TELEPHONE-SUPPORTED ACCEPTANCE AND COMMITMENT BIBLIOTHERAPY FOR PEOPLE WITH MULTIPLE SCLEROSIS AND PSYCHOLOGICAL DISTRESS: A RANDOMISED CONTROLLED FEASIBILITY STUDY

BARNABY PROCTOR, BSc.

Thesis submitted in part fulfilment of the requirements for the degree of Doctor of Clinical Psychology to the University of Nottingham

DECEMBER 2016

Thesis Abstract

Objective: Telephone-supported self-help Acceptance and Commitment Therapy (ACT) may be a way of providing accessible and effective psychotherapy to people with Multiple Sclerosis (MS). The aim of this trial was to determine the feasibility of a randomised controlled trial (RCT) of telephone-supported ACT bibliotherapy compared to treatment-as-usual (TAU), explore the effectiveness of the intervention and track individual changes.

Design: The study was a randomised controlled feasibility trial. The intervention consisted of eight weekly support calls guiding participants through an ACT self-help text. Participants were assessed at baseline and post-intervention using the Generalised Anxiety Disorder measure (GAD) and the Patient Health Questionnaire (PHQ) as primary outcome measures. The EuroQol (EQ-5D-5L) and Multiple Sclerosis Impact Scale (MSIS-29) were secondary measures, and the Acceptance and Action Questionnaire (AAQ-II) was a process measure. A sample of participants were interviewed and analysed using framework analysis to assess RCT feasibility.

Results: Twenty seven participants with MS with anxiety and/or depression were recruited from an outpatient MS clinic and an MS charity. The majority of participants found all components of the RCT acceptable. Overall attrition was 33%, and 64% in the intervention group. Linear mixed model analysis and effect size calculation found a significant effect (p=0.004) and large effect size (0.84 (95% confidence intervals 0.02-1.66)) at post-intervention in favour of the intervention on anxiety. Smaller non-significant positive effects were found on other measures. Participants in both groups exhibited clinically significant improvements and deteriorations. Intervention completers had significantly lower baseline scores on the MSIS and the AAQ-II.

Conclusions: Telephone-supported ACT bibliotherapy delivered in a RCT format may be a feasible research method for people with MS if significant changes to the method of delivery are made. The intervention has the potential to be effective in reducing anxiety, however there are limitations in sample size. Future research directions and the applicability of ACT in this population are discussed. Finally, personal reflections on methodology and intervention delivery are made.

Acknowledgements

I would like to thank Roshan das Nair and Nima Moghaddam for their guidance and support throughout the duration of the training programme. I would like to thank Dr Nikos Evangelou and other clinicians and researchers in the Division of Clinical Neurology for their enthusiasm in the study and in assisting with recruitment.

I would like to thank peers in my training cohort both for their support and words of motivation towards completing my research and their friendship outside of the course.

Statement of Contribution

Drs Roshan das Nair (RdN) and Nima Moghaddam (NM) assisted with trial design and application for ethical approval. Dr Nikos Evangelou and his neurology team assisted with participant recruitment. Margareta Clarke, Research Assistant in the Division of Clinical Neurology at Queen's Medical Centre assisted with data collection from clinical files. William Vogt (WV), Trainee Clinical Psychologist, conducted feasibility interviews. Drs Roshan das Nair and Nima Moghaddam assisted with data analysis and trial write-up.

Table of Contents

Thesis Abstract 1
Acknowledgements 2
Statement of Contribution 3
List of Tables and Figures 8
List of Appendices 10
Systematic Literature Review 11
Abstract 12
Impact and Implications Statement 13
Introduction 14
Methods 16
Results 19
Discussion 34
References 36
Journal article 41
Abstract 42
Impact and Implications Statement 43
Introduction 44
Multiple Sclerosis 44
Acceptance and Commitment Therapy 45
Teletherapy 46
Bibliotherapy 47
Aims 47
Methods 48
Participants 48
Assessment 48
Design 49
Intervention 49
Analysis 49
Results 52
Sample 52
Feasibility 54
Effectiveness 57

Sample Size Estimation 59
Discussion 60
Attrition 60
Effectiveness 62
Sample Size 62
Strengths and Limitations 63
Research implications 63
Clinical Messages 64
References 65
Extended Paper 70
1. Extended Introduction 71
1.1 The Aetiology of Psychological Distress in Multiple Sclerosis 71
1.2 MS and Psychotherapy 72
1.3 Acceptance and Commitment Therapy 72
1.3.1 Theory 72
1.3.2 Relational Frame Theory and Functional Contextualism 73
1.3.3 Research on ACT 74
1.3.4 ACT Studies in MS 75
1.3.5 Rationale for ACT in MS 76
1.3.6 ACT Summary 77
1.4 Teletherapy 77
1.4.1 Telepsychotherapeutic Mechanisms of Change 78
1.4.2 Teletherapy vs Face-to-face Therapy 78
1.4.3 Rationale for Teletherapy in MS 78
1.5 Bibliotherapy 79
1.5.1 Rationale for Bibliotherapy in MS 79
1.5.2 Bibliotherapy and teletherapy in MS 79
1.6.1 Feasibility Randomised Controlled Trials 80
1.6.2 Feasibility Aims 81
1.6.3 Secondary Objectives 81
1.7 Epistemology 82
2. Extended Methods 83
2.1 Recruitment 83

2.2 Sample Size 84
2.3.1 Inclusion Criteria 85
2.3.2 Exclusion Criteria 86
2.4.1 Demographic Measures 86
2.4.2 Primary Outcome Measures 87
2.4.3 Secondary Outcome Measures 88
2.4.4 Process Measures 88
2.4.5 Service-use Measures 89
2.5 Randomisation 89
2.6 Purposive Sampling 89
2.7 Procedure 90
2.8.1 Framework Analysis 91
2.8.2 Quantitative Data Analysis 91
2.8.3 Multiple Comparisons 93
2.8.4 Service-Use Analysis 93
2.8.5 Sample Size Estimates 93
2.8.6 Individual Changes 94
2.9.1 Ethical Approval 95
2.9.2 Informed Consent 95
2.9.3 Confidentiality 95
2.9.4 Further Considerations 95
3. Extended Results 97
3.1 Baseline Correlation Results 97
3.2 Missing Data 97
3.3 Attrition Reasons 97
3.4 Normality and Variance Testing 98
3.5 Per-protocol Analysis 98
3.6.1 Individual Changes 101
3.6.2 Case Examples 103
4. Extended Discussion 104
4.1 Feasibility 104
4.2 Sample 107
4.3 Quantitative Results 108

4.4.1 Attrition 113
4.4.2 Attrition Reasons 114
4.5.1 Individual Change Results 115
4.5.2 Case Examples 116
4.6 Extended Strengths 117
4.7 Extended Limitations 118
4.8 Research Implications 119
4.9 Implications for Clinical Practice 122
Extended References 124
Appendices 134
Poster 149

List of Tables and Figures

Figure 1: PRISMA diagram showing the flow of the review……..23

Figure 2: Methodological quality summary: review authors' judgements about each study's methodological quality. A positive symbol indicates low risk, a negative symbol indicates high risk and a question mark indicates unclear risk……...…28

Figure 3: Methodological quality graph: review authors' judgements about each study's methodological quality item presented as percentages across all included studies…….29

Figure 4: Forest plot showing results of studies with outcomes of short-term measures of depression……..30

Figure 5: Forest plot showing results of studies with outcomes of short-term measures of fatigue ……....31

Figure 6: Forest Plot showing results of studies with outcomes of short-term measures of QOL……..31

Figure 7: Forest Plot showing results of studies with outcomes of short-term measures of physical health……32

Figure 8: Flow of participants through the study……..51

Table 1: A Description of the included studies……..…20

Table 2: Risk of bias of the included studies……24

Table 3: Baseline demographic characteristics of the control and intervention groups…….53

Table 4: Baseline clinical characteristics of the control and intervention groups…….53

Table 5: Completers and non-completers in the intervention group. ……..55

Table 6: Baseline characteristics of intervention completers and non-completers……..56

Table 7: Baseline and post-intervention means between and within groups, results of linear model analysis of interaction effects of allocation and time and effect sizes of intervention vs TAU at post-intervention……...…58

Table 8: The breakdown of the self-help book…….....90

Table 9: Per-protocol analysis displaying baseline and post-intervention means between and within groups, results of linear model analysis of interaction effects of allocation and time and effect sizes of intervention vs TAU at post-intervention……..100

Table 10: Individual baseline and post-intervention scores for the TAU group…….…..….101

Table 11: Individual baseline and post-intervention scores for the intervention group……..102

List of Appendices

Appendix A: Ethics Approval Letter……135

Appendix B: Participant Information Sheet……139

Appendix C: Consent Form……...142

Appendix D: Telephone Support Call Guide……..143

Appendix E: Feasibility Interview Schedule……...144

Appendix F: An example of a transcript of a feasibility interview arranged into the predefined framework of feasibility……..145

Appendix G: Service-Use Questionnaire……...….146

Appendix H. Example search strategy……148

Systematic Literature Review

Abstract

Objective: To review the evidence for the effectiveness of telephone-psychotherapy on psychological outcomes in people with Multiple Sclerosis (MS).
Methods: We conducted a systematic search of EMBASE, PsycINFO, PsycARTICLES, MEDLINE, CINHAL, Web of Science, and hand-searched relevant journals to identify randomised controlled trials (RCTs) that evaluated the effectiveness of telephone-psychotherapy on psychological outcomes in people with MS (last search completed on 1st October 2015). The methodological quality of each included trial was assessed, based on a standardised list of methodological criteria. Where available, data were extracted and combined in meta-analysis to compute effect size estimates.
Results: Eleven RCTs and 1104 participants were identified. Meta-analysis found a moderate effect of the intervention on depression (SMD of 0.47 (95% CI of 0.21 to 0.73)). Meta-analysis also found small to moderate short-term effects of the intervention on fatigue, quality of life (QOL), MS-symptoms, physical activity, and medication adherence, compared to controls and other interventions. RCT designs were heterogeneous. All studies had at least one high or unclear risk of bias.
Conclusion: Telephone-psychotherapy provides small and moderate benefits in depression, fatigue, QOL, MS-symptoms, physical activity and medication adherence in the short-term. Few gains were sustained in the long term. Studies of better quality are needed.

Key Words: Multiple Sclerosis, teletherapy, psychotherapy.

Impact and Implications Statement

- There is some evidence that providing telephone-psychotherapy for people with MS has small-to-moderate benefits on depression, fatigue, physical activity, medication adherence, and MS symptoms in the short-term.
- Telephone-psychotherapy may be an effective and feasible method for clinicians to support people with MS.

Introduction

Multiple Sclerosis (MS) is a progressive neurological condition with no cure that affects two and half million people worldwide (MS Trust, 2015). The majority of those with MS have a relapsing-remitting form, whereby symptoms develop during a relapse, typically lasting two to six weeks, before remitting. Eventually, symptoms become permanent and the condition becomes worse over time, which is called secondary progressive MS. MS can have diverse and unpredictable effects on physical and psychological functioning (Wilkinson & das Nair, 2013), so there is a need for accessible and effective psychotherapeutic support. Psychological and psychosocial problems frequently arise in areas such as physical functioning, fatigue, pain, cognition, and problems with the support they receive from people around them (Khan, Turner-Stokes, Ng, & Kilpatrick, 2007). These types of problems are thought to be highly prevalent in the MS population. The lifetime prevalence of depression in MS, for instance, is estimated at 50% (NICE, 2003), compared to 17% in a non-clinical population (Blazer & Kessler, 1994). Psychosocial distress may arise through various interacting pathways, making the precise aetiology of psychological distress difficult to discern.

Many people with MS already take multiple medications for their condition and physical sequelae, and the pharmacological management of mood problems adds to their medical regimen. Psychotherapy, which has the potential to be effective in this population (Thomas, Thomas, Hillier, Galvin, & Baker, 2006), may provide an alternative treatment of choice for many. However, those with MS may not be able to access face-to-face psychological therapies due to fatigue, reduced mobility and other condition-related limitations. Furthermore, clinical experience suggests that psychological interventions may be perceived as costly and therefore not always funded by healthcare providers. Therefore, research into other ways of making such care available is warranted.

Telephone-psychotherapy is an intervention that offers the opportunity to deliver psychological therapies to people in their own homes who otherwise might find it difficult to travel to a healthcare location to receive face-to-face therapy, or where there are limited resources to allow therapists to conduct home-visits. Previous systematic reviews have demonstrated the potential effectiveness of telephone-

based interventions across a broad range of physical (Hailey, Roine, Ohinmaa, & Dennett, 2011) and mental health domains (Leach & Christensen, 2006), including stroke (Johansson & Wild, 2011; Paré, Jaana, & Sicotte, 2007) and spinal cord injury (Dorstyn, Mathias, & Denson, 2013; Hailey, Roine, Ohinmaa, & Dennett, 2013). Telephone-psychotherapy is thought to work in a similar way to face-to-face delivered psychotherapy, but may provide lower attrition rates (Mohr, Vella, Hart, Heckman, & Simon, 2008). Client satisfaction and acceptance of telephone psychotherapy has also found to be high (Bee et al., 2008). While there are studies which have explored the usefulness of telephone-psychotherapy, there is no consensus as to whether it can provide a similar quality of care compared to face-to-face interventions at a reduced cost (Mistry, 2012).

To our knowledge, there is no systematic review that evaluates the clinical effectiveness of telephone psychotherapies on psychological outcomes in MS. Results from this review will direct future research and practice on the potential applicability of this type of intervention with people with MS.

This systematic literature review aims to determine the effectiveness of telephone-based psychotherapies for people with MS, compared to those receiving no treatment, standard care or other control, on psychological and physical outcomes.

Methods

We searched the following electronic databases (from inception to 1st October 2015) to identify potential studies: EMBASE, PsycINFO, PsycARTICLES, MEDLINE, CINHAL, and Web of Science. The search strategy was based around the subjects: MS, telephone-based psychotherapies, and RCTs. An example of the search strategy is presented in Appendix 1. Manual citation tracking of all primary studies, forward citation tracking, and scanning references lists from review articles were conducted as another search strategy. The WHO International Clinical Trials Registry Platform (ICTRP) and www.clinicaltrials.com were searched to identify registered trials that met the inclusion criteria but with no data published. If any trials appeared to meet the inclusion criteria, the authors were contacted to request their data.

Trials including people with MS in which a telephone-delivered psychological therapy was compared to a control, were sought for inclusion in the review. RCTs and the pre-crossover component of randomised crossover trials were considered for inclusion if they met other criteria. Papers reporting secondary analysis of studies were included if they included between-group comparisons of outcomes of interest not reported in the original paper. Studies from conference presentations, dissertations or other grey literature were excluded.

We included trials with patients with all sub-types of MS. Trials with mixed diagnosis populations where MS data were not separable were excluded. Trials in which there was a comparison between a treatment group that received a telephone-based psychological therapy and a control group that either received no intervention or another type of intervention were included. To be considered a 'psychological therapy' the interventions should have been described as wholly or partially based on established psychological theories, models or principles. Therapy was considered to consist of a minimum of four sessions, so as to eliminate evaluations of telephone hotlines or crisis counselling services. Studies that delivered therapy via video-conference technologies were excluded. Studies that delivered support via web/internet technologies without adjunct teletherapy were excluded. Therapies could be delivered by any trained clinician (e.g. doctors, nurses, therapists).

The primary outcome of interest was depression. If there was more than one outcome measure measuring this construct, we used the following hierarchy of commonly used tests:

a) Beck Depression Inventory (BDI) (Beck, Steer, & Carbin, 1988).

b) Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960).

c) Any other depression outcomes.

Secondary outcomes were anxiety, fatigue, quality of life (QOL), MS symptoms, medication adherence, and level of physical activity.

All outcomes were either defined as short-term or long-term. Short-term outcomes were assessed immediately post-intervention. Long-term outcomes were defined as the outcome assessed nearest to 12 months post-randomisation, within a range of 6 to 18 months. Separate analyses were conducted for each of these time-points where possible. Total scores were taken over domain scores (subtest sections) if both were available. If subscale scores were reported without total scale scores, then first individual effect sizes were calculated for each subscale, then combined using the Rosenthal and Rubin (Rosenthal & Rubin, 1986) method for computing accurate combination of effect sizes incorporating the estimated inter-correlation between the subscales. Self-report scores were taken over clinician-rated scores if both were available.

Included trials were assessed for methodological quality, and rated using the "Risk of Bias Table" from the Cochrane Handbook for Systematic Reviews of Interventions, guidelines 5.1.0 (Higgins & Green, 2008). Potential sources of bias were judged to be low risk, high risk, or unclear risk by one researcher (BP) and checked by another researcher (WV). RdN and NM arbitrated if there were any discrepancies. An overall evaluation of the risk for all included studies was completed.

The review was conducted using the Cochrane Review Manager software, RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Standardised Mean Difference (SMD) was used as a summary statistic.

Only data that were deemed to be similar or comparable enough to meaningfully pool, on the basis of the outcome measures, were entered into the meta-analysis. Depending on the heterogeneity of the data, fixed-effect or random-effects models were considered. Where continuous data were available, means and standard deviations (SD) were entered into RevMan (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), and the effect estimate (with 95% confidence intervals) was calculated using inverse variance method to apply a weighting to each analysis and displayed as a SMD. Where data were dichotomous, Mantel-Haenszel analysis was completed to produce an Odds Ratio effect estimate, with 95% confidence intervals.

Where medians with upper and lower quartiles were reported, medians were treated as means and interquartile ranges were used to estimate the SD, according to the formula: SD= interquartile range / 1.35.

The data were estimated to be of a roughly normal distribution, if, by subtracting the lowest value on each scale from the estimated median and dividing this by the estimated SD, the value produced was higher than one. The I^2 statistic (Higgins & Green, 2008) was used to assess heterogeneity in meta-analysis.

Results

A description of the included studies can be seen in Table 1. A total of 125 studies were identified after removing duplicates. Based on our inclusion criteria, 11 studies, comprising 1104 participants were included in the review, with 1032 participants from 10 studies included in the meta-analysis (Berger, Liang, & Hudmon, 2004; Bombardier et al., 2008, 2013; Cosio, Jin, Siddique, & Mohr, 2011; Egner, Phillips, Vora, & Wiggers, 2003; Finlayson, Preissner, Cho, & Plow, 2011; Mohr et al., 2000, 2005; Mohr, Hart, & Vella, 2007; Turner, Sloan, Kivlahan, & Haselkorn, 2014). The PRISMA (Liberati et al., 2009) diagram in Figure 1 details the flow of the search strategy and reasons for exclusion.

Table 1. A Description of the included studies

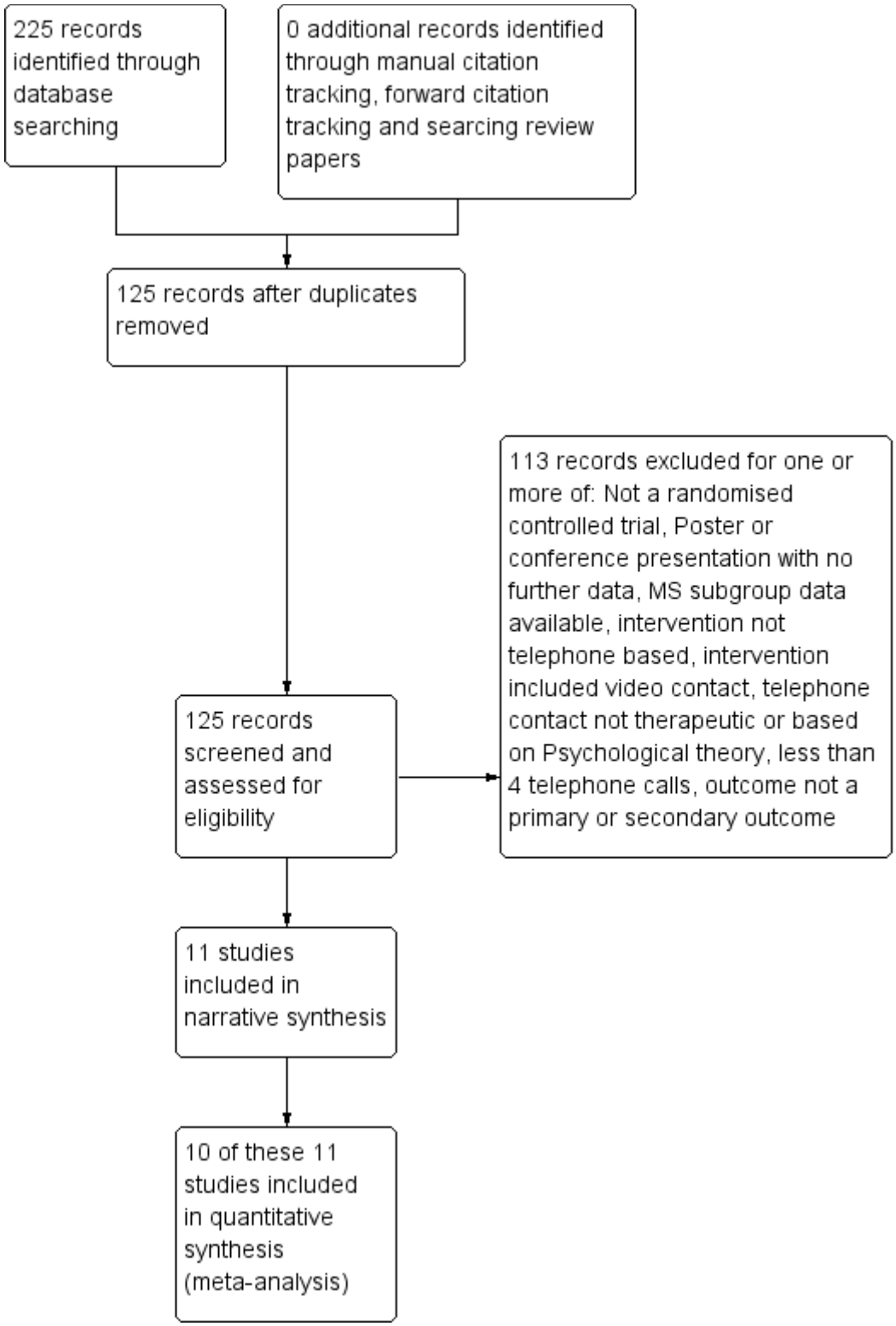
Study	Methods	Participants	Interventions	Outcomes
(Baron et al., 2011)	Secondary Analysis of "Mohr et al 2005"	From California, USA. Diagnosis of MS confirmed by a Neurologist. Inclusion Criteria: Functional impairment (on GNDS) and low mood (measured on BDI and HDRS). 127 Participants (T-CBT: 62, T-SEFT: 65). Groups comparable on baseline variables.	16 weekly 50 minute telephone calls with trained and supervised psychologist T-CBT as intervention with T-SEFT as control	SCID, BDI, HDRS- 3 Insomnia sub-items, HADS, GNDS, SF36, Digit Span, California Verbal Learning Test, Controlled Oral Word Association Test
(Berger et al., 2004)	Randomised Control Trial	From a USA-based MS network. Not specified how diagnosis of MS confirmed. MS patients currently using Avonex medication. 424 participants (E:212, C:212). Randomisation stratified on stage of readiness to discontinue Avonex. No analysis or available data to check if groups comparable at baseline.	E: Web-based motivational interviewing software with telephone calls every 2-4 weeks, up to 3 months C: Standard Care	Discontinuation of Avonex treatment and movement among stages of the Transtheoretical Model of Change
(Bombardier et al., 2008)	Single blind randomised control trial	From community setting in Pacific Northwest, USA. Diagnosis of MS confirmed by a Neurologist. Inclusion criteria: score of over 5.5 on EDSS. 130 participants (70 in E, 60 in C). Groups comparable at baseline, except on fatigue and TMT-B.	E: Initial 60-90 min motivational interviewing and goal setting, then 5 x 30 min phone calls over 12 weeks, delivered by a trained care manager supervised by a Clinical Psychologist C: Waiting list	HPLP-II, MFIS, SF36, MS QOL, CHART, lower limb strength, fitness on bicycle ergometer, walking speed, MSFC, TMT-A and TMT-B at 12 weeks post-randomisation
(Bombardier et al., 2013)	Single blind randomised control trial	Primarily from community setting in Washington, USA. Physician confirmed diagnosis of MS. Inclusion criteria: less than 5.5 on the EDSS, depressive symptoms as defined by the PHQ-9, a diagnosis of MDD or dysthymia and exercising less than 150 mins per week. 92 participants (E: 44, C: 48). Groups comparable on baseline variables except HAM-D, however controlling for this did not influence outcome analyses.	E: Telephone-counselling and physical activity promotion; In-person session then 6 calls of 30 mins and 1 call of 60 mins, from a counsellor supervised by a clinical psychologist C: Waiting list control	7-Day PAR, HAM-D, SCID, PANAS, MS-Related Symptom Checklist

(Cosio et al., 2011)	Secondary Analysis of "Mohr et al 2005"	From California, USA. Diagnosis of MS confirmed by a Neurologist. Inclusion Criteria: Functional impairment (on GNDS) and low mood (measured on BDI and HDRS). 127 Participants (T-CBT: 62, T-SEFT: 65). Groups comparable on baseline variables.	16 weekly 50 minute telephone calls with trained and supervised psychologistT-CBT as intervention with T-SEFT as control	SCID, BDI, HDRS- 3 Insomnia sub-items, HADS, GNDS, SF36, Digit Span, California Verbal Learning Test, Controlled Oral Word Association Test
(Egner et al., 2003)	Randomised Control Trial	From Atlanta, USA. Recruited from MS outpatient clinic. Not specified how diagnosis of MS confirmed. Inclusion Criteria: a recent exacerbation and a EDSS score of 7 or greater. 18 participants (E:11, C:5). Groups comparable on baseline characteristics.	E: 5 weekly psycheducation and counselling 30-40 min telephone calls, then two fortnightly sessions, delivered by nurses C: Standard Care A third video-telephone group was excluded from this review	FSS, QWB, CES-D at week 9 and months 6, 9, 12, 18 and 24
(Finlayson et al., 2011)	Randomised Control Trial	From Illinois, USA. Self-reported diagnosis of MS. Inclusion Criteria: a score of 4 or more on the FFS and a score of 12 or more on the BOMC. 190 participants randomised (E:77, C:74). Participants comparable on baseline characteristics.	E: 6 weeks on 70 minute group-based teleconference calls C: Waiting list	FIS, FSS, SF-36, SEECQ
(Mohr et al., 2000)	Randomised Control Trial (Participants not blind to allocation)	From California, USA. MS Diagnosis confirmed by a Neurologist. Inclusion criteria: Score of at least 15 on the POMS (depression-rejection subscale) and currently in taking medication or receiving psychotherapy for depression. 32 participants randomised (E: 16, C:16). Groups comparable on baseline characteristics.	E: 8 weekly sessions of CBT-based telephone therapy with a therapist supervised by the study authors. C: Usual Care	SC90, HDRS, SCID, POMS, Short-D, GNDS

(Mohr et al., 2005)	Randomised double blind study. Stratified randomisation based on MDD and use of anti-depressants	From California, USA. Diagnosis of MS confirmed by a Neurologist. Inclusion Criteria: Functional impairment (on GNDS) and low mood (measured on BDI and HDRS). 127 Participants (T-CBT: 62, T-SEFT: 65). Groups comparable on baseline variables.	16 weekly 50 minute telephone calls with a trained and supervised psychologist. T-CBT as intervention with T-SEFT as control	SCID, BDI, HDRS- 3 Insomnia sub-items, HADS, GNDS, SF36, Digit Span, California Verbal Learning Test, Controlled Oral Word Association Test
(Mohr et al., 2007)	Secondary Analysis of "Mohr et al 2005"	From California, USADiagnosis of MS confirmed by a Neurologist. Inclusion Criteria: Functional impairment (on GNDS) and low mood (measured on BDI and HDRS). 127 Participants (T-CBT: 62, T-SEFT: 65). Groups comparable on baseline variables.	16 weekly 50 minute telephone calls with a trained and supervised psychologist. T-CBT as intervention with T-SEFT as control	SCID, BDI, HDRS- 3 Insomnia sub-items, HADS, GNDS, SF36, Digit Span, California Verbal Learning Test, Controlled Oral Word Association Test
(Turner et al., 2014)	Pilot Randomised Controlled Trial	From Virginia, USA. Not specified how diagnosis of MS confirmed. Inclusion criteria: a military veteran struggling to adhere to DMT medication. 19 participants randomised (E:12, C:7). Participants comparable on baseline characteristic.	E: an average of 4 x 9 minute sessions of telephone counselling based on motivational interviewing, with home telehealth monitor delivering supportive text messages, over a total of 6 months. Delivered by a supervised "therapist". C: Care as usual	Adherence to DMT medication at 1, 3 and 6 months, NARCOMS, MFIS-5, PHQ-9, Short Delay recall task, Digit Span, Controlled Oral Word Association Task

7-Day PARL: 7 Day Physical Activity Recall, AIMS- DASA: Arthritis Impact Measurement Scale - Depression, anxiety and social activity subscales, BDI: Beck Depression Inventory, BOMC: Blessed Orientation Memory Concentration test, C: Control, CES-D: Centre for Epidemiologic Studies Depression Scale, CHART: Craig Handicap Assessment and Reporting Technique, DMT: Disease modifying therapies, E: Experimental, EDSS: Expanded Disability Severity Scale, FIS, Fatigue Impact Scale, FSS: Fatigue Severity Scale, GNDS: Guy's Neurological Disability Scale, HADS: Hospital Anxiety and Depression Scale- Anxiety sub-scale, HAM-D: Hamilton Rating Scale for Depression, HDRS: Hamilton Depression Rating Scale, HPLP-II: Health Promotion Lifestyle Profile, MDD: Major Depressive Disorder, MFIS-5: Modified Fatigue Impact Scale, MHLC-I: Multidimensional Health Locus of Control- Internal subscale, MS QOL: Multiple Sclerosis Quality of Life Inventory, MSFC: Multiple Sclerosis functional composite, MSSE-FC: MS Self-efficacy- function and control subscales, NARCOMS: North American Research Committee on MS, a disability measure, PANAS: Positive and Negative Affect Scale, PHQ-9: Patient Health Questionnaire 9, POMS: Depression-rejection scale, QWB: Quality of Wellbeing Scale, SC90: Symptom Checklist 90, SCID: Structured Clinical Interview , SEEQC: Self-efficacy for energy conservation questionnaire, SF: Medical Outcomes Study measure, SF36: Medical Outcomes Study measure, Short-D: Short Word List-Delay, SIP-PP: Sickness Impact Profile-Physical and Psychological composites, T-CBT: Telephone-administrated cognitive-behavioural therapy, TMT-A/B: Trial Making Test, T-SEFT: Telephone-administered support emotion-focused therapy, WCCC: Ways of Coping Checklist.

