; van der Gaag et al., 2011; Zhang et al., 2014; Haddock et al., 2003), two studies considered costs from both a societal and health and social care perspective (Patel et al., 2010; Patel et al., 2013) and two studies adopted the health and social care perspective alone (Barton et al., 2009; Priebe et al., 2015).

All studies were conducted across multiple sites, with one study involving multi-national sites (Patel et al., 2013). Sample sizes varied, ranging between 36 (Haddock et al., 2003) and 1184 (Zhang et al., 2014). In the four papers where power was discussed and/or a power calculation was reported, the studies were powered on the primary outcome measure, not on costs (van der Gaag et al., 2011; van Oosterhout et al., 2014; Patel et al., 2010; Priebe et al., 2015), this is common in trial-based economic evaluations (Briggs, 2000).

Four studies carried out cost-effectiveness analysis, CEA (van der Gaag et al., 2011; Patel et al., 2010; Priebe et al., 2015; Haddock et al., 2003), three carried out

cost-utility analyses, CUA (van Oosterhout et al., 2014; Barton et al., 2009; Zhang et al., 2014) and one study completed CEA and CUA (Patel et al., 2013). No study used cost benefit analysis (CBA). Time horizons varied between 24 weeks and 18 months. The psychological interventions considered included: Cognitive Behavioural Therapy (van der Gaag et al., 2011; Barton et al., 2009), CBT with motivational intervention (Haddock et al., 2003), Metacognitive training (van Oosterhout et al., 2014), Adherence Therapy (Patel et al., 2013), Cognitive Remediation Therapy (Patel et al., 2010), a brief intervention informed by Solution-Focused Therapy (Priebe et al., 2015) and a combined package consisting of psychoeducation, CBT, family intervention and skills training (Zhang et al., 2014). Table 1 presents a summary of these results.

Quality assessment

The methodological quality varied between studies. Quality ratings are summarised fully in Appendix 1.4. The total criteria met, expressed as a percentage for each study, is summarised in Table 2. All eight included studies had an appropriate study design and were full economic evaluations - as per the inclusion criteria. All studies identified all important and relevant outcomes for each alternative and measured and valued these appropriately. Conclusions that followed from the data were reported in every case. All but one study (Patel et al., 2010) clearly described the study population and all but one study (Priebe et al., 2015) posed a well-defined research question. The chosen time horizon was deemed to be appropriate, with the exception of one study (van Oosterhout et al., 2014). All important and relevant costs for each alternative were deemed to have been identified with the exception of two studies (van Oosterhout et al., 2014; Priebe et al., 2015). Costs were deemed to have been measured and valued appropriately in all but one instance (Priebe et al., 2015). In three out of the eight studies the competing alternatives were not clearly described (Patel et al., 2013; Patel et al., 2010; Zhang et al. 2014). Two studies did not adopt an appropriate perspective based on CHEC criteria (Barton et al. 2009; Priebe et al.2015). Three studies did not complete sufficient sensitivity analysis (Patel et al., 2010; Priebe et al. 2015; Zhang et al., 2014). Only three studies appropriately discussed generalisability of the results (van der Gaag et al. 2011, Patel et al. 2013; Patel et al. 2010). In the two studies with a time horizon

Table 1: Summary of study characteristics and results

Study, country	Population, age (mean), gender (male)	Interventions, sample size	Analysis	Perspective	Horizon	Outcomes	Cost-effectiveness results
van Oosterhout et al. (2014), Netherlands	Psychotic disorder in DSM-IV schizophrenia spectrum, 38, 60%	Metacognitive training (MCT) + Treatment as Usual (TAU), 75 TAU, 79	CUA	Societal	24 weeks	QALYs	• Mean total costs were €13325 in the MCT+TAU group and €12827 in the TAU group. • QALYs were lower in the MCT+TAU group (value not reported) • TAU dominated MCT+TAU.
van der Gaag et al. (2011), Netherlands	Schizophrenia or schizoaffective disorder with persistent symptoms, 37, 71%	Cognitive Behavioural Therapy (CBT),110 TAU, 106	CEA	Societal	18 months	Number of days patients functioned within the normal range	• Mean total costs were €33130 in the CBT group and €29578 in the TAU group. • The CBT group had on average 183 days of normal functioning compared to 106 days in the TAU group. • ICER was €47 per day with normal functioning gained.

Barton et al. (2009), United Kingdom	Diagnosis of affective or non-affective psychosis, 29, 71.4%	Social recovery orientated CBT(SRCBT), 35 Case Management Alone (CMA), 42	CUA	Health/social care	9 months	QALYs	• Mean total costs were £4866 in the SRCBT group and £3254 in the CMA group. • Mean QALY gain was estimated to be 0.041 for SRCBT compared to 0.006 for CMA. The ICER for SRCBT was £18844 which was below the assumed threshold of £20000 per QALY suggesting SRCBT is cost-effective.
Patel et al. (2013), Netherlands, United Kingdom, Germany, Italy	Clinical and research diagnosis of schizophrenia, 42, 60%	Adherence Therapy (AT), 204 Health Education (HE), 205	CEA and CUA	Health/social care and societal	12 months	Short Form 36 (SF-36) mental component score (MCS) and QALYs	• For Health/social care perspective, mean total costs were £20115 in the AT group and £22597 in the HE group. • From societal perspective, mean total costs were £25346 in the AT group and £26787 in the HE group. • Mean QALY gain was 0.67 in AT and 0.68 in HE. • Mean MCS score was 40.24 for AT and 41.32 for HE • ICERs not calculated • AT found to be equivalent to HE

Patel et al. (2010), United Kingdom	DSM-IV diagnosis of schizophrenia, 36, 73%	Cognitive Remediation Therapy (CRT) + Usual Care (UC), 43 UC alone, 42	CEA	Health/social care and societal	40 weeks	Improvement in working memory: total raw score from Digit Span subtest of the WAIS-III	• For Health/social care perspective, mean total costs were £14391 in the CRT group and £13029 in the UC group. • From societal perspective, mean total costs were £16338 in the CRT group and £15338 in the CU group. • 39% of participants gained ≥2 points in WAIS-III Digit Span total raw score since baseline compared to 15% in the UC group. • At the end of the study, the likelihood of cost-effectiveness peaked at 30% even for investments up to £5000.
Priebe et al. (2015), United Kingdom	Schizophrenia or related disorder according to ICD-10, 42, 70%	DIALOG+ (patient-centred assessment and brief psychological intervention informed by Solution Focused Therapy), 94 Active Control (AC), 85	CEA	Health/social care	12 months	Subjective Quality of Life (SQoL): mean score on MANSA, Manchester short assessment of quality of life	• Mean total costs were £3279 in the DIALOG+ group and £4624 in the AC group. • Mean MANSA score in the DIALOG+ group at 12 months post treatment was 4.4 and 4.1 in the AC group. • There was a 72.4% probability of the intervention both improving

							outcomes and saving costs.
Zhang et al. (2014), China	Schizophrenia or schizophreniform disorder according to DSM-IV criteria, 26, 55%	Combined Treatment (CT) 'Psychosocial Intervention programme' (Included: psychoeducation, family intervention, skills training, CBT), 580 TAU, 604	CUA	Societal	12 months	QALYs	• Mean monthly total costs in the CT group were US$213.3 and US$ 213.2 in the TAU group. • Mean QALYs gained in the CT group were 0.676 and 0.658 in the TAU group • CT was associated with an ICER of US$1819.4 per QALY gained. This is below the threshold accepted in China (US$5,100 per QALY gained), indicating that the intervention is cost-effective.
Haddock et al. (2003), United Kingdom	Diagnosis of schizophrenia, schizoaffective disorder or delusional disorder according to DSM-IV and ICD-10 and a diagnosis of substance dependence or misuse according to DSM-IV	CBT + Motivational Intervention (CBT+MI), 18 patient-carer pairs Routine Care (RC), 18 patient-carer pairs	CEA	Societal	18 months	Global Assessment of Functioning (GAF) score	• Mean total costs were £8753 in the CBT+MI group and £10013 in the RC group. • Total GAF score in the CBT group at 18 months was 60.12 versus 53.44 in the RC group. • CBT+MI dominated RC.

	Mean age and gender proportion not reported for patients						

QALYs: quality-adjusted life years; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition; ICD-10: International Statistical Classification of Diseases and Related Health Problems – Tenth Edition; CEA: cost-effectiveness analysis, CUA: cost-utility analysis, WAIS-III: Wechsler Adult Intelligence Scale – Third Edition

greater than one year, future costs and outcomes were discounted appropriately (van der Gaag et al., 2001; Haddock et al., 2003). No studies included in this review discussed ethical and distributional issues.

Table 2: Percentage of CHEC-list quality criteria met within each study

Study	**Total criteria met (%)**
van Oosterhout et al. (2014)	78
van der Gaag et al. (2011)	95
Barton et al. (2009)	83
Patel et al. (2013)	89
Patel et al. (2010)	78
Priebe et al. (2015)	56
Zhang et al. (2014)	78
Haddock et al. (2003)	89

Cost-effectiveness of psychological interventions for psychosis

Due to heterogeneity of the studies in terms of the interventions, comparators and the methodologies used, the results of each study will be discussed briefly in turn. van der Gaag et al. (2011) compared CBT with Treatment as Usual (TAU). The primary outcome was number of days functioning within the normal range. Results indicated that although costs were higher in the CBT group, CBT was also associated with better outcomes. They reported an incremental cost-effectiveness ratio (ICER) of €47 per day of normal functioning gained. Drawing from the cost-effectiveness acceptability curve (CEAC), the authors indicated that a willingness to pay of €84 per additional day of normal functioning would be associated with 70% probability that CBT was more cost-effective than TAU.

Another study compared social recovery orientated CBT (SRCBT) and Case Management Alone (CMA). Barton et al. (2009) found that costs were higher in the SRCBT group but that SRCBT was associated with better outcomes, i.e. greater gain in quality-adjusted life years (QALYs). The ICER for SRCBT was £18,844 which, being below the assumed threshold of willingness to pay £20,000 per QALY endorsed by NICE, indicated that SRCBT is cost-effective. When uncertainty was explored, the probability of cost-effectiveness was 54.3% at the assumed threshold.

In a large study (n=1184), Zhang et al. (2014) compared Combined Treatment (CT, a psychosocial intervention programme which included psychoeducation, family intervention, skills training, CBT) with TAU. CT was associated with more QALYs gained. Cost differences were not statistically significant. The ICER for CT was US$1819.4 per QALY gained (the common threshold accepted in China is US$5,100 per QALY gained, Zhang et al., 2014). As the ICER is below the accepted threshold, CT was considered to be a cost-effective option compared to TAU.

In a study which compared DIALOG+ (patient-centred assessment and brief psychological intervention informed by Solution Focused Therapy) with an active control (AC), Priebe et al. (2015) found that DIALOG+ was associated with lower costs and better outcomes in terms of Subjective Quality of Life (SQoL: mean score on MANSA, Manchester short assessment of quality of life) and that it therefore dominated AC. The authors reported a 72.4% probability of the DIALOG+ intervention both improving outcomes and saving costs. The probability reported here was not based on a CEAC and is not related to a willingness to pay threshold, which was not reported.

Haddock et al. (2003) considered the cost-effectiveness of CBT+Motivational Intervention (CBT+MI) compared to routine care (RC) in patient-carer pairs. Patients met diagnostic criteria for substance misuse or dependence in addition to a diagnosed psychotic disorder. The primary outcome for the CEA was Global assessment of functioning (GAF) score. Results indicated that CBT+MI was associated with lower costs and better outcomes, thereby dominating RC. Based on the presented CEAC, the probability of CBT+MI being cost-effective when the decision maker is unwilling to pay anything additional for an extra point increase in the GAF was 69.3%. If the decision maker was prepared to pay at least £30 per point increase in the GAF score then the probability of the treatment programme being cost-effective increased to 70% with probability further rising to 90% at a figure of £655 per point increase in GAF score (Haddock et al., 2003).

Patel et al. (2013) considered the cost-effectiveness of Adherence Therapy (AT) compared to a Health Education intervention (HE). The authors reported that AT appeared to be equivalent to HE in terms of costs and outcomes. AT may also have been dominated by HE or involve lower costs alongside worse outcomes, which the authors acknowledged is an unlikely basis for choosing a treatment (Patel et al.,

2013). Based on the CEAC, probabilities of AT being the most cost-effective option ranged between 30 and 60% for both cost perspectives and for both outcomes measured (QALYs, MCS score) for the willingness to pay thresholds examined (range €0-5000). Based on these results, AT was not considered to be a cost-effective treatment.

Patel et al. (2010) considered the cost-effectiveness of Cognitive Remediation Therapy (CRT) and Usual Care (UC) compared to UC alone. The primary outcome used for the CEA was working memory improvement. There was more than an 80% probability that CRT would be cost-effective compared to UC at time 2 (14 weeks post-randomisation) however at time 3 (40 weeks post-randomisation), at the end of the study period, the likelihood of cost-effectiveness peaked at 30% even for investments up to £5000 per 1% of patients improving their working memory. These results indicated that CRT may not be the most cost-effective option in the longer term (Patel et al., 2010).

Another study considered the cost-effectiveness of Metacognitive training (MCT) + TAU compared to TAU alone. TAU was found to dominate MCT+TAU, i.e. TAU alone was associated with both less costs and better outcomes leading the authors to conclude that MCT+TAU is not cost-effective (van Oosterhout et al., 2014).

Discussion

The current review explored the cost-effectiveness of psychological interventions for people with psychosis. This is the first known review of economic evaluations in this area. In order to decide if an intervention offers 'good' value for money, a reported ICER must be compared to a specified monetary threshold, this threshold representing the maximum amount that a decision-maker is willing to pay for health effects (Fenwick et al., 2006). It is not possible to make any definitive statements about what is and what is not cost-effective where willingness to pay thresholds are hypothetical (i.e. as reported in CEACs), or indeed are not reported at all. Final interpretation remains subjective and will depend on the decision maker. Whilst methodological differences and a lack of commonly accepted cost-effectiveness thresholds for certain measures of effect complicate synthesis and the overall

conclusions which can be made, it is possible to draw some preliminary conclusions from the studies reviewed.

Interventions with a strong CBT component

CBT+Motivational Intervention had a high probability of being cost-effective when compared to routine treatment (RT), with CBT+MI dominating RT (Haddock et al. 2013). In another study, CBT was associated with greater costs and better outcomes and was likely to be more cost-effective than TAU as long as the willingness to pay for an additional day of normal functioning gained was higher than €47 (van der Gaag et al., 2011). There is no consensus on an acceptable benchmark threshold in relation to an additional day of normal functioning (van der Gaag et al., 2011). The critical issue that will determine whether this treatment is deemed to be cost-effective based on this result will depend on what a given decision maker is indeed prepared to pay for an additional day of normal functioning. Social recovery orientated CBT (SRCBT) was also associated with greater costs and better outcomes and was reported to be a cost-effective treatment for people with psychosis when compared to Case Management Alone (Barton et al., 2009). However, as the probability of cost-effectiveness was only 54.3% (as indicated by the CEAC) at the assumed threshold of £20,000 per QALY, this suggests the need for caution regarding the cost-effectiveness of SRCBT.

Combined treatment packages

A treatment combining several psychological treatment approaches was also reported to be cost-effective as the ICER reported was below the common threshold accepted in China. In this case though, Zhang et al. (2014) did not present a cost-effectiveness plane and/or CEACs therefore the uncertainty associated with this result is not known.

Solution Focused Therapy

An intervention informed by Solution Focused Therapy combined with patient-centred assessment (DIALOG+) was found to dominate the active control (AC) with a 72.4% probability of being cost-effective (Priebe et al., 2015). In this study, Priebe et al. (2015) addressed uncertainty by plotting cost-outcome combinations onto a

cost-effectiveness plane however the extent of uncertainty can be difficult to assess using the cost-effectiveness plane alone (Drummond et al., 2015). CEACs were not reported. A decision maker would likely require further information regarding the uncertainty associated with this result prior to making a decision in relation to the implementation of this treatment.

Metacognitive training

Metacognitive training (MCT) was dominated by TAU (van Oosterhout et al. 2014) and therefore is not likely to be a cost-effective treatment option based on this study and in comparison with the other psychological interventions reported above.