Figure 1. PRISMA diagram showing the flow of the review.



Overall the risk of bias was mixed across the 11 included studies, detailed in Table 2 and summarised in Figures 2 and 3.

Table 2. Risk of bias of the included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
(Baron et al., 2011)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	No description provided.	No description provided.	"Psychologists were nested in, rather than crossed with, treatment arm. This was done to avoid the influence of systematic therapist effects, such as treatment preferences, therapeutic orientation, or incremental therapist bias resulting from observation of the superiority of one treatment over another".	To facilitate preservation of the blinding, all assessment interviews commenced with a request by the interviewer that the participants not discuss any aspects of their treatment"	Attrition= T-CBT:5% (59 completers of 62), T-SEFT:6% (61 completers of 65). Drop-outs: 6 due to desire to drop out, 1 due to deterioration in mental health due to external trauma. Intention to treat analysis done. 3 in T-CBT and 4 in T-SEFT did not complete follow up assessments so were excluded from analysis.	All outcomes reported.
(Berger et al., 2004)*	Unclear risk	Unclear risk	Low risk	Unclear risk	High Risk	Low risk
	No description provided.	No description provided.	"The study investigators had no contact with patients and did not have access to patient names or other identifiers".	No description provided.	Attrition: E=19% (172 completers of 212), C=8% (195 completers of 212). No analysis on the 68 who did not provide final data. "Our analyses focus on 367 participants for whom complete follow-up data were available".	All outcomes reported
(Bombardier et al., 2008)	Low risk	Low risk	High Risk	Unclear risk	Low risk	Low risk
	"The randomization sequence was computer generated was blocked to yield equal allocation of every 50 participants, without stratification"	"The research care manager opened the next numbered randomisation envelope"	Single blind design; participants told of allocation group. Personnel knew of allocation group.	Outcome assessments were conducted by research assistants. No mention if they were blind	Attrition, E=9% (64 completers of 70), C=2% (59 completers of 60). 2 lost to follow up, 3 withdrew due to time constraints, 2 withdrew as they felt the intervention was of no use to them. Intent to treat analysis completed.	All outcomes reported
(Bombardier et al., 2013)	Low risk	Low risk	High Risk	Low risk	Low risk	Low risk

	"The randomization sequence was computer generated and blocked to yield equal allocation of every 50 participants without stratification,". The SNOSE method was used.	"Upon completion of the baseline assessment, participants met with the study counselor and underwent randomization. The study counselor would open the next consecutively numbered randomization envelope..."	Both participants and personnel knew of allocation during study.	"outcome assessments were conducted in person at the medical center by a trained research coordinator (RW) who was kept blind to participants' group assignments"	Attrition rate=5% in experimental (42 completers out of 44), 19% in control (39 completers out of 48). 1 due to travel, 1 due to burden and 9 due to unknown reasons. Intention to treat analysis done. No other exclusions from analysis.	All outcomes reported
(Cosio et al., 2011)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	No description provided.	No description provided.	Psychologists were nested in, rather than crossed with, treatment arm. This was done to avoid the influence of systematic therapist effects, such as treatment preferences, therapeutic orientation, or incremental therapist bias resulting from observation of the superiority of one treatment over another".	"To facilitate preservation of the blinding, all assessment interviews commenced with a request by the interviewer that the participants not discuss any aspects of their treatment"	Attrition= T-CBT:5% (59 completers of 62), T-SEFT:6% (61 completers of 65). Drop-outs: 6 due to desire to drop out,1 due to deterioration in mental health due to external trauma. Intention to treat analysis done. 3 in T-CBT and 4 in T-SEFT did not complete follow up assessments so were excluded from analysis.	All outcomes reported
(Egner et al., 2003)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk
	No description provided.	No description provided.	No description provided.	Unclear if "separate" indicates blinding: "interviews were conducted by telephone only and were completely separate from the intervention interviews"	0% attrition	All outcomes reported
(Finlayson et al., 2011)	High Risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk

	Was not described if they w ere randomly prepared: "One hundred and forty opaque envelopes w ere prepared in advance of recruitment"	As consent forms w ere returned to the study office, they w ere numbered sequentially and matched to one of the opaque envelopes. When the research assistant contacted the participant, the appropriate envelope w as opened and the participant"...[w as randomised]	No description provided	No description provided	Attrition=E:18% (77 completers of 94), C=4% (92 completers of 96).	All outcomes reported
(Mohr et al., 2000)	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	High Risk
	No description provided	No description provided	No description provided	Assessment conducted by a "clinical evaluator", w ith suggestion that they w here unaw are of blinding.	Attrition E=31% (11/16 completers), C=25% (12/16 completers). 5 dropped out due to inability to make phone appointments, 3 declined final assessment, 1 in the control group died.	Short-D and GNDS not reported
(Mohr et al., 2005)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	No description provided.	No description provided.	Psychologists w ere nested in, rather than crossed w ith, treatment arm. This w as done to avoid the influence of systematic therapist effects, such as treatment preferences, therapeutic orientation, or incremental therapist bias resulting from observation of the superiority of one treatment over another".	"To facilitate preservation of the blinding, all assessment interview s commenced w ith a request by the interview er that the participants not discuss any aspects of their treatment"	Attrition= T-CBT:5% (59 completers of 62), T-SEFT:6% (61 completers of 65). Drop-outs: 6 due to desire to drop out,1 due to deterioration in mental health due to external trauma. Intention to treat analysis done. 3 in T-CBT and 4 in T-SEFT did not complete follow up assessments so were excluded from analysis.	All outcomes reported
(Mohr et al., 2007)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk

	No description provided.	No description provided.	Psychologists were nested in, rather than crossed with, treatment arm. This was done to avoid the influence of systematic therapist effects, such as treatment preferences, therapeutic orientation, or incremental therapist bias resulting from observation of the superiority of one treatment over another".	"To facilitate preservation of the blinding, all assessment interviews commenced with a request by the interviewer that the participants not discuss any aspects of their treatment"	Attrition= T-CBT:5% (59 completers of 62), T-SEFT:6% (61 completers of 65). Drop-outs: 6 due to desire to drop out,1 due to deterioration in mental health due to external trauma. Intention to treat analysis done. 3 in T-CBT and 4 in T-SEFT did not complete follow up assessments so were excluded from analysis.	All outcomes reported
(Turner et al., 2014)	Low risk	Low risk	Unclear risk	Low risk	Low risk	High Risk
	"..individuals were individually randomized via computer algorithm to the intervention or the control condition"	Appears participants were allocated by the same computer algorithm that generated the sequence.	Unclear what personell knew of allocation after assignment. "Prior to assignment, treatment condition was unknown to the project coordinator to ensure concealment of allocation."	"Treatment condition was concealed from the telephone interviewer for all outcome assessments"	Attrition=0%. All included in analysis.	Only medication adherence reported, no other outcomes

* The Berger (2005) study had an additional unclear bias: Research was funded by "Biogen, Inc" who manufacture Avonex, with adherence to this medication being the primary outcome. However, the authors declare no financial conflict of interests. SNOSE: Sequentially numbered sealed envelopes

Figure 2. Methodological quality summary: review authors' judgements about each study's methodological quality. A positive symbol indicates low risk, a negative symbol indicates high risk and a question mark indicates unclear risk.

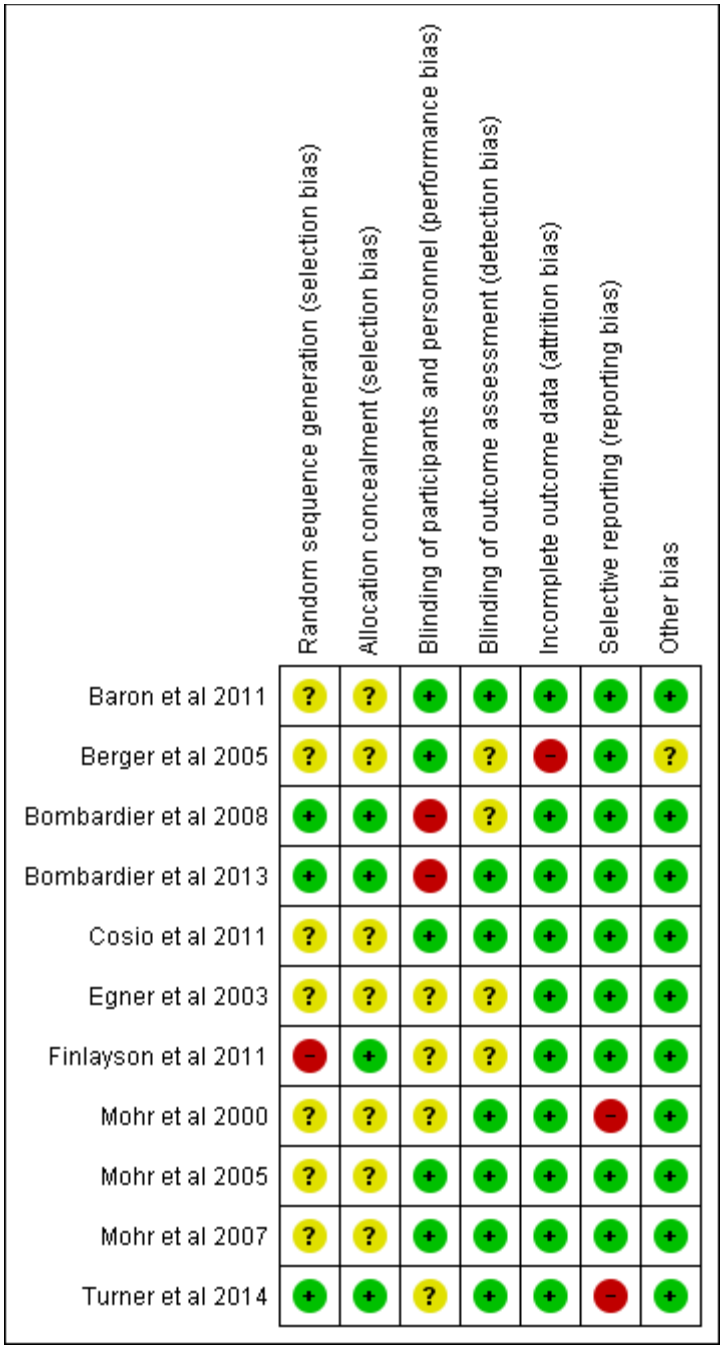
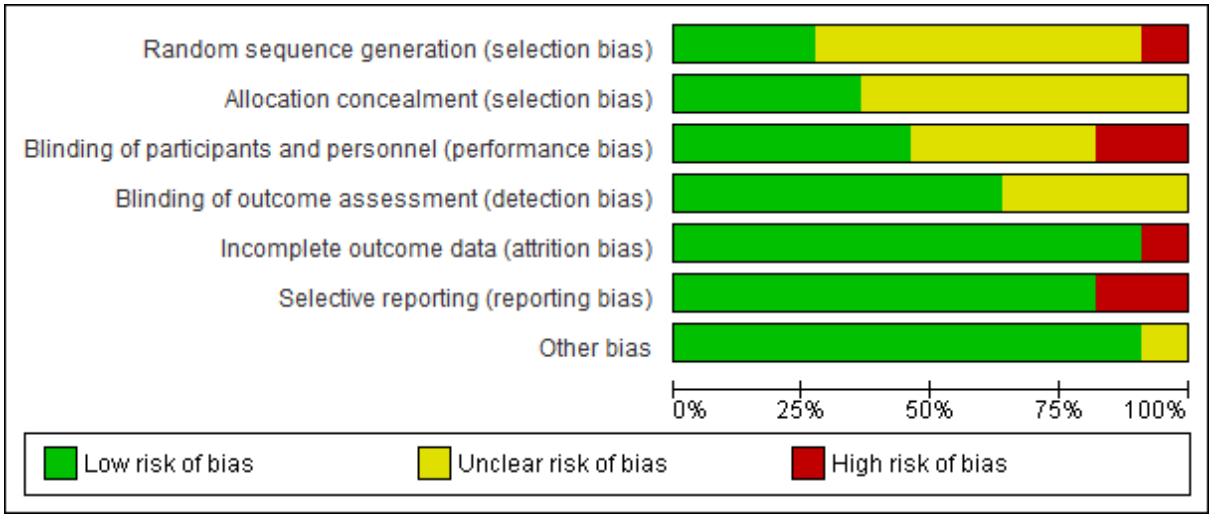


Figure 3. Methodological quality graph: review authors' judgements about each study's methodological quality item presented as percentages across all included studies.



Comparisons were split into two categories: comparisons of telephone-psychotherapy to waiting lists or no intervention controls and comparisons of telephone cognitive-behaviour therapy (T-CBT) to Telephone Support Emotion Focused Therapy (T-SEFT).

Of the included studies, one was not considered for the meta-analysis: The Baron study (Baron, Corden, Jin, & Mohr, 2011) was not included because it did not present sufficient data on between-group differences. It reported no significant difference between the T-CBT and T-SEFT groups on insomnia, measured using the three insomnia sub-items of the HDRS (Hamilton, 1960).

Where applicable, visual inspections of funnel plots revealed symmetrical distributions.

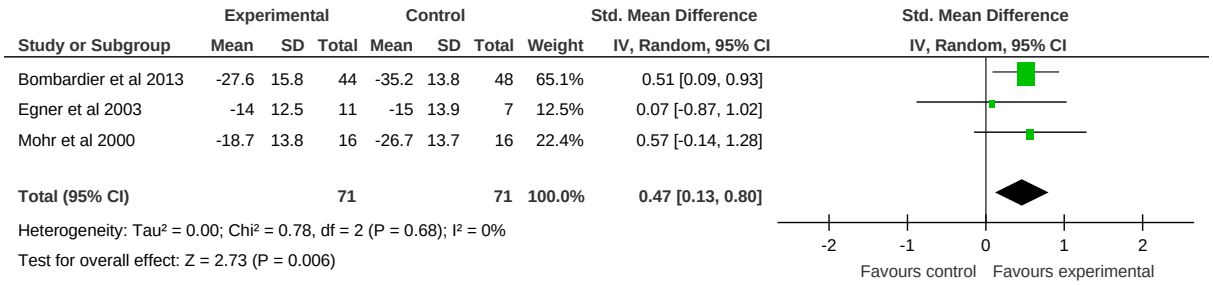
Comparisons of interventions to waiting list or no intervention controls

Depression

Three studies (Bombardier et al., 2013; Egner et al., 2003; Mohr et al., 2000) included short-term measures of depression using HDRS (Hamilton, 1960), Centre for Epidemiologic Studies Depression Scale (CES-D) (Orme, Reis, & Herz, 1986) and the BDI (Beck et al., 1988). A moderate effect on depression was found (SMD of

0.47 (95% CI of 0.21 to 0.73)), as seen in figure 4 below. Statistical heterogeneity assessed using I^2 was 0%. The Egner study (Egner et al., 2003) included long-term measurement of depression using the CES-D (Orme et al., 1986). A small non-significant treatment effect was found on depression favouring the control group (SMD of -0.33, (95% CI of -1.22 to 0.56)).

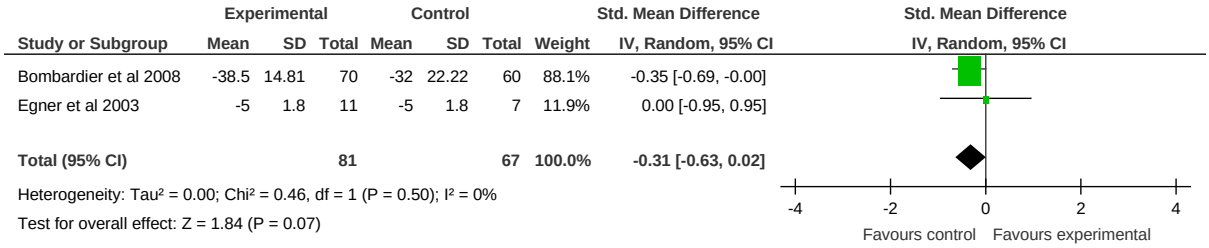
Figure 4. Forest plot showing results of studies with outcomes of short-term measures of depression.



Fatigue

The Finlayson study (Finlayson et al., 2011) reported short-term effect estimates and standard errors for three subscales of the Fatigue Impact Scale (FIS) (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994). The three subscales were converted into effect sizes and averaged, taking into account the sub-scale intercorrelation of 0.87 (Fisk, Ritvo, et al., 1994). A moderate composite effect size was found in favour of the intervention (SMD of 0.49 (95% CI 0.82 to 0.17)). One of the two Bombardier studies (Bombardier et al., 2008) and the Egner study (2003) reported short-term continuous data on fatigue using the Modified Fatigue Impact Scale (MFIS) (Fisk, Ritvo, et al., 1994) and the Fatigue Severity Scale (FSS) (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). A small non-significant effect favouring the control was found (SMD of -0.31 (95% CI of -0.63 and 0.02), as seen in figure 5 below. Statistical heterogeneity assessed using I^2 was 0%. The Egner study (2003) reported on the long-term effects on fatigue on the FSS (Krupp et al., 1989), with no effect found (SMD of 0.00 (95% CI of -0.95 and 0.95)).

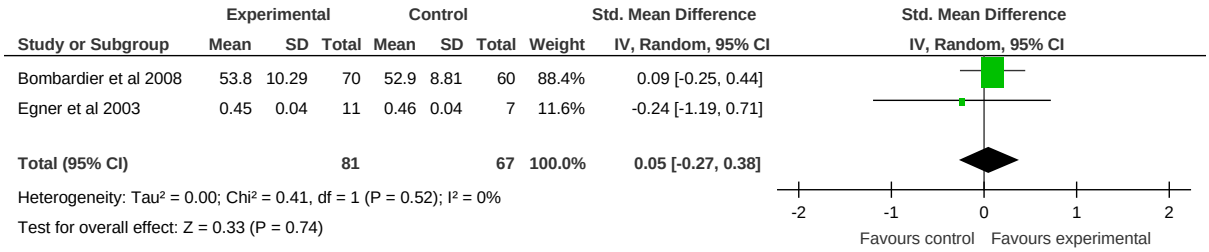
Figure 5. Forest plot showing results of studies with outcomes of short-term measures of fatigue.



Quality of life

Two studies (Bombardier et al., 2008; Egner et al., 2003) reported short-term data on QOL using the Short Form 36 measure (SF36) (Jenkinson, Coulter, & Wright, 1993) and the Quality of Wellbeing Scale (QWB) (McDowell, 2006). No effect was found (SMD of 0.05 (CI 95% of -0.27 to 0.38)), as shown in figure 6 below. Statistical heterogeneity assessed using I^2 was 0%.

Figure 6. Forest Plot showing results of studies with outcomes of short-term measures of QOL.



The Egner study (2003) reported long-term continuous data on QOL, using the QWB (McDowell, 2006), finding no effect (SMD of 0.00 (95% CI of -0.95 and 0.95)).

Medication adherence

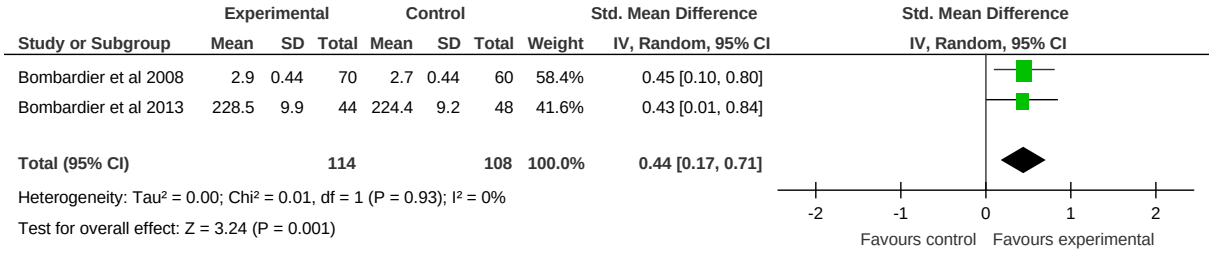
The Berger study (2004) study reported dichotomous data on medication adherence: the number of participants who had stopped taking their medication. A significant but negligible effect was found (SMD of 0.12 (95% CI of 0.03 and 0.54). The Turner study (2014) reported continuous data on medication adherence, asking how often participants had missed doses in the last month. A small non-significant effect was found in favour of the intervention (SMD of 0.33 (95% CI of -0.6 and 1.27). The same study reported long-term effects of medication adherence, finding a large but non-

significant effect in favour of the intervention (SMD of 0.89 (95% CI of -0.09 and 1.88)).

Physical health

Both Bombardier studies (2008; 2013) reported data on the short-term effects on physical health, using the Health Promotion Lifestyles Profile (HPLP-II) (Walker, Sechrist, & Pender, 1987,) and the 7 day physical activity recall measure (7-Day Par) (Sallis et al., 1985). A small effect was found favouring the intervention (SMD 0.44 (95% CI of 0.17 and 0.71)), as seen in figure 7 below. Statistical heterogeneity assessed using I^2 was 0%.

Figure 7. Forest Plot showing results of studies with outcomes of short-term measures of physical health.



One Bombardier study (2013) included short-term measures of MS symptoms using the MS-Related Symptoms Checklist (Gulick, 1989). A moderate effect was found favouring the intervention (SMD of 0.51 (95% CI of 0.09 and 0.93)).

Comparisons of T-CBT to T-SEFT

One Mohr study (2005) included short-term measures of depression, using the BDI (Beck et al., 1988). A small non-significant effect was found favouring T-CBT (SMD of 0.33 (95% CI of -0.03 to 0.69)) compared to T-SEFT. The same study included long-term measures of depression, using the BDI (Beck et al., 1988). No effect was found favouring either intervention (SMD of 0.06 (95% CI of -0.3 to 0.43)).

One Mohr study (2007) reported on short-term measures of fatigue, using the FIS (Fisk, Pontefract, et al., 1994). A small non-significant effect was found favouring T-CBT over T-SEFT (SMD of 0.18 (95% CI of -0.18 to 0.54)).

The Cosio study (2011) included short-term measures of QOL, which was a single-item question about QOL. A moderate effect favouring the T-CBT over T-SEFT was found (SMD of 0.60 (95% CI of 0.43 to 0.84)).

Discussion

There is some mixed and poor quality evidence that suggest that providing telephone-psychotherapy to people with MS has small-to-moderate benefits on depression, fatigue, physical activity, medication adherence and MS symptoms in the short-term. This finding appears to be roughly comparable to other systematic reviews of telephone therapies in chronic and neurological populations (Hailey et al., 2011; Johansson & Wild, 2011; Leach & Christensen, 2006), which also offer tentative evidence for the potential effectiveness of the intervention.

Where follow-up data were available, initial gains were not sustained in the long-term after the termination of telephone-psychotherapy. The results suggest there is some mostly poor quality evidence that providing T-CBT over T-SEFT will have small benefits on short-term QOL.

Overall, the majority of trials were of poor quality, with no studies fully adhering to the CONSORT guidelines (Moher, Schulz, & Altman, 2001). Mostly of small and moderate sample sizes, the majority of RCTs had high or unclear risks of selection bias and performance bias. Just over half had a low risk of detection bias. However, attrition, reporting and other biases were relatively low. All studies had at least one high or unclear risk of bias.

Like other systematic reviews, there is risk of potential publication bias. Any RCTs without positive results may not have been picked up by the search strategy. However, funnel plots of multiple comparisons were symmetrical, suggesting this may not be the case. The results of this study support the notion that many psychological variables in MS are correlated, as telephone-psychotherapy produced similar effects across different outcomes. Other psychosocial and functional outcomes may respond to similarly to telephone-psychotherapy. Due to limited data, sub-analyses on how sub-type of MS diagnosis, frequency of telephone calls or theoretical approach of therapy may interact with telephone-psychotherapy were not conducted. Future research may address these areas in hope of exploring what formats of therapy are most effective for whom.

Almost all studies were based on a specific psychological theory or model, commonly motivational interviewing or cognitive behaviour therapy, and demonstrate a similar small effect on psychological outcomes. However, the intervention in one

trial (Finlayson et al., 2011) only very briefly alluded to cognitive-behavioural principles and it was not at all explicit. Nevertheless, one could cautiously conclude that the specific theoretical modality of the telephone-support offered does not impact significantly upon outcome, much like face-to-face psychotherapy (Wampold et al., 1997). Although little evidence exists, it may be the case that, like face-to-face therapy (Norcross, 2002), telephone-psychotherapy relies upon therapeutic alliance for outcome change. Evidence for this comes from a study where better therapeutic alliance was found to predict better outcomes in telephone-psychotherapy for people with MS and depression (Beckner, Vella, Howard, & Mohr, 2007). Therapeutic alliance may feasibley be modified by frequency and intensity of telephone calls.

Overall, the current literature on telephone-psychotherapy for people with MS is sparse and methodologically poor, with most trials not adhering to CONSORT guidelines (Moher et al., 2001). Clinicians and researchers may recognise that telephone-psychotherapy interventions can have small-to-moderate short-term effects on mental and physical well-being. However, more well-conducted and reported RCTs following published guidance in this area are needed. Although not possible in this review due to small sample sizes and lack of information of diagnosing criteria, future reviews may also attempt to conduct sub-group analyses by MS sub-type or level of disability, theoretical approach and frequency/intensity of telephone support. Given potential advantages in terms of increased accessibility and reduced cost in telephone-based psychotherapy, findings to date warrant further investigation.

References

Baron, K. G., Corden, M., Jin, L., & Mohr, D. C. (2011). Impact of psychotherapy on insomnia symptoms in patients with depression and multiple sclerosis. *Journal of behavioral medicine*, *34*, 92–101.

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical psychology review*, *8*, 77–100.

Beckner, V., Vella, L., Howard, I., & Mohr, D. C. (2007). Alliance in two telephone-administered treatments: Relationship with depression and health outcomes. *Journal of consulting and clinical psychology*, *75*, 508.

Bee, P. E., Bower, P., Lovell, K., Gilbody, S., Richards, D., Gask, L., & Roach, P. (2008). Psychotherapy mediated by remote communication technologies: a meta-analytic review. *BMC psychiatry*, *8*, 60.

Berger, B. A., Liang, H., & Hudmon, K. S. (2004). Evaluation of software-based telephone counseling to enhance medication persistency among patients with multiple sclerosis. *Journal of the American Pharmacists Association: JAPhA*, *45*, 466–472.

Blazer, D. G., & Kessler, R. C. (1994). The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *Age (years)*, *15*, 24–27.

Bombardier, C. H., Cunniffe, M., Wadhwani, R., Gibbons, L. E., Blake, K. D., & Kraft, G. H. (2008). The efficacy of telephone counseling for health promotion in people with multiple sclerosis: a randomized controlled trial. *Archives of physical medicine and rehabilitation*, *89*, 1849–1856.

Bombardier, C. H., Ehde, D. M., Gibbons, L. E., Wadhwani, R., Sullivan, M. D., Rosenberg, D. E., & Kraft, G. H. (2013). Telephone-based physical activity counseling for major depression in people with multiple sclerosis. *Journal of consulting and clinical psychology*, *81*, 89.

Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. (2014). Review Manager.

Cosio, D., Jin, L., Siddique, J., & Mohr, D. C. (2011). The Effect of Telephone-Administered Cognitive–Behavioral Therapy on Quality of Life among Patients with Multiple Sclerosis. *Annals of Behavioral Medicine*, *41*, 227–234.

Dorstyn, D., Mathias, J., & Denson, L. (2013). Applications of telecounselling in spinal cord injury rehabilitation: a systematic review with effect sizes. *Clinical rehabilitation*, 1072–1083.

Egner, A., Phillips, V. L., Vora, R., & Wiggers, E. (2003). Depression, fatigue, and health-related quality of life among people with advanced multiple sclerosis: results from an exploratory telerehabilitation study. *NeuroRehabilitation*, *18*, 125–133.

Finlayson, M., Preissner, K., Cho, C., & Plow, M. (2011). Randomized trial of a teleconference-delivered fatigue management program for people with multiple sclerosis. *Multiple Sclerosis Journal*, *17*, 1130–1140.

Fisk, J. D., Pontefract, A., Ritvo, P. G., Archibald, C. J., & Murray, T. J. (1994). The impact of fatigue on patients with multiple sclerosis. *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques*, *21*, 9–14.

Fisk, J. D., Ritvo, P. G., Ross, L., Haase, D. A., Marrie, T. J., & Schlech, W. F. (1994). Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clinical Infectious Diseases*, *18*, S79–S83.

Gulick, E. E. (1989). Model confirmation of the MS-related symptom checklist. *Nursing research*, *38*, 147–153.

Hailey, D., Roine, R., Ohinmaa, A., & Dennett, L. (2011). Evidence of benefit from telerehabilitation in routine care: a systematic review. *Journal of telemedicine and telecare*, *17*, 281–287.

Hailey, D., Roine, R., Ohinmaa, A., & Dennett, L. (2013). The status of telerehabilitation in neurological applications. *Journal of telemedicine and telecare*, 307–310.

Hamilton, M. (1960). A rating scale for depression. *Journal of neurology, neurosurgery, and psychiatry*, *23*, 56.

Higgins, J. P. T., & Green, S. (2008). *Cochrane handbook for systematic reviews of interventions* (Vol. 5). Wiley Online Library.

Jenkinson, C., Coulter, A., & Wright, L. (1993). Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. *BMJ: British Medical Journal*, *306*, 1437.

Johansson, T., & Wild, C. (2011). Telerehabilitation in stroke care–a systematic review. *Journal of telemedicine and telecare*, *17*, 1–6.

Khan, F., Turner-Stokes, L., Ng, L., & Kilpatrick, T. (2007). Multidisciplinary rehabilitation for adults with multiple sclerosis. *Cochrane Database Syst Rev*, *2*.

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of neurology*, *46*, 1121–1123.

Leach, L. S., & Christensen, H. (2006). A systematic review of telephone-based interventions for mental disorders. *Journal of telemedicine and telecare*, *12*, 122–129.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., … Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Annals of internal medicine*, *151*, W–65.

McDowell, I. (2006). *Measuring health: a guide to rating scales and questionnaires*. Oxford University Press.

Mistry, H. (2012). Systematic review of studies of the cost-effectiveness of telemedicine and telecare. Changes in the economic evidence over twenty years. *Journal of telemedicine and telecare*, *18*, 1–6.

Moher, D., Schulz, K. F., & Altman, D. G. (2001). The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC Medical Research Methodology*, *1*, 2.

Mohr, D. C., Hart, S. L., Julian, L., Catledge, C., Honos-Webb, L., Vella, L., & Tasch, E. T. (2005). Telephone-administered psychotherapy for depression. *Archives of General Psychiatry*, *62*, 1007.

Mohr, D. C., Hart, S., & Vella, L. (2007). Reduction in disability in a randomized controlled trial of telephone-administered cognitive-behavioral therapy. *Health Psychology*, *26*, 554.

Mohr, D. C., Likosky, W., Bertagnolli, A., Goodkin, D. E., Van Der Wende, J., Dwyer, P., & Dick, L. P. (2000). Telephone-administered cognitive–behavioral therapy for the treatment of depressive symptoms in multiple sclerosis. *Journal of consulting and clinical psychology*, *68*, 356.

Mohr, D. C., Vella, L., Hart, S., Heckman, T., & Simon, G. (2008). The Effect of Telephone-Administered Psychotherapy on Symptoms of Depression and Attrition: A Meta-Analysis. *Clinical Psychology: Science and Practice*, *15*, 243–253.

MS Trust. (2015). Prevalence and incidence of multiple sclerosis. Retrieved October 16, 2015, from https://www.mstrust.org.uk/a-z/prevalence-and-incidence-multiple-sclerosis

NICE. (2003). *CG8 Multiple sclerosis: NICE guideline*. London: National Institute for Clinical Excellence.

Norcross, J. C. (2002). *Psychotherapy relationships that work: Therapist contributions and responsiveness to patients.* Oxford University Press.

Orme, J. G., Reis, J., & Herz, E. J. (1986). Factorial and discriminant validity of the center for epidemiological studies depression (CES-D) scale. *Journal of clinical psychology*, *42*, 28–33.

Paré, G., Jaana, M., & Sicotte, C. (2007). Systematic review of home telemonitoring for chronic diseases: the evidence base. *Journal of the American Medical Informatics Association*, *14*, 269–277.

Rosenthal, R., & Rubin, D. B. (1986). Meta-analytic procedures for combining studies with multiple effect sizes. *Psychological bulletin*, *99*, 400.

Sallis, J. F., Haskell, W. L., Wood, P. D., Fortman, S. P., Rogers, T., Blair, S. N., & Paffenbarger, R. S. (1985). Physical activity assessment methodology in the Five-City Project. *American journal of epidemiology*, *121*, 91–106.

Thomas, P. W., Thomas, S., Hillier, C., Galvin, K., & Baker, R. (2006). Psychological interventions for multiple sclerosis. *Cochrane Database Syst Rev*, CD004431.

Turner, A. P., Sloan, A. P., Kivlahan, D. R., & Haselkorn, J. K. (2014). Telephone counseling and home telehealth monitoring to improve medication adherence: Results of a pilot trial among individuals with multiple sclerosis. *Rehabilitation Psychology*, *59*, 136–146.

Walker, S. N., Sechrist, K. R., & Pender, N. J. (1987). The health-promoting lifestyle profile: development and psychometric characteristics. *Nursing research*, *36*, 76–81.

Wampold, B. E., Mondin, G. W., Moody, M., Stich, F., Benson, K., & Ahn, H. (1997). A meta-analysis of outcome studies comparing bona fide psychotherapies: Empiricially," all must have prizes." *Psychological bulletin*, *122*, 203.

Wilkinson, H. R., & das Nair, R. (2013). The psychological impact of the unpredictability of multiple sclerosis: a qualitative literature meta-synthesis. *British Journal of Neuroscience Nursing*, *9*, 172–178.

Journal article

Abstract

Objective: Telephone-supported self-help Acceptance and Commitment Therapy (ACT) may be a way of providing accessible and effective psychotherapy to people with Multiple Sclerosis (MS). The aim of this trial was to determine the feasibility of a randomised controlled trial (RCT) of telephone-supported ACT bibliotherapy compared to treatment-as-usual (TAU), and explore the effectiveness of the intervention.

Research Design: The study was a randomised controlled feasibility trial. The intervention was eight weekly support calls guiding participants through an ACT self-help text. Participants were assessed at baseline and post-intervention using the Generalised Anxiety Disorder Measure (GAD) and the Patient Health Questionnaire (PHQ) as primary outcome measures. The EuroQol (EQ-5D-5L) and Multiple Sclerosis Impact Scale (MSIS-29) were secondary outcome measures, and the Acceptance and Action Questionnaire (AAQ-II) was a process measure. A sample of participants were interviewed to assess RCT feasibility, using framework analysis.

Results: Twenty seven participants with MS with anxiety and/or depression were recruited from an outpatient MS clinic and an MS charity. The majority of participants found the different elements of the RCT acceptable. Overall attrition was 33%, and 64% in the intervention group. Linear mixed model analysis and effect size calculation found a significant effect (p=0.004) and large effect size (0.84 (95% confidence intervals 0.02-1.66)) at post-intervention in favour of the intervention on anxiety. Smaller non-significant positive effects were found on other measures. Intervention completers had significantly lower baseline scores on the MSIS and the AAQ-II.

Conclusions: Telephone-supported ACT bibliotherapy delivered in a RCT format may be a feasible research method for people with MS if significant changes to the method of delivery are made. The intervention has the potential to be effective in reducing anxiety, however there are limitations in sample size. Future research directions and the applicability of ACT in this population are discussed.

Key words: Acceptance and Commitment Therapy, Multiple Sclerosis, Teletherapy, Bibliotherapy, Randomised Controlled Trial, Guided Self-help.

Impact and Implications Statement

- This paper provides tentative evidence that ACT-based teletherapy and bibliotherapy interventions are feasible and potentially effective for people with Multiple Sclerosis in reducing anxiety.
- If significant changes to study design are made, a full trial of telephone-supported self-help Acceptance and Commitment Therapy for people with MS and psychological distress may be warranted.

Introduction

Multiple Sclerosis

Multiple Sclerosis (MS) is a central nervous system disease in which white matter is inflamed or destroyed by the immune system. It is estimated there are more than 100,000 people in the UK who are currently diagnosed with MS (MS Trust, 2015). The majority of those with MS have a relapsing-remitting form, whereby symptoms develop during a relapse, typically lasting two to six weeks, before remitting. Eventually, symptoms become permanent and the condition becomes worse over time, which is called secondary progressive MS.

MS can have diverse and unpredictable effects on psychological wellbeing (Wilkinson & das Nair, 2013), thus there is a need for accessible and effective psychotherapeutic support. Psychological and psychosocial problems frequently arise in areas such as physical functioning, fatigue, pain, cognition, and problems with support from others (Khan, Turner-Stokes, Ng, & Kilpatrick, 2007). These types of problems are thought to be highly prevalent in the MS population; for example, a recent study found a 41.8% point prevalence of depression in a large sample of people with MS, related to severity of disease (Chwastiak et al., 2014). This is higher than other neurological conditions, such as 33% lifetime prevalence after stroke (Hackett, Yapa, Parag, & Anderson, 2005), 17% in Parkinson's disease (Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008) and is higher than in the general population (16.2%) (Kessler et al., 2003). The lifetime prevalence of anxiety in MS is estimated at 37.5% (Korostil & Feinstein, 2007). Psychological distress may arise through various interacting pathways, making its precise aetiology difficult to discern.[1]

Many people with MS already take multiple medications for their condition and physical sequelae, so any pharmacological management of mood problems would add to their medical regimen. Psychological interventions, which have potential to be effective in this population (Thomas, Thomas, Hillier, Galvin, & Baker, 2006) may provide an alternative, or even preferred treatment.[2]

[1] See Extended Introduction 1.1 for further details on MS and the aetiology of psychological distress.
[2] See Extended Introduction 1.2 for further details on MS and psychotherapy.

Acceptance and Commitment Therapy

Acceptance and Commitment Therapy (ACT) is a model of therapy in the third-wave of Cognitive-Behavioural Therapies (CBT) and may be efficacious across a broad range of physical and psychological symptoms (Davis, Morina, Powers, Smits, & Emmelkamp, 2015). The authors present a meta-analysis of 39 RCTs and conclude ACT is effective in treating difficulties with anxiety, depression and somatic health problems. However, the RCTs reviewed were ACT against treatment-as-usual or placebo conditions and more research is needed on the effect of ACT on quality of life (QoL) outcomes. ACT is designed to improve functioning and QoL by increasing a person's ability to act in accordance with personally held values (Hayes, Strosahl, & Wilson, 1999). The model views experiential avoidance as a core pathogenic process, and attempts to increase acceptance of negative experiences and 'de-fuse' thoughts from feelings (Dahl, Wilson, & Nilsson, 2004).

Hayes and colleagues (2006) set out the six core processes of the ACT model. "Acceptance" is described as experiential engagement, rather than avoidance. "Cognitive defusion" is an attempt to change one's relationship or perspective on thoughts, without trying to alter their form. "Being present" is defined less clearly, but makes reference to a "non-judgemental" approach to psychological events, and mindfulness techniques. "Self-as-context" is a shift in standpoint away from the self as the central perspective. "Values" are chosen actions or directions in life. Lastly, "Committed Action" is the encouragement of the aforementioned values. As stated by the authors, "Values" and "Committed Action" are concepts and techniques very similar to behavioural theories of psychology and their associated psychotherapeutic techniques.

ACT may be particularly suited to those with chronic physical health conditions, as traditional CBT thought challenging of beliefs around illness and symptoms may be limited when such cognitions could be accurate (Dennison, Moss-Morris, & Chalder, 2009). Furthermore, there is evidence that avoidant coping strategies predict poor outcomes (Pakenham, 1999), and acceptance is the strongest predictor of adjustment to MS (Pakenham, 2006).

There is some limited literature suggesting the potential effectiveness of ACT for psychological problems related to MS.[3] Twelve weeks after a group ACT intervention for people with MS, significant improvements were observed in depression (np^2 = .29), extent of thought suppression (np^2 = .35), impact of pain on behaviour (np^2 = .37) and QoL (np^2 = .34) in participants, although no change on physical symptoms and mindfulness were observed (Sheppard, Forsyth, Hickling, & Bianchi, 2010). The study had a small sample size of 15 participants, no control group and the intervention was a one-off half-day session.

An RCT of ACT compared to relaxation therapy in MS outpatients with elevated symptoms of anxiety and/or depression (n=210) found no significant advantage of ACT over relaxation therapy on any outcome variable (Nordin & Rorsman, 2012). However within-group analyses on the ACT group showed improvement in BDI scores from pre-treatment to post treatment ($z = 2.2$, $p < 0.05$), and a maintained improvement in on the Acceptance and Action Questionnaire (AAQ-II) at post-treatment ($z = 2.2$, $p < 0.05$) and 3 month follow up ($z = 2.1$, $p < 0.05$).

Teletherapy

Aside from the traditional face-to-face provision of ACT therapy, other formats of delivery need to be investigated: this is due to the costs of providing ACT in this format and because of a lack of services (particularly for those who live in remote or rural areas). Furthermore, those with MS may not be able to access face-to-face psychological therapies due to the fatigue and reduced ability to travel associated with their condition. Telephone-psychotherapy (teletherapy) is an intervention that offers the opportunity to deliver psychological therapies to people in their own home. A recent systematic review and meta-analysis of the effectiveness of telephone-based psychotherapies for people with MS, compared to those receiving no treatment, standard care or other control, found a positive effect of the intervention on psychological outcomes, such depression, fatigue, quality of life (QoL), MS-symptoms, physical activity and medication adherence (Proctor, Moghaddam, Vogt & das Nair, in press). The therapies were largely CBT-orientated. A moderate effect size (SMD = 0.47, 95% CI 0.21- 0.73) of the intervention on depression was found, for example. Effects on anxiety could not be reviewed due to a lack of eligible

[3] See Extended Introduction 1.3 for ACT theory and research.

studies. Reviewed studies were of poor methodological quality, and the authors recommend studies of better methodological quality are required.[4]

Bibliotherapy

Bibliotherapy (self-help text) is another common alternative or adjunct to face-to-face therapy, which can be supplemented with teletherapy. Meta-analysis has shown bibliotherapy can improve psychological outcomes in mood disorders compared to control conditions (Den Boer, Wiersma, & Bosch, Van den, 2004). Within the MS population, a trial of an eight week telephone-supported CBT bibliotherapy compared to usual care where participants received a workbook and telephone-support found significant reductions in depression outcomes (Mohr et al., 2000).[5] However, the trial was specific to those with diagnoses of depression and did not consider the multitude of other mental health problems those in this population are vulnerable to, such as difficulties with anxiety.

Aims

A telephone-supported ACT bibliotherapy may be an effective and accessible way of delivering psychotherapy to people with MS and psychological distress. There have been no studies that have examined whether this format of ACT intervention is feasible within this population. The primary aim of this study was to explore the feasibility of people with MS and psychological distress completing a randomised control trial (RCT) of telephone-supported ACT bibliotherapy plus treatment as usual (TAU), compared with a control group receiving TAU. Secondary to this, was an exploration of between and within group differences, to generate parameters for designing future studies. [6]

[4] See Extended Introduction 1.4 for more information regarding teletherapy.
[5] See Extended Introduction 1.5 for more information regarding bibliotherapy.
[6] See Extended Introduction 1.6 for further details of the study aims and epistemology.

Methods

Participants

We aimed to recruit between 25 and 30 participants in order to generate significant parameters to design a full trial and allow for expected attrition (Julious, 2005; Lancaster, Dodd & Williamson, 2004).[7] Participants were recruited through a neurology outpatient clinic at an acute National Health Service (NHS) hospital in Nottingham, UK, and through an advertisement placed in a regional MS Society publication. Participants were adults with a verified diagnosis of MS, not within the last twelve months. Participants were screened for psychological distress using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983), which captures experiences of anxiety and depression. They were eligible if they scored above seven on their combined anxiety and depression score, indicating mild, moderate or severe distress. Participants unable to read and write, and participants receiving other psychotherapy were excluded.[8] This study was approved by the NHS Research Ethics Committee and The University of Nottingham, UK.[9]

Assessment

Basic demographic details, time since MS diagnosis, time since last relapse, the most recent Expanded Disability Status Scale score (EDSS) (Kurtzke, 1983) and current medication were captured from clinical files. Participants also self-reported current medications and contacts with health services through a bespoke service-use questionnaire.[10]

Baseline assessments were administered to all participants before randomisation and were used again as outcome measures twelve weeks after randomisation. The primary quantitative measures were the generalised anxiety disorder scale (GAD) (Spitzer, Kroenke, Williams, & Löwe, 2006) and the patient health questionnaire (PHQ) (Kroenke, Spitzer, & Williams, 2001), which captured anxiety and depression. Secondary outcomes were the Multiple Sclerosis Impact Scale (MSIS-29) (Hobart, Lamping, Fitzpatrick, Riazi, & Thompson, 2001), which was split into physical and psychological sub-scales (Ramp, Khan, Misajon, & Pallant, 2009). The EQ-5D-5L

[7] See Extended Methods 2.1 and 2.2 for further details about recruitment and sample size.
[8] See Extended Methods 2.3 for further details on inclusion and exclusion criteria.
[9] See Extended Methods 2.9 for ethical considerations.
[10] See Extended Methods 2.4 for further details of assessments.

(Herdman et al., 2011) was administered to capture QoL outcomes. All quantitative measures were administered securely online using www.esurv.org, except the EQ-5D-5L which was administered and collected via post.

Design

The trial was a feasibility RCT. Participants were randomly allocated to one of two groups. The randomisation sequence was computer generated by one researcher (NM).[11] Once all baseline measures were completed, participant allocation was uncovered by a separate researcher (BP), not blind to allocation, who informed the participant.

The primary outcome of feasibility was obtained via telephone-interviews conducted with a sample of participants (n=10) at post-intervention. Maximum variation purposive sampling was used to select five participants from each group, with a total of ten participants sufficient in providing qualitative nuance to this primarily quantitative study.[12] They were administered by a trainee clinical psychologist (WV), who was familiar with the trial protocol and format of the ACT intervention, but not otherwise involved with the trial. Appendix E details the feasibility interview guide.

Intervention

The intervention arm consisted of TAU plus the self-help book "Get out of your mind and into your life" (Hayes & Smith, 2005) with a guide of what chapters to read each week. This coincided with eight weekly support calls, theoretically orientated to the ACT model, from a trainee clinical psychologist (BP), who supported participants in understanding the text and engaging in model. A pro-forma detailing the structure and content of the support calls is reproduced in Appendix D. The second arm consisted of solely TAU. The flowchart in Figure 8 details the flow of participants through the study.[13]

Analysis

[11] See Extended Methods 2.5 for further details of randomisation.
[12] See Extended Methods 2.6 for details of purposive sampling.
[13] See Extended Methods 2.7 for further details of trial procedure.

To assess feasibility, framework analysis of qualitative telephone interviews was undertaken by BP (as per Gale, Heath, Cameron, Rashid, & Redwood, 2013). Pre-defined codes about the feasibility of the study were assigned to transcripts of the interviews, then codes were summarised into a framework of feasibility. An example of this can be seen in Appendix F.

To assess the success of the randomisation process, allocation groups were analysed using independent t-tests and their non-parametric equivalents for significant differences of socio-demographic measures, self-report clinical psychometrics and clinic obtained measures.

Contact with health services was explored between groups using independent t-tests. Self-report medication was cross-referenced against medication recorded in clinical notes. EQ-5D-5L scores were converted into normed scores between -0.59 and 1, using UK EQ-5D-5L value sets (van Hout et al., 2012). Independent t-tests were conducted to explore baseline differences on intervention completers vs non-completers.

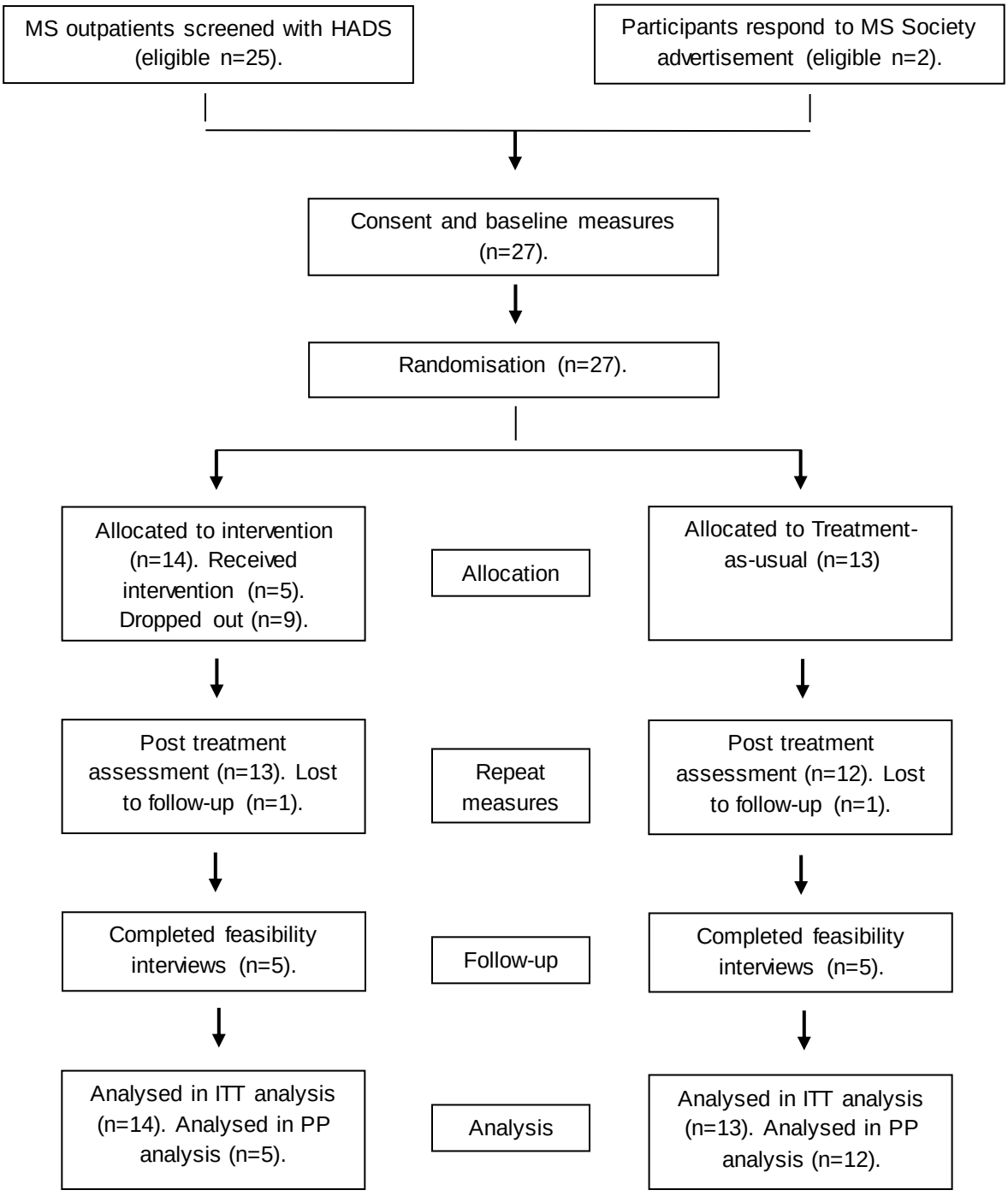
In intention-to-treat analysis, independent variables of 'group allocation' and 'time point' were entered into linear mixed models to explore interactions of intervention and time. Multiple comparisons were corrected with the Bonferroni method. Effect sizes were estimated through pooling standard deviations derived from estimated marginal means (Hedges, 2007).