Cognitive Remediation Therapy

With regards to CRT, results suggested that it was cost-effective in the short term (14 weeks) but was unlikely to be cost-effective in the longer term (40 weeks). It is unlikely therefore that CRT would be the preferred treatment option compared to, for example, a Solution Focused Therapy approach (DIALOG+) or CBT+MI which dominated the alternatives with which they were compared following time periods of 12 and 18 months respectively.

Adherence Therapy

AT was unlikely to be more cost effective than Health Education (Patel et al, 2013). Because AT was not compared to routine care, it is not possible to say whether it would be cost-effective in comparison to the other psychological interventions discussed above that did compare to routine care.

Implications

From the research reviewed, an intervention combining CBT+MI (Haddock et al., 2003) emerged as being the most likely to be cost-effective as it dominated in the economic evaluation, although it should be noted that the sample size was very small. An intervention that combined patient-centred assessment with SFT also dominated indicating that it was cost-effective however the degree of uncertainty was difficult to fully assess and there were other issues in relation to inadequate reporting that limit the conclusions which can be drawn about this treatment

currently. The current evidence does not support Metacognitive training, CRT or AT as being cost-effective options. Two further CBT-based treatments (CBT, van der Gaag et al., 2011; SCRBT, Barton et al., 2009) and a combined treatment (Zhang et al., 2014) were associated with greater costs and better outcomes and may be cost-effective however further research using improved methodology and comparison with an appropriate cost-effectiveness threshold (in the case of van der Gaag et al., 2011) is required before more definitive conclusions can be drawn regarding their cost-effectiveness.

Methodological issues

The overall quality of studies included in this review was reasonable when evaluated against health economics standards (see Table 2). In addition to some of the methodological issues already mentioned above however, quality assessment revealed some additional methodological issues that limit the conclusions which can be drawn from this review. One such issue relates to choice of outcome measure. The QALY is the outcome that is currently recommended within most guidelines for the purposes of economic evaluation (van der Gaag et al., 2011). The use of a single, generic measure such as the QALY allows for comparison of diverse healthcare interventions (Duarte et al., 2017). Half of the studies included in this review used QALYs. In the studies adopting different outcome measures (e.g. GAF, days functioning in the normal range, working memory) it is not possible to make comparisons across studies. Whilst there is an established cost-effectiveness threshold reported by NICE for QALYs which facilitates interpretation of ICERs, there are no useful threshold values for incremental costs per unit of other effect (Brettschneider et al., 2014). This means that some of the ICERs here were difficult to interpret.

The majority of studies included in this review adopted a societal perspective, this is the perspective often recommended within the wider health economics field (Drummond et al., 2015). Indirect costs have been found to constitute a substantial proportion of the costs associated with schizophrenia with evidence suggesting that taking a relatively broad approach to cost measurement in this area is important (Davies and Drummond, 1994; Knapp, 2000; Mangalore and Knapp, 2007). Two studies in this review adopted the health and social care perspective. Indirect costs are not considered within the health and social care approach. Of note however is that both of these studies were conducted in the UK where adopting the health and

social care perspective is preferred (NICE, 2012). This highlights one of the many examples of variability that exist between different countries and health care systems which can impact on how research is conducted. Cost estimates can vary significantly depending on the perspective adopted (Drummond et al., 2015; Luyten et al., 2016) therefore studies adopting different perspectives will not have comparable results. Given the indirect costs associated with schizophrenia, researchers within the UK may wish to consider measuring costs from both perspectives. This would facilitate comparison with research adopting a societal perspective and would arguably better capture the wider impact of treatment.

The time horizons of the studies included in this review ranged from 24 weeks to 18 months. As schizophrenia is a lifelong condition, it has been argued that the time horizon for assessing treatments in this area should cover a long period (Achilla and McCrone, 2013). Economic evaluation which occurs as part of a trial however is usually restricted to the follow-up period of the study. Whilst the time horizons used for the trial-based economic evaluations reviewed here were largely deemed to be appropriate given their context, it is nevertheless important to acknowledge this limitation of trial-based analyses. Any conclusions drawn about cost-effectiveness of an intervention based on trial-based analyses alone may be vulnerable to change over time. One study included in this review indicated reduced cost-effectiveness of CRT over time (Patel et al., 2010). Whilst it was not possible to determine whether this occurred in the other studies included in this review due to analysis only occurring at one time point, there may be merit in considering longer time horizons and methods of analyses which allow for potential decline in cost-effectiveness in the post-treatment phase to be quantified.

When assessing the quality of studies included in this review, some criteria were difficult to assess due to limitations with reporting. For example, Priebe et al. (2015) provided insufficient information to establish whether all important and relevant costs had been identified, measured and valued appropriately. The CHEERS (Consolidated Health Economic Evaluation Reporting Standards) statement makes recommendations in relation to the minimum amount of information to be included when reporting health economic evaluations. Recommendations are presented in a 24-item checklist based on the format of the CONSORT statement checklist (Husereau et al., 2013). A recommendation of the current review is that researchers should endeavour to meet these minimum reporting standards in order to facilitate

interpretation of their results and thereby maximise the value of the research. Greater consistency and transparency in reporting should also allow for comparisons across interventions to be made more easily and should thereby facilitate the decision making process overall.

Strengths, limitations and future research

This review has several strengths. First, a broad search strategy was used in order to increase search sensitivity. Studies reporting partial economic evaluations (costs and effects not considered together) and studies that did not report an incremental analysis of costs and effects were also excluded thereby ensuring greater quality and associated utility of the results reported. The review also only included RCTs which are considered the gold standard for assessing both effectiveness and cost-effectiveness (Edwards et al., 2015).

With regards to limitations, modelling studies were excluded from this review therefore the full range of evidence available in relation to the cost-effectiveness of psychological interventions may not have been captured. In addition, the review did not attempt to transform currency values to a single value in order to better facilitate comparison and interpretation. There was also no independent assessor of study eligibility or data extraction, with quality ratings the only aspect of the review independently assessed. Finally, whist an assessment of the methodological quality of the economic evaluations was completed, this review did not appraise methodological quality or risk of bias associated with the RCTs to which the economic evaluations were attached. It is therefore not possible to quantify or evaluate the impact of such issues on the conclusions drawn within this review.

Finally, the studies included in this review were not all conducted within the same country. Differences in health care systems in terms of, for example, costs and willingness to pay thresholds, mean that it is not always possible to generalise the results of cost-effectiveness analyses beyond the country of investigation. The format and design of interventions and comparators also varied across studies, as did the cost perspective adopted which further impacts on the extent to which these results can be generalised.

Conclusions

Despite the importance of economic evaluation for resource allocation decisions, there remain relatively few studies of psychological interventions for people with psychosis which include economic evaluations. Whilst eight papers were identified for this review, a recent review of effectiveness of psychological interventions for psychosis included 72 papers (Lutgens et al., 2017), highlighting the relative infancy of focus on cost-effectiveness. Whilst two interventions, (CBT+MI and patient-centred assessment and SFT) were promising given their association with reduced costs and better outcomes, small sample size and methodological limitations means that the cost-effectiveness of these interventions will need to be replicated in larger, more robust trials. The current evidence does not support Metacognitive training, CRT or AT as being cost-effective options. The overall small study number, diversity across studies and methodological limitations mean that these conclusions are tentative and should be considered preliminary.

Further robust economic evaluations of psychological interventions will be able to further elucidate their potential cost-effectiveness and will help commissioners allocating scare health resources to consider their added value in terms of their potential to deliver better outcomes and cost-offsets in comparison to other treatment options for psychosis. In guiding the commissioning and design of more robust evaluations, pilot data and pre-trial economic modelling can provide important information about the likely cost-effectiveness of an intervention and thus instances where a full-scale evaluation is or is not likely to be worthwhile.

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Chapter Two: Major Research Project

Exploring the cost-effectiveness of psychological therapies: Analysis of a pilot Randomised Controlled Trial (RCT) of Acceptance and Commitment Therapy (ACT) for depression in the context of psychosis

Prepared in accordance with the requirements for submission to Schizophrenia Bulletin (see Appendix 1.1)

Word count: 6997

Plain English Summary

Background

Schizophrenia and related psychotic disorders pose challenges not only in terms of clinical management but also in terms of costs which fall to healthcare systems and wider society. Depression is common in people with psychotic disorders and contributes to poorer outcomes. It is important that effective treatments are developed to treat depression in the context of psychosis.

The ADAPT trial was a pilot randomised controlled trial (RCT) of Acceptance and Commitment Therapy (ACT) for depression after psychosis (ACTdp) for individuals with a diagnosis of schizophrenia who also met diagnostic criteria for major depression. The trial was undertaken by a group of researchers in Glasgow in 2014/15. ACT aims to help people relate to difficult thoughts and feelings in more adaptive ways and helps them to commit to behavioural change that is consistent with personally held values. The ADAPT trial included 29 participants, with 15 people receiving ACTdp and 14 people receiving Standard Care (SC). Data were collected from participants at three time points: the beginning of the trial, after 5 months (post-treatment) and at 10 months (follow-up).

Economic evaluation relates to the comparative analysis of alternative treatments in terms of both their costs and consequences and is the process through which cost-effectiveness can be established (Drummond et al., 2015). In the context of resource constraints in health care, it is not only important to determine whether a treatment is effective, but also whether it is cost-effective and ‘value for money’.

Aims

The aim of this study was to use data collected as part of the ADAPT trial to explore whether ACTdp is cost-effective and whether it would be feasible to conduct an economic evaluation alongside a larger trial of ACTdp.

Methods

The main outcome for the cost-effectiveness analysis was the quality-adjusted life year (QALY). QALYs are an overall measure of health outcome that weight the life expectancy of a patient with an estimate of their health-related quality of life.
The total cost of the use of health and social care services over the 10-month study period was calculated for participants in each group. The cost of providing ACT was included in the ACTdp group total, with total costs and QALYs then compared between the groups.

Main findings and conclusions

Preliminary results indicated that ACTdp may be a cost-effective treatment option. Although costs were higher in the ACTdp group, it was promising that some of the additional costs associated with providing ACT were offset by reduced use of some health and social care services in this group. Whilst there was no significant difference between the groups in terms of QALYs, the data suggested a trend towards better outcomes in the ACTdp group. The overall results indicate that a larger trial of ACTdp to confirm these preliminary results is justified.

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Abstract

Health, social, and economic burden related to schizophrenia is significant for both patients and wider society (Knapp, 2000; Chong et al., 2016). Depression is common in people with schizophrenia (Whitehead et al., 2002) and is associated with particularly high levels of health care use (Steel et al., 2015). Developing and disseminating cost-effective interventions for people with depression in the context of psychosis is therefore indicated. The ADAPT trial was a pilot randomised controlled trial (RCT) of Acceptance and Commitment Therapy for depression after psychosis (ACTdp) for individuals with a diagnosis of schizophrenia who also met diagnostic criteria for major depression (Gumley et al., 2015; Gumley et al., 2017). A total of 29 participants were randomised to ACTdp+ Standard Care (SC) (n=15) or SC alone (n=14). The aim of the present study was to explore outcomes relating to cost-effectiveness of ACTdp and to consider the feasibility of conducting an economic evaluation alongside a larger, definitive trial. Cost-effectiveness was explored in a cost-utility analysis (CUA) with quality-adjusted life years (QALYs) as the primary outcome. QALYs were calculated from the EuroQol (EQ-5D-5L) and cost data were collected using the Client Service Receipt Inventory (CSRI). The incremental cost-effectiveness ratio (ICER) for ACTdp was £8,339 which falls below the assumed threshold of £20,000 per incremental QALY used by NICE (2012). A trend towards better outcomes and partial cost-offsets in the ACTdp group suggests that ACTdp may be a cost-effective treatment and that a larger, definitive trial to explore this further would be justified.

Keywords: Schizophrenia, cost-analysis, cost-utility analysis, health economics

Introduction

Schizophrenia and related psychotic disorders can be chronic, severe and disabling illnesses which pose challenges not only in terms of clinical management but also in terms of costs. As well as being associated with a significant cost to the patient in terms of personal suffering (Jin and Mosweu, 2017), there is also a considerable economic burden to healthcare systems (Mangalore and Knapp, 2007), families, other caregivers and wider society (Knapp, 2000; Chong et al., 2016). Whilst the lifetime prevalence is low (median 4.0 per 1,000 persons; Saha et al., 2005), within the United Kingdom (UK), the annual cost of treatment of schizophrenia has been estimated to exceed £2billion, which is approximately 3% of the overall National Health Service (NHS) budget (Mangalore and Knapp, 2007). Comorbid conditions can be associated with additional personal and economic burden.

Depression is common in people with schizophrenia with prevalence data indicating depressive symptoms in 50% of people newly diagnosed with schizophrenia and 33% of people with chronic schizophrenia who have relapsed (Whitehead et al., 2002). Depression contributes to poorer quality of life in people with psychosis (Connell et al., 2014; Saarni et al., 2010) and is associated with poorer outcomes (Vorontsova et al., 2013) and greater health care use (Steel et al., 2015). Schizophrenia comorbid with depression is also associated with a suicide rate of approximately 5% which is significantly higher than the general population (Palmer et al., 2005; Hor and Taylor 2010). The need to develop and disseminate cost-effective interventions for people with depression in the context of psychosis is therefore clearly indicated.

Acceptance and Commitment Therapy

Acceptance and Commitment Therapy (ACT) is a contextual cognitive-behavioural approach which incorporates mindfulness and acceptance techniques to help people relate to difficult thoughts and feelings in more adaptive ways and helps them to commit to behavioural change that is consistent with personally held values (Morris et al., 2013). A recent meta-analysis which focused on mindfulness and acceptance-based therapies for psychosis, including ACT, showed small to

moderate effect sizes when compared with a control condition (Khoury et al., 2013). Randomised controlled trials have also shown that ACT can lead to reduced depression in non-psychotic populations (Hacker et al., 2016). In a feasibility study of ACT for emotional dysfunction following psychosis, White et al. (2011) found that, relative to a group receiving treatment as usual (TAU), a significantly greater proportion of those who received ACT changed from being depressed at baseline to not being depressed at 3-month follow-up. In a post hoc analysis, White et al. (2015) found that those receiving ACT were 15 times more likely to achieve a clinically significant improvement in depression scores than those receiving TAU.

ADAPT trial

The ADAPT trial was a pilot randomised controlled trial of Acceptance and Commitment Therapy for depression after psychosis (ACTdp) for individuals with a diagnosis of schizophrenia who also met diagnostic criteria for major depression (Gumley et al., 2015; Gumley et al., 2017). This pilot trial followed the feasibility work described above (White et al., 2011). The trial methodology and the clinical results have previously been reported (see Gumley et al., 2015 and Gumley et al., 2017). In brief, a total of 29 participants were randomised to ACTdp+Standard Care (SC) (n=15) or SC alone (n=14). There were no significant differences between groups in terms of the Calgary Depression Scale for Schizophrenia (CDSS) total score at 5-months (immediately post-treatment) or at 10-months (follow-up). In terms of the other primary outcome measure, the Beck Depression Inventory (BDI-II), a statistically significant effect in favour of ACTdp + SC at 5-months but not at 10-months was noted.

Economic evaluation

In the context of resource constraints, decision makers increasingly rely on economic evaluations to guide decision making processes (Garcla-Altes et al., 2004) and are increasingly asking economic as well as clinical questions in relation to new treatment developments (Knapp, 2000). Where there are competing healthcare interventions, economic evaluation informs policymakers, payers and others on how to make efficient allocation decisions (Luyten et al., 2016). Although there is now a promising evidence base which supports the effectiveness of

psychological interventions for psychosis (Garety, 2003), it is very rare for there to be a cost-effectiveness analysis in published trials.

Whilst preliminary results suggest that ACTdp has potential to improve outcomes in people with depression in the context of psychosis, the question of whether this treatment can be considered cost-effective remains unexplored. There are currently three preferred methods of economic evaluation: cost-benefit analysis (CBA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) (Drummond et al., 2015). All three subtypes may be referred to as cost-effectiveness analyses in the literature. These approaches vary in the effect measure employed. In CEA, effects or benefits are expressed in natural units (e.g. changes on a symptom severity scale); in CUA a preference-based measure of health is used (such as quality-adjusted life years, QALYs); in CBA effects are measured in monetary units (Drummond et al., 2015). The aim of the present study is to explore preliminary outcomes relating to cost-effectiveness of ACT for depression after psychosis and to consider the feasibility of conducting an economic evaluation alongside a larger, definitive trial. Cost-effectiveness will be explored in a cost-utility analysis.