Sample size estimates for a full trial were carried out using the standard deviations of the GAD and PHQ at post-intervention across all participants and published clinically significant change (CSC) values.[14]

[14] See Extended Methods 2.8 for full details of qualitative and quantitative analysis.

Figure 8. Flow of participants through the study

.



MS: Multiple Sclerosis, HADS: Hospital Anxiety and Depression Scale, ITT: Intention-to-treat, PP: Per-protocol.

Results

In the following section, where relevant, we have collated both quantitative and qualitative data under relevant sub-headings, rather than present these data separately, in order to provide a more integrated narrative and fuller description of each aspect of our findings.

Sample

Two participants responded to the advertisement in a regional MS Society publication. From the weekly neurology outpatient's clinic, consultants referred 33 patients to be recruited, 25 of whom consented, to make up 27 enrolled participants. Analysis used an intention-to-treat (ITT) approach. Overall demographic and baseline clinical characteristics of the sample are shown in Tables 3 and 4 below.

Normal distributions and homogeneity of variances were found in all groups. Independent t-tests and their non-parametric equivalents found no significant differences between the allocation groups.

The HADS was split into anxiety and depression sub-scales. Across all participants (n=27) a paired samples t-test found there was significantly higher levels of anxiety 11.5 (SD=3.1) than depression 8.2 (SD=3.7) as measured on the HADS subscales (t=3.827, p=0.001).[15]

[15] See Extended Results 3.1 for further analysis of baseline data.

Table 3. Baseline demographic characteristics of the control and intervention groups.

Characteristic	TAU group (n=13) *Mean (SD)*	Intervention group (n=14) *Mean (SD)*	p value
Age, years, mean *(SD)*	45.8 *(8.8)*	46 *(12.4)*	0.984a
Male/Female	0/13	3/11	0.22b
Diagnosis, *n* (%)			0.61c
Relapsing Remitting	10 (77%)	9 (64%)	
Primary Progressive	2 (15%)	2 (14%)	
Secondary Progressive	1 (8%)	3 (21%)	
Years since MS diagnosis *(SD)*	6.2 *(4.7)*	9.7 *(7.5)*	0.16a
Years since last relapse *(SD)*	2.5 *(1.9)*	2.2 *(3.9)*	0.83a
Marital Status			0.152c
Single	3	2	
Married/Civil Partnership	7	12	
Divorced/Dissolved Partnership	2	0	
Widowed	1	0	
Employment Status			0.746c
Full Time	3	2	
Part Time	3	3	
Unpaid Work	0	1	
Not Employed	6	5	
Retired	1	2	
In Education	0	1	

a=Independent t-test, b=Fisher's exact test, c=Pearson's chi squared.

Table 4. Baseline clinical characteristics of the control and intervention groups.

Characteristic	TAU (n=13) *Mean (SD)*	Intervention group (n=14) *Mean (SD)*	p value
HADS	18.5 *(5.5)*	20.8 *(4.8)*	0.24a
EDSS	4.9 *(2)*	5.4 *(1.6)*	0.51a
GAD	16.8 *(4.8)*	18.3 *(5)*	0.45a
PHQ	21.2 *(5.9)*	22.1 *(7.1)*	0.72a
MSIS-Physical	63.8 *(14.3)*	60.6 *(20.2)*	0.63a
MSIS-Psych	28.7 *(7.8)*	29.9 *(8.9)*	0.7a
EQ-5D-5L	0.356 *(0.253)*	0.408 *(0.292)*	0.62a
AAQ-II	23.8 *(12.9)*	27.4 *(9.5)*	0.41a

HADS: Hospital Anxiety and Depression Scale, EDSS: Expanded Disability Status Scale, EQ-5D: Quality of Life Measure, GAD: Generalised Anxiety Disorder Scale, PHQ: Patient Health Questionnaire, MSIS-Physical: Multiple Sclerosis Impact Scale - Physical health subscale, MSIS-Psych: Multiple Sclerosis Impact Scale - Psychological subscale, AAQ-II: Acceptance and Action Questionnaire, a: Independent t-test.

Feasibility

Although all interviewed participants (n=10) were asked the same questions in the feasibility interviews, not all participants made reference to all pre-defined codes of feasibility, therefore if reporting specific numbers of participants one could not assume the remaining participants thought the opposite. Thus the results of the framework analysis refer to the number of participants endorsing particular codes using the terms “majority”, “some” and “minority”, meaning more than 75%, 50-75% and under 50% respectively, of all participants who referenced that code, and not all 10 participants (Braun and Clarke, 2013).

Recruitment

The majority of interviewed participants found the pathway to recruitment appropriate and the recruitment process straightforward. A minority reported that they thought their neurologist using their appointment to speak about the trial was inappropriate. The majority thought the information provided by the recruiter (BP) was clear. A minority of participants reported they wanted more information about the commitment and work required from participants.

Randomisation

Whilst all interviewed participants agreed that randomisation was fair, some participants reported they did not fully understand of the minutia of the process.

Measures

After the intervention, 25 of 27 participants (93%) completed online questionnaires, and 24 participants (89%) completed postal questionnaires. On average, online questionnaires took 14 minutes to complete (SD=9).[16]

The majority of interviewed participants found the questions clear, easy and quick to complete, and thought questions asked were appropriate for the study. Some participants reported wanting more space to add text to clarify their responses, when they felt the options available did not accurately capture their experiences.

Self-report data

[16] See Extended Results 3.2 for details of missing data.

At post-intervention, 25 of 27 participants (93%) reported the amount of contacts they had with health services in the last three months that were specifically related to their MS. In the intervention group, the mean number of contacts was 10.8 (SD=6.6) and in the TAU group it was 7.4 (SD=6.2), which was not a significance difference (p=0.2). Across 23 participants self-reporting medications, there were 45 instances where clinical notes described a medication a participant had not listed. There were 20 instances where participants had self-reported a drug that was not listed in clinical notes.

Attrition

Overall, nine of 27 (33%) participants dropped out of the study. All nine were participants randomised to receive the intervention, therefore the attrition rate was 64% in this group. Of non-completers, six (66%) did not start the book at all and three (33%) dropped out after reading the first few chapters and receiving one support-call. Table 5 summarises the reasons participants did not complete the intervention. [17]

Table 5. Completers and non-completers in the intervention group.

	Intervention group (n=14)
Completed Intervention	5 (36%)
Non-completers:	9 (64%)
Too busy	4 (29%)
Lost to follow-up	2 (14%)
Book described as inappropriate	2 (14%)
Too unwell	1 (7%)

Independent t-tests of baseline characteristics between completers and non-completers revealed that non-completers scored significantly higher on the MSIS -physical and -psychological subscales, and the AAQ-II, as shown in Table 6.[18] However, these effects were not significant after correcting for multiple comparisons.

[17] See Extended Results 3.3 for further details of attrition reasons.
[18] See Extended Results 3.4 for details of assumption testing of quantitative data.

Table 6. Baseline characteristics of intervention completers and non-completers.

	Group		
	Completers (n=5)	**Non-completers (n=9)**	
Characteristic/Measure	Mean *(SD)*	Mean *(SD)*	p value
Age, (years)	51.8 *(6)*	42.7 *(14)*	0.2a
Years since MS diagnosis	11.2 (7.8)	8.9 (7.7)	0.62a
Years since last relapse	2.2 (2.6)	2.3 (4.4)	0.96a
Diagnosis, *n* (%)			0.9c
Relapsing Remitting	3	6	
Primary Progressive	1	1	
Secondary Progressive	1	2	
HADS	19.4 (4.6)	21.7 (5)	0.42a
EDSS**	4.5 (2)	5.8 (1.1)	0.3a
GAD7	15.2 (2.9)	20 (5)	0.85a
PHQ9	18.8 (6.9)	24 (6.9)	0.2a
MSIS-Physical	45.2 (15)	69 17.9)	0.027a*
MSIS-Psych	22.6 (7.6)	34 (6.9)	0.014a*
EQ-5D-5L	0.49 (0.18)	0.36 (0.33)	0.44a
AAQ-II	19.6 (6.9)	31.8 (7.9)	0.014a*
Service use (no of contacts)	8.4 (5)	12.2 (7.2)	0.28a

a=Student's t test, b=Fisher's exact test, c=Pearson's chi squared.

**completers: n=5; non-completers: n=8. *= significant at p=0.05

Support calls

Of the five participants who completed the self-help book, three (60%) received the eight scheduled support calls and completed the book within the expected seven weeks. Two (40%) received an extra phone call, due to not completing chapters within the allotted time period, therefore one participant (7%) took 10 weeks to complete the book and one participant (7%) took 12 weeks to complete the book.

The average time of a support call was 14 minutes (SD=6). Among participants completing the intervention, there was a total of eight from a possible 42 (19%) occasions where a participant rescheduled their scheduled support call time, and one occasion (2%) where a scheduled call was missed.

The majority of participants agreed that support calls were helpful, appropriate in their length and that the clinician was curious and friendly. Those completing the support calls agreed that either slightly less text to read each week, or calls spaced further apart would have been a better pace for the intervention.

Self-help text

The majority of interviewed participants found the language used in the self-help text understandable, and a few found it too complex. The majority thought that the language was "Americanised", and a considerable amount of re-reading was required. No participants reported they skipped ahead of the chapters they were scheduled to read.

With regards to the helpfulness of specific elements of the self-help text, there was disparity amongst the sample; e.g. one participant found the values chapter most helpful, one found mindfulness the most helpful, and one found mindfulness not helpful. The majority of interviewed participants thought that other people with MS would find the book and the phone support helpful. This included two participants who dropped out because of illness and other stresses.

Effectiveness

As shown in Table 7, ITT[19] linear mixed model analyses[20] found a significant interaction effect for time and allocation on the GAD in favour of the intervention at post-intervention (F=10.34, p=0.004). This remained significant after a Bonferroni correction for six multiple comparisons *(0.05/6=0.0083).* No other interaction effects reached statistical significance, however, an interaction effect for time and allocation for the MSIS psychological scale approached significance at the 0.05 level.

The intervention vs TAU effect sizes at post-intervention, with 95% confidence intervals, are displayed in Table 7. A large and significant effect size (d=0.84, 95%s CIs = 0.02-1.66) was found in favour of the intervention on GAD scores at post-intervention. The strengths of the effect estimates vary, however, all estimates of outcome and process measures were positive, in favour of the intervention.

[19] See Extended Results 3.5 for full results of the per-protocol linear mixed model analysis.
[20] Mixed ANOVAs of all dependent variables were also carried out. A similar trend of results was found to the linear mixed models; there was a significant interaction of time and group allocation for the GAD and no other significant effects.

Table 7. Baseline and post-intervention means between and within groups, results of linear model analysis of interaction effects of allocation and time and effect sizes of intervention vs TAU at post-intervention.

	Time					
	Pre-randomisation			**Post-intervention**		
	TAU (n=13)	Intervention (n=14)		TAU (n=12)	Intervention (n=13)	F *(p value)*	Effect size *(95% CIs)* at post-
Measure	Mean *(SD)*	Mean *(SD)*		Mean *(SD)*	Mean *(SD)*	Interaction effect	intervention
GAD	16.8 *(4.8)*	18.3 *(5)*	GAD	16.8 *(4.6)*	12.7 *(5.2)*	10.34 *(0.004)*	0.84 *(0.02-1.66)*
PHQ	21.2 *(5.9)*	22.1 *(7.1)*	PHQ	19.6 *(6.3)*	18.4 *(7.5)*	0.74 *(0.39)*	0.2 *(-0.59-0.99)*
MSIS-Physical	63.8 *(14.3)*	60.6 *(20.2)*	MSIS-Physical	60.6 *(16.7)*	57.5 *(21.7)*	0.016 *(0.9)*	0.14 *(-0.65-0.92)*
MSIS-Psych	28.7 *(7.8)*	29.9 *(8.9)*	MSIS-Psych	28.1 *(9.3)*	24.5 *(10.6)*	3.82 *(0.063)*	0.46 *(0.34-1.25)*
EQ-5D-5L	0.36 *(0.25)*	0.41 *(0.29)*	EQ-5D-5L*	0.44 *(0.2)*	0.45 *(0.22)*	0.099 *(0.756)*	0.11 *(-0.71-0.93)*
AAQ-II	23.8 *(12.9)*	27.4 *(9.5)*	AAQ-II**	23.4 *(12.5)*	20.9 *(13.2)*	2.868 *(0.105)*	0.23 *(-0.58-1.03)*

*: n for TAU = 11, n for Intervention = 12, **: n for TAU = 11, n for Intervention = 13.

HADS: Hospital Anxiety and Depression Scale, EDSS: The Expanded Disability Status Scale, EQ-5D-5L: Quality of Life Measure, GAD: Generalised Anxiety Disorder Scale, PHQ: Patient Health Questionnaire, MSIS-Physical: Multiple Sclerosis Impact Scale - Physical health subscale, MSIS-Psych: Multiple Sclerosis Impact Scale - Psychological subscale, AAQ-II: Acceptance and Action Questionnaire.

Sample Size Estimation

Thirty four participants would need to be required to have a 90% chance of detecting, as significant at the 5% level, a decrease of 5 points on the GAD. Seventy six participants would need to be required to have a 90% chance of detecting, as significant at the 5% level, a decrease of 5 points on the PHQ. These figures are higher (52 and 116) if expecting an attrition rate of 33%.

Discussion

To our knowledge, this is the first study to evaluate telephone-supported ACT bibliotherapy for people with MS and psychological distress. Overall, we found that if high attrition rates can be addressed this type of intervention is a feasible and potentially effective way of delivering psychotherapy in this population, and a full trial is warranted.

Feasibility

The high attrition rate means that this trial is not feasible in its current format, despite results from the feasibility interviews suggesting that the trial is feasible with regards to recruitment, randomisation, and data collection. There may have been experimenter demand effects in the interviews and only a small sample of participants provided this qualitative data. The self-help book and telephone-support calls were mostly acceptable to participants. Changes in a full trial may be considered, such as recruiting solely through an outpatient clinic, moving QoL measures online, including space for qualitative responses alongside psychometrics and changes to the intensity/pace and complexity of the self-help text.[21]

Attrition

The trial has unusually high attrition rate (33% overall, 64% in the intervention group), compared to other teletherapy and bibliotherapy trials in MS and similar populations (Mohr, Vella, Hart, Heckman, & Simon, 2008), although difference in trial methodology exist. There were a mixture of external factors and trial-related factors influencing participant drop-out. Most participants dropped out due to MS-related illness or not being able to commit to the programme and some dropped out as they found the self-help text inappropriate. Additionally, attrition may have been a product of the recruitment environment: an increased self-focus on wellbeing during participant's outpatient appointments may have led to a greater uptake of patients willing to participate, with motivation decreasing away from the hospital leading to drop-out.

[21] See Extended Discussion 4.1 for further discussion of feasibility data

Participants who dropped out had higher baseline rates of MS-related physical and psychological distress compared to intervention-completers. Engagement with psychotherapy requires effort and concentration, and psychotherapy may initially increase distress as the ACT model encourages participants to engage in negative experiences. People with higher rates of physical and psychological distress were potentially unable to tolerate and/or engage with the intervention, in addition to their illness-related distress.

Psychological distress is related to physical disability in MS (Chwastiak et al., 2014), meaning those who could benefit most overall from psychological intervention maybe those most likely to disengage from treatment. Practically, this may be addressed by having additional face-to-face individual sessions with participants to acculturate them to the ACT model and prepare them for the work involved. Alternatively, video-conferencing technologies may be a way to increase engagement with highly disabled people with MS who struggle to attend face-to-face therapy, with some existing literature suggesting efficacy (e.g. Yuen et al., 2013).

Non-completers also had significantly higher baseline scores on the AAQ-II than completers. Therefore ACT-based interventions may be less acceptable to people with high rates of experiential-avoidance and cognitive-fusion, components ACT attempts to reduce, although the literature on predictors and mediators of treatment outcome is mixed (Wolitzky-Taylor, Arch, Rosenfield, & Craske, 2012). People with lower rates of experiential-avoidance and cognitive-fusion benefited more from the intervention. The ACT model may be more syntonic with their pre-existing coping styles, so they go on to engage, further increase their levels of healthy ACT processes and reduce their distress. Alternatively, it may be that they find the ACT model more syntonic with their pre-existing coping styles, are motivated to continue the program but improve via more general psychotherapy factors (Duncan, Miller, Wampold, & Hubble, 2010). Some literature suggests that those with the highest rates of unhealthy ACT processes may benefit more from CBT (Wolitzky-Taylor et al., 2012), although more research is needed. There was no significant time and allocation interaction for the AAQ-II, so exact mechanisms of change remain

unknown. Studies powered to detect mechanisms of change in ACT interventions are warranted. [22]

Effectiveness

A lack of power and multiple comparisons make the detection of significant differences unlikely, however, despite this, a significant (p=0.004) time and allocation effect was found in favour of the intervention group at post-intervention for anxiety with a large effect size (0.84 and 95% CIs 0.02-1.66). Ostensibly, this could initially be interpreted as evidence for the success of the intervention, supporting existing literature of the effectiveness of the ACT model (Davis et al., 2015) and is very similar to meta-analytic review for ACT on anxiety where an effect size of 0.83 was found (Vøllestad, Nielsen, & Nielsen, 2012). This is promising for future research on the benefits for ACT on anxiety in MS.

Less effect was found on measures of depression. There were higher levels of anxiety than depression in the sample; whereas most research reports the reverse (Korostil & Feinstein, 2007; Mohr & Cox, 2001). Therefore this sample may be less representative of the population.[23] Participants may have used the intervention to tackle their prominence of anxiety over depression, hence the significant reduction in anxiety and not depression, which parallels the experience of the researcher (BP) providing the support calls, where participants mostly brought examples of anxiety to discussions.[24]

Sample Size

Adjusting for a potential attrition rate of 33%, 52 participants would be needed to have a 90% chance of detecting, as significant at the 5% level, a decrease of five points on the GAD, which would be clinically significant. It may be prudent to focus on GAD over the PHQ in full scale RCT design, given the greater effect in this trial, the less participants required to be recruited, the predominance of participants using the book for anxiety and the higher levels of anxiety over depression found in this sample. However, a future trial would aim to reduce the attrition rate found in this study, through practical changes to the protocol such as those previously suggested,

[22] See Extended Discussion 4.3 for further discussion around mechanisms of change in ACT.
[23] See Extended Discussion 4.2 for a discussion of findings on the sample.
[24] See Extended Discussion 4.3 for a discussion of quantitative results.

and more feasibility work to more accurately calculate full trial sample size is needed.

Strengths and Limitations

The study's RCT design allowed the comparison of the intervention to a control group, therefore significant between group differences, effect sizes and sample size calculations for larger trials could be conducted. The study was further strengthened by its mixed-methods design, whereby feasibility questions could be triangulated with quantitative. This allowed for a more detailed exploration of the practicalities of running the study and reasons for drop-out, potentially improving participant retention in future studies.

The main limitation is the high attrition rate in the intervention group, meaning a small sample size in the completer sub-group in completer vs non-completer comparisons, therefore less accurate estimates of who may benefit most from this type of intervention. Whether it is feasible to collect longer-term follow up data and explore whether any gains were sustained remains unknown. A further limitation is that the RCT design meant it was hard to unpick what elements of the intervention participants found the most useful.[25]

Research implications[26]

From the results, we can make the follow specific recommendations for future trials:

- Overall, a more feasibility work is required before proceeding to a full trial. Practical changes resulting from the findings suggest how this further work may proceed are listed below.
- Consider the use of face-to-face sessions at the beginning of the intervention (as an adjunct to the book and phone calls) to orient the participant to the model, increase motivation and reduce attrition.
- Make clear the amount of commitment required in working through the self-help text during recruitment; participants must be active in their treatment, not passive recipients.

[25] See Extended Methods 4.6 and 4.7 for further details on strengths and limitations of this study.
[26] See Extended Methods 4.8 for details of research implications.

- Do not rely on self-report prescription medication, instead use clinical records to improve accuracy.
- Reduce the amount of reading required each week. Be more flexible with intervention duration. E.g. Participants could put treatment on hold if they feel they need a break.
- Consider active control arms and different ways of capturing change processes to further add to the mechanism of change literature.
- More research is needed into whether teleconferencing or other technologies are a feasible way of reaching the most highly disabled people with MS, and whether other types of psychotherapy, such as CBT, may be a more feasible way of providing support to those with highest levels of experiential avoidance.

Clinical Messages[27]

- This specific method of telephone-supported ACT bibliotherapy is not currently a feasible format for delivering psychotherapy to people with MS and low mood.
- Telephone-supported ACT bibliotherapy does have the potential to be effective in reducing levels of psychological distress within a sub-population of people with MS.

[27] See Extended Methods 4.9 for details of clinical implications.

References

Braun, V., & Clarke, V. (2013). *Successful qualitative research: A practical guide for beginners*. London, UK: Sage.

Chwastiak, L., Ehde, D. M., Gibbons, L. E., Sullivan, M., Bowen, J. D., & Kraft, G. H. (2014). Depressive symptoms and severity of illness in multiple sclerosis: epidemiologic study of a large community sample. *American Journal of Psychiatry. 159*(11), 1862-1868.

Dahl, J., Wilson, K. G., & Nilsson, A. (2004). Acceptance and commitment therapy and the treatment of persons at risk for long-term disability resulting from stress and pain symptoms: A preliminary randomized trial. *Behavior Therapy, 35*, 785–801.

Davis, M. L., Morina, N., Powers, M. B., Smits, J. A. J., & Emmelkamp, P. M. G. (2015). A meta-analysis of the efficacy of acceptance and commitment therapy for clinically relevant mental and physical health problems. *Psychotherapy and Psychosomatics, 84*, 30–36.

Den Boer, P. C. A. M., Wiersma, D., & Bosch, Van den, R. J. (2004). Why is self-help neglected in the treatment of emotional disorders? A meta-analysis. *Psychological Medicine, 34*, 959–971.

Dennison, L., Moss-Morris, R., & Chalder, T. (2009). A review of psychological correlates of adjustment in patients with multiple sclerosis. *Clinical Psychology review, 29*, 141–153.

Duncan, B. L., Miller, S. D., Wampold, B. E., & Hubble, M. A. (2010). *The heart and soul of change: Delivering what works in therapy.* Washington, DC: American Psychological Association.

Gale, N. K., Heath, G., Cameron, E., Rashid, S., & Redwood, S. (2013). Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology*, *13,* 117.

Hackett, M. L., Yapa, C., Parag, V., & Anderson, C. S. (2005). Frequency of depression after stroke. A systematic review of observational studies. *Stroke. 36*(6), 1330-1340.

Hayes, S. C., & Smith, S. (2005). *Get out of your mind and into your life: The new acceptance and commitment therapy*. Oakland, CA: New Harbinger Publications.

Hayes, S. C., Strosahl, K. D., & Wilson, K. G. (1999). *Acceptance and commitment therapy: An experiential approach to behavior change*. New York, NY: Guilford Press.

Hedges, L. V. (2007). Effect sizes in cluster-randomized designs. *Journal of Educational and Behavioral Statistics, 32,* 341–370.

Herdman, M., Gudex, C., Lloyd, A., Janssen, M. F., Kind, P., Parkin, D., … Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research, 20*, 1727–1736.

Hobart, J., Lamping, D., Fitzpatrick, R., Riazi, A., & Thompson, A. (2001). The multiple sclerosis impact scale (MSIS-29) a new patient-based outcome measure. *Brain, 124*, 962–973.

Julious, S. A. (2005). Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceutical Statistics, 4*, 287–291

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., … Wang, P. S. (2003). The epidemiology of major depressive disorder: results from the national comorbidity survey replication (NCS-R). *Journal of the American Medical Association, 289*, 3095–3105.

Khan, F., Turner-Stokes, L., Ng, L., & Kilpatrick, T. (2007). Multidisciplinary rehabilitation for adults with multiple sclerosis. *Cochrane Database of Systematic Reviews, (2),* CD006036.

Korostil, M., & Feinstein, A. (2007). Anxiety disorders and their clinical correlates in multiple sclerosis patients. *Multiple Sclerosis, 13*, 67–72.

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *Journal of General Internal Medicine, 16,* 606–613.

Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology, 33,* 1444.

Lancaster, G. A., Dodd, S., & Williamson, P. R. (2004). Design and analysis of pilot studies: Recommendations for good practice. *Journal of Evaluative Clinical Practice, 10,* 307-312.

Mohr, D. C., & Cox, D. (2001). Multiple sclerosis: empirical literature for the clinical health psychologist. *Journal of Clinical Psychology, 57*, 479–99.

Mohr, D. C., Likosky, W., Bertagnolli, A., Goodkin, D. E., Van Der Wende, J., Dwyer, P., & Dick, L. P. (2000). Telephone-administered cognitive–behavioral therapy for the treatment of depressive symptoms in multiple sclerosis. *Journal of Consulting and Clinical Psychology, 68,* 356.

Mohr, D. C., Vella, L., Hart, S., Heckman, T., & Simon, G. (2008). The effect of telephone-administered psychotherapy on symptoms of depression and attrition: A meta-analysis. *Clinical Psychology: Science and Practice, 15*, 243–253.

MS Trust. (2015). *Introduction to MS.* Retrieved January 5, 2016. From http://www.mstrust.org.uk/news/article.jsp?id=3082

Nordin, L., & Rorsman, I. (2012). Cognitive behavioural therapy in multiple sclerosis: a randomized controlled pilot study of acceptance and commitment therapy. *Journal of Rehabilitation Medicine, 44*, 87–90.

Pakenham. (2006). Investigation of the coping antecedents to positive outcomes and distress in multiple sclerosis (MS). *Psychology & Health, 21*, 633–649.

Pakenham, K. I. (1999). Adjustment to multiple sclerosis: application of a stress and coping model. *Health Psychology, 18*, 383–392.

Proctor, B, J., Moghaddam, N., Vogt, W., & das Nair, R. (in press). Telephone-psychotherapy in multiple sclerosis: A systematic review and meta-analysis. *Rehabilitation Psychology.*

Ramp, M., Khan, F., Misajon, R. A., & Pallant, J. F. (2009). Rasch analysis of the multiple sclerosis impact scale (MSIS-29). *Health and Quality of Life Outcomes, 7*, 58.

Reijnders, J. S. A. M., Ehrt, U., Weber, W. E. J., Aarsland, D., & Leentjens, A. F. G. (2008). A systematic review of prevalence studies of depression in parkinson's disease. *Movement Disorders, 23*, 183–189.

Ruiz, F. (2010). A review of acceptance and commitment therapy (ACT) empirical evidence: Correlational, experimental psychopathology, component and outcome studies. *International Journal of Psychology and Psychological Therapy, 10,* 125–162.

Sheppard, S. C., Forsyth, J. P., Hickling, E. J., & Bianchi, J. (2010). A novel application of acceptance and commitment therapy for psychosocial problems associated with multiple sclerosis: Results from a half-day workshop intervention. *International Journal of MS Care, 12*, 200–206.

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of Internal Medicine, 166*, 1092–1097.

Thomas, P. W., Thomas, S., Hillier, C., Galvin, K., & Baker, R. (2006). Psychological interventions for multiple sclerosis. *Cochrane Database of Systematic Reviews,* CD004431.

Van Hout, B., Janssen, M. F., Feng, Y.-S., Kohlmann, T., Busschbach, J., Golicki, D., … Pickard, A. S. (2012). Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value in Health, 15*, 708–715.

Vøllestad, J., Nielsen, M. B., & Nielsen, G. H. (2012). Mindfulness-and acceptance-based interventions for anxiety disorders: A systematic review and meta-analysis. *British Journal of Clinical Psychology, 51*, 239–260.

Wilkinson, H. R., & das Nair, R. (2013). The psychological impact of the unpredictability of multiple sclerosis: a qualitative literature meta-synthesis. *British Journal of Neuroscience Nursing, 9,* 172–178.

Wolitzky-Taylor, K. B., Arch, J. J., Rosenfield, D., & Craske, M. G. (2012). Moderators and non-specific predictors of treatment outcome for anxiety disorders: A comparison of cognitive behavioral therapy to acceptance and commitment therapy. *Journal of Consulting and Clinical Psychology, 80*, 786.

Yuen, E. K., Herbert, J. D., Forman, E. M., Goetter, E. M., Juarascio, A. S., Rabin, S., … Bouchard, S. (2013). Acceptance based behavior therapy for social anxiety disorder through videoconferencing. *Journal of Anxiety Disorders, 27*, 389–397.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67*, 361–370.

Extended Paper

1. Extended Introduction

The extended introduction provides further details on how Multiple Sclerosis (MS) relates to psychological functioning and in-depth review of Acceptance and Commitment Therapy (ACT), teletherapy and bibliotherapy. It then discusses the study aims and objectives in more detail before touching upon the epistemological position of the trial.

1.1 The Aetiology of Psychological Distress in Multiple Sclerosis

The short paper states that (MS) can have diverse and unpredictable effects on physical and psychological functioning. Further physical symptoms include problems with vision, balance, fatigue and sexual dysfunction (Mohr, Goodkin, Islar, Hauser, & Genain, 2001). MS causes psychological distress, such as in MS outpatients reporting higher level of mood related psychiatric disorders compared to matched controls (odds ratio 3.17) (Galeazzi et al., 2005). Depression is one of the more common and well-studied of these emotional problems.

From studies with small sample sizes, point prevalence estimates of depression in MS vary between 14-57% (Mohr & Cox, 2001). Lifetime prevalence of major depressive disorder in MS is estimated to be 50% (Mohr & Cox, 2001). Depression may have multiple aetiologies, including MS-specific immune dysregulation, neurological damage, iatrogenic effects of MS medication (Mohr & Cox, 2001). It may be a coincidental effect, independent of MS, but potentially maintained by the disease (Galeazzi et al., 2005). Psychosocial variables associated with depression include high perceptions of uncertainty, high perceived intrusiveness on daily functioning (Mullins et al., 2001), and loss of social support (Barnwell & Kavanagh, 1997).

A complicating factor in studying MS and depression is that symptoms of MS such as fatigue are also common in depression, making it hard to attribute these symptoms to MS-specific or depression-specific aetiologies. (Thomas et al., 2006).

Although less well studied, high levels of uncertainty and the perceived threat of MS leads to a prevalence of anxiety that is higher in MS than in non-clinical populations (Mohr & Cox, 2001). The aetiology of anxiety in MS remains unknown, although is

thought unlikely to arise from any specific brain lesions. Studies of anxiety disorders estimate point prevalence at 19.3% (Beiske et al., 2008) and lifetime prevalence at 37.5%, with generalised anxiety disorder being most common (Korostil & Feinstein, 2007). Whether anxiety is a direct consequence of MS or a product of psychological adjustment to the disease remains unclear (Thomas et al., 2006). Overall, the relationship between MS and mood in MS is complicated and multifactorial.

1.2 MS and Psychotherapy

NICE guidelines state that there is insufficient evidence to firmly recommend formal therapeutic interventions for low mood in MS, however they recognise the possible benefits of providing emotional support in some way (NICE, 2003). A Cochrane review assessed 16 trials of psychological treatments for MS (Thomas et al., 2006) on outcomes of depression, anxiety, self-efficacy, self-esteem, disability, cognitive functioning and the MS Impact Scale (MSIS) (Hobart et al., 2001). They concluded there is reasonable evidence for cognitive behavioural approaches in the treatment of depression and coping in MS. However, there was less evidence for any beneficial effect of psychotherapy for anxiety, cognitive impairment or physical disability.

1.3 Acceptance and Commitment Therapy

This section critiques the theoretical underpinnings and major theoretical components of Acceptance and Commitment Therapy (ACT), before reviewing its evidence and finally discussing why the model may be psychotherapeutically relevant in an MS population, with reference to traditional Cognitive Behaviour Therapy (CBT).

1.3.1 Theory

ACT sits within the third-wave of CBT interventions; it is particularly sensitive to the context and functions of psychological phenomena, not just their form. Rather than seeking to change psychological events themselves, ACT seeks to change an individual's relationship to them and the function of the events (Hayes, Luoma, Bond, Masuda, & Lillis, 2006).

Psychotherapeutically, ACT views experiential avoidance as a core pathogenic process, and attempts to increase acceptance of negative experiences and de-fuse thoughts from feelings (Dahl et al., 2004). It purports to improve functioning and

quality of life by increasing a person's ability to act in concordance with personally held values (Hayes et al., 1999).

In meta-analysis, significant positive effect sizes have been observed for acceptance, defusion, present moment, values and mindfulness compared to inactive comparison conditions (Levin, Hildebrandt, Lillis, & Hayes, 2012). However, a recent randomised controlled trial (RCT) investigating ACT for anxiety concluded there was limited support for these six purported ACT mechanisms (Swain, Hancock, Hainsworth, & Bowman, 2015). Despite their theoretical differences, ACT and CBT may be underpinned by analogous mechanisms; e.g. the ACT process of cognitive defusion may play a role in CBT (Arch, Wolitzky-Taylor, Eifert, & Craske, 2012). Harris (2009) suggests the six ACT process factors may collapse down into three factors of "defusion and acceptance", "self-as-context" and "values and committed action", and these three make up the overall concept of psychological flexibility.

1.3.2 Relational Frame Theory and Functional Contextualism

ACT is rooted in a behavioural theory of human language called relational frame theory (RFT), which sits within a wider epistemology of functional contextualism, which attempts to predict behaviour as a product of contextual factors.
RFT stipulates that humans can derive bidirectional stimulus relations (Torneke, 2010); they learn to arbitrarily relate events, and to change the functions of events based on these relations (Hayes et al., 2006). There are an arbitrary number of dimensions, or frames, along which stimuli can be related, which serve as the building blocks for human language and cognition. This ability to arbitrarily relate objects is useful for problem solving in the physical world, however, this becomes problematic when the same skills are applied to internal events. Through relational frames, any stimulus can invoke negative emotions, feelings or thoughts (Hayes & Smith, 2005).

This has important implications for psychopathology and ACT intervention. Relational networks developed over time can influence behaviour through the process of derived relations. Previously neutral thoughts, feelings, memories and sensations can come to acquire aversive functions and dominate overt behaviour. For example, through an aversive experience, particular thoughts may become fused with anxiety. In the future, that same or a similar thought or memory may invoke

anxiety. ACT therefore targets these relational networks during psychotherapy, and attempts to widen the narrowing effects language can have, for example, through de-fusion of thought from emotion.

1.3.3 Research on ACT

Hayes, Louma, Bond, Masuda and Lilis (2006), proponents of the approach, review ACT, with their findings tending to favour the model. For example, the Acceptance and Action Questionnaire (AAQ) is moderately correlated with a host of psychopathological and quality of life (Qol) outcomes, which could be interpreted as support for core act processes in psychological well-being. However, the AAQ-II has been critiqued on its construct validity. Wolgast (2014) reviews the broad empirical support for the role of the construct of experiential avoidance across various domains of psychopathology, but questions the validity of the AAQ which has been relied upon to make claims about the role of acceptance, in review papers such as Hayes and colleagues 2006 paper The author found the measure more strongly related to items designed to measure distress than to items designed to measure acceptance and experiential avoidance. Overall, the measure does not clearly make the distinction between process and outcome, and may capture psychological distress rather than core ACT processes. These findings undermine correlational research concluding the importance of ACT processes in emotional well-being.

Hayes et al (2006) point out that large-scale component analyses of therapies are resource intensive, therefore in their paper they review component micro-studies. They find evidence for concepts of acceptance, defusion and values in experimental studies. Research on mindfulness, closely linked to the ACT process of "present moment awareness", and a technique the model encourages, shows strong evidence for its effectiveness (Hofmann, Sawyer, Witt, & Oh, 2010). Hayes and colleagues (2006) note that observer, rather than self-report measures would strengthen these studies.

With regards to outcome studies, Hayes et al (2006) report within-condition effect sizes of 1.11 at post-intervention and 1.26 at follow up (Cohen's d), and report larger effect sizes for ACT when ACT is compared to CBT. However, a recently updated meta-analysis of ACT (Öst, 2014) includes 60 RCTs and reported a smaller effect size (0.42). Compared to cognitive and behavioural treatments they found no

significant differences. Overall there is currently a mixed picture of how ACT compares to CBT with regards to effectiveness.

Most psychometrics are influenced by currently predominating theories and therapies, such as CBT, where cognition takes temporal predominance over affective change; a change in cognition is assumed as a proxy for symptomatic amelioration. ACT views functional change as primary and is less concerned with shifts in cognitive content, therefore traditional CBT-informed measures of change may be less sensitive to functional changes. Therefore ACT may underperform in equivalence trials against CBT. QoL measures were included in this study in attempt to capture functional changes which may be exhibited by those engaging in the intervention.

Overall, the use of static measurement approaches, such as the AAQ-II, are problematic, and likely to lead to misunderstandings of antecedents, correlates, and consequences of change processes (Kashdan & Rottenberg, 2010). Alternative ways of capturing dynamic psychological processes may come from aggregated single case experimental designs, objective-observer ratings or Q-sort methods.

1.3.4 ACT Studies in MS

As outlined in the main paper, there has been one encouraging study of the effect of ACT on MS; In twelve week follow-up significant improvements were observed in depression (np^2 = .29), extent of thought suppression (np^2 = .35), impact of pain on behaviour (np^2 = .37) and QoL (np^2 = .34), although no change on physical symptoms and mindfulness were observed (Sheppard et al., 2010). However, with a small sample size of 15 participants, no control group and duration of half a day for the actual intervention, caution would be advised if taking this study as evidence for potential efficacy of ACT on low mood in MS.

As mentioned in the main paper, an RCT of ACT compared to relaxation therapy in MS outpatients with elevated symptoms of anxiety and/or depression (n=210) found no significant advantage of ACT over relaxation therapy on any outcome variable (Nordin & Rorsman, 2012). However within-group analyses on the ACT group showed improvement in BDI scores from pre-treatment to post treatment ($z = 2.2$, $p < 0.05$), and a maintained improvement in on the Acceptance and Action

Questionnaire (AAQ-II) at post-treatment ($z = 2.2$, $p < 0.05$) and 3 month follow up ($z = 2.1$, $p < 0.05$). The authors note that outcome variables assessing aspects of QoL, such as social and physical participation and impact on daily functioning may have been more appropriate than symptom scales given the breadth of difficulties associated with MS and the theoretical emphasis on behavioural change rather than symptom reduction. Therefore a QoL measure has been included as a secondary measure in this study.

1.3.5 Rationale for ACT in MS

Whilst both CBT and ACT support problem-focused coping, they are distinct in that CBT is antecedent orientated, whereas ACT is response oriented (Hofmann & Asmundson, 2008). CBT employs antecedent orientated strategies such as cognitive reappraisal, whereas ACT focuses on response, and encourages emotional acceptance, which may be particularly useful in a MS population where beliefs about illness or symptoms may actually be *true*, and traditional CBT belief challenging may be of limited usefulness (Dennison et al., 2009).

A review of 72 quantitative studies examining psychological factors relating to psychological adjustment in MS found that denial and avoidance, two concepts ACT attempts to reduce, are related to poorer psychological adjustment (Dennison et al., 2009). Acceptance has been found to be the strongest predictor of adjustment to MS (Pakenham, 2006). Whilst these studies are limited to adjustment to diagnosis which not the focus of this trial, it may be reasonable to extend theoretical explanations of psychopathology at time of adjustment to people with MS years after formal diagnosis: those with MS could be conceptualised as undergoing a continual adjustment to the progressive nature of the disease as their physical health worsens. Therefore this literature supporting the role of acceptance in MS is relevant to this trial.

Whilst CBT interventions have been found to improve outcomes in chronic health conditions, evidence that mediation of effects is achieved through cognitive reappraisals is questionable (Hayes et al., 2006). CBT interventions may improve outcomes in chronic conditions through increasing acceptance (Poppe, Petrovic, Vogelaers, & Crombez, 2013). Thus acceptance appears critical in this population, and it is prudent to trial a therapy such as ACT that targets acceptance directly.

1.3.6 ACT Summary

Evidence from meta-analyses appears mixed, and potentially related to the theoretical orientation of the researcher. Correlational research is weakened by challenges to the validity of ACT process measures. There is a small but encouraging body of literature on ACT in MS populations, and a theoretically sound rationale for why ACT could be effective in chronic and progressive conditions, therefore trials exploring its potential effectiveness are warranted.

1.4 Teletherapy

The term "telephone-psychotherapy" is often used interchangeably with overlapping terms such as "teletherapy", "telecare", "telehealth" and "telemedicine". It can be defined as providing therapy at a distance with the use of Information Technology (Bashshur, Shannon, Krupinski, & Grigsby, 2011). Broadly, the telephone can be used for a range of healthcare-related activities, such as diagnosis, monitoring symptoms and medications, administering measures, or providing counselling, rehabilitative or psychological support. Telephone-psychotherapy offers the opportunity to deliver psychological therapies to people in their own homes who otherwise might find it difficult to travel to a healthcare location to receive face-to-face therapy. Likewise, it also facilitates the provision of psychotherapy to those at home where there is a scarcity of resources to allow therapists to visit people in their homes.

Previous systematic reviews have demonstrated the potential effectiveness of telephone-based interventions across a broad range of physical (Hailey, Roine, Ohinmaa, & Dennett, 2011) and mental health domains (Leach & Christensen, 2006), including stroke (Johansson & Wild, 2011; Paré, Jaana, & Sicotte, 2007) and spinal cord injury (Dorstyn, Mathias, & Denson, 2013; Hailey, Roine, Ohinmaa, & Dennett, 2013). Therefore teletherapy may be applicable to chronic physical health conditions, such as MS.

The short paper cites a recent systematic review and meta-analysis of eleven trials investigating the effectiveness of telephone-based psychotherapies for people with MS, compared to those receiving no treatment, standard care or other control (Proctor, Moghaddam, Vogt & das Nair, in press). The therapies were largely CBT-

orientated. Whilst the review found that the interventions had positive effects on depression, fatigue, QoL, MS-symptoms, physical activity and medication adherence, how clinically significant these effects are was not examined. Furthermore, the small to moderate effect sizes that were found immediately post-intervention, were mostly not sustained in the long term. Included trials were of poor methodological quality, and the authors recommended studies of better methodological quality are required. This trial would be eligible to be included in a future update of this systematic review and meta-analysis.

1.4.1 Telepsychotherapeutic Mechanisms of Change

Telephone-psychotherapy is thought to work in a similar way to face-to-face delivered psychotherapy, which broadly speaking, relies on psycho-education, modality-specific techniques and the relationship between therapist and client. Therapeutic alliance has been found to be high as measured by both client and therapist in telephone-psychotherapy (Reese, Conoley, & Brossart, 2002) and has been found to predict outcomes in telephone psychotherapies with an MS population (Beckner, Vella, Howard, & Mohr, 2007). However, RCTs may not be the best methodology for dissecting precise mechanisms of change, and different research designs investigating the phenomena are needed.

1.4.2 Teletherapy vs Face-to-face Therapy

Randomised controlled trials (RCTs) have found similar therapeutic effects between face-to-face and telephone delivered psychotherapies (Brenes, Ingram, & Danhauer, 2011), and one systematic review of telephone psychotherapies found lower attrition rates compared to face-to-face therapies in people with depression (Mohr et al., 2008). Client satisfaction and acceptance of telephone psychotherapy has also found to be high (Bee et al., 2008).

1.4.3 Rationale for Teletherapy in MS

Overall, teletherapy may work in similar ways to face-to-face therapy. There is evidence from meta-analyses that it can be effective for a variety of health conditions, including evidence of small but significant gains in the MS population (Proctor, Moghaddam, Vogt & das Nair, in press) Furthermore, it may be more acceptable to those who are unable to travel to a clinic due to MS-related symptoms,

such as pain and fatigue, therefore may be a method to reach those with higher levels of disability, which are associated with higher levels of psychological distress (Beiske et al., 2008).

1.5 Bibliotherapy

Various models of therapy have been adapted into self-help texts (bibliotherapy). A meta-analysis of bibliotherapy for anxiety disorders in adults found moderate to large effect size (g = 0.78) compared to placebos and waiting listings (Haug, Nordgreen, Öst, & Havik, 2012). When compared to face-to-face therapy, there was a small effect that favoured the face-to-face group. However, another meta-analysis of bibliotherapy for anxiety and depression concluded that bibliotherapy and face-to-face therapy have comparable effects and comparable attrition rates (Cuijpers, Donker, van Straten, Li, & Andersson, 2010).

With specific regard to ACT, a systematic review and meta-analysis of ACT and mindfulness bibliotherapies found significant effects on anxiety (Hedges g=-0.34), depression (Hedges g=-0.37) and acceptance measures (Hedges g=-0.49) compared to controls (Cavanagh, Strauss, Forder, & Jones, 2014). Overall, research is mixed as to how bibliotherapy compares to face-to-face therapy, but there is evidence to suggest that bibliotherapy, and ACT-based bibliotherapy may have positive effects on psychological outcomes such as depression and anxiety.

1.5.1 Rationale for Bibliotherapy in MS

The James Lind Alliance is a non-profit initiative that brings patients and clinicians together in prioritising the most important research questions in particular fields. In 2013, and in partnership with the MS Society, number four in their top ten research priorities was the question “How can people with MS be best supported to self-manage their condition?” (2013). Bibliotherapy is one such method attempting to help people with MS self-manage their condition, and research into the feasibility and effectiveness of supporting people in this self-management addresses this prioritised question laid out by clinicians and patients alike.

1.5.2 Bibliotherapy and teletherapy in MS

Within an MS population, Mohr and colleagues (2000) examined the effect of eight week telephone-supported CBT bibliotherapy compared to usual care. Patients

(n=32) in the intervention group received telephone-support, including a workbook and homework assignments. In this group there was a significant reduction between pre- and post-treatment scores ($F(1, 21) = 15.37$, $p = .0008$) on their depression measure. Therefore telephone-supported CBT bibliotherapy may be effective for depression in MS, and research into the effectiveness of third-wave CBT bibliotherapies on depression and other outcomes is warranted. Of particular relevance to this trial, the authors note that telephone support might be more appropriate for those who cannot make a regular therapeutic group due to symptoms such as fatigue resulting from their MS.

Ehde and colleagues (2015) recently conducted an RCT combining both teletherapy and bibliotherapy for a MS population. They designed a control against their telephone-support CBT intervention that consisted of a telephone-based programme of education on MS symptoms and care in attempt to control for common factors such as therapeutic relationship, treatment dosing, and participation in a manualized intervention. All participants significantly improved on fatigue, pain and depression measures from baseline to post-intervention, however, contrary to hypotheses, they found no significant differences between groups. However, those in the CBT condition reported significantly higher treatment satisfaction and greater improvements in activation, positive affect, and social roles, which were generally maintained at long term follow up. They suggest their rigorous control group may have masked CBT benefits as it could have provided many common ingredients associated with positive psychotherapeutic outcomes.

Rigby, Thorton and Young (2008) found that if bibliography is provided without any social support then mood outcomes worsen in MS, compared to those receiving bibliography and social support (Rigby et al., 2008). We may be able to conceptualise the provision of telephone support as similar to the social support provided in this study, although differences exist. Nevertheless, clinician support may play an important role in bibliotherapy, hence providing telephone-support alongside the self-help text, rather than solely providing the self-help text.

1.6.1 Feasibility Randomised Controlled Trials

Feasibility studies have different aims from RCTs. A feasibility study is research done before a main study which is used to estimate important parameters that are

needed to design the main study (Arain, Campbell, Cooper, & Lancaster, 2010). Guidance on developing and evaluating complex interventions describe feasibility work as vital in testing procedures for their acceptability, estimating rates of recruitment, retention of subjects and calculating appropriate sample sizes (Craig et al., 2008). Evaluations of full clinical trials are often undermined by problems of acceptability, compliance, recruitment and retention that could be anticipated by thorough feasibility studies.

Before a large scale RCT of telephone-supported ACT bibliography for people with low mood and MS can be run, a feasibility study is vital. The feasibility outcomes can then be used to streamline or redesign larger studies, powered to detect significant group differences, in the knowledge that future evaluations should not be hampered by problems of acceptability, compliance, recruitment and retention.

1.6.2 Feasibility Aims

The specific elements of feasibility the study was designed to assess were laid out during the conception of the trial. From the participants we wanted to assess the acceptability of the recruitment process, the randomisation process, the self-help text, the telephone-support calls and acceptability of the assessment batteries. Other data could inform us of the practicalities of recruitment (e.g. eligibility and uptake), the practicalities of providing telephone support (e.g. length of telephone calls) and the reliability of using self-report measures (e.g. comparing self-report data to clinical notes).

1.6.3 Secondary Objectives

A review of feasibility studies suggested that there is often an over-emphasis of reporting results of quantitative hypotheses in published feasibility trials (Arain et al., 2010). The authors suggest feasibility studies should either mainly be descriptive or focus on sample size estimation, while results from hypothesis testing must be interpreted with caution, as feasibility studies are not designed to evaluate the outcome of interest; that is left to the main study. Therefore the primary outcome of the study was the feasibility and calculations for a larger trial. Exploratory analyses of between and within group differences of were secondary to these main outcomes.

Analysis of potential change mechanisms using the AAQ-II are also secondary to aims of feasibility.

1.7 Epistemology

Despite ACT being grounded in a functional contextualist epistemology, which is considered pragmatic, this study will be conducted from a realist position. Post-positivism aims to pursue an objective account of reality, whilst acknowledging that the background, knowledge and values of the researchers can affect what is observed (Robson, 2002). Data taken may not give an exact account of what is experienced by the participants, but there should be a high probability that it is a close representation. Whilst caution is advised over blending different epistemological perspectives, it can be pragmatically useful to adopt a realist approach (Long, 2013).

2. Extended Methods

The extended methods section provides further details of participant included in the trial, the assessment measures used, details of the randomisation, intervention and analysis and finally further ethical considerations.

2.1 Recruitment

Participants were identified from two sources. Firstly though the Neurology Department at Queens Medical Centre (QMC), Nottingham, and secondly through the MS Society (a UK registered charity). This was firstly to maximise the potential to recruit participants in a short time period, and secondly so the sample is more representative of the types of settings people with MS can access support, making any clinical recommendations coming from the study more applicable to the UK MS population.

The MS service at QMC agreed to use the HADS as a regular measure for all patients attending their weekly MS outpatient clinic. This meant patients were given the screening measure by NHS clinicians, rather than myself, which is considered more ethical.

Patients completed the HADS prior to their scheduled appointment with a neurology doctor. Those scoring above the cut-off were informed of their eligibility to take part in the study by their physician, and asked if they would like to speak to myself in another room after their appointment. I then re-confirmed the patients HADS score, before going through the details of the study, checking inclusion and exclusion criteria, and providing information sheets and consent forms if appropriate.

The study was also advertised to members of the Nottingham branch of the MS society via their quarterly newsletter. Individuals were invited to contact myself if they were interested. They were then posted the HADS, along with a patient information sheet, consent form and exclusion/inclusion criteria checklist to complete and return in a provided stamped and addressed envelope.

Unusually, this meant there was no face-to-face contact whatsoever with individuals recruited through this pathway. However, speaking on the phone with the participants was an opportunity to start building a therapeutic relationships with

myself, which would be important if they went on to be randomised to the intervention group. The therapeutic relationship has found to be an important factor in telepsychotherapy (Beckner et al., 2007), so it was necessary to attempt to build a relationship with participants who were recruited through this route. It could be argued that participants who met with myself face-to-face may build better relationships and therefore have better outcomes. Whilst a full trial may include a sub-analysis testing this hypothesis, this feasibility study was underpowered to assess this.

2.2 Sample Size

For feasibility studies a sample size of twelve per group has been suggested as it is thought to be enough to ascertain reliable parameters of the mean and variance for each group; requirements when designing a fully powered RCT (Julious, 2005). Thirty participants per arm has been found to be median arm size for feasibility studies in the UK (Billingham, Whitehead, & Julious, 2013), which could be a recruitment target to make the study of a more acceptable standard, making a maximum of 60 total participants a potential target. However, to pragmatically recruit an acceptable sample within the time constraints, a target of twelve per group plus allowance for expected attrition was used to calculate a recruitment target. Attrition rates were expected to be low; a meta-analysis of telephone psychotherapy for depression found a mean attrition rate of 7.5%, much lower than face to face psychotherapy (Mohr et al., 2008), so a minimum of 26 participants was the recruitment aim to allow for a similar attrition rate.