Methods

Participants and recruitment procedures

Participants were consecutively recruited, assessed and randomised and included inpatients or outpatients aged 16 or over who were receiving (a) anti-psychotic medication (b) psychiatric follow-up and (c) follow-up from secondary mental health care community based services (Gumley et al., 2017). Participants met DSM-IV-TR criteria for schizophrenia and major depression which was confirmed via Structured Clinical Interview for DSM/SCID-I & Calgary Depression Scale/CDSS for Schizophrenia (score N 7; Kim et al., 2006) (Gumley et al., 2017). Individuals with significant learning disability or who were unable to speak English were not eligible (Gumley et al., 2017).

Measures

The EuroQol (EQ-5D-5L; Herdman et al., 2011) is a preference-based quality of life instrument which assesses five dimensions of health-related quality of life (HRQoL): mobility, self-care, usual activities, pain, and anxiety/depression. Utility scores can be calculated by attaching nation-specific values (also called weights) to the EQ-5D raw data. Value sets for several countries are provided by the EuroQoL group. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). The EQ-5D is the preferred measure of HRQoL in adults (NICE, 2012) and has been found to be a valid and reliable measure for use in people with psychosis (Konig et al., 2007; Barton et al., 2009; Stochl et al., 2013). Utility scores are widely used for calculating QALYs.

The Client Service Receipt Inventory (CSRI) is an instrument used to collect retrospective information on service utilisation (including standard health services and psychiatric services) which was developed specifically for capturing service use among psychiatric patients (Beecham and Knapp, 2001). The instrument can be adapted to capture data for pre-specified time durations and different service categories. The CSRI in this study captured data for the preceding five months.

Intervention: Acceptance and Commitment Therapy for depression after psychosis (ACTdp)

Individuals received up to five months of individual ACTdp+Standard Care (hereafter referred to as ACTdp). The intervention has been described elsewhere (Gumley et al., 2015). In brief, the ACTdp intervention aimed to enhance engagement with valued life activities via increasing mindfulness and psychological flexibility, values clarification and reducing experiential avoidance (Gumley et al., 2017).

Standard Care (SC)

Treatment received by all participants in the trial was examined in order to establish the parameters of Standard Care. For inclusion, all participants had to be in receipt of antipsychotic medication and follow-up from a secondary specialist mental health service.

Design

The study was designed as a Parallel-group Randomised Open Blinded Evaluation (PROBE) of Acceptance and Commitment Therapy for depression after psychosis (ACTdp).

Research Procedures

CSRI and health-related quality of life data were collected at three time points: entry, pre-randomisation; 5-months; and 10-months. Research Assistants collecting the data were masked to treatment allocation.

Outcomes

Health-related quality of life

The main outcome for the cost-effectiveness analysis will be the quality-adjusted life year (QALY). QALYs are an overall measure of health outcome that weight the life expectancy of a patient with an estimate of their health-related quality of life. The EQ-5D-5L health states will be assigned a utility score using responses published by the EuroQol group. QALYs will be calculated as the amount of time spent in a health state weighted by the corresponding utility (U).

Resource use and costs

The economic evaluation will adopt the NHS and Personal Social Services (PSS) perspective preferred by NICE (i.e. 'health and social care perspective') which includes all direct medical and other health-related costs. Indirect costs such as those associated with loss of productivity and costs incurred by patients and carers are not included within this perspective (should a societal perspective have been adopted all of these costs would have been included). From the CSRI data, service utilisation costs will be estimated by multiplying the resource use by the appropriate unit cost using UK unit cost estimates routinely published by the Personal Social Services Research Unit (PSSRU) for the year 2014–2015 (Curtis and Burns, 2015). Medications will be costed using the British National Formulary.

ACTdp

Intervention costs will be calculated using available data on unit cost of a Clinical Psychologist, as published by PSSRU. The average length of session offered by a Clinical Psychologist delivering ACTdp was 1 hour. To account for preparation time

and patient-related administration, 1 ½ hours was added to every 1 hour session thus, for every session attended, the cost of a psychologist per minute was multiplied by 150 minutes. Similarly, to reflect costs which are still incurred when a session is cancelled by a patient, cancelled sessions were costed by multiplying the cost of a Clinical Psychologist per minute by 90.

Data Analysis

A health economist was consulted when formulating the data analysis plan. The proportion of patients using services included in the CSRI will be reported. Mean total costs by service and total costs within each group will be calculated. Due to the small sample size of this study and the tendency for cost data to have a highly skewed distribution (Briggs and Gray, 1998), differences between total costs will not be explored statistically. The importance of controlling for imbalance in baseline utility in the calculation of mean differential QALYs has previously been emphasised (Manca et al., 2005). Mean difference in QALYs will therefore be explored using a regression model adjusting for baseline utility scores. The focus of analysis is on preliminary estimation rather than hypothesis testing.

Cost-effectiveness will be assessed through the calculation of an incremental cost-effectiveness ratio (ICER). This will be calculated by dividing the difference in total costs between the ACTdp and the SC group by the difference in effects (i.e. QALYs). Given the small sample size and pilot nature of this trial, this will be exploratory and hypothesis-generating only. NICE suggest that, in general, interventions with an ICER of less than £20,000 per QALY gained should be considered to be cost-effective (NICE, 2012). The stated figure is also referred to as the cost-effectiveness threshold or the willingness to pay threshold (WTPT).

Results

Participants

The full characteristics of the sample and the range of outcomes from the ADAPT trial have been reported elsewhere (Gumley et al., 2017) therefore only a summary is reported here. Of the 55 participants referred to the study, 38 gave their informed

consent to enter. Of these, seven were not eligible and two participants declined continued participation prior to randomisation. This left 29 participants who were randomised to ACTdp+SC (n=15) or SC alone (n=14). The mean age of the sample was 46.2 years old in the SC group and 46.8 in the ACTdp group. Men accounted for 64.3% of the SC group and 66.7% of the ACTdp group.

Missing data

At baseline, data were available for all participants in relation to service use and quality of life. Two participants in the ACtdp group declined follow-up at 5-months with a further participant lost to follow-up at 10-months (total n=3). Data were available for all participants in the SC group at 5-months with one declining follow-up at 10-months (total n=1). Missing cost and quality of life responses were managed by imputation using median answers from other participants in the same group and time point.[2]

Service use and costs

The proportion of participants using each service and total resource use for each service is presented in Table 1. Mean costs of each service used at the three study time points are summarised in Table 2. A table containing the unit costs used in the cost calculations is available in Appendix 2.1. At baseline, whilst overall patterns of service use between the two groups appeared to be broadly similar, which would be expected given randomisation, some differences were observed. One participant in the ACTdp group and two in the SC group had a hospitalisation in the five months prior to study entry. The individual in the ACTdp group had an admission of 12 days whilst the combined number of days for the two participants hospitalised in the SC group was 17. This was associated with a mean cost of £178.40 in the ACTdp group and £270.79 in the SC group (Table 2). Whilst the proportion of participants who saw a Community Psychiatric Nurse (CPN) was the same within each group (n=12), the number of contact minutes varied with participants in the SC group accruing 4319 minutes (£256.06) of contact compared to 7,485 (£414.17) in the ACTdp group. Total overall costs at baseline were £832.31 in the SC group and £1237.4 in the ACTdp group.

In the 5 months following randomisation during which time ACTdp was delivered, there were further observable differences in service use and associated costs

[2] This was completed by Bruno Riveros prior to the transfer of data to the writer

between the two groups. Three participants in the SC group had periods of hospitalisation which totalled 83 days when combined. No participants in the ACTdp group were hospitalised in this period. Hospitalisation contributed £1369.86 to the total costs for the SC group in this period. There was also increased use of Voluntary Organisation Day Activity services in the SC group compared to ACTdp in this time-period. Four participants were recorded to have used a total of 510 hours (£364.20) of this service compared to 60 hours (£40) accrued by one participant in the ACTdp group. Between baseline and 5-months, the difference in CPN use observed at baseline appeared to lessen with service use and associated cost now also slightly higher in the SC group (4971 hours, £294.71) than in the ACTdp group (4013 hours, £222.05). Contact with Social Work was also observed to increase in the ACtdp group with three participants accruing 1490 minutes (£84.43) compared to 80 minutes (£4.86) accrued by one participant in the SC group. Contact with General Practitioner (GP) also changed between groups. Whilst at baseline contact with and therefore associated costs of GP use was greater in the ACTdp group (370 minutes, £93.73) compared to SC (230 minutes, £ 62.43), at 5-months post-treatment, GP use had increased in the SC group (415 minutes, £112.64) but decreased in the ACTdp group (170 minutes, £43.07).

At 10-months follow-up, there were no hospitalisations within either group. Use of Voluntary Organisation Day Activity within the SC group decreased slightly (296 hours compared to 510 hours at 5-months) and increased slightly within the ACTdp group (110 compared to 60 hours at 5-months). CPN use also decreased by a similar margin in both groups with use and associated costs still slightly less in the ACTdp group (3167 minutes, £175.24) than the SC group (4260 minutes, £252.56). GP contact further decreased in the ACTdp group at 10-months (35, £8.87) and also decreased slightly in the SC group although with overall use still higher than in the ACTdp group (354 minutes, £96.09). The total cost difference between the groups at 10-months was £375.55 (95% CI -£1,379 to £2,129). Total costs are summarised in Table 3.

Participants in both groups reported being on at least one medication during all three time periods with the exception of two people in the ACTdp group, one of whom was only recorded as using medication during one time period (5-10months) and another participant who used medication during the baseline period and 5-months of

treatment but who was not recorded as using medication during the final 5 months of study.

Table 1: Total resource use and proportion of participants (pts) using each service for each 5-month time-period

	Baseline (5-months prior to baseline)				**End of treatment** (baseline-5 months)				**Follow-up** (5-10 months)			
	SC		ACTdp		SC		ACTdp		SC		ACTdp	
Service	Total	Pts	Total	Pts	Total	Pts	Total	Pts	Total	Pts	Total	Pts
Psychiatric ward (days)	17	2	12	1	86	3	0	0	0	0	0	0
Psychiatric outpatient visit (appt)	0	0	8	2	1	1	0	0	0	0	0	0
Other hospital outpatient visit (appt)	1	1	8	1	2	2	1	1	5	3	0	0
CMHT (hours)	0.75	1	27	3	0	0	0	0	0	0	3	1
Voluntary Organisation Day activity (hours)	0	0	40	1	510	4	60	1	296	2	110	1
Consultant Psychiatrist (mins)	670	12	790	13	485	12	655	11	465	10	545	10
Psychiatrist Registrar (mins)	0	0	45	1	0	0	60	1	0	0	0	0
Psychologist (mins)	0	0	60	1	330	2	360	1	600	2	210	2
CPN (mins)	4,319	12	7,485	12	4,971	13	4,013	11	4,260	12	3,167	10
Social Worker (mins)	0	0	90	1	80	1	1,490	3	0	0	245	1
OT (mins)	60	1	1,870	3	295	3	185	2	135	2	462	1
Chiropodist (mins)	0	0	85	3	0	0	140	2	30	1	20	1
GP (mins)	230	9	370	10	415	10	170	6	354	8	35	4
Dentist (mins)	90	5	205	8	140	6	96	5	280	7	255	5
Optician (mins)	55	2	80	1	80	2	30	1	65	3	60	1
ACTdp Treatment (mins)	-		-	-	0	0	36,570	15	-		-	
Medication	-	14	-	14	-	14	-	14	-	13	-	11

GP: General Practitioner, CPN: Community Psychiatric Nurse, CMHT: Community Mental Health Team, OT: Occupational Therapist, appt: appointment, mins: minutes (Note: data on ACTdp delivery and medication was available for the two ACTdp participants who declined follow-up at 5-months.)

Table 2: Summary of mean (s.d.) costs (£) per patient for each 5-month time-period

	Baseline (5-months prior to baseline)		**End of treatment** (baseline-5 months)		**Follow-up** (5-10 months)	
	SC	ACTdp	SC	ACTdp	SC	ACTdp
Service						
Psychiatric ward	270.79 (809)	178.40 (668)	1,369.86 (2,634)	-	-	-
Psychiatric outpatient visit	-	57.07 (156)	7.64 (28)	-	-	-
Other hospital outpatient visit	7.50 (27)	56.00 (209)	15.00 (37)	7.00 (27)	37.50 (21)	-
CMHT	2.25 (8)	75.60 (193)	-	-	-	8.40 (23)
Voluntary Organisation Day activity	-	26.67 (103)	364.29 (438)	40.00 (52.10)	211.43 (438)	73.33 (52.10)
Consultant Psychiatrist	85.19 (60)	93.75 (69)	59.12 (46)	77.73 (48)	61.66 (46)	64.67 (48)
Psychiatrist Registrar	-	5.34 (21)	-	7.12 (28)	-	-
Psychologist	-	4.12 (16)	24.28 (59)	24.72 (53)	44.14 (61)	14.42 (28)
CPN	256.06 (11)	414.17 (19)	294.71 (18)	222.05 (13)	252.56 (33)	175.24 (32)
Social Worker	-	5.10 (20)	4.86 (18)	84.43 (236)	-	13.88 (29)
Occupational Therapist	2.91 (11)	84.77 (315)	14.33 (62)	8.39 (73)	6.56 (19)	20.94 (36)
Chiropodist	-	3.40 (8)	-	5.90 (19)	1.29 (4)	0.80 (1)
General Practitioner	62.43 (81)	93.73 (154)	112.64 (212)	43.07 (69)	96.09 (145)	8.87 (17)
Dentist	7.59 (12)	16.13 (20)	11.80 (28)	7.55 (11)	23.60 (45)	20.06 (32)
Optician	4.64 (13)	6.29 (24)	6.74 (18)	2.36 (16)	5.48 (9)	4.72 (7)
ACTdp Treatment	-	-	-	2,511.14 [1,080]	-	-
Medication	132.95(104)	116.86 (121)	147.69 (98)	118.12 (120)	137.73 (107)	121.64 (112)
Total costs	832.31	1237.4	2432.96	3159.58	878.04	526.97

CPN: Community Psychiatric Nurse, CMHT: Community Mental Health Team, s.d.: standard deviation

Table 3: Total costs from baseline to 10-months			
	SC	ACTdp	Difference
Total cost	£3311	£3686.55	£375.55

ACTdp

Participants attended an average of 15.4 (s.d.= 6.2) sessions with 0.7 (s.d.=1.4) cancelled and 1.2 (s.d.=-1.5) not attended. The total cost of providing ACTdp over the 5-month treatment period was £37,667 with a mean cost per participant of £2,511 (s.d.= £1,112, min: £92; max: £3,708).

Quality of Life

Utility values were assigned to each participant at each time point based on EQ-5D-5L responses[3]. Table 4 summarises the mean utility scores for each group at the three time points in the study.

Table 4: Mean (standard deviation) utility scores at each study time-point (Scale range: 0, death, to 1, optimal or 'perfect' health)						
	Baseline		5-months		10-months	
	SC	ACTdp	SC	ACTdp	SC	ACTdp
Utility score	0.55 (0.33)	0.62 (0.24)	0.55 (0.29)	0.69 (0.27)	0.64 (0.27)	0.66 (0.24)

Within the ACTdp group, there appeared to be a slight improvement in utility score between baseline (0.62) and end of treatment (0.69). By 10-month follow-up, the mean utility score had decreased slightly from the post-treatment stage but was still slightly higher than at baseline and was similar to the mean utility score in the SC group. Within the SC group, utility scores appeared to improve slightly between baseline (0.55) and 10-month follow-up (0.64).

Table 5 summarises the quality-adjusted life years (QALYs) accrued in each group across 10 months from baseline to follow-up.

[3] Utility values were assigned and QALY calculations completed by Bruno Riveros

Table 5: Summary of QALYs accrued during 10-month study period				
	Mean	*Standard Deviation*	*Min*	*Max*
SC	0.477	0.224	0.019	0.754
ACTdp	0.557	0.165	0.207	0.765

Difference in QALYs between the groups was explored using a regression model, adjusting for baseline utility score. ACTdp was associated with a mean incremental QALY gain of 0.045 QALYs, although the difference between groups was not significant (95% CI -0.062 to 0.152). Table 6 summarises the regression output.