The recommendation of twelve per group given by Julious (2005) is primarily for drug trials, so perhaps less appropriate for this psychotherapy trial. Looking to other literature, there is considerable debate around what sample size is appropriate for determining parameters for a full trial. They are suggestions of a total sample size of 30 as appropriate for a feasibility study (Lancaster, Dodd & Williamson, 2004) and other suggestions of 50 participants (Sim & Lewis, 2012). Overall, a total sample of 24-50 has been suggested as reasonable, therefore a minimum of 26 participants for this trial is justified.

I was unable to collect data on ineligible participants who scored under the HADS cut-off; the measure was being delivered as part of normal service delivery, and data

only became accessible to me if the participant consented to take part in the study. Therefore HADS questionnaires from participants that were ineligible were inaccessible to me, so I was unable to calculate a percentage of all MS outpatients who would be eligible to participate in a full study. This data would be of interest to a full study, for example, in estimating how many outpatient clinics, with an average attendance, a recruiter may have to attend to reach a desired sample size. (At time of writing this is piece of research is something the neurology clinicians and researchers are considering undertaking, potentially with my involvement).

With regards to the sample size of ten participants for the feasibility interviews, it was considered a pragmatic approach in order to add some nuance to the quantitative findings. The study was primarily and quantitative study, therefore less formal methods and more pragmatic methods were used when adding this qualitative data to further inform the primary objectives of the trial.

2.3.1 Inclusion Criteria

Participants must have had a diagnosis of MS, as verified by their GP or secondary care service. Sub-diagnosis of MS type was also obtained. A feasibility trial would not be powered to carry out sub-group analyses, but it was important to ascertain the feasibility of collecting this data, as a full trial may attempt such an analysis; e.g. are their differences in intervention effectiveness for relapsing vs progressive types of MS? Furthermore, the psychotherapy research methodology scale (Öst, 2008), a measure of study quality, specifies that trials should state how diagnoses are confirmed.

Participants were only eligible if they were deemed to be experiencing psychological distress, as measured by scoring above seven on the HADS (Zigmond & Snaith, 1983), as anxious and depressed people are more likely to request and benefit from psychotherapy. The HADS consists of seven anxiety items and seven depression items. Its high internal consistency of 0.9 and its brevity makes the HADS a useful screening tool (Herrero et al., 2003), which is especially relevant for a busy outpatient recruitment environment.

The published cut-off for the measure is eight and above, with further suggested cut-offs for mild, moderate and severe. This same cut-off has been previously used as

when recruiting MS patients with low mood into a psychotherapy RCT (Forman & Lincoln, 2010). The measure can also be scored to produce separate scores for anxiety and depression, therefore the measure may be particularly useful as it allows exploration of any differences between anxiety and depression in the sample.

Participants had to be able to read, write and speak English, which were all necessary, firstly for giving informed consent, and secondly for undertaking the intervention if allocated to that group.

2.3.2 Exclusion Criteria

The first exclusion criteria was that participants must have not had their diagnosis of MS in the last twelve months. It has been suggested that there is a natural period of psychological adjustment after diagnosis which would affect scores on the HADS screening tool and outcome measures by processes unrelated to the intervention (N. Evangelou, Consultant Neurologist, personal communication, January 21st 2014; Janssens et al., 2003).

Participants must have not been receiving psychotherapy for a mood disorder. This would be adding another uncontrolled variable to the study which could affect scores. For example, a participant's baseline and post-intervention scores could be affected by another psychotherapy, and not by the telephone-support ACT bibliotherapy. Equally, scores in the TAU group could be artificially elevated if participants were engaging in psychotherapy, therefore underestimating any positive effect of the intervention in between group analyses. In clinical practice, a client could be accessing adjunct bibliotherapy or face-to-face psychotherapy, and other events external to psychotherapy can frequently occur and often account for improvement or deterioration in a client. However, the more variables under control, the more accurate estimates of the effect of the intervention can be.

2.4.1 Demographic Measures

The following clinical and demographic information was taken; age, gender, time since diagnosis, date of last relapse, last EDSS (Expanded Disability Status Scale) score, current medications, employment status and marital status. Current medications were taken from the participant and from their clinical notes to test the reliability of self-report data. Employment and marital status were recorded as this

data would be used to aid cost-effectiveness evaluation in a full trial. Careful consideration was given only to take demographic information that could be useful in potential sub-analyses in fuller trials.

2.4.2 Primary Outcome Measures

The primary outcome measures were the GAD (Spitzer et al., 2006) and the PHQ (Kroenke, Spitzer, & Williams, 2001); both recommended in NICE guidelines for assessing outcomes in mental health research (NICE, 2011). ACT is hypothesised to mediate depressive responses to physical symptoms and aversive cognitions. Any changes in depressive emotions and cognitions were tested using the Patient Health Questionnaire 9 (PHQ-9); a self-report measure of depression containing nine items the participant must rate from "not at all" (0) to "nearly every day" (3) (Kroenke et al., 2001). It has an internal consistency of 0.83-0.92 (Cameron, Crawford, Lawton, & Reid, 2008).

ACT is also hypothesised to mediate anxious responses to physical symptoms and cognitions. Any changes in anxious feelings or thoughts were assessed using the Generalised Anxiety Disorder 7 (GAD-7); a seven item self-report measure of generalised anxiety with an internal consistency of 0.92 (Spitzer et al., 2006). Participants must rate from "not at all" (0) to "nearly every day" (3).

Other trials of ACT in MS have used alternative measures of depression, such as Becks Depression Inventory (BDI) or the HADS as an outcome measure (e.g. Nordin & Rorsman, 2012). Evidence suggests the BDI and the PHQ are very closely correlated statistically, and the PHQ is shorter and without licence restrictions so chosen over the BDI (Kung et al, 2013).

The HADS was considered the best screening measure to capture overall psychological distress as it measures both anxiety and depression: in a busy recruitment environment it was better to use one brief measure rather than using two separate psychometrics.

With regards to anxiety, there are few psychotherapy RCTs investigating anxiety in the MS population. However, recently the GAD psychometric has found to be a reliable a valid measure within the MS population (Terrill, Hartoonian, Beier, Salem, & Alschuler, 2015).

2.4.3 Secondary Outcome Measures

To assess whether the intervention can affect the aversive impact of MS, the MSIS-29 (Hobart et al., 2001) was used. It is a 29-item scale that has been specifically designed to measure physical and psychological effects of MS on an individual. It has be found to be reliable in community and hospital settings (McGuigan & Hutchinson, 2004) therefore applicable to both recruitment streams in this trial. It is responsive to change in both physical and psychological symptoms (Hobart, Riazi, Lamping, Fitzpatrick, & Thompson, 2005). Estimates of internal consistency are over 0.8. Rasch analysis suggests splitting the two subscales of physical and psychological impact, rather than combining them to form a total score (Ramp et al., 2009).

Nordin and Rorsman (2012) suggest that outcome variables assessing aspects in QoL may be more appropriate than symptom scales given the breadth of difficulties associated with MS and the emphasis on behavioural change rather than symptom reduction in ACT. They define QoL as a measure of social and physical participation and daily functioning. The EQ-5D-5L (Herdman et al., 2011), in which participants rate their health from one to five in five health dimensions creating a single index value, was used to measure QoL and meet this suggestion of using measures potentially more appropriate to the theoretical model and clinical population. The change to five levels from the original three is thought to combat ceiling effects found in the original measures. Using UK data sets the EQ-5D-5L scores were converted into a single score, ranging from -0.59 to 1, where -0.59 indicates worst possible health and 1 indicates perfect health.

2.4.4 Process Measures

ACT is hypothesised to modulate depressive and anxious emotional responses to physical symptoms and unwanted cognitions, for example, a participant feeling depressed as a result of their fatigue. ACT should counteract maladaptive response-focused emotional regulation by increasing acceptance (Hofmann & Asmundson, 2008). To assess whether any changes in mood may be due to ACT processes, rather than via CBT or other process, the AAQ-II (Bond et al., 2011) was used. It contains seven items each scored on a seven point scale and it measures acceptance and experiential avoidance. It has an internal consistency of 0.84 and

test-retest reliability of 0.81 at 3 months. The AAQ-II has been found to change in the predicted direction in response to therapy, thus is should be sensitive to change of theoretical ACT processes (Forman, Herbert, Moitra, Yeomans, & Geller, 2007).

Limitations of the AAQ-II are discussed in detail in extended introduction section 1.3.3. Despite aforementioned limitations, the AAQ-II is still the most ubiquitous measure in ACT research and likely to be acceptable to- and understood by editors, reviewers and readers of ACT peer-reviewed publications and have the most impact, therefore it was used in this trial.

2.4.5 Service-use Measures

To assess whether cost-effectiveness measures can be used well in this study participants completed service-use questionnaires similar to those previously used in an evaluation of cost-effectiveness of psychotherapy in MS (Humphreys, Drummond, Phillips, & Lincoln, 2013). The questions ask about number of contacts with all health and social services in the last three months that were specifically to do with the person's MS. This measure is reproduced in Appendix G.

2.5 Randomisation

Only after participants had completed all baseline measures were they randomised. They were randomised to either TAU and telephone-supported ACT bibliotherapy or TAU, with a 1:1 ratio. A separate researcher (NM) generated a randomisation code, which was kept blind to myself until a participant finished their baseline measures and their allocation was requested. Participants were notified via phone, letter and email of their allocation randomisation group.

One researcher (NM) was blind to group allocation as they verified statistical analysis done by myself. Another researcher (RdN) was not blind to allocation as they assisted with clinical issues that arose from my contact with participants.

2.6 Purposive Sampling

At twelve weeks post-randomisation, maximum variation purposive sampling (Coyne, 1997) was used to select five participants from each group who completed qualitative semi-structured telephone interviews about their experiences in taking part in the study. This method of sampling was used in attempt to analyse a variety

of typical and non-typical perspectives on the study. Five participants from each allocation group were selected: from those in the intervention arm, two that completed the trial were invited to take part, in order of participant number until two participants agreed. One participant that dropped out from each of the categories of illness, commitment and belief that intervention inappropriate were were invited to be interviewed, again in order of participant number until one from each of these three groups was reached. From the TAU group, five participants were invited, contacted in order of participant number, until five agreed. This was in attempt of obtaining a pseudo-random and varied sample, so to avoid only contacting participants that I believed may only have favourable opinions on the study. To avoid experimenter demand effects these interviews were conducted by another Trainee Clinical Psychologist (WV) who was familiar with the trial methodology, the workbook and the ACT model.

2.7 Procedure

Those randomised to the active intervention arm were called to schedule an initial telephone support session to take place in the preceding three weeks and posted a copy of "Get Out of Your Mind and into Your Life" (Hayes & Smith, 2005). The intervention was split into eight sessions, shown in table 8 below.

Table 8. The breakdown of the self-help book.

Week	**Chapters**	**Topic(s)**
1	Introduction, 1 & 2	Human Suffering and Language
2	3 & 4	Avoidance and Letting Go
3	5	Introduction to Thoughts
4	6 & 7	Defusion and the Observing-Self
5	8	Mindfulness
6	9 & 10	Willingness
7	11 & 12	Values
8	13 and Conclusion	Commitment

Participants in the intervention arm received eight accompanying telephone-support calls after each section had been completed. The calls were provided by myself, who was familiar with the workbook and the ACT model. Each phone call asked how the

participant had found the week's content, whether they had completed the exercises, what they did and didn't like and answered any questions they had in understanding the content. A pro-forma detailing the structure and content of the support calls is reproduced in Appendix D.

Those in the control arm received no contact from the study team after being informed of their group allocation, until twelve weeks post-randomisation. At this point, the intervention group had finished their workbook, and both groups were telephoned and emailed to remind them to complete post-intervention measures.

2.8.1 Framework Analysis

The feasibility interviews were analysed using framework analysis, a method frequently used for the analysis of semi-structured interviews (Gale et al., 2013). It is a useful approach when working deductively to answer a predefined question, as it is in this case to answer questions about the feasibility of a study.

Themes were pre-selected on the basis of the research question. They were feasibility and acceptability of recruitment, randomisation, measures, self-help text, telephone support, and changes to the study protocol. Appendix E details the interview guide based around these themes of feasibility.

Analysis commenced with transcription of the audio interviews, whereby participants spoke in relation to one or more of the predefined codes. This was also an opportunity to start becoming immersed in the text. Next a code was applied to each phrase of text. Within each pre-selected theme of feasibility, codes were analysed for patterns, and arranged into a matrix of feasibility themes as columns and participant codes as rows. An example is provided in Appendix F.

2.8.2 Quantitative Data Analysis

Whether baseline HADS, PHQ and GAD scores were correlated with the baseline AAQ-II scores at the start of the study was investigated with correlational analysis.

Data on the length of each telephone call, missed calls, and the time it took participants to complete online measures were collated and means and standard deviations calculated to answer questions about the feasibility of conducting the study.

As recommended in CONSORT guidelines (Moher, Schulz, & Altman, 2001), the main quantitative analysis was the intention-to-treat (ITT) analysis, consisting of data from all 27 participants who provided baseline data. The repeated measures RCT design of the trial suggests two main types of analyses may be used to explore the data; a mixed ANOVA or a linear mixed model.

A mixed ANOVA, also known as a split-plot ANOVA, is used to test for differences between two or more independent groups whilst subjecting participants to repeated measures, whereby variance between and within groups is analysed. A linear mixed model. A linear mixed model is an extension to the generalized linear model in which the linear predictor contains random effects in addition to the usual fixed effects.

Both a mixed ANOVA and a linear mixed model are valid ways to explore repeated measures in RCTs, however linear models convey some important advantages. Linear models treat time as a continuous variable, so do not exclude an entire participant's data if one value is missing. Mixed ANOVAs treat missing data differently; the multiple-imputation method being one of the more robust and popular methods. However there is no agreed method of how to pool effect sizes for mixed ANOVAs from the various estimates generated from the multiple-imputations. Linear models are also more robust when handling samples of different sizes, which is useful for planned per-protocol (PP) analyses where attrition rates between allocation groups may lead to unequal sample sizes. Therefore mixed linear models were the main ITT analysis and variables of group allocation and time point were entered into linear mixed models to explore interactions of intervention and time. PP analysis, where participants who dropped out of the study were excluded, preceded in the same way to the ITT analysis.

To demonstrate the different methods of analysing data and to explore any differences in choice of analysis, mixed ANOVAs were also run on the data, and a summary of results are reported in a footnote in the main journal paper.

2.8.3 Multiple Comparisons

The trial included six different psychometrics; the more measures taken in a study, the higher the chance of making a Type I error, that is assuming there is a significant effect where none exists. Various statistical methods exist that attempt to adjust for this problem. Whilst it can be conservative, the Bonferroni method is one popular method of adjusting for multiple comparisons. In the case of this study, the significance value of 0.05 is divided by six. Therefore analyses have to reach a 'p value' of 0.0083 to be considered significant.

Achieving such a small p value is unlikely in a trial not powered to detect significant between group differences, therefore trends in the data and comparisons approaching significance can also be informative when considering what may be significant in the data of a higher powered trial.

2.8.4 Service-Use Analysis

Results on the service-use questionnaire were converted into an overall number; each contact with a health or social service was counted as one. Contact with health service was then explored between groups using independent t-tests. Self-report medication was cross-referenced against use medication recorded in clinical notes to search for instances where clinical notes reported medications that participants did not, and instances where participants reported medications that clinical notes did not.

2.8.5 Sample Size Estimates

Due to the imprecision inherent in data from small samples, estimates of the intervention effect made in feasibility studies are not used to plan sample sizes for full RCTs (Leon, Davis, & Kraemer, 2011). An alternative approach is to base sample size estimates for a full scale RCT on what is deemed a ***clinically meaningful effect***. For example, from published parameters for the GAD and PHQ, which are a change of five points. Then a full RCT is designed to detect the smallest difference that is generally agreed to be ***clinically meaningful.***

Using the standard deviations of the GAD and PHQ at post-intervention across all participants, sample sizes for both primary measures were calculated in order to have 90% power to detect a change of five points at the 5% significance level.

The calculations are based on a trial design with parallel groups attempting to demonstrate superiority of one arm over another, and assume continuous data and a normal distribution (Julious, 2004).

2.8.6 Individual Changes

People vary in their responses to psychotherapy. Traditional analysis of RCT involves comparing central tendencies between groups, relying on large sample sizes to account for differing individual responses within groups. Whilst a well-designed and conducted RCT finding a significant group difference may reasonably attribute the difference to the intervention, this does not necessarily mean the change is clinically significant for the patients involved.

Analysis of individual changes allows us to estimate, within the constraints of the measures used, whether changes are reliable and clinically significant for each participant providing adequate data. This applies to both improvements and deteriorations.

Where possible, the clinical significance of individual participant change was explored using the Leeds Reliable Index Change Analysis method (Agostinis, Morley, Dowzer, 2008). This involved analysis of both individual reliable change (RCI) and clinically significant change (CSC) for all participants providing baseline and post-intervention data. Using data on the reliability and the error of measurement for the each specified measures, it was calculated whether individual participants exhibited any reliable improvement or deterioration from baseline to post-intervention.

To achieve CSC on the GAD and PHQ, the post-intervention score had to be five or less, as per the published cut-offs.

No clinical cut-offs for the MSIS or EQ5D are suggested in the literature, but suggested minimally important differences (MID) are published, whereby a participant must show an drop of eight points on the combined MSIS (adjusted for EDSS), or an increase of 0.07 on the EQ5D, to be considered as achieving a clinically significant improvement (Costelloe et al., 2007; Walters & Brazier, 2005).

Two case examples were put together where individual change scores on clinical measures were linked with feasibility interviews and other behavioural data in order to highlight methodological issues of conducting psychotherapy trials and issues of interpreting results.

2.9.1 Ethical Approval

In order to recruit participants from the MS Society, ethical permission was granted from the University of Nottingham. In order to recruit participants from the QMC, ethical permission was granted from an NHS Research Ethics Committee (REC) and the Nottingham University Hospital Trust Research and Development department. See Appendix A for a copy of this approval letter.

2.9.2 Informed Consent

Informed consent was obtained in accordance with Good Clinical Practice (GCP) and REC guidance. Participants were first approached by an NHS clinician before speaking with myself. They read the study information sheet and asked any questions they had before giving consent to take part. See Appendices B and C for copies of the patient information sheet and the consent form. Participants were explicitly advised that they could withdraw from the study at any time without needing to provide a reason, and that doing so would not affect their regular care.

2.9.3 Confidentiality

All hardcopy participant data was stored securely in the trial master file and kept in a locked office at the University of Nottingham. All electronic participant data was kept on password protected University of Nottingham secure servers. Each participant was assigned a study identity code number, for use on study forms, other study documents and the electronic database.

2.9.4 Further Considerations

The nature of the model meant that that those receiving the intervention were invited to expose themselves to psychologically aversive experiences, such as depressing memories, future worries and anxious physiology. The theoretical basis is that the person's relationship to these experiences changes, so they experience less suffering. This might be initially distressing, difficult to do and increase psychological

distress, however, there is considerable evidence that ACT can achieve this change and reduce psychological suffering (Hayes et al., 2006).

It was hypothesized that some of those in the intervention group would benefit from the self-help book, therefore it was offered to the control group after their participation in the study had finished. However, due to limited resources this was unfortunately without the additional telephone-support that the intervention group received.

3. Extended Results

The extended results section provides further details on reasons why participants dropped out of the study, assumption testing, full per-protocol results, discussion on missing data and individual change results and case examples.

3.1 Baseline Correlation Results

At baseline, analysis revealed that AAQ-II score was significantly correlated with the HADS (r=0.435, n=27, p=0.24), the GAD (r=0.642, n=27, p=0.0001) and the PHQ (r=0.642, n=27, p=0.0001).

3.2 Missing Data

Longitudinal trials are frequently subject to missing data. Whilst every attempt was made to contact participants, there were still instances of missing data. With questionnaires administered online, there was one participant from the intervention group and one participant from the TAU group that did not supply any data, from 27 randomised. Among questionnaires administered via post, there were two participants from the intervention group and four participants from the control group that did not return questionnaires.

3.3 Attrition Reasons

Reasons participants dropped out of the study are briefly tabulated in the short paper. Purposive sampling meant that participants dropping out were invited for telephone interviews (n=3) and the reasons they dropped out are reported in more detail below.

One participant reported too much external stress to commit to starting the intervention. They reported that the weekly schedule felt like too much like a deadline and it was too overwhelming. They reported they struggle to commit to other things too, and they were having problems in their significant relationships which was another contributing factor to dropping out.

Another participant briefly reported they were not feeling very well at the time, due to an MS related illness, and did not get round to starting the self-help book at all.

Another participant started reading the book, and believed it was aimed at people with “panic attacks” and thought it not “reasonable” to send such a text to someone with a progressive disease like MS, saying that MS should not be grouped with other mental health problems. They were concerned that the text did not mention MS or chronic illness, therefore the authors did not understand the nature of MS.

3.4 Normality and Variance Testing

Both samples having relatively normal distributions is an assumption of independent t-tests. For baseline data, samples were split into TAU and intervention groups and assessed on the normality of their distributions. Samples were assumed as possessing a normal distribution if the Shapiro-Wilk p value was over 0.05, and the skew and kurtosis z score divided by their standard error was between -1.96 and 1.96. The distribution of the HADS, GAD, PHQ, MSIS physical and psychological subscales, EQ-5D-5L and AAQ-II was approximately normal. Therefore independent t-tests were carried out.

The above checks for normality were repeated for data split into intervention completers and non-completers. All groups were normally distributed except the EDSS non-completer group, the PHQ non-completer group and the MSIS-psychological completer group, making these sub-tests less robust and less reliable.

With regards to the assumptions of linear mixed models, it has been argued that the normality or other residuals do not affect the parameter estimates; Gelman & Hill (2007) advise against normality tests of regression residuals as no adjustments would be made if they were found to be violated.

3.5 Per-protocol Analysis

Independent t-tests are less robust when the two groups are unequal in size, as was the case in the per-protocol (PP) analysis (TAU=13, intervention=5). Nevertheless, the distribution of the PHQ, MSIS -physical and -psychological subscales, EQ-5D-5L and AAQ-II were approximately normal, as confirmed by the Shapiro-Wilk test and skew and kurtosis z score division.

Table 9 details the results of the PP linear model analyses and effect sizes. There was a significant interaction for allocation and time for the GAD (F=8.7, p=0.011) in

favour of the intervention at post-intervention. There were no significant interactions for the PHQ, EQ-5D-5L, either MSIS subscale or the AAQ-II. The MSIS psychological subscale interaction effect size almost reached significance (f=4, p = 0.063) at the 0.05 level, as did the AAQ-II interaction effect (f=4.2, p=0.06), in terms of there being a post-intervention effect in favour of the intervention group. All effect sizes were positive.

Table 9. Per-protocol analysis displaying baseline and post-intervention means between and within groups, results of linear model analysis of interaction effects of allocation and time and effect sizes of intervention vs TAU at post-intervention.

	Time					
	Pre-randomisation			**Post-intervention**		
	TAU (n=13)	Intervention (n=5)		TAU (n=12)	Intervention (n=5)	F *(p value)*	Effect size *(95% CIs)* at post-intervention
Measure	Mean *(SD)*	Mean *(SD)*		Mean *(SD)*	Mean *(SD)*	Interaction effect	
GAD	9.85 *(4.83)*	8.2 *(2.95)*	GAD	9.83 *(4.36)*	1.6 *(1.81)*	8.75 *(0.011)*	2.05 *(0.8-3.3)*
PHQ	12.23 *(5.87)*	9.4 *(7.13)*	PHQ	10.58 *(6.3)*	6 *(5.57)*	0.23 *(0.639)*	0.78 *(-0.3-1.85)*
MSIS-Physical	63.84 *(14.28)*	45.2 *(15)*	MSIS-Physical	60.75 *(16.71)*	43 *(22.77)*	0.007 *(0.934)*	1.03 *(-0.07-2.12)*
MSIS-Psych	28.69 *(7.78)*	22.6 *(7.63)*	MSIS-Psych	28 *(9.29)*	15.4 *(6.42)*	4 *(0.063)*	1.53 *(0.36-2.69)*
EQ-5D-5L*	0.36 *(0.25)*	0.49 *(0.17)*	EQ-5D-5L*	0.44 *(0.2)*	0.59 *(0.2)*	0.019 *(0.894)*	0.74 *(-0.34-1.82)*
AAQ-II	23.8 *(12.9)*	19.6 *(6.8)*	AAQ-II*	23.4 *(12.5)*	11.4 *(6.3)*	4.2 *(0.06)*	1.2 *(0.06-2.34)*

*: n for TAU = 11 at post-intervention.

HADS: Hospital Anxiety and Depression Scale, EDSS: The Expanded Disability Status Scale, EQ-5D-5L: Quality of Life Measure, GAD: Generalised Anxiety Disorder Scale, PHQ: Patient Health Questionnaire, MSIS-Physical: Multiple Sclerosis Impact Scale - Physical health subscale, MSIS-Psych: Multiple Sclerosis Impact Scale - Psychological subscale, AAQ-II: Acceptance and Action Questionnaire.

3.6.1 Individual Changes

Table 10 summarises individual pre- and post- scores across five measures for the TAU group, and indicates instances of reliable change and where clinically significant change (CSC) or minimally important differences (MID) are achieved.

Table 10. Individual baseline and post-intervention scores for the TAU group.

Participant	Time	GAD	PHQ	MSIS	AAQ-II	EQ-5D-5L
			TAU group			
3	Pre	8	9	82	22	0.32
	Post	9	14	77	21	0.32
8	Pre	4	6	68	18	0.74
	Post	6	4	65	16	0.64
13	Pre	10	8	87	9	0.55
	Post	9	3	70 $^{MID\uparrow}$	10	0.66 $^{MID\uparrow}$
14	Pre	10	16	94	16	0.42
	Post	3 $^{R\uparrow,C\uparrow}$	3 $^{R\uparrow,C\uparrow}$	76 $^{R\uparrow0,MID\uparrow}$	8	0.52 $^{MID\uparrow}$
17	Pre	7	11	115	34	-0.08
	Post	17 $^{R\downarrow}$	18 $^{R\downarrow}$	122	44	0.54 $^{R\uparrow,MID\uparrow}$
20	Pre	2	7	74	10	0.54
	Post	4	8	73	7	0.65 $^{MID\uparrow}$
21	Pre	6	7	n/a	21	n/a
	Post	7	12	n/a	23	n/a
22	Pre	14	15	82	24	0.43
	Post	12	15	92	28	0.43
23	Pre	10	12	85	32	0.26
	Post	12	10	68 $^{MID\uparrow}$	39	0.42 $^{MID\uparrow}$
24	Pre	9	9 $^{R\downarrow}$	101	7	0.29
	Post	14 $^{R\downarrow}$	18	122 $^{R\downarrow}$	27 $_{R\downarrow}$	-0.02 $^{R\downarrow}$
26	Pre	12	12	119	n/a	0.22
	Post	8	3 $^{R\uparrow,C\uparrow}$	121	n/a	0.29
29	Pre	17	25	109	46	0.31
	Post	17	19	114	34 $^{R\uparrow}$	0.34

^{R} denotes Reliable Change at $p<.05$; ^{C} denotes Clinically Significant Change (from clinical to non-clinical range); ^{MID} denotes a minimally important (clinical) difference; ↑ indicates an improvement and ↓ indicates a deterioration.