Table 6: Summary of regression output						
					95% confidence interval for B	
Unstandardised Coefficients						
	B	*Standard Error*	*t*	*Sig.*	*Lower bound*	*Upper bound*
Baseline Utility	0.481	0.091	5.288	0.000	0.294	0.667
Group	0.045	0.052	0.868	0.394	-0.062	0.152

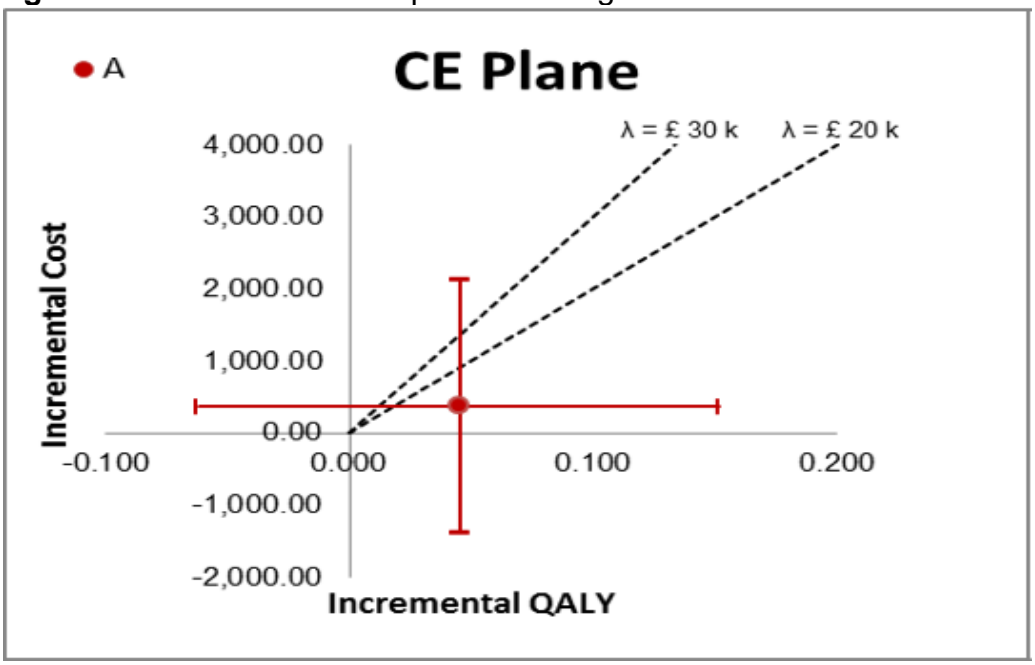
Cost-effectiveness

The numerical trends in the data indicate that ACTdp is associated with greater costs but also better outcomes. Whilst differences in costs were not explored statistically and there was not a significant difference between the groups in terms of QALYs gained, calculation of an ICER is still recommended (Claxton, 1999; Briggs and O'Brien, 2001). Taking the mean difference in costs between the two groups (£375) and the mean difference in QALYs (0.045) over a time horizon of 10-months, the incremental cost-effectiveness ratio (ICER) for ACTdp was calculated

to be £8,339. ACTdp is therefore associated with a cost of £8,339 for every QALY gained. Assuming a threshold of £20,000 per incremental QALY (as per NICE), the results suggest that ACTdp is cost-effective as the ICER falls below the value of this assumed threshold.

A cost-effectiveness plane was plotted (Figure 1) which shows the ICER point estimate along with 95% confidence intervals for costs and effects. Two ceiling ratios (£20,000 and £30,000), i.e. the maximum values that a decision maker might be willing to pay for an additional QALY, were added. Whilst the confidence intervals for the point estimate are wide, as would be expected in a small sample, it is promising that the point estimate nevertheless falls below the 20k threshold. This suggests that there is likely to be value in exploring cost-effectiveness in a larger, definitive trial.

Figure 1: Cost-effectiveness plane showing ICER and 95% confidence intervals[4].



[4] This chart was produced by Bruno Riveros in STATA

Discussion

This is the first known trial and economic evaluation of ACT for depression in the context of psychosis. As would be expected, there was an increase in costs in the time-period over which ACT was provided in the ACTdp group, however the cost pattern over the 10 months of study suggests that some of these additional costs were partially offset by reduced costs elsewhere. As the calculated ICER fell below the threshold of £20,000 recommended by NICE, this suggests that there is potential that ACTdp may be cost-effective and that a larger trial of ACTdp to further explore these preliminary findings is justified.

Implications

Due to the pilot nature of this trial, making any firm conclusions about cost-effectiveness of ACTdp from this evaluation would be premature. It is not possible to determine from these results whether reduced hospitalisation and associated costs in the ACTdp group at the post-treatment stage is linked to ACTdp delivery or whether this occurred by chance. However, this pattern is consistent with previous trial results where inpatients with psychosis who received four sessions of ACT plus treatment as usual (TAU) had half the rate of rehospitalisation than that of participants receiving TAU over a 4-month period (Bach et al., 2012). Inpatient care is the most costly component of healthcare in the overall treatment of psychosis. Knapp et al. (2000) consulted evidence from a number of countries and reported that inpatient care accounted for 56.5% of the total care costs of schizophrenia compared to 2.5% for outpatient care. In this study, hospitalisation was the second largest contributor to overall mean costs second to the cost of providing ACTdp. It will be important for future trials to confirm whether ACTdp has an impact on rates of hospitalisation. Any meaningful impact on hospitalisation rates is likely to significantly increase the likelihood that an intervention will be cost-effective. Other positive signals in the data that warrant future investigation include the reduction in use of GP and CPN services observed within the ACTdp group.

Uncertainty surrounds estimates of effectiveness, costs and the resulting cost-effectiveness ratios (Edejer, 2003). As ICERs are point-estimates, they do not capture uncertainty in the sample data on which they are based (Miller et al., 2003). Due to the small sample size and pilot nature of the ADAPT trial, exploring

uncertainty by conducting the comprehensive sensitivity analyses that are usually recommended (Drummond et al., 2015) would not be appropriate. However, this will be an important feature of a larger trial. Overall, the partial cost offsets and the trend towards improved quality of life observed in this study will need to be confirmed in a larger trial, the undertaking of which appears justified by the present results.

The study results observed here also have important implications with regards to the overall objectives of the pilot trial which included confirming the feasibility of conducting an economic evaluation alongside a larger trial. Whilst drop-outs inevitably occur within any study (Villeneuve, 2009), and here resulted in missing data for some participants (n=4), there were no missing data in terms of unanswered items within the CSRI or EQ-5D-5L. This suggests that it is feasible to use these measures to facilitate economic evaluation. Also, within the UK, routinely published unit cost information (PSSRU: Curtis and Burns, 2015) means that the process of costing resource use is relatively straightforward and would be feasible in a larger trial. Similarly, as there are widely used EQ-5D value sets which could be easily obtained through EuroQol report to calculate utility scores, this study confirms that it would be feasible to use this measure for the purposes of economic evaluation in a larger, definitive trial of ACTdp.

Comparison with other research

This study joins a small group of studies which have carried out economic evaluations of psychological therapies for people with psychosis. Whilst there are no known studies that have conducted a formal cost-effectiveness analysis of ACT for psychosis, other studies have considered Cognitive Behavioural Therapy, CBT (van der Gaag et al., 2011; Barton et al., 2009), CBT+Motivational Intervention, MI, (Haddock et el., 2003), a combined multi-component treatment package (Zhang et al., 2014), Cognitive Remediation Therapy, CRT (Patel et al., 2010), Adherence Therapy, AT, (Patel et al., 2013), a brief intervention informed by Solution Focused Therapy (SFT) alongside patient-centred assessment (Priebe et al., 2015) and Metacognitive training (van Oosterhout et al., 2014).

From the studies referred to above, there were two instances where the psychological interventions *dominated* in the economic evaluation, i.e. were associated with both lower costs and better outcomes: CBT+MI (Haddock et al., 2003) and an intervention which combined patient-centred assessment with SFT

(Priebe et al., 2015). Two further CBT-based treatments (CBT, van der Gaag et al., 2011; social recovery CBT, SRCBT, Barton et al., 2009) and a combined treatment (Zhang et al., 2014) were associated with greater costs and better outcomes, as with the present study. In two of these studies in which QALYs were used as the primary outcome measure, the mean difference in QALYs between groups was 0.035 (SRCBT, Barton et al. 2009) and 0.031 (Combined treatment, Zhang et al. 2014) compared to 0.045 in the present study. None of the studies referred to above found significant differences in costs between the comparison groups, a common finding in health economics research. As well as further research looking specifically at ACT, further research which considers the cost-effectiveness of psychological interventions overall is required.

Limitations

This study has several limitations. The results which are reported here may not be generalisable to other study locations or different health service contexts due to potential differences in costs and service use patterns. Some participants also declined (n=3) or were lost to follow-up (1), the reasons for which are not clear at this stage. Positively however, no one in the ACTdp group dropped out during treatment suggesting that ACTdp is a well tolerated intervention. The low cancellation and non-attendance rates further confirm this (Gumley et al., 2017).

As stated earlier in this paper, NICE (2012) recommend that the perspective on costs should be that of the NHS and Personal Social Services, PSS (i.e. 'health and social care' perspective). They also specify that if broader costs must be included then they should not be combined into the ICER (NICE, 2012). This study has followed these recommendations however it should be noted that within the health economics literature, adopting the broader societal perspective is often encouraged (Drummond et al., 2015). In the case of schizophrenia, research indicates that there may be pertinence in capturing the wide-ranging impact of the illness beyond costs which are incurred directly by the health service alone (Davies and Drummond, 1994; Knapp, 2000; Mangalore and Knapp, 2007). One recommendation for future research may therefore be to capture costs from both a societal and health and social care perspective and to explore the impact of adopting the differing perspectives on resulting ICERs and conclusions. This may elucidate whether, despite NICE recommendations, research in relation to psychosis should indeed incorporate broader cost categories within the cost-effectiveness analyses. Also,

given that ACT aims to enhance engagement with valued life activities, rather than completely eradicating symptoms, it is possible that this type of treatment may conceivably have more of an impact on the type of broader societal level outcomes that would not be captured within the health and social care perspective alone.

Strengths

A key strength of this paper is that it is thought to be the first study to estimate the cost-effectiveness of providing ACT to treat depression in the context of psychosis. Including an economic evaluation alongside trials is likely to make the results of the overall evaluation much more useful for decision-makers (Craig et al., 2006). ACTdp was also compared to standard care which makes it more informative than if it was compared to a placebo (Craig et al., 2006). Another strength is the use of the QALY as the primary outcome for the cost-effectiveness analysis. This is the outcome preferred by NICE and also allows comparison across studies.

Conclusions

Psychosis and depression present a significant burden to the individual in terms of personal suffering and reduced quality of life and are also associated with a significant economic burden. Preliminary indications suggest that ACTdp has the potential to be a cost-effective treatment given patterns observed in terms of partial cost-offsets and a trend towards improved quality of life. This adds another valuable dimension to the evaluation of this promising treatment. Whilst the pilot nature of this trial precludes firm conclusions being made, the present results provide signals that ACTdp might reduce hospital admission costs and suggests that conducting a larger trial is warranted.

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Vorontsova, N., Garety, P. and Freeman, D., 2013. Cognitive factors maintaining persecutory delusions in psychosis: The contribution of depression. *Journal of abnormal psychology*, *122*(4), pp.1121-1131.

White, R., Gumley, A., McTaggart, J., Rattrie, L., McConville, D., Cleare, S. and Mitchell, G., 2011. A feasibility study of Acceptance and Commitment Therapy for emotional dysfunction following psychosis. *Behaviour research and therapy*, *49*(12), pp.901-907.

White, R.G., Gumley, A.I., McTaggart, J., Rattrie, L., McConville, D., Cleare, S., McLeod, H.J. and Mitchell, G., 2015. Acceptance and commitment therapy for depression following psychosis: an examination of clinically significant change. *Journal of Contextual Behavioral Science*, *4*(3), pp.203-209.

Whitehead, C., Moss, S., Cardno, A. and Lewis, G., 2002. Antidepressants for people with both schizophrenia and depression. *The Cochrane database of systematic reviews*, (2), pp.CD002305-CD002305.

Zhang, Z., Zhai, J., Wei, Q., Qi, J., Guo, X. and Zhao, J., 2014. Cost-effectiveness analysis of psychosocial intervention for early stage schizophrenia in China: a randomized, one-year study. *BMC psychiatry*, *14*(1), p.212.

Chapter 1 Appendices

Appendix 1.1: Schizophrenia Bulletin: Information for authors

Schizophrenia Bulletin is an international peer-reviewed journal that publishes unsolicited and invited reports and reviews of clinical and experimental research relating to all aspects of schizophrenia. *First Person Accounts* , Historical perspectives from patients and their families, are also welcome.

EDITORIAL POLICIES

Manuscripts must be written in English and are accepted for consideration with an explicit understanding that the material has not been previously published in whole or substantial part and is not currently under consideration for publication by any other journal. All matters relating to the editorial policies of *Schizophrenia Bulletin* should be addressed in writing to Prof. William Carpenter, M.D., Editor-in Chief, *Schizophrenia Bulletin* Editorial Office, Maryland Psychiatric Research Center, PO Box 21247, Baltimore, MD 21228, USA. Manuscripts should be submitted through the journal's web-based manuscript submission system as instructed below.

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Manuscripts reporting experiments on patients or healthy volunteers must record the fact that the subjects' consent was obtained and include a statement that the research was approved by the responsible ethical committee of the institution (e.g., an institutional

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Laboratory Animals

Manuscripts reporting the results of experiments involving laboratory animals must be contain a statement indicating that the procedures used were in accordance with the guidelines published in the Institute of Laboratory Animals Resources Commission on Life Sciences' 1996 *Guide for the Care and Use of Laboratory Animals* (Washington, DC: National Academic Press; http://www.nap.edu/readingroom/books/labrats) or a similar internationally recognized standard. The species, sex, source, and genetic background of the animals as well as a detailed description of the experimental procedures, including any anesthetics and/or analgesics, must be provided in the Methods section of the manuscript.

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Originality

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By submitting your manuscript to the journal it is understood that this is an original manuscript and is unpublished work not under consideration elsewhere. Plagiarism, including duplicate publication of the author’s own work, in whole or in part without

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At the point of submission, *Schizophrenia Bulletin's* policy requires that each author reveal any financial interests or connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated - including pertinent commercial or other sources of funding for the individual author(s) or for the associated department(s) or organization(s), personal relationships, or direct academic competition. When considering whether you should declare a conflicting interest or connection please consider the conflict of interest test: Is there any arrangement that would embarrass you or any of your co-authors if it was to emerge after publication and you had not declared it?

Examples of potential conflicts include a proprietary interest in a drug or product mentioned in the study, equity interest in the sponsor of the study or any other commercial entity with a potential financial interest in its outcome, or payments with a cumulative monetary value exceeding $2,000 made by the sponsor to the investigators or their family members during or within two years of the completion of the study. Institutional support for the study should be included in the Acknowledgments section of the manuscript.

Funding

All manuscripts submitted for publication will contain a Conflict of Interest statement. The corresponding author will describe each circumstance in sufficient detail to enable the editors and reviewers to assess its scope and to identify the author(s) with whom the conflict(s) exist. If the corresponding author has indicated that no conflict exists, the following statement will be inserted by the publisher and will appear at the end of the published manuscript:

- The sentence should begin: ‘This work was supported by …’
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- Grant numbers should be complete and accurate and provided in parentheses as follows: '(grant number xxxx)'
- Multiple grant numbers should be separated by a comma as follows: '(grant numbers xxxx, yyyy)'
- Agencies should be separated by a semi-colon (plus 'and' before the last funding agency)
- Where individuals need to be specified for certain sources of funding the following text should be added after the relevant agency or grant number 'to [author initials]'.

"The Authors have declared that there are no conflicts of interest in relation to the subject of this study."

Details of all funding sources for the work in question should be given in a separate section entitled 'Funding'. This should appear before the 'Acknowledgments' section.

The following rules should be followed:

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In order to meet your funding requirements authors are required to name their funding sources, or state if there are none, during the submission process. For further information on this process or to find out more about the CHORUS initiative please click here .

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Title Page

This page should consist of (i) the complete title of the manuscript, (ii) a running title not to exceed 50 characters including spaces, (iii) the full name of each author and the authors' institutional affiliations, (iv) name, complete address, telephone, fax, and e-mail address of the corresponding author, and (v) separate word counts of the abstract and text body. Please note that there can only be one corresponding author, per journal style

Manuscript Length

Manuscripts should be concisely worded and **should not exceed 5,000 words for major reviews, 4,000 words for regular articles, or 2,500 words for invited special features**. The word count should include the abstract, text body, figure legends, and acknowledgments and must appear together with the abstract word count on the title page of the manuscript. Supplementary data, including additional methods, results, tables, or figures will be published online.