Among the TAU group seven participants (58%) achieved a reliable change, clinically significant change or MID on one or more outcome measure, and two (17%) showed a reliable or clinically significant deterioration. One participant (8%)

achieved a reliable improvement in ACT process and one (8%) a reliable deterioration.

Table 11 summarises individual pre- and post- scores across five measures for the intervention group, split into completers and non-completers, and indicates instances of reliable change and where CSC or MID are achieved.

Table 11. Individual baseline and post-intervention scores for the intervention group.

Participant	Time	GAD	PHQ	MSIS	AAQ-II	EQ-5D-5L
			Intervention: Non-completers			
4	Pre	18	21	104	34	-0.17
	Post	12 $^{R\uparrow}$	16	96 $^{MID\uparrow}$	45	0.35 $^{R\uparrow, MID\uparrow}$
6	Pre	18	2	n/a	25	n/a
	Post	5 $^{R\uparrow}$	1	n/a	8 $^{R\uparrow, C\uparrow}$	n/a
12	Pre	4	7	108	24	0.31
	Post	3	5	110	20	0.10
18	Pre	9	20	94	23	0.55
	Post	9	16	115 $^{R\uparrow}$	31	0.55
25	Pre	8	17	100	34	0.62
	Post	1 $^{C\uparrow}$	1 $^{R\uparrow, C\uparrow}$	94	12 $^{R\uparrow, C\uparrow}$	0.50
27	Pre	13	10	96	29	0.65
	Post	14	13	104	30	0.29 $^{R\downarrow}$
28	Pre	16	21	127	40	-0.02
	Post	14	22	116 $^{MID\uparrow}$	42	0.12 $^{MID\uparrow}$
30	Pre	12	18	116	30	0.26
	Post	8	18	96 $^{R\uparrow, MID\uparrow}$	27	0.53 $^{R\uparrow, MID\uparrow}$
			Intervention: Completers			
5	Pre	10	2	51	18	0.48
	Post	0 $^{R\uparrow,C\uparrow}$	1	33 $^{R\uparrow, MID\uparrow}$	9	0.71 $^{MID\uparrow}$
7	Pre	5	8	52	11	0.71
	Post	1	7	53	7	0.70
11	Pre	11	10	73	18	0.64
	Post	0 $^{R\uparrow, C\uparrow}$	2 $^{R\uparrow, C\uparrow}$	32 $^{R\uparrow, MID\uparrow}$	7	0.72 $^{MID\uparrow}$
15	Pre	5	8	58	30	0.32
	Post	4	15 $^{R\downarrow}$	99 $^{R\downarrow}$	12 $^{R\uparrow, C\uparrow}$	0.25
19	Pre	10	21	105	21	0.32
	Post	3 $^{R\uparrow, C\uparrow}$	5 $^{R\uparrow}$	75 $^{R\uparrow, MID\uparrow}$	22	0.56 $^{MID\uparrow}$

^{R} denotes Reliable Change at $p<.05$; ^{C} denotes Clinically Significant Change (from clinical to non-clinical range); ^{MID} denotes a minimally important (clinical) difference; ↑ indicates an improvement and ↓ indicates a deterioration.

Among the intervention non-completers six participants (75%) achieved a reliable change, clinically significant change or MID on one or more outcome measure, and one (20%) showed a reliable or clinically significant deterioration. Two participants (25%) achieved a reliable improvement in ACT process and there were no reliable or clinically significant deteriorations.

Among the intervention completers three participants (60%) achieved a reliable change, clinically significant change or MID on one or more outcome measure, and one (20%) showed a reliable or clinically significant deterioration. One participant (20%) achieved a reliable improvement in ACT process and there were no reliable or clinically significant deteriorations.

3.6.2 Case Examples

In attempt to illustrate different individual journeys through the trial and highlight the limitations in RCT design and analysis, two participant case examples are reported below.

Participant 11 completed the intervention. They showed reliable and clinically significant (CSC) improvement on the GAD and PHQ, reliable and clinically important (MID) improvement on the MSIS, clinically important (MID) improvement on the EQ-5D-5L and a non-significant reduction on the AAQ-II. In the feasibility interview they were asked what changes they noticed in themselves. They reported they no longer take painkillers, but deal with pain by “putting it on the bus”; a technique taught in the self-help text. They said they no longer sit and watch TV anymore, but engage in valued activities, such as speaking more with family. They reported they realised that they were “not living their life”, attributed their improvements to “working out what I was missing out on” and reported they are now “living my life and enjoying myself”.

Participant 15 completed the intervention. They showed a reliable and clinically significant (CSC) improvement in their AAQ-II. However, they showed reliable deteriorations on the PHQ and MSIS. This is unexpected finding is discussed in the extended discussion section.

4. Extended Discussion

In this section primary and secondary findings of the study will be expanded and interpreted in relation to psychological theory. Attrition will be examined in detail. Throughout, the findings will be discussed with regards to their impact on future research and clinical practice, however there are stand-alone sections making practical research recommendations and discussing clinical implications. Finally, the strengths and limitations of the trial are discussed in detail.

4.1 Feasibility

Recruitment

Most participants found it acceptable to be recruited through their MS outpatient clinic, suggesting that filling out screening measures whilst they wait and a brief conversation with their consultant referring them to a separate researcher would be a viable route for future recruitment. Close liaison with a neurologist who understood the trial and was motivated to assist was crucial, as was being continually proactive with clinical and secretarial staff to remind them of the inclusion criteria and troubleshoot any difficulties. One participant thought it was inappropriate to discuss research opportunities with their neurologist; they felt that they only had one brief appointment with a consultant each year and that there were more important issues she wanted to discuss in this valued time. However, the vast majority of participants had no such issues, and it could be argued that offering patients with high levels of psychological distress the opportunity to participate in a study with the potential to reduce this suffering is a valuable use of clinician time, given that increased rates of psychological suffering are correlated with increased physical disability (Chwastiak et al., 2014), therefore an increased cost to the health system. Whilst the outpatient clinic was a fruitful source for recruitment into the trial, advertising through the MS Society produced much lower numbers. Therefore future trials may consider recruiting through outpatient departments in the first instance to maximise trial enrolment.

Randomisation

Most participants thought randomisation was fair, however some did not understand exactly how participants were allocated. At the time of recruitment, it was stressed by the recruiter (BP) that there was a 50% chance of receiving the intervention, and that it is was decided completely at random. Participants were also given information sheets outlining the process. Therefore the process was already as transparent as possible to potential participants.

Measures

At post-intervention, 93% of participants completed online measures. Slightly less (89%) completed postal measures, which might be expected given the increased time required for most participants to complete and post a measure compared to completing measures online. Licence restrictions and limited resources meant that the EQ-5D-5L could not be used online, however, future trials with more resources may consider including this measure in the online psychometric battery to increase data retention.

The 93% of participants completing post-intervention measures is much higher that than the 64% of participants completing the trial: people who had stopped the intervention were still amenable to completing measures. This is helpful for reflecting a more accurate estimate of the effectiveness of being allocated to the intervention in the ITT analysis.

Participants took on average 14 minutes to complete online questionnaires, which they found acceptable. Some participants wanted space next to ordinal questionnaires to clarify or stipulate their responses; future studies may consider collecting more qualitative data, as long as an appropriate qualitative framework for analysing such responses is carefully designed beforehand and it is decided what questions this data will answer.

Self-report Data

With regards to the feasibility of self-report data, results comparing the self-reported and clinic-reported prescribed medication showed there was discrepancies between the two methods. However, this may be obscured by some over-the-counter

medication not being recorded by clinic, recent changes to medications that may not be up to date is clinic records, and problems with participants remembering all their prescribed medications, especially if they are prescribed a lot, as is frequently the case in people with MS. However, where possible future trials should continue to collect data on prescribed medications from clinic notes in the first instance, as this would be the most accurate.

Support-Calls

Support-calls were originally scheduled to take place over seven weeks, however two from the five participants receiving the calls required more calls and more time to complete the book. This may suggest that the support calls and text could be re-designed to be read over a longer period of time, however, we should be wary of spreading out the text too much and potentially losing interest and momentum from participants who wish to read at a faster pace. Overall, flexibility to the participant's wants and needs is likely the best method of providing support. Future studies may stipulate that the book is designed to be read over a certain amount of weeks, but emphasize this is just a guideline that can be adapted. This may also reduce initial concerns over committing to the intervention, which was a reason one participant dropped out. Therefore more flexibility with intervention delivery may be a means to both provide a better quality of psychological support and reduce attrition.

Self-help Text

Hayes's (1999) self-help text employs a lot of "Americanised" language, as one participant stated, which means it may be less acceptable to a UK population. Furthermore, the book uses a lot of theoretical language and concepts, including references to other work and studies. Despite this, the majority of participants found the language used was understandable, although some found it complex and many reported it required a lot of effort to read. The complex language may have made it harder to read, meaning more investment is required in the model and potentially meaning more therapeutic benefit, however this is very speculative. Problems with participants finding the book inapplicable to their experiences may be better dealt with at recruitment, rather than suggesting using a different text entirely, as is discussed in the section on attrition.

The book was chosen for its interactivity; it included a lot of exercises to involve the reader. The book is also authored by a chief proponent of ACT, suggesting close fidelity to the theoretical model. However, this may have come at some cost to the accessibility of the text to this population. Future studies may choose to review and refine what is included in bibliography interventions, with the caution that different participants found different elements of the text helpful.

Protocol Redesign

Results from the interviews suggest that overall, the various components of the trial are largely feasible and acceptable, and the data provides us with clear indications of how to streamline future study protocols. Specifically to the running of a full trial emulating from the results of this feasibility study, researchers may consider recruiting solely through the outpatient clinic, moving QoL measures online and including space for qualitative responses to sit alongside psychometrics. The self-help text may be spread over nine or ten sessions instead of eight. However, there may have been experimenter demand effects during the telephone-feasibility interviews, despite the interviewer (WV) not being otherwise involved in the trial. Furthermore, only ten participants were interviewed, meaning the findings may be less representative of the sample, and weakening the strength of the recommendations that come from this data.

Despite overall apparent acceptability of the components of the trial, because of the large attrition rate in the intervention group meaning this trial is unfeasible in its current format. The reported high feasibility of the trial may suggest the high attrition rate is attributable to external factors outside of the trial. This is discussed in section 4.4.1.

4.2 Sample

The short paper reports significantly higher anxious than depressive symptomology in the sample. This is a surprising finding: existing literature suggests greater point and lifetime prevalence of depression compared to anxiety in MS (Beiske et al., 2008; Korostil & Feinstein, 2007; Mohr & Cox, 2001). Although from a small sample, this may be an important prompt for future epidemiological and clinical studies. Depression is more typically the therapeutic target in published psychotherapy trials

in MS. For example, Proctor and colleagues (in press) were unable to review the effect of teletherapy on anxiety due to lack of eligible RCTs. This is also a prompt for researchers to consider anxiety as a valid therapeutic target, or at least include anxiety psychometrics. Hayes's (2005) self-help text does not specify differing aetiologies for depressive and anxious symptomology, and allows the reader to tailor the intervention to whatever they would like to examine. Therefore the provision of this ACT bibliotherapy may be more suitable than a therapy for a specific mental health difficulty in a population where there is mixed evidence on the levels of anxiety and depression.

The AAQ-II was correlated with the HADS, GAD and PHQ at baseline, ostensibly suggesting that ACT processes may go some way to explaining psychological distress and therefore ACT interventions may be viable. However, the AAQ-II has been critiqued for capturing psychological distress as an outcome rather than measuring ACT process (Wolgast, 2014), therefore one may expect these measures to correlate, and this correlational data alone cannot be used to justify an ACT approach in this instance and further rational is needed.

4.3 Quantitative Results

The short paper reports that the main finding from the linear mixed model analysis was a significant drop (p=0.004) in GAD scores at post-intervention for the intervention group along with a large effect size (0.84 and 95% Cis 0.02-1.66). Ostensibly, this could be interpreted as evidence for the success of the intervention, supports existing literature of the effectiveness of the ACT model (Davis et al., 2015) and is incredibly similar to meta-analytic review for ACT on anxiety where an effect size of 0.83 was found (Vøllestad et al., 2012).

It could be argued that the control arm of "treatment-as-usual", is effectively "no treatment", which one would expect most psychotherapies to beat in a RCT, therefore other psychotherapies aside from ACT may achieve similar results. However, in feasibility work, such an inactive control arm is appropriate; only when proceeding to a full trial would equivalence trials of ACT vs CBT, for example, be considered, as per recommendations (Thomas et al., 2006), so to best use resources.

This research does little to add to the literature on bibliography or teletherapy, due to the package nature of the intervention, however, it does add to the *telebibliography* literature; these interventions can have positive effects (Proctor, Moghaddam, Vogt & das Nair, in press). Unfortunately, this small body of literature may soon be less relevant due to advances and accessibility to ICT methods of delivering psychotherapy, as discussed in directions for future research.

In linear mixed model analysis, there was no significant effect on the PHQ, either MSIS measure, the QoL measure or the AAQ-II in ITT analysis. This is harder to interpret, given previously outlined criticisms of the AAQ-II capturing psychological distress rather than ACT processes, and potential overlap between the GAD and the MSIS-psychological subscale and the GAD effect being significant. Even if we assume the AAQ-II can capture ACT processes, a drop in GAD scores with no significant drop in ACT scores suggests an amelioration of anxiety may have been achieved through other means outside of the ACT model, or undetectable on the AAQ-II, although this RCT was not powered to detect significant differences. It is rare that a single mediator might be able to completely explain the relationship between an independent and a dependent variable, particularly in therapies as complex as ACT (Luciano et al., 2014). Indeed, as the authors suggest, it may take decades to identify all the psychological constructs that partially or fully mediate the causal relationships between ACT and clinical improvement.

The PP analysis is only conducted with participants that completed the trial and post-intervention measures. This was 13 participants in the TAU group and five participants in the intervention group. PP analyses do not account for reasons participants did not complete the trial or provide data; they exclude data from participants who may have dropped out due to poor acceptability or effectiveness of the intervention, for example. Therefore, this type of analysis is not favoured over ITT analyses. Nevertheless, PP analysis can give us some estimate of the efficacy of the intervention in a scenario whereby all participants stick to the protocol and there is no missing data. It may also elucidate individual differences in completers vs non-completers when the PP analysis is compared to the ITT analysis.

Completers and Non-completers

The PP analysis found a significant effect in favour of the intervention at post-intervention for the intervention group on GAD scores. Effect sizes varied from 0.75 to 2.05 and confidence intervals were very large. As PP analysis drops non-completers, significant baseline differences between completers and non-completers are not accounted for; those that completed the intervention tended to benefit, hence the overall increase in effect sizes. The MSIS-psychological and AAQ-II came close to reaching significance. The main difference in findings between the ITT and the PP analysis is the difference in the AAQ-II scores; if we exclude participants who dropped out of the intervention group, we see a close to significant reduction in ACT process scores, alongside a drop in anxiety and MS related psychological distress. This trend suggests that those who completed the intervention may have benefited through employing ACT processes, and this trend is masked in the ITT analysis.

When examining the pre-randomisation characteristics of completers vs non-completers, we see that those that went on to drop-out of the intervention group had higher rates of physical and psychological distress on the MSIS. This suggests that those with higher rates of physical disability and MS-related distress are less likely to engage with the intervention. The most physically and psychologically unwell people; those who need support the most, are more likely to drop out. Interventions to reach this population need to be explored and trialled, which is discussed later in this chapter.

Non-completers also had higher baseline rates on the AAQ-II, leading to the hypothesis that participants may need some level of healthy ACT processes at the start of the intervention if they are to *complete* it. Those that completed the intervention tended to benefit from it, as demonstrated in the PP analysis, so this extends this hypothesis to that participants may need some level of healthy ACT process if they are to *benefit* from the intervention.

Participants with high levels of ACT processes are more cognitively fused, less accepting and more avoidant. One may expect significantly higher GAD and PHQ scores in this sub-group of those with significantly higher ACT scores who went on to drop-out, if ACT process predicts psychological wellbeing and the AAQ-II and other distress measures are correlated. However, only MS related measures were

significantly higher and not the GAD or PHQ: Speculatively, within this subgroup psychological suffering arises directly from their illness and therefore differences are not found on general psychological wellbeing measures. Distress may arise from their MS and not independently of it, and acceptance may play an important role (Pakenham, 1999; 2006). More research is needed into the aetiology of distress and what ACT theory may be able to add.

Whilst people with high AAQ-II may have more to gain from ACT psychotherapy, the text is more removed from their perspective and coping mechanisms so may they completely reject it and drop-out of treatment. There is limited literature on what predicts attrition in ACT therapies, as typically participants who drop-out of trials are lost to follow-up. However, participants in this trial who dropped out still completed post-intervention measures and feasibility interviews. The data provided by this trial contributes to this little explored facet of psychological theory and there is a unique opportunity to explore factors what may predict retention and what may predict attrition.

Previous literature is mixed as to the moderating effect of baseline levels of unhealthy ACT process on treatment outcome. Zettle (2012) found that higher baseline levels of experiential avoidance positively predicted outcomes in a small sample of students with mathematics anxiety who were treated with ACT, similarly to Arch and colleagues (2012) who found that those high in experimental avoidance showed more improvement in ACT treatment. However, the converse has been found, whereby moderate, but not high levels of experiential avoidance were optimal for outcome in ACT treatment (Wolitzky-Taylor et al., 2012). The authors recommend that those with high baseline experiential avoidance may be best suited for CBT and those with moderate baseline experiential avoidance may be best suited for ACT. In their equivalence trial they found that long-term improvement in CBT was greatest for those with high experiential avoidance at baseline, and moderate levels of experience avoidance at baseline were optimal for outcome for those allocated to ACT. However, these trends were not statistically significant and the authors do not attempt to suggest theoretically why this may be the case. Their findings and those from this study suggest that patients and participants could be assessed on ACT and other process measures at baseline and matched to a treatment more likely to benefit them; an idea which is elaborated in the section on recommendations for

research. There is little literature on baseline ACT process characteristics and trial *completion* rate; however, the findings of the current study appear to fit with findings that moderate, but not high levels of baseline unhealthy ACT processes are optimal for participant retention and positive treatment outcome.

People who are the most physically and psychologically unwell are more likely to drop out. This intervention attempted to provide support to people where there is a barrier to accessing face-to-face support, however, in doing so may have marginalised those suffering physical and psychologically the most. Those who are more unwell find it harder to access face-to-face support; so suggesting more face-to-face sessions may not be a way around this barrier. Those with high amounts of unhealthy ACT processes also may need alternative methods to increase engagement. Alternatively, the ACT model itself may not be suitable for this population compared to other psychological models potentially more acceptable to those with high amounts of experiential avoidance, such as CBT (Wolitzky-Taylor et al., 2012), although more research is needed.

Overall, all effect sizes in the ITT and PP analyses were positive and one significant interaction effect was found, which considering the trial was not designed to detect between and within group differences is of great credit to the power of the intervention. However, not all of these effects are statistically or clinically meaningful, although this was not the main aim of the study.

In conclusion, the ITT showed that intervention had a significant effect on lowering anxiety, compared to TAU. A correlated drop in unhealthy ACT processes only starts to become significant when drop-outs are removed, as in the PP analysis. This may be because a sub-group benefitted greatly from the intervention, evidenced by the drop in GAD scores, but had with smaller shifts on the AAQ-II, which are masked when this sub-group is pooled with drop-outs.

Alternatively, it may be because we know that those with high pre-randomisation AAQ-II scores were more likely to drop out, but not those with higher GAD scores: there was a lot of variation between completers and non-completers in the intervention group on AAQ-II scores, meaning ITT interaction effects were not significant. Only when the PP analysis removes participants with high baseline AAQ-II scores do we see an interaction effect approaching significant. Therefore,

participants who do not already have high levels of unhealthy ACT process at the start of the trial, went on to have a significant reduction in their anxiety as a result of engaging in the intervention, compared to those receiving TAU.

Functional Measures and Mechanism of Change Conclusions

The ACT model would hypothesise change on the AAQ-II first and change on functional measures, such as the EQ-5D-5L, before changes on symptom measures. However, whilst there were significant changes in anxious symptomology there were no differences on the EQ-5D-5L, which includes items on functioning and activity. Were those achieving decreases in anxiety doing without engaging more in valued activities? The QoL measure may not be sensitive enough to detect differences, particularly in a trial underpowered to do so. So whilst there is some evidence from the ITT and PP analyses that changes were achieved through ACT process, no trends in QoL measures between groups cloud this conclusion, as does a lack of trend in tracking individual changes (See 4.5.1) and we cannot conclude with any certainty how those who benefited did so. A full trial would be more equipped to elucidate mechanisms of change, as would longer term follow up.

4.4.1 Attrition

There was a large attrition rate in the intervention group, and because of this the trial is currently unfeasible in its current format. The attrition rate is an important finding relating to the question of feasibility. Upon first inspection, participant reports of high feasibility seems discordant with a high attrition rate. There may have been experimenter demand effects during the telephone-feasibility interviews, despite the interviewer (WV) not being otherwise involved in the trial. Furthermore, only ten participants were interviewed, meaning the findings may be less representative of the sample, and weakening the strength of the recommendations that come from this data. Written responses instead of telephone interviews may have provided less biased data, however, richness of data would have been lost as answers could not be explored in more detail as they came up, which the interviewer was able to do.

The minimum sample size of 26 was designed so to leave 12 participants in each group after drop-out. The drop-out estimate of 7.5% was derived from a previous attrition rate reported in a meta-analysis of telephone-support bibliotherapy trials

(Mohr et al., 2008). However, the meta-analysis includes studies done in a variety of physical and mental health populations, not just MS, and therefore in hindsight a more cautious approach may have been to use a higher estimate, although little literature on this topic exists. The attrition rate in this study was 33% and 64% in the intervention arm, and the fact that all participants had MS may be one reason contributing to the higher than expected drop-out. However attrition in the TAU group was much lower, suggesting that a more predictive factor leading to a high attrition rate than participants having MS was the requirement to engage in this intervention.

4.4.2 Attrition Reasons

Overall, examination of attrition reasons suggests that not all, but the majority of drop-out was due to external factors and not trial specific factors. Some participants dropped-out due to illness; there is little researchers can do to avoid participants dropping out due to illness, MS-related or otherwise. The relapsing-remitting nature of some diagnoses of MS means participants can unexpectedly and rapidly deteriorate. Furthermore, exacerbations frequently coincide with difficulties in concentration, making engagement with psychotherapy hard. These cognitive and attentional factors related to MS may make it harder for participants to engage in long periods of reading. Future studies may benefit from allowing participants to take breaks from treatment so they can continue when they are more able and motivated to engage.

Some participants cited outside stressors as a reason to dropping out of the intervention group. It was made clear during recruitment the amount of commitment involved in taking part in the study. Therefore, speculatively it may be a product of the outpatient recruitment environment; participants had just seen their neurology consultant and may have been attending more to their physical and mental health, so may have been more willing to consent to a psychotherapy trial. However, outside of this context their motivation may have decreased, meaning they are more likely to drop out.

Two participants dropped out as they thought the book not inappropriate for their needs; for example, not MS specific. Both found it “insulting” that their MS was being grouped with other mental health difficulties such as obsessive compulsive disorder. There is a serious risk here of further alienating these participants through

crystalizing their view of mental health services; will they be less likely to access support in the future now because of their involvement in the trial? These participants were contacted with apologies about the miscommunication during the recruitment stage. The offence that the participants reported could have triggered a deterioration in psychological wellbeing, however, at post-intervention one of these two participants showed reliable and clinically significant improvements on the GAD, PHQ and AAQ-II and the other showed reliable and minimally important improvements on the MSIS and EQ-5D-5L. Therefore in this instance taking part in the study did not adversely affect these participants, at least on the battery of psychological and physical outcomes employed in this study. However, considering how this risk could be avoided in future research would be prudent, perhaps through increased face-to-face engagement.

The face-to-face ACT psychotherapist would be more equipped to deal with resistance to engage in the model. ACT is seen as a basic theory of human behaviour and experience, adaptable to individual circumstance, so the therapist may be able to help the participant tailor the book to their specific needs. They could use participant's in-session thoughts as a way to explore the model and motivate the client. Future trials should emphasise that the ACT model is not MS-specific, but is adaptable to personal experience. Therefore, future studies may benefit from initial face-to-face or trial intervention to answer any questions and deal with such challenges. Practically, this could take the form of one, two or three face-to-face sessions before starting the self-help text and continuing with telephone-support calls from the same therapist, which is an avenue for future research.

4.5.1 Individual Change Results

The results of the individual change analyses shows clinically significant changes, minimally important difference and reliable improvements and deteriorations in TAU and intervention groups, and among completers and non-completers. Four from five intervention completers showed some significant improvement, although one of these had a significant deterioration on another measure. One showed no changes whatsoever.

Across participants in the TAU group and intervention completers and non-completers there are no clear trends. Many individuals in the TAU and the non-

completer group showed improvements, which may link to the nature of MS and that many were diagnosed with the relapsing-remitting form of the condition. A lack of clear differences in individual changes between groups suggests that those not receiving the intervention may be experiencing similar clinically important improvements and deteriorations to those receiving it, although the sample size is small. A lack of clear between group differences when taking into account all six measures may also detract from the initial success of the findings on anxiety in the linear mixed model analysis and effect size estimates.

The individual change results add little to any clinical or research implications we can draw from this study. Tracking individual changes in a larger study may result in the emergence of clearer trends.

4.5.2 Case Examples

Participant 11, an intervention completer, engaged in core ACT processes which may account for their significant improvement on outcome measures. Whilst their change on the AAQ was not reliable, their post-intervention score of seven is the lowest value it is possible to score on the measure. It is likely that ACT processes were a mechanism of change for this individual. This also illustrates that the reliable change methodology is not infallible and needs to be triangulated with other methods for tracking change.

Participant 15, an intervention completer, showed improvements on the AAQ-II, but deterioration on the PHQ and MSIS, the opposite of what the ACT model would predict. This is problematic when speculating on mechanisms of change; it highlights individual differences in response to treatment as well as evidence in opposition to the ACT model in this instance.

These two case studies highlight the problem of firstly attributing clinical changes to specific psychological mechanisms, and also methodological issues of grouping individuals together in traditional analyses; it can mask this issue of individual differences in response to treatment and underemphasise the finding that some individuals experience reliable deteriorations in physical and psychological wellbeing.