Abstract

Provide a summary of **no more than 250 words** describing why and how the study, analysis, or review was done, a summary of the essential results, and what the authors have concluded from the data. The abstract should not contain unexplained abbreviations. Up to six key words that do not appear as part of the title should be provided at the end of the abstract.

Main Text

Unsolicited original manuscripts reporting novel experimental findings should be comprised of these sections, in this order: Abstract, Introduction, Methods, Results, Discussion, Acknowledgments, References, and Figure Legends. Review articles must contain an abstract; however, the body of the text can be organized in a less structured format. Authors of review articles are encouraged to use section headers to improve the readability of their manuscript.

Number pages consecutively beginning with the title page. Spelling should conform to that used in *Merriam-Webster's Collegiate Dictionary* , eleventh edition. Clinical laboratory data may be expressed in conventional rather than Système International (SI) units.

Acknowledgments

These should be as brief as possible but include the names of sources of logistical support.

References

Authors are encouraged to be circumspect in compiling the reference section of their manuscripts.
Please note: references to other articles appearing in the same issue of the journal must be cited fully in the reference list.

Each reference should be cited in consecutive numerical order using superscript arabic numerals, and reference style should follow the recommendations in the *American Medical Association Manual of Style* , 10th edition, with one exception: in the reference list, the name of all authors should be given unless there are more than 6, in which case the names of the first 3 authors are used, followed by "et al."

- Book: Talairach J, Tournoux P. *Co-planar stereotaxic atlas of the human brain* . New York, NY: Thieme Medical Publishers; 1998.
- Book chapter: Goldberg TE, David A, Gold JM. Neurocognitive deficits in schizophrenia. In: Hirsch SR, Weinberger DR, eds. *Schizophrenia* . Oxford, England: Blackwell Science; 2003:168-184.
- Journal article: Thaker GK, Carpenter WT. Advances in schizophrenia. *Nat Med* 2001;7:667-671.
- Journal article with more than 6 authors: Egan MF, Straub RE, Goldberg TE, et al. Variation in GRM3 affects cognition, prefrontal gluatamate, and risk for schizophrenia. *Proc Natl Acad Sci USA* 2004;101:12604-12609.
- Article published on Advance Access only: Gilad, Y. and Lancet, D. March 5, 2003. Population Differences in the Human Functional Olfactory Repertoire. *Mol Biol Evol* doi:10.1093/molbev/msg013.
- Article first published on Advance Access: Gilad, Y. and Lancet, D. 2003. Population Differences in the Human Functional Olfactory Repertoire *Mol Biol Evol* 2003;20:307-314. First published on March 5, 2003, doi:10.1093/molbev/msg013.

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Tables should be created with the table function of a word processing program; spreadsheets are not acceptable. Include only essential data, and format the table in a manner in which it should appear in the text. Each table must fit on a single manuscript page and have a short title that is self-explanatory without reference to the text. Footnotes can be used to explain any symbols or abbreviations appearing in the table. Do not duplicate data in tables and figures.

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Note : All tables and figures reproduced from a previously published manuscript must cite the original source (in the figure legend or table footnote) and be accompanied by a letter of permission from the publisher of record or the copyright owner.

Appendix 1.2: Full systematic review search strategy

Ovid MEDLINE(R) 1946 to Present with Daily Update and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations June 23, 2017

Search Number	Search Terms	Search Results
1	exp Psychotic Disorders/ or exp Schizophrenia/	134113
2	(schizo* or psychosis or psychoses or psychotic or (severe* adj2 mental*)).ti,ab,kw.	171319
3	1 or 2	203537
4	"costs and cost analysis"/ or exp cost-benefit analysis/	115897
5	(cost* adj2 (analysis or analyses or comparison or effective* or utility or benefit or minimi*)).ti,ab,kw.	127867
6	(economic* adj2 (evaluation* or health or analysis or analyses)).ti,ab,kw.	27837
7	4 or 5 or 6	214990
8	3 and 7	1695
9	Limit 1 to English Language	1538

Ovid Embase 1974 to 2017 June 23

Search Number	Search Terms	Search Results
1	exp psychosis/	272397
2	exp schizophrenia/	176169
3	(schizo* or psychosis or psychoses or psychotic or (severe* adj2 mental*)).ti,ab,kw.	236893
4	1 or 2 or 3	325730
5	"cost benefit analysis"/ or economic evaluation/ or "cost effectiveness analysis"/	199055
6	"cost utility analysis"/	7637
7	"cost minimization analysis"/	2999
8	(cost* adj2 (analysis or analyses or comparison or effective* or utility or benefit or minimi*)).ti,ab,kw.	177441
9	(economic* adj2 (evaluation* or health or analysis or analyses)).ti,ab,kw.	35117
10	5 or 6 or 7 or 8 or 9	298088
11	4 and 10	3405
12	limit 11 to english language	3172
13	limit 12 to exclude medline journals	372

EBSCO PsychINFO 23rd June 2017

Search Number	Search Terms	Search Results
1	DE "Psychosis" OR DE "Acute Psychosis" OR DE "Chronic Psychosis" OR DE "Schizophrenia" OR DE "Paranoid Schizophrenia" OR DE "Schizophrenia (Disorganized Type)" OR DE "Schizophreniform Disorder" OR DE "Undifferentiated Schizophrenia"	108358
2	TI ((schizo* or psychosis or psychoses or psychotic or (severe* N2 mental*))) OR AB ((schizo* or psychosis or psychoses or psychotic or (severe* N2 mental*))) OR KW ((schizo* or psychosis or psychoses or psychotic or (severe* N2 mental*)))	168008
3	1 OR 2	172174
4	((DE "Costs and Cost Analysis") OR (DE "Health Care Economics")	16613
5	TI ((cost* N2 (analysis or analyses or comparison or effective* or utility or benefit or minimi*))) OR AB ((cost* N2 (analysis or analyses or comparison or effective* or utility or benefit or minimi*))) OR KW ((cost* N2 (analysis or analyses or comparison or effective* or utility or benefit or minimi*))	23157
6	TI ((economic* N2 (evaluation* or health or analysis or analyses))) OR AB ((economic* N2 (evaluation* or health or analysis or analyses))) OR KW ((economic* N2 (evaluation* or health or analysis or analyses)))	6756
7	4 OR 5 OR 6	38386
8	3 AND 7	1480
9	Narrow 8 by English Language	1396

NHS Economic Evaluation Database accessed via Cochrane resources on 23.06.17
The NHS EED database ceased to continue publishing new bibliographic records following the end of March 2015 however the database can still be accessed to search for studies published prior to then.

Search Number	Search Terms	Search Results
1	In Title, Abstract, Keyword: psychosis or psychotic or psychoses or schizo*	195

Appendix 1.3: List of excluded studies

Study reference	Reason for exclusion
Abbass, A., Bernier, D., Kisely, S., Town, J. and Johansson, R., 2015. Sustained reduction in health care costs after adjunctive treatment of graded intensive short-term dynamic psychotherapy in patients with psychotic disorders. *Psychiatry research*, *228*(3), pp.538-543.	Not an RCT
Almond, S., Knapp, M., Francois, C., Toumi, M. and Brugha, T., 2004. Relapse in schizophrenia: costs, clinical outcomes and quality of life. *The British Journal of Psychiatry*, *184*(4), pp.346-351.	Not a psychological intervention
Bin, Z.H.O.U. and Yiwei, G.U., 2014. Effect of self-management training on adherence to medications among community residents with chronic schizophrenia: a singleblind randomized controlled trial in Shanghai, China. *Shanghai archives of psychiatry*, *26*(6), pp.332-338.	No cost data
Bin, Z.H.O.U., Zhang, P. and Yiwei, G.U., 2014. Effectiveness of self-management training in community residents with chronic schizophrenia: a single-blind randomized controlled trial in Shanghai, China. *Shanghai archives of psychiatry*, *26*(2), pp.81-87.	No cost data
Boyd, J.L., Mcgill, C.W. and Falloon, I.R., 1981. Family participation in the community rehabilitation of schizophrenics. *Psychiatric Services*, *32*(9), pp.629-632.	Not an RCT
Breitborde, N.J., Bell, E.K., Dawley, D., Woolverton, C., Ceaser, A., Waters, A.C., Dawson, S.C., Bismark, A.W., Polsinelli, A.J., Bartolomeo, L. and Simmons, J., 2015. The Early Psychosis Intervention Center (EPICENTER): development and six-month outcomes of an American first-episode psychosis clinical service. *BMC psychiatry*, *15*(1), p.266.	Not an RCT
Breitborde, N.J., Woods, S.W. and Srihari, V.H., 2009. Multifamily psychoeducation for first-episode psychosis: A cost-effectiveness analysis. *Psychiatric Services*, *60*(11), pp.1477-1483.	Modelling study
Brunette, M.F., Rotondi, A.J., Ben-Zeev, D., Gottlieb, J.D., Mueser, K.T., Robinson, D.G., Achtyes, E.D., Gingerich, S., Marcy, P., Schooler, N.R. and Meyer-Kalos, P., 2016. Coordinated technology-delivered treatment to prevent rehospitalization in schizophrenia: a novel model of care. *Psychiatric Services, 67*(4), pp.444-447.	Not an RCT

Burns, T. and Raftery, J., 1991. Cost of schizophrenia in a randomized trial of home-based treatment. *Schizophrenia Bulletin*, *17*(3), p.407.	Partial economic evaluation
Burti, L., Amaddeo, F., Ambrosi, M., Bonetto, C., Cristofalo, D., Ruggeri, M. and Tansella, M., 2005. Does additional care provided by a consumer self-help group improve psychiatric outcome? A study in an Italian community-based psychiatric service. *Community mental health journal*, *41*(6), pp.705-720.	Not a psychological intervention
Craig, T.K., Johnson, S., McCrone, P., Afuwape, S., Hughes, E., Gournay, K., White, I., Wanigaratne, S., Leese, M. and Thornicroft, G., 2008. Integrated care for co-occurring disorders: psychiatric symptoms, social functioning, and service costs at 18 months. *Psychiatric Services*, *59*(3), pp.276-282.	No integrated analysis of costs and effects
Crawford, M.J., Killaspy, H., Barnes, T.R., Barrett, B., Byford, S., Clayton, K., Dinsmore, J., Floyd, S., Hoadley, A., Johnson, T. and Kalaitzaki, E., 2012. Group art therapy as an adjunctive treatment for people with schizophrenia: a randomised controlled trial (MATISSE). *Health Technology Assessment*, *16*(8), pp.1-76.	Not a psychological intervention
Crawford, M.J., Killaspy, H., Kalaitzaki, E., Barrett, B., Byford, S., Patterson, S., Soteriou, T., O'Neill, F.A., Clayton, K., Maratos, A. and Barnes, T.R., 2010. The MATISSE study: a randomised trial of group art therapy for people with schizophrenia. *BMC psychiatry*, *10*(1), p.65.	Not a psychological intervention
Depp, C.A., Mausbach, B., Granholm, E., Cardenas, V., Ben-Zeev, D., Patterson, T.L., Lebowitz, B.D. and Jeste, D.V., 2010. Mobile interventions for severe mental illness: design and preliminary data from three approaches. *The Journal of nervous and mental disease*, *198*(10), p.715.	No cost data
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. *The British Journal of Psychiatry*, *192*(6), pp.412-423.	No cost data
Garrido, G., Penadés, R., Barrios, M., Aragay, N., Ramos, I., Vallès, V., Faixa, C. and Vendrell, J.M., 2017. Computer-assisted cognitive remediation therapy in schizophrenia: Durability of the effects and cost-utility analysis. *Psychiatry Research*, *254*, pp.198-204.	No integrated analysis of costs and effects
Gilden, J., Staring, A.B.P., Van der Gaag, M. and Mulder, C.L., 2011. Does Treatment Adherence Therapy reduce expense of healthcare use in patients with psychotic disorders? Cost-minimization analysis in a randomized controlled trial. *Schizophrenia research*, *133*(1), pp.47-53.	Partial economic evaluation

Glynn, S. and Mueser, K.T., 1986. Social learning for chronic mental inpatients. *Schizophrenia Bulletin*, *12*(4), p.648.	No economic evaluation reported
Gottlieb, J.D., Pryzgoda, J., Neal, A. and Schuldberg, D., 2005. Generalization of skills through the addition of individualized coaching: Development and evaluation of a social skills training program in a rural setting. *Cognitive and Behavioral Practice*, *12*(3), pp.324-337.	No cost data
Guo, X., Zhai, J., Liu, Z., Fang, M., Wang, B., Wang, C., Hu, B., Sun, X., Lv, L., Lu, Z. and Ma, C., 2010. Effect of antipsychotic medication alone vs combined with psychosocial intervention on outcomes of early-stage schizophrenia: a randomized, 1-year study. *Archives of general psychiatry*, *67*(9), pp.895-904.	No cost data
Gray, R., Leese, M., Bindman, J., Becker, T., Burti, L., David, A., Gournay, K., Kikkert, M., Koeter, M., Puschner, B. and Schene, A., 2006. Adherence therapy for people with schizophrenia. *The British journal of psychiatry*, *189*(6), pp.508-514.	No cost data
Hastrup, L.H., Kronborg, C., Bertelsen, M., Jeppesen, P., Jorgensen, P., Petersen, L., Thorup, A., Simonsen, E. and Nordentoft, M., 2013. Cost-effectiveness of early intervention in first-episode psychosis: economic evaluation of a randomised controlled trial (the OPUS study). *The British Journal of Psychiatry*, *202*(1), pp.35-41.	Combined treatment package
Healey, A., Knapp, M., Astin, J., Beecham, J., Kemp, R., Kirov, G. and David, A., 1998. Cost-effectiveness evaluation of compliance therapy for people with psychosis. *The British Journal of Psychiatry*, *172*(5), pp.420-424.	Not an RCT
Jenner, J.A., Nienhuis, F.J., Wiersma, D. and van de Willige, G., 2004. Hallucination focused integrative treatment: a randomized controlled trial. *Schizophrenia Bulletin*, *30*(1), p.133.	No economic evaluation reported
Jerrell, J.M., 1996. Toward cost-effective care for persons with dual diagnoses. *The journal of mental health administration*, *23*(3), pp.329-337.	Included non-psychotic diagnoses
Jerrell, J.M. and Hu, T.W., 1996. Estimating the cost impact of three dual diagnosis treatment programs. *Evaluation Review*, *20*(2), pp.160-180.	Included non-psychotic diagnoses
Jerrell, J.M., Hu, T.W. and Ridgely, M.S., 1994. Cost-effectiveness of substance disorder interventions for people with severe mental illness. *The journal of mental health administration*, *21*(3), pp.283-297.	Included non-psychotic diagnoses
Jerrell, J.M. and Ridgely, M.S., 1995. Comparative effectiveness of three approaches to serving people with severe mental illness and substance abuse disorders. *The Journal of nervous and mental disease*, *183*(9), pp.566-576.	Included non-psychotic diagnoses

Jerrell, J.M. and Ridgely, M.S., 1997. Dual diagnosis care for severe and persistent disorders. A comparison of three methods. *Behavioral healthcare tomorrow*, *6*(3), pp.26-33.	Included non-psychotic diagnoses
Johns, L.C., Oliver, J.E., Khondoker, M., Byrne, M., Jolley, S., Wykes, T., Joseph, C., Butler, L., Craig, T. and Morris, E.M., 2016. The feasibility and acceptability of a brief Acceptance and Commitment Therapy (ACT) group intervention for people with psychosis: the 'ACT for life'study. *Journal of behavior therapy and experimental psychiatry*, *50*, pp.257-263.	Not an RCT
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. *Bmj*, *322*(7290), pp.835-840.	No integrated analysis of costs and effects
Karon, B.P. and Vandenbos, G.R., 1975. Treatment costs of psychotherapy versus medication for schizophrenics. *Professional Psychology*, *6*(3), p.293.	No integrated analysis of costs and outcomes
Klingberg, S., Wittorf, A., Meisner, C., Wölwer, W., Wiedemann, G., Herrlich, J., Bechdolf, A., Müller, B.W., Sartory, G., Wagner, M. and Kircher, T., 2010. Cognitive behavioural therapy versus supportive therapy for persistent positive symptoms in psychotic disorders: The POSITIVE Study, a multicenter, prospective, single-blind, randomised controlled clinical trial. *Trials*, *11*(1), p.123.	Study protocol
Kuipers, E., Fowler, D., Garety, P., Chisholm, D., Freeman, D., Dunn, G., Bebbington, P. and Hadley, C., 1998. London-east Anglia randomised controlled trial of cognitive-behavioural therapy for psychosis. III: Follow-up and economic evaluation at 18 months. *The British Journal of Psychiatry*, *173*(1), pp.61-68.	No integrated analysis of costs and effects
Leff, J., Berkowitz, R., Shavit, N., Strachan, A., Glass, I. and Vaughn, C., 1989. A trial of family therapy v. a relatives group for schizophrenia. *The British Journal of Psychiatry*, *154*(1), pp.58-66.	No cost data
Leff, Mandy Sharpley, Daniel Chisholm, Ray Bell, Catherine Gamble, J., 2001. Training community psychiatric nurses in schizophrenia family work: a study of clinical and economic outcomes for patients and relatives. *Journal of Mental Health*, *10*(2), pp.189-197.	No integrated analysis of costs and effects
Li, C. and He, Y., 2008. Morita therapy for schizophrenia. *Schizophrenia bulletin*, *34*(6), pp.1021-1023.	Systematic review
Lobban, F., Glentworth, D., Chapman, L., Wainwright, L., Postlethwaite, A., Dunn, G., Pinfold, V., Larkin, W. and Haddock, G., 2013. Feasibility of a supported self-management	Outcomes not reported for people

intervention for relatives of people with recent-onset psychosis: REACT study. *The British Journal of Psychiatry*, *203*(5), pp.366-372.	with psychosis
Lund, C., Waruguru, M., Kingori, J., Kippen-Wood, S., Breuer, E., Mannarath, S. and Raja, S., 2013. Outcomes of the mental health and development model in rural Kenya: a 2-year prospective cohort intervention study. *International Health*, *5*(1), pp.43-50.	Combined treatment package
May, P.R., 1971. Cost efficiency of treatments for the schizophrenic patient. *American journal of Psychiatry*, *127*(10), pp.1382-1385.	No integrated analysis of costs and effects
McFarlane, W.R., Link, B., Dushay, R., Marchal, J. and Crilly, J., 1995. Psychoeducational Multiple Family Groups: Four-Year Relapse Outcome in Schizophrenia. *Family process*, *34*(2), pp.127-144.	No cost data
Mihalopoulos, C., Magnus, A., Carter, R. and Vos, T., 2004. Assessing cost-effectiveness in mental health: family interventions for schizophrenia and related conditions. *Australian and New Zealand Journal of Psychiatry*, *38*(7), pp.511-519.	Modelling study
Mino, Y., Shimodera, S., Inoue, S., Fujita, H. and Fukuzawa, K., 2007. Medical cost analysis of family psychoeducation for schizophrenia. *Psychiatry and Clinical Neurosciences*, *61*(1), pp.20-24.	Not an RCT
Miran, M.D. and Miran, E.R., 1999. Neuropsychological therapeutic community treatment for individuals with schizophrenia. *Psychiatric Rehabilitation Journal*, *22*(3), pp.277282.	Not an RCT
Mlcoch, T., Kruntorádová, K., Mandelíková, M. and Dolezal, T., 2015. Cost-Effectiveness Analysis of the Information Technology Aided Relaps Prevention Programme in Schizophrenia (Itareps) in the Czech Republic. *Value in Health*, *18*(7), p.A410.	Modelling study
Moradi-Lakeh, M., Yaghoubi, M., Hajebi, A., Malakouti, S.K. and Vasfi, M.G., 2017. Cost-effectiveness of aftercare services for people with severe mental disorders: an analysis parallel to a randomised controlled clinical trial in Iran. *Health & Social Care in the Community*, *25*(3), pp.1151-1159.	Included non-psychotic diagnoses
Peters, E., Landau, S., McCrone, P., Cooke, M., Fisher, P., Steel, C., Evans, R., Carswell, K., Dawson, K., Williams, S. and Howard, A., 2010. A randomised controlled trial of cognitive behaviour therapy for psychosis in a routine clinical service. *Acta Psychiatrica Scandinavica*, *122*(4), pp.302-318.	No integrated analysis of costs and effects

Phanthunane, P., Vos, T., Whiteford, H. and Bertram, M., 2011. Cost-effectiveness of pharmacological and psychosocial interventions for schizophrenia. *Cost Effectiveness and Resource Allocation*, *9*(1), p.6.	Modelling study
Priebe, S., Savill, M., Reininghaus, U., Wykes, T., Bentall, R., Lauber, C., McCrone, P., Röhricht, F. and Eldridge, S., 2013. Effectiveness and cost-effectiveness of body psychotherapy in the treatment of negative symptoms of schizophrenia–a multi-centre randomised controlled trial. *BMC psychiatry*, *13*(1), p.26.	Study protocol
Ranger, M., Tyrer, P., Miloseska, K., Fourie, H., Khaleel, I., North, B. and Barrett, B., 2009. Cost-effectiveness of nidotherapy for comorbid personality disorder and severe mental illness: randomized controlled trial. *Epidemiology and Psychiatric Sciences*, *18*(2), pp.128-136.	Included non-psychotic diagnoses
Rund, B.R., Moe, L., Sollien, T., Fjell, A., Borchgrevink, T., Hallert, M. and Naess, P.O., 1994. The Psychosis Project: outcome and cost-effectiveness of a psychoeducational treatment programme for schizophrenic adolescents. *Acta Psychiatrica Scandinavica*, *89*(3), pp.211-218.	Not an RCT
So, S.H.W., Chan, A.P., Chong, C.S.Y., Wong, M.H.M., Lo, W.T.L., Chung, D.W.S. and Chan, S.S., 2015. Metacognitive training for delusions (MCTd): effectiveness on data-gathering and belief flexibility in a Chinese sample. *Frontiers in psychology*, *6*, p.730	No cost data
Španiel, F., Hrdlicka, J., Novák, T., KOŽENÝ, J., Hoeschl, C., Mohr, P. and Motlova, L.B., 2012. Effectiveness of the information technology-aided program of relapse prevention in schizophrenia (ITAREPS): a randomized, controlled, double-blind study. *Journal of Psychiatric Practice®*, *18*(4), pp.269-280.	Not a psychological intervention
Stant, A.D., TenVergert, E.M., Groen, H., Jenner, J.A., Nienhuis, F.J., Willige, G. and Wiersma, D., 2003. Cost-effectiveness of the HIT programme in patients with schizophrenia and persistent auditory hallucinations. *Acta Psychiatrica Scandinavica*, *107*(5), pp.361-368.	Combined treatment package
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. *The British Journal of Psychiatry*, *197*(6), pp.448-455.	No cost data
Startup, M., Jackson, M.C., Evans, K.E. and Bendix, S., 2005. North Wales randomized controlled trial of cognitive behaviour therapy for acute schizophrenia spectrum disorders: two-year follow-up and economic evaluation. *Psychological Medicine*, *35*(9), pp.1307-1316.	No integrated analysis of costs and effects

Tarrier, N., Lowson, K. and Barrowclough, C., 1991. Some aspects of family interventions in schizophrenia. II: Financial considerations. *The British Journal of Psychiatry*, *159*(4), pp.481-484.	Partial economic evaluation
Tong, A.C.Y., Lin, J.J.X., Cheung, V.Y.K., Lau, N.K.M., Chang, W.C., Chan, S.K.W., Hui, C.L.M., Lee, E.H.M. and Chen, E.Y.H., 2016. A Low-Intensity Mindfulness-Based Intervention for Mood Symptoms in People with Early Psychosis: Development and Pilot Evaluation. *Clinical psychology & psychotherapy*, *23*(6), pp.550-560.	No cost data
van der Gaag, M., 2014. The efficacy of CBT for severe mental illness and the challenge of dissemination in routine care. *World Psychiatry*, *13*(3), pp.257-258.	Not an RCT
Vasiliadis, H., Briand, C., Lesage, A., Reinharz, D., Stip, E., Nicole, L. and Lalonde, P., 2006. Health care resource use associated with integrated psychological treatment. *Journal of Mental Health Policy and Economics*, *9*(4), p.201.	Partial economic evaluation
Vickar, G.M., North, C.S., Downs, D. and Marshall, D.L., 2009. A randomized controlled trial of a private-sector inpatient-initiated psychoeducation program for schizophrenia. *Psychiatric services*, *60*(1), pp.117-120.	No integrated analysis of costs and effects
Welfare-Wilson, A. and Jones, A., 2015. A CBT-based anxiety management workshop in first-episode psychosis. *British Journal of Nursing*, *24*(7).	No cost data
Wykes, T., Reeder, C., Williams, C., Corner, J., Rice, C. and Everitt, B., 2003. Are the effects of cognitive remediation therapy (CRT) durable? Results from an exploratory trial in schizophrenia. *Schizophrenia research*, *61*(2), pp.163-174.	No integrated analysis of costs and effects
Wykes, T., Hayward, P., Thomas, N., Green, N., Surguladze, S., Fannon, D. and Landau, S., 2005. What are the effects of group cognitive behaviour therapy for voices? A randomised control trial. *Schizophrenia research*, *77*(2), pp.201-210.	No cost data
Yamaguchi, S., Sato, S., Horio, N., Yoshida, K., Shimodaira, M., Taneda, A., Ikebuchi, E., Nishio, M. and Ito, J., 2017. Cost-effectiveness of cognitive remediation and supported employment for people with mental illness: a randomized controlled trial. *Psychological medicine*, *47*(1), pp.53-65.	Combined treatment package

Appendix 1.4: Full table of quality ratings

		Study							
Item		a	b	c	d	e	f	g	h
1	Is the study population clearly described?	Y	Y	Y	Y	N	Y	Y	Y
2	Are competing alternatives clearly described?	Y	Y	Y	N	N	Y	N	Y
3	Is a well-defined research question posed in answerable form?	Y	Y	Y	Y	Y	N	Y	Y
4	Is the economic study design appropriate to the stated objective?	Y	Y	Y	Y	Y	Y	Y	Y
5	Is the chosen time horizon appropriate in order to include relevant costs and consequences?	N	Y	Y	Y	Y	Y	Y	Y
6	Is the actual perspective chosen appropriate?	Y	Y	N	Y	Y	N	Y	Y
7	Are all important and relevant costs for each alternative identified?	N	Y	Y	Y	Y	N	Y	Y
8	Are all costs measured appropriately in physical units?	Y	Y	Y	Y	Y	N	Y	Y
9	Are costs valued appropriately?	Y	Y	Y	Y	Y	N	Y	Y
10	Are all important and relevant outcomes for each alternative identified?	Y	Y	Y	Y	Y	Y	Y	Y
11	Are all outcomes measured appropriately?	Y	Y	Y	Y	Y	Y	Y	Y
12	Are outcomes valued appropriately?	Y	Y	Y	Y	Y	Y	Y	Y
13	Is an incremental analysis of costs and outcomes of alternatives performed?	Y	Y	Y	Y	Y	Y	Y	Y
14	Are all future costs and outcomes discounted appropriately?	NA	Y	NA	NA	NA	NA	NA	Y
15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Y	Y	Y	Y	N	N	N	Y
16	Do the conclusions follow from the data reported?	Y	Y	Y	Y	Y	Y	Y	Y
17	Does the study discuss the generalizability of the results to other settings and patient/client groups?	N	Y	N	Y	Y	N	N	N
18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Y	Y	Y	Y	Y	Y	Y	Y
19	Are ethical and distributional issues discussed appropriately?	N	N	N	N	N	N	N	N
	Percentage of criteria met	78	95	83	89	78	56	78	89

Y: yes; N: no; NA: Not applicable a: van Oosterhout et al. (2014); b: van der Gaag et al. (2011); c: Barton et al. (2009); d: Patel et al. (2013); e: Patel et al. (2010); f: Priebe et al. (2015); g: Zhang et al. (2014); h: Haddock et al. (2003)

Chapter 2 Appendices

Appendix 2.1: Table of unit costs

Taken from: Curtis, L. and Burns, A., 2015. Unit costs of health and social care 2015. Personal Social Services Research Unit; 2015.

Service/Resource	Unit	Cost
Acute psychiatric ward	Day	£223.00
Psychiatric outpatient visit	Appointment	£107.00
Other hospital outpatient visit	Appointment	£ 105.00
Community Mental Health Centre	Hour	£ 42.00
Voluntary Organisation Day Activity Facility	Hour	£ 10.00
Consultant/Registrar Psychiatrist	Minute	£ 1.78
Psychologist	Minute	£ 1.03
Community Psychiatric Nurse	Minute	£ 0.83
Social Worker	Minute	£ 0.85
Occupational Therapist	Minute	£ 0.68
Chiropodist	Minute	£ 0.60
General Practitioner	Minute	£ 3.80
Dentist	Minute	£ 1.18
Optician	Minute	£ 1.18

Appendix 2.2: Project Proposal

MRP Proposal

Title: Exploring the cost-effectiveness of psychological therapies: Analysis of a pilot RCT of ACT for depression after psychosis.

Matriculation number: 2166401

University Supervisor: Dr Hamish McLeod

Date of submission: 19.05.2017

Version number: 1

Word count: 3621

Abstract

Background

Depression is common in people with schizophrenia. It contributes to poorer quality of life (Saarni et al., 2010) and is associated with poorer functional outcomes. The ADAPT trial was a pilot randomised controlled trial of Acceptance and Commitment Therapy for depression after psychosis (ACTdp) for individuals with a diagnosis of schizophrenia who also met diagnostic criteria for major depression.

Aims

This study will use data from a randomised controlled trial to conduct an economic analysis to explore the potential cost-effectiveness of ACTdp.

Methods

A total of 29 participants were randomised to ACTdp+Standard Care (SC) (n=15) or SC alone (n=14). Individuals received up to 5 months of individual ACTdp. Health related quality of life was measured using the EuroQol (EQ-5D-5L; Herdman et al., 2011). Service use was described using the Client Service Receipt Inventory (CSRI; Chisolm et al., 2000). Data were collected at entry pre-randomisation, 5-months and 10-months. Healthcare and other service costs will be estimated by multiplying resource use by the appropriate unit cost. This will allow differences to be described between the ACTdp and SC groups in service utilisation and associated costs. Health economic analysis focused on quality of life outcomes and the costs of providing care will be calculated and used to evaluate the cost effectiveness of ACTdp.

Applications

This study will contribute to our understanding of how psychological therapies for complex mental health problems can be evaluated from a health economic perspective. This is an increasingly important but generally under researched aspect of psychological treatment development.

Introduction

Schizophrenia and related psychotic disorders are among the most disabling illnesses worldwide (World Health Organization; WHO, 2001) and pose a considerable economic burden to healthcare systems (Mangalore & Knapp, 2007; Stant et al., 2007). Despite its low lifetime prevalence (median 4.0 per 1,000 persons; Saha et al., 2005), health, social, and economic burden related to schizophrenia is significant, not only for patients but also for families, other caregivers, and wider society (Chong et al., 2016). The World Health Organization (WHO) estimated that direct costs of schizophrenia in Western countries ranges from 1.6% to 2.6% of total health care expenditures (Barbato et al., 1998).

Clinical depression is the second largest cause of global disability (Ferrari et al., 2010). Globally, the drag effect of depression on aggregate economic output is predicted to be US$5.36 trillion between 2011 and 2030 (Bloom et al, 2011). Depression is common in people with schizophrenia with prevalence data indicating depressive symptoms in 50% of people newly diagnosed with schizophrenia and 33% of people with chronic schizophrenia who have relapsed (Whitehead et al., 2002). Depression has been implicated in all stages of psychosis: as a vulnerability factor, a predictor of transition, as a maintaining factor and as a response to having experienced a psychotic episode (Vorontsova et al., 2013). Depression may occur independently of the symptoms of psychosis and several months after recovery from an acute episode in up to 30% of cases (Siris, 1995). Depression contributes to poorer quality of life (Saarni et al., 2010) and is associated with poorer outcomes in people with psychosis including: poorer adherence to treatment (Conley et al., 2007), lack of response to neuroleptics (Gasquet et al., 2005), increased relapses (Birchwood et al.,1993) and reduced functioning (Conley et al., 2007) (Vorontsova et al., 2013).

An analysis of the comparative effectiveness and costs of pharmacological and psychosocial interventions for reducing the burden of mental disorders (WHO, 2006a) concluded that there are modest extra costs (for training and intervention) of providing psychosocial treatment alongside pharmacological treatment for severe mental disorders such as schizophrenia and bipolar affective disorder but that providing this treatment is expected to result in substantial extra health gain,

therefore making a combined strategy more cost-effective than pharmacotherapy alone (WHO, 2006b). The benefits associated with the introduction of cost-effective treatments are numerous and include not only reduced psychiatric morbidity but also reductions in family burden at the household level and higher rates of participation in the labour force and reduced levels of crime and antisocial behaviour at the community level (WHO, 2006b). At present, there is a lack of robust evidence supporting the use of antidepressants (Whitehead et al., 2002) and psychological (Wykes et al., 2008) interventions for depression in people diagnosed with schizophrenia (Gumley et al., 2017). Although there is preliminary evidence that depression symptoms improve in people receiving CBT for psychosis (CBTp) (Wykes et al., 2008) this important outcome domain is not typically assessed in CBTp trials (Jauhar et al., 2014) so there is a need to build the treatment evidence base (Gumley et al., 2017).

Acceptance and Commitment Therapy (ACT) could offer a promising psychological intervention that helps individuals to disengage from unhelpful coping strategies including rumination and avoidance and enables them to commit to behavioural change consistent with personally held values (Gumley et al., 2017). There is preliminary evidence of clinical and cost-effectiveness of ACT when delivered individually to people with psychosis (Johns et al., 2015). Randomised controlled trials have also shown that ACT can lead to reduced depression in non-psychotic populations (Hacker et al., 2016). In a feasibility study, White et al. (2011) investigated ACT for psychosis with the primary outcome focused on emotional distress. They found a trend on the limit of significance for differences between the groups in depression ($p=0.051$) (White et al., 2011). In a later analysis, White et al. (2015) found that ACT was associated with significantly greater likelihood of achieving a clinically significant improvement in depression.

The ADAPT trial was a pilot randomised controlled trial of Acceptance and Commitment Therapy for depression after psychosis (ACTdp) for individuals with a diagnosis of schizophrenia who also met DSM-IV diagnostic criteria for major depression. This trial followed the feasibility study conducted by White et al. (2011) described above. An additional aim of the ADAPT trial was to capture data that could be used to assess the cost-effectiveness of ACTdp – an increasingly important aspect of treatment development and evaluation (Gumley et al., 2015). The trial methodology and the clinical results have previously been reported (see Gumley et

al., 2015 and Gumley et al., 2017) so will not be discussed comprehensively here. In brief, a total of 29 participants were randomised to ACTdp+ Standard Care (SC) (n=15) or SC alone (n=14). There were no significant differences between groups in terms of the Calgary Depression Scale for Schizophrenia (CDSS) total score at 5-months or at 10-months. In terms of the other primary outcome measure, the Beck Depression Inventory (BDI-II), a statistically significant effect in favour of ACTdp + SC at 5-months but not at 10-months was noted. Psychological flexibility showed significant improvement at 5-months but not 10-months (Gumley et al., 2017).

What remains unknown is whether any potential health gain associated with ACTdp offsets the additional cost of providing the treatment. In the context of resource scarcity which is inherent within any healthcare system, health economic evaluation has been developed as a methodology to inform policymakers, payers and others on how to make efficient allocation decisions over competing healthcare interventions or programmes (Luyten et al., 2016). Rather than dictating and prescribing particular decisions, it aims to establish an economic evidence base for discussions (Luyten et al., 2016). The overall aim of the current project therefore will be to pilot methods and approaches for determining cost-effectiveness analyses of ACT for depression after psychosis.

Aim

The aim of this study is to use data from a randomised controlled trial to conduct an economic analysis to explore the potential cost-effectiveness of ACT for depression after psychosis. Differences between the ACTdp and SC groups in service utilisation and associated costs will be explored. Quality adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) will be calculated.

Plan of investigation

Participants and recruitment procedures

Participants were consecutively recruited, assessed and randomised and included inpatients or outpatients, aged 16 or over and receiving (a) anti-psychotic medication (b) psychiatric follow-up and (c) follow-up from secondary mental health care community based services (Gumley et al., 2017). Participants met DSM-IV-TR criteria for schizophrenia and major depression (confirmed by Structured Clinical Interview for DSM/SCID-I & Calgary Depression Scale/CDSS for Schizophrenia;

score N 7; Kim et al., 2006). Individuals with substance use problems were eligible for inclusion but those with significant learning disability, or who were unable to speak English were not included (Gumley et al., 2017).

Measures

The EuroQol (EQ-5D-5L; Herdman et al., 2011) is a preference-based quality of life instrument that has been successfully used with people diagnosed with schizophrenia and can be used to calculate quality adjusted life years for the purposes of health economic analyses (Gumley et al., 2015). It is the preferred measure of health-related quality of life in adults (NICE, 2012).

The Client Service Receipt Inventory (CSRI; Chisolm et al., 2000) is an instrument developed specifically for capturing service use among psychiatric patients. In addition to standard health service resource use (e.g. GP, specialist, hospital visits), the CSRI also includes specific psychiatric resource use (both hospital and community-based) plus contacts with the judicial system (Gumley et al., 2015). The tool also collects data on employment, income and receipt of benefits.

Intervention: Acceptance and Commitment Therapy for depression after psychosis (ACTdp)

Individuals received up to 5 months of individual ACTdp. ACTdp is based on the rationale that the experience of psychosis can undermine progress in valued life domains. The ACTdp intervention protocol was to identify problematic appraisals; highlight how attempts to avoid these appraisals can paradoxically increase their frequency; develop individuals' ability to let go of appraisals rather than get caught up
reacting to them; facilitate understanding about how distress can inform values; explore valued life domains; and help individuals to commit to behaviours consistent with these valued life domains (Gumley et al., 2015).

Standard Care

Treatment received by all participants in the trial was examined in order to establish the parameters of Standard Care. For inclusion, all participants had to be in receipt of antipsychotic medication and follow-up from a secondary specialist mental health

service (Gumley et al., 2015).

Design

The study was designed as a Parallel-group Randomised Open Blinded Evaluation (PROBE) of Acceptance and Commitment Therapy for depression after psychosis (ACTdp).

Research Procedures

CSRI and health-related quality of life data were collected at entry pre-randomisation, 5-months and 10-months by a Research Assistant who was masked to treatment allocation. Healthcare and other service resource use data relates to three time-frames: (1) from entry at pre-randomisation relating to the previous 5 months, (2) At 5-months (post treatment) for the preceding 5 months and (3) at 10-months (follow-up) for the preceding 5 months.

Justification of sample size

Given that the focus of the current project is to conduct an economic analysis on pre-existing data, conducting a sample size calculation was not within the remit of the current project. In line with Medical Research Council (MRC) guidance on developing and evaluating complex interventions, an overall aim of the pilot study from which this project has stemmed was to estimate the sample size requirements for a future trial (Gumley et al., 2015).

Outcomes

Health-related quality of life

The main outcome for the cost-effectiveness analysis will be the quality-adjusted life year (QALY) assessed using the EQ-5D-5L. The use of a single, generic measure of health benefit such as the QALY enables diverse healthcare interventions to be compared, thus enabling broader questions of efficiency to be addressed (Duarte et al., 2017). QALYs are an overall measure of health outcome that weight the life expectancy of a patient with an estimate of their health-related quality of life (measured on a 0–1 scale) (NICE, 2012). Cost-effectiveness analysis with the units of effectiveness expressed in cost per QALY gained (cost–utility analysis) is widely recognised as a useful approach for measuring and comparing the efficiency of

different health interventions (NICE 2012). The NICE technology appraisal programme uses the QALY approach (NICE, 2012).

Resource use and costs

The economic evaluation will take the NHS and Personal Social Services (PSS) perspective preferred by NICE (NICE, 2012). From the CSRI data, service utilisation costs will be estimated by multiplying the resource use by the appropriate unit cost, using routinely published UK unit cost estimates (pounds sterling at 2014–2015 prices). Information on unit costs will be obtained from national list prices such as the PSSRU (Personal Social Services Research Unit) Unit costs of health and social care and/or Department of Health reference costs, in-line with NICE recommendations (NICE, 2012). Intervention costs will be calculated using available data on unit cost of a clinical psychologist multiplied with corresponding activity levels.

Data Analysis

A statistician and/or health economist will be consulted prior to finalising the analysis plan. The following comparisons between the ACTdp and SC groups at 5- and 10-months will be assessed: (i) proportion of patients using each service included in the Client Service Receipt Inventory; (ii) mean number of contacts with each service; (iii) mean cost of each service; (iv) mean total cost. The focus will be on the comparison of total costs. Cost comparisons at 5- and 10-months will be made using regression models with bootstrap methods used to generate confidence intervals around the cost differences.

Cost-effectiveness will be assessed through the calculation of incremental cost-effectiveness ratios (ICERs) and will be explored in terms of cost utility by using QALYs as the measure of effect, as derived from the EQ-5D-5L. Uncertainty around cost-effectiveness estimates will be explored using cost-effectiveness planes (through generating a large number of cost-outcome combinations using bootstrap methods) and cost-effectiveness acceptability curves (CEACs). As well as showing the probability of the intervention being cost-effective at various levels of willingness to pay for health benefits, the CEAC also represents uncertainty in the estimation of the ICER, including in circumstances where statistical power limits significance testing (Briggs, 2000). Cost-effectiveness planes will indicate the probability that the

intervention is (i) cost saving with better outcomes; (ii) cost saving with worse outcomes; (iii) cost increasing with worse outcomes or (iv) cost increasing with better outcomes.

Settings and equipment

As this project uses archival data a computer and SPSS are the only things required.

Researcher and Participant Safety Issues

Given the nature of this project there are no safety issues.

Ethical issues

Ethical approval was provided by West of Scotland Research Ethics Committee (12/WS/0311).

Timetable

May: Proposal

May-July 2017: Data analysis and write-up

July 2017: Final project submitted

Practical Applications

In the context of resource constraints it is important that efficient allocation decisions regarding competing healthcare interventions are made. Although it does not intend to dictate particular decisions, economic evaluation aims to establish an economic evidence base for discussions (Luyten et al., 2016). When any new treatment in a given context is proposed, it is essential not only to demonstrate the new treatment's effectiveness but also to establish its cost and compare this with the established treatment, whether that is treatment in terms of standard care or another treatment (Ising et al., 2014). The use of a single RCT as a vehicle for economic analysis would be inadequate for decision making however it is one of the key sources of evidence which must then be placed in a broader framework of evidence synthesis and decision analysis (Sculpher et al., 2006). The economic evidence that this study will report will contribute to this broader framework of evidence and our

understanding of the potential for the therapy under evaluation to be considered cost-effective. It will also help inform the design of a larger definitive trial.

Clinical Psychologists need to be able to show that interventions they provide or support are not only effective but cost-effective if decision makers are going to support implementation of such interventions (Baker et al., 2009). If we are to make a good business case for the value of our services and interventions, it follows that, as a profession, we must improve our capacity to understand and evaluate cost-effectiveness, not just efficacy, of psychological interventions.

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Additional Appendices

Appendix 3.1: Original project proposal

Explanatory Note

The following proposal relates to a major research project which was initially undertaken prior to the project which has been presented in this portfolio. This project was developed to the point of study commencement and recruitment. The ethics application process was completed and approval received. However, difficulties with recruitment over January – April 2017 led to the project being terminated. The intention had been to recruit 15 participants for this feasibility study however by April 2017, only one potential participant was eligible based on screening questions. Other potential participants who had expressed an interest in taking part in the research did not meet inclusion criteria. In order to be able to meet the research portfolio requirements, it was necessary to undertake a new Major Research Project and Systematic Review. The new project uses data from a previous trial.

MRP Proposal

Title: A brief behavioural intervention for insomnia in family carers of people with dementia: a feasibility study

Matriculation number: 2166401

University Supervisor: Dr Maria Gardani

Field Supervisor: Dr Stephanie Crawford

Date of submission: 16/05/2016

Version number: 3

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Abstract

Background

Between 50-74% of dementia carers report some sleep disturbance (Peng and Chang, 2013) however relatively few studies have explored interventions for dementia carers where insomnia symptoms have been the primary focus of intervention.

Aims

This study aims to explore the feasibility of delivering a brief behavioural intervention for insomnia (BBTI) to family carers of people with dementia. Recruitment and retention rates and the acceptability of the intervention will be explored. Outcomes on a range of measures will also be explored and effect sizes reported in order to inform sample size calculation in future studies.

Method

Participants: Family carers of people with dementia who have insomnia.

Intervention: The BBTI described in Buysee et al. (2011) and Troxel et al. (2012) will be adapted for carers and delivered across three group sessions.

Design and Procedure: This is a within-subjects feasibility study. Assessments will be completed at baseline, immediately post-treatment and at 4 weeks post-treatment. Sleep diaries will be kept throughout.

Measures: Semi-structured sleep interview, Pittsburgh Sleep Quality Index (PSQI), Sleep Condition Indicator (SCI), Zarit Burden Interview (ZBI), Hospital Anxiety and Depression Scale (HADS), Stanford Sleepiness Scale (SSS).

Applications

Given the well documented negative impact of insomnia symptoms in carers and given the time constraints they face due to their caring role, a brief intervention for insomnia may be both a time- and cost-effective way of improving sleep in this group.

Introduction

Approximately one third of the general population presents with at least one insomnia symptom, such as difficulty with sleep initiation or maintenance (Ohayon, 2002). In the UK, the results of the Great British Sleep Survey (GBBS) indicated that, of 11,129 participants who completed the GBSS between March 2010 and April 2011, 5,083 were considered to have possible insomnia disorder (Espie et al., 2012).

Between 50-74% of dementia carers report sleep disturbance (Peng and Chang, 2013). Dementia carers may be particularly at risk for suffering negative consequences from the impact of chronic sleep loss on top of the stress of their carer role (McCurry, 2009). Sleep disturbance in carers has been linked to carers experiencing physical and emotional role limitations, reduced quality of life, poorer mental health outcomes, risk for premature mortality, lowered immune function and increased risk for cardiovascular disease (McCurry et al., 2009; Lee and Thomas, 2011; Peng and Chang, 2013). Sleep disturbance associated with caring for someone with dementia has also been reported to be a major reason for institutionalisation of the person with dementia (Hope et al., 1998).

Insomnia Interventions

Cognitive Behavioural Therapy for Insomnia (CBTI) is currently the first line psychological treatment for insomnia and has been shown to be equal to pharmacotherapy during acute treatment and more effective in the long term (Reimann, 2015). Efficacy has been reported for individually delivered CBT for chronic insomnia that is not comorbid with any medical or psychiatric disorders

(Trauer et al., 2015) and for both individual and group delivered CBT for insomnia comborbid with psychiatric and medical conditions, such as cancer, arthritis, chronic pain, depression and anxiety (Geiger-Brown et al., 2015; Wu et al., 2015; Koffel et al., 2015). Gains from behavioural treatments have shown to be sustained for months to years following treatment and are not associated with the variety of side effects seen with sleep medication (Irwin et al., 2006).

Insomnia Interventions in carers

Relatively few studies have explored interventions for dementia carers where insomnia symptoms have been the primary focus of intervention, however, findings from research to date are promising (McCurry et al., 2015). McCurry et al. (1998) found that a behavioural treatment for sleep problems in older dementia carers delivered over six weekly sessions led to significant improvements in sleep quality and sleep efficiency at post-treatment and 3-month follow-up (McCurry et al., 1998). The intervention included sleep hygiene, stimulus control, sleep restriction, stress management and also guidance in relation to the management of behaviour problems in the person with dementia (McCurry et al., 1998).

In another study, a brief behavioural intervention delivered to a small sample of carers of both community-dwelling and institutionalized individuals with dementia indicated a trend towards improvement in sleep quality and depression (Simpson and Carter, 2010). The intervention was well received and carers reported no increased burden from engaging in the intervention (Simpson and Carter, 2010).

BBTI

In the context of concerns regarding the resources necessary to deliver typical CBT interventions for insomnia and the impact that this has on dissemination, Buysee et

al. (2011) developed a brief behavioural intervention for insomnia (BBTI). BBTI is based on the same core principles which are key to other empirically supported treatments, including CBTI (Troxel et al., 2012). The basic rationale for BBTI is that it is possible to have a direct impact on the two major physiological systems that regulate sleep: the homeostatic and circadian drive, by modifying waking behaviours (Troxel et al., 2012). The key intervention components derive from sleep restriction and stimulus control techniques and include instructions to: reduce time in bed; get up at the same time each day, regardless of sleep duration; to not stay in bed unless sleepy and not to go to bed unless sleepy (Buysee et al., 2011).

Several studies support the use of BBTI to treat insomnia. Germain et al. (2006) randomly assigned 35 older adults to BBTI or an information only control. At 4 weeks post-intervention, significant improvements in sleep diary and self report measures were found. In another study, Buysee et al. (2011) explored the efficacy of BBTI versus an information control condition in a sample of 79 older adults. The BBTI produced significantly better outcomes in self reported sleep and actigraphy with improvements maintained at 6 months.

In a recent cluster-randomized controlled trial, Fuller et al. (2015) tested the feasibility of modified BBTI delivered by pharmacists (Fuller et al., 2015). They found a significant decrease in Insomnia Severity Index (ISI) scores from baseline to 3 month follow-up in the intervention group (n-17) relative to controls (n=19). Although the difference in ISI between intervention versus controls was not found to be significant when cluster effects were taken into account, the results nevertheless indicated that reductions in insomnia severity can be gained using non-sleep professionals to deliver a brief behavioural intervention (Fuller et al., 2015).

Relatively few studies have explored interventions for dementia carers where insomnia symptoms have been the primary focus of intervention (McCurry et al.,

2015). Given the well documented negative impact of poor sleep in carers (McCurry et al., 2009; Lee and Thomas, 2011; Peng and Chang, 2013) and given the time constraints they face due to their caring role, a brief intervention for insomnia may be both a time-and cost-effective way of improving sleep in this group. This study will explore the feasibility of delivering adapted BBTI in a group setting to family carers of people with dementia.

Aims and Research Questions

Aims

As stipulated in the Medical Research Council (2008) guidelines on developing complex interventions, the feasibility and piloting stage includes: estimating the likely rates of recruitment and retention of participants, testing procedures for their acceptability and calculation of appropriate sample sizes. Based on these guidelines, the current study aims to explore how many eligible participants consent to participate, how many are retained and whether the adapted intervention is acceptable. The study will also explore outcomes on a range of measures and report effect sizes to inform sample size calculation in future studies although it is acknowledged that the lack of control group in the current study will preclude any firm conclusions regarding treatment efficacy being made.

Parameters of interest

- What proportion of eligible participants consent to participate in BBTI?
- What are the rates of retention for the treatment and follow-up stages?
- Are improvements in sleep observed, as measured by the Pittsburgh Sleep Quality Index (PSQI), the Sleep Condition Indicator (SCI) and sleep diary parameters such as Sleep Efficiency?

- Are changes in anxiety, depression and carer burden observed?

- Do those who participate in BBTI report the intervention to be acceptable and what modifications may be required for future studies?

It is hypothesised that there will be a reduction in scores on the Pittsburgh Sleep Quality Index (PSQI), an increase in scores on the Sleep Condition Indicator (SCI), and an improvement in sleep diary parameters (increased sleep efficiency, a reduction in sleep latency and a reduction in wake time after sleep onset) following participation in BBTI. Total sleep time is not expected to increase significantly (Irwin et al., 2006).

Plan of investigation:

Participants

Inclusion Criteria: Both the patient and the carer must live together. Carers must meet DSM-V criteria for insomnia disorder (American Psychiatric Association, 2013) with the exception that carers who do not meet the frequency criterion of 3 times per week or duration criterion of 3 months will still be included if frequency is at least twice per week and duration 2 months. Carers must be competent in English language and have good basic literacy skills.

Exclusion Criteria: Carers with unstable, moderate to severe mental health issues (particularly Major Depressive Disorder and Bipolar Disorder) and/or carers already receiving a psychological intervention will be excluded as will carers with untreated sleep disorders like obstructive sleep apnoea, restless legs syndrome and periodic limb movement disorders. Carers with a current serious medical condition such as cancer will be excluded as will people with cancer who have only recently entered remission. Carers with a Learning Disability or a neurological condition (e.g. Multiple Sclerosis, Parkinson's disease, epilepsy) will be excluded as will carers who are

being investigated for a degenerative condition. In order to be as inclusive as possible, carers who have previously had a stroke will not be excluded. In instances where a potential participant has had a stroke, consent will be requested to consult with the individual's GP to discuss suitability for inclusion where this is felt to be necessary.

Intervention

The intervention described in Buysee et al. (2011) and Troxel et al. (2012) and also described earlier in this proposal will be adapted to be delivered to carers in a group setting.

Recruitment procedures

Individuals who are caring for a family member with dementia who is known to one of two NHS Greater Glasgow and Clyde Older People's Community Mental Health Teams (OPCMHT) will be recruited via multidisciplinary team members.

Justification of sample size

The Pittsburgh Sleep Quality Index (PSQI) was deemed the most appropriate measure upon which to base the sample size calculation due to its coverage of a number of relevant sleep variables. To our knowledge, only two studies, those by McCurry et al. (1998) and Simpson and Carter (2010) described earlier, have reported on a brief behavioral intervention for insomnia delivered to dementia carers. The McCurry et al. (1998) study was deemed most appropriate to inform the current sample size calculation. Whilst the study by McCurry et al. (1998) used a between subjects design, it was possible to calculate the within subjects effect size from the data reported in their paper. The within subjects effect size calculated for the PSQI was large (d=0.9). Using this effect size (d=0.9), power of 0.8, and a significance level of 0.05, the sample size required is estimated to be 11. Given that

some participants may withdraw from the study or not be able to complete the intervention, the study will aim to recruit 15 participants. Whilst the measurement of treatment effects is a secondary aim, effect sizes reported in the McCurry et al. (1998) study suggest that there will be a statistically significant result recruiting this sample size.

Design and research procedure

It was not possible to access local data to inform likely recruitment rates across the two bases prior to the study as this is the first study of its kind to be undertaken at those locations. However, a number of potential barriers to recruitment were considered to be relevant, including whether a carer would be able to ensure alternative care provision for the person with dementia whilst they attended a group and also general time constraints they might face due to the nature of their carer role. Given this, and given the relatively restricted time available for recruitment to the study, it was felt that it would most likely not be possible to recruit sufficient numbers to include a control group in the current study. The current study therefore utilises a within-subjects design and focuses on parameters relating to feasibility.

The intervention will be delivered across 3, weekly group sessions of approximately 1 ½ hours duration. In order to maximize the groups which can be delivered and to reduce the time recruited participants have to wait, each group will be started as soon as there are 3 participants to make up a group, with 3 being the minimum number required. Given that the intervention includes delivering the group material and reviewing individual sleep diaries, groups will have a maximum of 5 participants. Delivering the intervention to groups of a larger size across 3 sessions with only two facilitators would impose difficulties in terms of delivering all aspects of the intervention adequately and in terms of providing adequate support to each individual during the sessions. Assessment measures will be completed at baseline

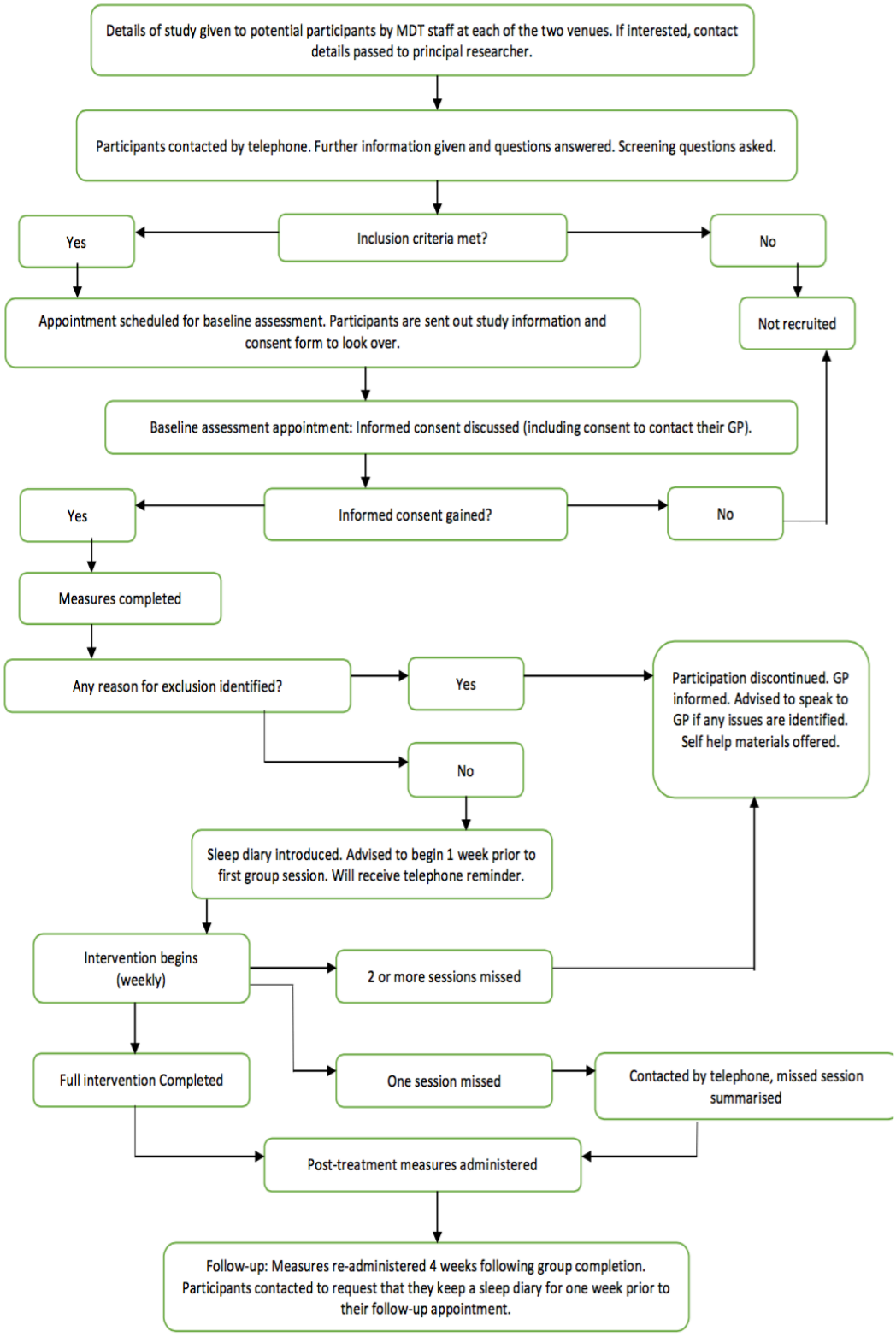
and immediately post treatment with sleep diaries being kept throughout the intervention. Follow-up assessment will be undertaken at 4 weeks post-treatment. Both those who complete BBTI and those who do not will be invited to attend a focus group for the purposes of exploring acceptability of treatment and the study procedures in general. The flow chart in Figure 1 outlines the research procedure.

In order to reduce disruption to carers' normal routine and caregiving responsibilities, initial screening will be conducted via telephone in order to assess whether they meet inclusion criteria. Thereafter, if assessed as safe to do so following consultation with the Older People's Community Mental Health Team, baseline assessment will be completed at the participant's home, again, to reduce burden on the caregiver. In any instance where risk associated with completing a home visit is identified, baseline assessment will be conducted within the two identified OPCMHT bases: Parkview Resource Centre (North East Glasgow) and the Argyll Centre (Greenock). Post-treatment, follow-up assessment and groups will also be conducted within the two bases.

Should a participant miss a group session, they will be contacted by telephone so that the session can be summarised. In the event that two sessions are missed by an individual, participation will be discontinued given that the total duration is only 3 sessions. They will however be provided with self help materials and encouraged to speak to their GP about alternative treatment should they wish to pursue this. As part of the consent taking process, consent will be requested to inform the participant's GP of their involvement in the study. Any participant who is not able to complete the BBTI will be offered the opportunity to take part in another group so long as another group is due to run in their area prior to the study ending and that planned groups are not already at full capacity.

The principal researcher will complete the telephone screening and all assessments. The principal researcher will also facilitate the group intervention along with one of the research team and/or a mental health nurse.

Figure 1: Flow chart summarising the research procedure



Measures

Basic demographic information: Age; Gender; Years in education; Length of time in caring role; Relationship to patient

Burden measure: Zarit Burden Interview (Zarit et al., 1985)

Medical information: Current medication; Medical conditions

Drug and alcohol information: Alcohol Use Disorders Identification Test (AUDIT, Bohn et al., 1995); Drug Use Disorders Identification Test (DUDIT, Berman et al., 2005)

Anxiety/Depression: Hospital Anxiety and Depression Scale (HADS, Zigmond & Snaith, 1983)

Sleep related measures: Semi-structured sleep interview (adapted from Gardani et al. 2015); The Pittsburgh Sleep Quality Index (PSQI, Buysee et al., 1989); Sleep Condition Indicator (SCI, Espie et al., 2014); Stanford Sleepiness Scale (SSS, Hoddes et al. 1972); sleep and daytime functioning diary (adapted from Espie & Morin, 2006) - the diary will include a basic numeric pain rating scale and a section to record whether any nighttime behaviour of the person with dementia occurred during the sleep period with a scale to rate the level of disturbance this was felt to cause.

Qualitative

A short evaluation questionnaire (designed by the research team) will be given to participants to provide feedback on their experience of the group. In addition, both those who completed and did not complete BBTI will be invited to take part in a focus group, the primary aim of which will be to explore aspects of acceptability such as: how accessible the content was, factors relating to how the groups were

facilitated and factors relating to variables such as session duration and location. Focus group discussion will be recorded and analysed for themes.

Data Analysis

A statistician will be consulted prior to finalising the analysis plan. Descriptive statistics will be reported. It is anticipated that a within-subjects t-test will be used to explore changes in the primary variable of interest, namely sleep quality as measured by the PSQI. In the event that parametric assumptions are not met, a Wilcoxin test will be performed.

Settings and equipment

Groups and face-to-face assessment will take place within the Argyll Centre or Parkview Resource Centre. Baseline assessment may be completed within the participant's home where identified as being safe to do so.

Equipment required: NHS phone line, projector, psychometric questionnaires, sleep diaries and psychoeducation materials.

Health and safety issues

Researcher safety issues

The client group are not a high-risk group and thus researcher safety issues are deemed to be minimal. Groups and assessments will take place during working hours and standard organisational and local safety procedures will be followed at all times.

Participant Safety Issues

When undertaking behavioural sleep treatment there may be a temporary increase in daytime sleepiness as a result of mild sleep deprivation associated with sleep restriction strategies (Troxel et al., 2012). Specific guidance will be given to

participants regarding this prior to them giving consent. Assessment of the severity of daytime sleepiness will be undertaken at each contact using the Stanford Sleepiness Scale and via review of sleep diaries. Treatment will be discontinued where any concerns regarding excessive sleepiness are identified.

Should any new or worsening physical or mental health conditions be identified, the participant will be encouraged to speak to their GP about this and their participation in the study discontinued if necessary. If a participant should become distressed or upset at any time they will be supported by one of the group facilitators, and should they require further support, will be signposted to their GP. If issues arise that suggest it is no longer advisable for them to continue in the study, this will be explained. Should a participant express suicidal ideation, the Glasgow Clinical Risk Screening and Management Tool will be used to guide risk assessment and will guide decisions regarding appropriate management thereafter. The participant's GP will be contacted as necessary. Given that the content of assessment and group sessions does not involve the discussion of difficult or distressing subject matter it is anticipated that incidence of distress during assessment and intervention should be minimal.

Ethical issues

Information about the study and the right to withdraw will be given to participants in advance of consent being sought. Data will be held in-line with NHS and university policies on data protection and confidentiality. NHS Ethics and R & D approval will be sought.

Financial issues

Printing and photocopying costs. Tea/coffee to be provided at groups.

Timetable

16th May 2016: Final approved proposal due for submission. Await 'Proceed to Ethics' letter from Research Director.

May/June 2016: Apply to ethics

Summer 2016: Group materials developed

Autumn 2016 to Spring 2017: Data collection

May-July 2017: Data analysis and write-up

July 2017: Final project submitted

Practical Applications

Given the well documented negative impact of poor sleep in carers and given the time constraints they face due to their caring role, a brief intervention for insomnia may be both a time-and cost-effective way of improving sleep and may help reduce overall caregiver burden. Also, given that the client group recruited is likely to be older (McCurry et al., 2007), they may also benefit from other aspects associated with group treatment in older people such as: reduced social isolation, normalisation of their difficulties and peer support (Finkel, 1990; Agronin, 2009). A feasibility study will be able to provide key information regarding whether the intervention is acceptable and will provide information and data which can inform future studies.

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