4.6 Extended Strengths

The methodological design of the study is strong; an RCT allows for the testing of the intervention against a control group, therefore increasing our accuracy in attributing changes to the actual intervention rather than placebo effects of being involved in a trial or external factors. The randomisation of 27 participants between allocation groups and high post-intervention measure completion percentage means parameters for a full trial can be estimated. (Julious, 2005). The randomisation procedure took place after the completion of baseline and pre-randomisation measures were completed, and the randomisation key was held securely and only revealed on a participant-by-participant basis as they completed measures. Therefore, the potential for bias drops as the participants were randomised purely by chance.

Quantitative analyses of between and within groups pooled data, coupled with individual analysis of reliable and clinically significant change and content analysis of qualitative feasibility data provides a rich dataset to triangulate responses and explore questions of feasibility and potential effectiveness. Individual change analysis allowed estimation of whether any changes were meaningful for participants, rather than solely reporting statistically significant between group differences which may be less clinically relevant to individual participants. Framework analysis was methodologically sufficient to answer questions about the feasibility of the trial. However, in this type of analysis some participant responses that do not fit into pre-defined frames are dropped, and inductive qualitative methods that explore how people with MS construct their disease, which likely has implications for psychotherapy, could be a valid alternative method of fully capturing how participants experienced the taking part in the trial and the intervention.

Recruitment was successful with regards to uptake, meaning the assessment, intervention and evaluation phases of the trial were completed within the expected time-frame laid out in the protocol. This uptake in the trial also reminds us that many people with MS do suffer from difficulties with anxiety and depression, as shown by those scoring over the cut-off on the HADS, and there is a need for mental health service provision in this area. The vast majority of participants were recruited via NHS services, increasing the impact of the research on clinical practice within the

UK health system. Lastly, quantitative data can be included in systematic reviews and meta-analyses, therefore potentially influencing future guidelines directing service provision.

4.7 Extended Limitations

This study suffers from considerable limitations. Firstly, methodological difficulties with regards to unpacking the active, or most active ingredients of the intervention. Secondly, a high attrition rate and thirdly a lack of long-term follow-up.

Implications for theory

There are limitations on what the trial may be able to add to existing literature on ACT theory. Whilst RCT designs are adept at quantifying the effectiveness of a therapeutic intervention, they are less equipped to explore change processes and mechanisms of change. Unpicking the active ingredients of the intervention is important to advance theoretical understanding of why psychotherapy works. The self-help text directly links to ACT theory and the feasibility interviews suggested some, but not all participants may have benefitted through ACT processes. A fidelity analysis of the adherence of the telephone calls to ACT principles would have further helped dissect the intervention. Other variables such as therapeutic relationship were not measured, and problems with attributing change using AAQ-II have been discussed. Feasibility interviews suggested different participants found different elements of the ACT model more helpful than others. RCTs can add valuable contributions to theory, such as who may or may not benefit from therapy, however RCTs need to be triangulated with single case designs and studies employing other methods of measuring complex dynamic change processes.

Unfortunately, there is no way of clearly discriminating between the telephone-support calls and the self-help text in terms of their effect as the support participants received was a package intervention. For example, did people benefit from weekly social support over the telephone rather than ACT bibliotherapy? Employing a TAU only group rules out change due to extra care and attention from being involved in a trial, but nothing else. Unpacking the active ingredients of change is beyond the scope of this particular trial, although potential changes to the design of the study are discussed in the section on recommendations for future research.

Attrition

The trial suffers from an attrition rate much higher than expected. However, this is useful data in informing us that participants may drop-out from the trial due to the nature of the intervention, therefore prompts the exploration of ways the intervention may be adapted. It is also useful in estimating recruitment parameters for future trials, knowing that participants may drop out due to the disabling nature of their MS and other factors. However, it does limit the main ITT analysis as changes during the trial are harder to pin on the intervention if many participants dropped out. The PP analysis also suffers from small and unequal group sizes therefore effect sizes have very large confidence intervals. Qualitative comparisons of feasibility-interviews between completers and non-completers are also limited due to only a small sample of non-completers providing feasibility-interview data. Therefore the understanding of why participants dropped out is limited, and issues of participant retention in future trials can only be addressed to some extent.

Length of follow-up

Participants were assessed immediately post-intervention on clinical measures, which only gives us a cross-sectional estimation of the effects of the intervention. Ideally, all participants would be followed up and assessed again to estimate the effects of the intervention some months after the intervention has terminated, so to investigate if any long-term psychotherapeutic gains are sustained, again compared to TAU. A recent meta-analysis and systematic review of teletherapy interventions for psychological distress in MS reported that few gains are sustained in the long-term (Proctor, Moghaddam, Vogt & das Nair, in press). None of the included trials employed ACT interventions, therefore longer term follow up of whether this modality of psychotherapy is comparable with the literature on long-term effects of teletherapy interventions within this population is warranted.

4.8 Research Implications

Findings from this study suggest multiple directions for future research. Running a full RCT with some minor adjustments would be risky, despite potential to see psychotherapeutic gains in the intervention group and the relatively low numbers required to be recruited. (Sample size calculations to power a full trial to detect

significant between-group differences estimate 52 participants would be needed. Anecdotally, this would be a feasible recruitment target if recruiting from the weekly neurology outpatient clinic and could be achieved relatively quickly). However, the more the current protocol is changed, the less the feasibility findings can be used to justify a full trial.

No significant differences were found between groups on number of contacts with health services. A full RCT would also collect health service use data to evaluate cost-effectiveness of intervention, to evaluate the potential savings to the health system made from reducing psychological distress, which would make a better case for this format of intervention to be introduced into routine care.

Adding a third arm to the full RCT whereby participants receive just the self-help book without telephone support calls could be way to investigate what the most helpful aspects of the intervention are, with a view to being able to recommend the most effective type of support that uses the least resources. However, with anecdotal evidence from myself, I would suggest there may be no completers at all in this third arm; many of those receiving the calls said they were vital to motivate them to keep going through the book and without weekly calls they would not be able to complete the book. This would still be useful data in terms of proof-of-concept and would be robust evidence that teletherapy is an active and necessary ingredient in bibliotherapeutic change processes. Therefore this is a firm recommendation for future research. Furthermore, a larger trial could have a more active control arm, such as that used by Ehde and colleagues (2015) whose control arm consisted of a telephone-based programme of education on MS symptoms and symptom management in attempt to control for common factors such as therapeutic relationship, treatment dosing, and participation in a manualized intervention. This could further help elucidate mechanisms of change.

This feasibility trial has also highlighted a sub-group of non-completers who may not engage with the ACT model, possibly due to high levels of MS related physical and psychological support and possibly due to high levels of unhealthy ACT processes. Future research may be designed to provide support to this group of people. The ideas below would require new feasibility trials themselves as they deviate

significantly from the protocol of this study, and the feasibility data wouldn't extrapolate to these new designs.

A trial involving face-to-face starter sessions before ongoing telephone-support could be conceived. The rationale for this would be to decrease the high attrition rate found in this study. Starter sessions may increase the therapeutic relationship, a known predictor of positive therapeutic outcome, and starter sessions may help participants with high levels of ACT processes acculturate to the ACT model; a set of ideas they would be unfamiliar and maybe resistant to, and something a text-book may not be able to deal with.

Another option may be to redesign the self-help text. Future trials may consider pre-existing ACT books written by British authors or with less complex language to make the book more accessible. However some participants thought that the book should be MS-specific, so an MS-specific book could be used. However, Haye's (2005) book allows the reader to work on whatever they wish and is not prescriptive; for the sample in this trial, this was unexpectedly anxiety. An MS-specific book may be too prescriptive in dictating what participants should be working on. One way designing a different book may be to do focus group with people with MS and psychological distress to explore what participants would find most helpful (as per Ehde et al., 2015).

Part of the rationale for the current RCT was that people with MS can find it hard to travel to face-to-face sessions. Adding face-to-face starter sessions obviously is not an option for the most unwell people with MS. To increase engagement and reduce attrition in this group, a study may be designed where clinicians do home visits, at least at first. This would be more resource intensive. Another alternative to augment bibliotherapy could be to use audio-visual and computer technologies. There have been some promising studies of the use of videoconferencing technologies in the delivery of ACT therapies for mental health problems (e.g. Yuen et al., 2013). Therapeutic alliance, if poor can lead to drop-out: systematic analysis has rated therapeutic alliance in video-therapy as high (Simpson & Reid, 2014), although whether it increases participant retention and/or therapeutic outcome more than telephone-support requires further research.

This study found that those with the highest levels of unhealthy ACT processes went on to drop out and those with moderate levels completed the intervention and benefited from it. Wolitzky-Taylor and colleagues (2012) found that those with highest levels of experiential avoidance had better long-term outcomes when allocated to CBT rather than ACT. Future research may consider assessing participants at baseline on the AAQ-II, for example, and splitting them into high and low subgroups. These two groups could then be randomly allocated to either ACT bibliotherapy or CBT bibliotherapy, to create a four arm trial. The hypothesis would be that those in the "high" group allocated to CBT and those in the "low" group allocated to ACT would outperform those in the "high" group allocated to ACT and those in the "low" group allocated to CBT.

Overall, this trial suggest multiple research avenues, and is not particularly directive in suggesting one over another. Future research may wish to consider using other measures instead of the AAQ-II, such as the CompACT (Francis, Dawson and Golijani-Mogghaddam, submitted) which may more accurately capture ACT processes. If trialling ACT against CBT, CBT process measures could also be used for a more thorough investigation of change mechanisms.

4.9 Implications for Clinical Practice

The vast majority of participants were recruited directly from a regular NHS neurology outpatient clinic, therefore recommendations emulating from the findings of this trial should be applicable to routine practice within the UK healthcare system. However, as the trial sits within a research framework of conducting feasibility trials with a view to designing larger trials, the findings generate many more research recommendations than implications for clinical practice.

Nevertheless, providing access to psychological studies at weekly neurology outpatient clinics is feasible, and furthermore, the interventions have demonstrated the potential to reduce patient's anxious symptomology. Data from this trial can be included in future meta-analysis and systematic review which can influence clinical guidelines. Therefore the results from this study should demonstrate to those commissioning services that there is a demand for psychological support and a feasible means of providing such support, albeit further investigation as to the clinical significance of the support needs to be done.

Specifically to the consultants, registrars, MS nurses and secretarial staff at the QMC with whom I worked, they can see that the routine delivery of a psychometric is feasible, and to the consultants and registrars highlights the high levels of psychological distress in their patient population. This impact will be more through them working directly with myself, rather than from the published findings, and furthermore there will be high staff-turnover. However, for the consultants with whom I worked who lead the service, conducting this research ideally should mean that they continue to maintain working relationships with local clinical psychology doctorate courses and work with trainees undergoing research, as they have seen it is feasible. Future research may consider neurologist views as to how psychological research can be further integrated into routine clinical practice.

Extended References

Arain, M., Campbell, M. J., Cooper, C. L., & Lancaster, G. A. (2010). What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Medical Research Methodology, 10*, 67.

Arch, J. J., Wolitzky-Taylor, K. B., Eifert, G. H., & Craske, M. G. (2012). Longitudinal treatment mediation of traditional cognitive behavioral therapy and acceptance and commitment therapy for anxiety disorders. *Behaviour Research and Therapy, 50,* 469–478.

Barnwell, A. M., & Kavanagh, D. J. (1997). Prediction of psychological adjustment to multiple sclerosis. *Social Science & Medicine, 45,* 411–418.

Bashshur, R., Shannon, G., Krupinski, E., & Grigsby, J. (2011). The taxonomy of telemedicine. *Telemedicine and e-Health, 17*, 484–494.

Beckner, V., Vella, L., Howard, I., & Mohr, D. C. (2007). Alliance in two telephone-administered treatments: Relationship with depression and health outcomes. *Journal of Consulting and Clinical Psychology, 75*, 508.

Bee, P. E., Bower, P., Lovell, K., Gilbody, S., Richards, D., Gask, L., & Roach, P. (2008). Psychotherapy mediated by remote communication technologies: a meta-analytic review. *BMC Psychiatry, 8*, 60.

Beiske, A. G., Svensson, E., Sandanger, I., Czujko, B., Pedersen, E. D., Aarseth, J. H., & Myhr, K. M. (2008). Depression and anxiety amongst multiple sclerosis patients. *European Journal of Neurology, 15,* 239–245.

Billingham, S. a M., Whitehead, A. L., & Julious, S. (2013). An audit of sample sizes for pilot and feasibility trials being undertaken in the united kingdom registered in the united kingdom clinical research network database. *BMC Medical Research Methodology, 13*, 104.

Bond, F. W., Hayes, S. C., Baer, R. A., Carpenter, K. M., Guenole, N., Orcutt, H. K., … Zettle, R. D. (2011). Preliminary psychometric properties of the acceptance and action questionnaire–II: A revised measure of psychological inflexibility and experiential avoidance. *Behavior Therapy, 42,* 676–688.

Brenes, G. A., Ingram, C. W., & Danhauer, S. C. (2011). Benefits and challenges of conducting psychotherapy by telephone. *Professional Psychology: Research and Practice, 42,* 543.

Cameron, I. M., Crawford, J. R., Lawton, K., & Reid, I. C. (2008). Psychometric comparison of PHQ-9 and HADS for measuring depression severity in primary care. *The British Journal of General Practice, 58,* 32–36.

Cavanagh, K., Strauss, C., Forder, L., & Jones, F. (2014). Can mindfulness and acceptance be learnt by self-help?: A systematic review and meta-analysis of mindfulness and acceptance-based self-help interventions. *Clinical psychology Review, 34*, 118–129.

Chwastiak, L., Ehde, D. M., Gibbons, L. E., Sullivan, M., Bowen, J. D., & Kraft, G. H. (2014). Depressive symptoms and severity of illness in multiple sclerosis: epidemiologic study of a large community sample. *American Journal of Psychiatry, 159*(11), 1862-1868.

Costelloe, L., O'Rourke, K., Kearney, H., McGuigan, C., Gribbin, L., Duggan, M., … Hutchinson, M. (2007). The patient knows best: significant change in the physical component of the multiple sclerosis impact scale (MSIS-29 physical). *Journal of Neurology, Neurosurgery & Psychiatry, 78*, 841–844.

Coyne, I. T. (1997). Sampling in qualitative research: Purposeful and theoretical sampling; merging or clear boundaries*? Journal of Advanced Nursing, 26*, 623–630.

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., & Petticrew, M. (2008). Developing and evaluating complex interventions: the new medical research council guidance*. BMJ, 337,* a1655.

Cuijpers, P., Donker, T., van Straten, A., Li, J., & Andersson, G. (2010). Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety disorders? A systematic review and meta-analysis of comparative outcome studies. *Psychological Medicine, 40*, 1943–1957.

Dahl, J., Wilson, K. G., & Nilsson, A. (2004). Acceptance and commitment therapy and the treatment of persons at risk for long-term disability resulting from stress

and pain symptoms: A preliminary randomized trial. *Behavior Therapy, 35*, 785–801.

Davis, M. L., Morina, N., Powers, M. B., Smits, J. A. J., & Emmelkamp, P. M. G. (2015). A meta-analysis of the efficacy of acceptance and commitment therapy for clinically relevant mental and physical health problems. *Psychotherapy and Psychosomatics, 84,* 30–36.

Dennison, L., Moss-Morris, R., & Chalder, T. (2009). A review of psychological correlates of adjustment in patients with multiple sclerosis. *Clinical Psychology Review, 29,* 141–153.

Dorstyn, D., Mathias, J., & Denson, L. (2013). Applications of telecounselling in spinal cord injury rehabilitation: a systematic review with effect sizes. *Clinical Rehabilitation, 27*(12) 1072–1083.

Ehde, D. M., Elzea, J. L., Verrall, A. M., Gibbons, L. E., Smith, A. E., & Amtmann, D. (2015). Efficacy of a telephone-delivered self-management intervention for persons with multiple sclerosis: a randomized controlled trial with a one-year follow-up. *Archives of Physical Medicine and Rehabilitation, 96,* 1945–1958.

Forman, A. C., & Lincoln, N. B. (2010). Evaluation of an adjustment group for people with multiple sclerosis: a pilot randomized controlled trial. *Clinical Rehabilitation, 24*, 211–221.

Forman, Herbert, J. D., Moitra, E., Yeomans, P. D., & Geller, P. A. (2007). A randomized controlled effectiveness trial of acceptance and commitment therapy and cognitive therapy for anxiety and depression. *Behavior Modification, 31*, 772–799.

Francis, A., Dawson, D., & Golijani-Mogghaddam, N. (Submitted). The development and validation of the comprehensive assessment acceptance and commitment processes (CompACT). *Journal of Contextual Behavioral Science.*

Gale, N. K., Heath, G., Cameron, E., Rashid, S., & Redwood, S. (2013). Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology, 13*, 117.

Galeazzi, G. M., Ferrari, S., Giaroli, G., Mackinnon, A., Merelli, E., Motti, L., & Rigatelli, M. (2005). Psychiatric disorders and depression in multiple sclerosis outpatients: impact of disability and interferon beta therapy. *Neurological Sciences, 26*, 255–62.

Gelman, A., Hill, J., 2007. *Data analysis using regression and multilevel/hierarchical models*. Cambridge, UK: Cambridge University Press.

Harris, R. (2009*). ACT made simple: An easy to read primer on acceptance and commitment therapy.* Oakland, CA: New Harbinger.

Hailey, D., Roine, R., Ohinmaa, A., & Dennett, L. (2011). Evidence of benefit from telerehabilitation in routine care: a systematic review. *Journal of Telemedicine and Telecare, 17,* 281–287.

Hailey, D., Roine, R., Ohinmaa, A., & Dennett, L. (2013). The status of telerehabilitation in neurological applications. J*ournal of Telemedicine and Telecare, 19*(6) 307–310.

Haug, T., Nordgreen, T., Öst, L. G., & Havik, O. E. (2012). Self-help treatment of anxiety disorders: a meta-analysis and meta-regression of effects and potential moderators. *Clinical Psychology Review, 32*, 425–445.

Hayes, S. C., Luoma, J. B., Bond, F. W., Masuda, A., & Lillis, J. (2006). Acceptance and commitment therapy: model, processes and outcomes*. Behaviour Research and Therapy, 44,* 1–25.

Hayes, S. C., & Smith, S. (2005). *Get out of your mind and into your life: The new acceptance and commitment therapy*. Oakland, CAL New Harbinger Publications.

Hayes, S. C., Strosahl, K. D., & Wilson, K. G. (1999). *Acceptance and commitment therapy: An experiential approach to behavior change*. New York, NY: Guilford Press.

Herdman, M., Gudex, C., Lloyd, A., Janssen, M. F., Kind, P., Parkin, D., … Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research, 20,* 1727–1736.

Herrero, M. J., Blanch, J., Peri, J. M., De Pablo, J., Pintor, L., & Bulbena, A. (2003). A validation study of the hospital anxiety and depression scale (HADS) in a spanish population. *General Hospital Psychiatry, 25*, 277–283.

Hobart, J., Lamping, D., Fitzpatrick, R., Riazi, A., & Thompson, A. (2001). The multiple sclerosis impact scale (MSIS-29) a new patient-based outcome measure. *Brain, 124,* 962–973.

Hobart, Riazi, A., Lamping, D. L., Fitzpatrick, R., & Thompson, A. J. (2005). How responsive is the multiple sclerosis impact scale (MSIS-29)? A comparison with some other self report scales. *Journal of Neurology, Neurosurgery & Psychiatry, 76*, 1539–1543.

Hofmann, S. G., & Asmundson, G. J. G. (2008). Acceptance and mindfulness-based therapy: new wave or old hat? *Clinical Psychology Review, 28*, 1–16.

Hofmann, S. G., Sawyer, A. T., Witt, A. A., & Oh, D. (2010). The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *Journal of Consulting and Clinical Psychology, 78*, 169.

Humphreys, I., Drummond, A. E. R., Phillips, C., & Lincoln, N. B. (2013). Cost-effectiveness of an adjustment group for people with multiple sclerosis and low mood: a randomized trial. *Clinical Rehabilitation, 27*, 963–971.

James Lind Alliance. (2013). *Top Tens: Multiple Sclerosis.* Retrived January 5, 2016. From, http://www.jla.nihr.ac.uk/top-tens/ms-psp-top-10

Johansson, T., & Wild, C. (2011). Telerehabilitation in stroke care–a systematic review. *Journal of Telemedicine and Telecare, 17*, 1–6.

Julious S, A. (2004). Sample sizes for clinical trials with normal data. *Statistics in Medicine(23),*1921-1986.

Julious, S. A. (2005). Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceutical Statistics, 4*, 287–291.

Kashdan, T. B., & Rottenberg, J. (2010). Psychological flexibility as a fundamental aspect of health. *Clinical Psychology Review, 30,* 865–878.

Korostil, M., & Feinstein, A. (2007). Anxiety disorders and their clinical correlates in multiple sclerosis patients. *Multiple Sclerosis, 13*, 67–72.

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *Journal of General Internal Medicine, 16,* 606–613.

Kung, S., Alarcon, R. D., Williams, M. D., Poppe, K. A., Jo Moore, M., & Frye, M. A. (2013). Comparing the beck depression inventory-II (BDI-II) and patient health questionnaire (PHQ-9) depression measures in an integrated mood disorders practice. *Journal of Affective Disorders, 145*(3), 341-343.

Lancaster, G. A., Dodd, S., & Williamson, P. R. (2004). Design and analysis of pilot studies: Recommendations for good practice. *Journal of Evaluative Clinical Practice, 10,* 307-312.

Leach, L. S., & Christensen, H. (2006). A systematic review of telephone-based interventions for mental disorders. *Journal of Telemedicine and Telecare, 12*, 122–129.

Leon, A. C., Davis, L. L., & Kraemer, H. C. (2011). The role and interpretation of pilot studies in clinical research. *Journal of Psychiatric Research, 45*, 626–629.

Levin, M. E., Hildebrandt, M. J., Lillis, J., & Hayes, S. C. (2012). The impact of treatment components suggested by the psychological flexibility model: A meta-analysis of laboratory-based component studies. *Behavior Therapy, 43,* 741–756.

Long, D. M. (2013). Pragmatism, realism, and psychology: Understanding theory selection criteria. *Journal of Contextual Behavioral Science, 2*, 61–67.

Luciano, J. V, Guallar, J. A., Aguado, J., López-del-Hoyo, Y., Olivan, B., Magallón, R., … Garcia-Campayo, J. (2014). Effectiveness of group acceptance and commitment therapy for fibromyalgia: A 6-month randomized controlled trial (EFFIGACT study). *Pain, 155*, 693–702.

McGuigan, C., & Hutchinson, M. (2004). The multiple sclerosis impact scale (MSIS-29) is a reliable and sensitive measure. *Journal of Neurology, Neurosurgery & Psychiatry, 75,* 266–269.

Moher, D., Schulz, K. F., & Altman, D. G. (2001). The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC Medical Research Methodology, 1*(1), 2.

Mohr, D. C., & Cox, D. (2001). Multiple sclerosis: empirical literature for the clinical health psychologist. *Journal of Clinical Psychology, 57*, 479–99.

Mohr, D. C., Goodkin, D. E., Islar, J., Hauser, S. L., & Genain, C. P. (2001). Treatment of depression is associated with suppression of nonspecific and antigen-specific TH1 responses in multiple sclerosis. *Archives of Neurology, 58*, 1081.

Mohr, D. C., Likosky, W., Bertagnolli, A., Goodkin, D. E., Van Der Wende, J., Dwyer, P., & Dick, L. P. (2000). Telephone-administered cognitive–behavioral therapy for the treatment of depressive symptoms in multiple sclerosis. *Journal of Consulting and Clinical Psychology, 68,* 356.

Mohr, D. C., Vella, L., Hart, S., Heckman, T., & Simon, G. (2008). The effect of telephone-administered psychotherapy on symptoms of depression and attrition: A meta-analysis. *Clinical Psychology: Science and Practice, 15*, 243–253.

Mullins, L. L., Cote, M. P., Fuemmeler, B. F., Jean, V. M., Beatty, W. W., & Paul, R. H. (2001). Illness intrusiveness, uncertainty, and distress in individuals with multiple sclerosis. *Rehabilitation Psychology, 46*(2), 139-153.

NICE. (2003). CG8 Multiple sclerosis: NICE guideline. London: National Institute for Clinical Excellence.

Nordin, L., & Rorsman, I. (2012). Cognitive behavioural therapy in multiple sclerosis: a randomized controlled pilot study of acceptance and commitment therapy. *Journal of Rehabilitation Medicine, 44*, 87–90.

Öst, L.-G. (2008). Efficacy of the third wave of behavioral therapies: A systematic review and meta-analysis. *Behaviour Research and Therapy, 46*, 296–321.

Öst, L.-G. (2014). The efficacy of acceptance and commitment therapy: An updated systematic review and meta-analysis. *Behaviour Research and Therapy, 61,* 105–121.

Pakenham. (2006). Investigation of the coping antecedents to positive outcomes and distress in multiple sclerosis (MS). *Psychology & Health, 21*, 633–649.

Paré, G., Jaana, M., & Sicotte, C. (2007). Systematic review of home telemonitoring for chronic diseases: the evidence base. *Journal of the American Medical Informatics Association, 14*, 269–277.

Poppe, C., Petrovic, M., Vogelaers, D., & Crombez, G. (2013). Cognitive behavior therapy in patients with chronic fatigue syndrome: the role of illness acceptance and neuroticism. *Journal of Psychosomatic Research, 74,* 367–72.

Proctor, B, J., Moghaddam, N., Vogt, W., & das Nair, R. (in press). Telephone-psychotherapy in multiple sclerosis: A systematic review and meta-analysis. *Rehabilitation Psychology.*

Ramp, M., Khan, F., Misajon, R. A., & Pallant, J. F. (2009). Rasch analysis of the Multiple Sclerosis Impact Scale MSIS-29. *Health and Quality of Life Outcomes, 7*, 58.

Reese, R. J., Conoley, C. W., & Brossart, D. F. (2002). Effectiveness of telephone counseling: A field-based investigation. *Journal of Counseling Psychology, 49*, 233.

Rigby, S. A., Thornton, E. W., & Young, C. A. (2008). A randomized group intervention trial to enhance mood and self-efficacy in people with multiple sclerosis. *British Journal of Health Psychology, 13*, 619–31.

Robson, C. (2002). *Real world research: a resource for social scientists and practitioner-researchers* (2nd Ed). Madlen, MA: Blackwell.

Rosner, A. L. (2012). Evidence-based medicine: revisiting the pyramid of priorities. *Journal of Bodywork and Movement Therapies, 16*, 42–49.

Sheppard, S. C., Forsyth, J. P., Hickling, E. J., & Bianchi, J. (2010). A novel application of acceptance and commitment therapy for psychosocial problems associated with multiple sclerosis: Results from a half-day workshop intervention. *International Journal of MS Care, 12*, 200–206.

Sim, J. & Lewis, M. (2012). The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *Journal of Clinical Epidemiology, 65,* 301-308.

Simpson, S. G., & Reid, C. L. (2014). Therapeutic alliance in videoconferencing psychotherapy: A review. *Australian Journal of Rural Health, 22*, 280–299.

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of Internal Medicine, 166*, 1092–1097.

Swain, J., Hancock, K., Hainsworth, C., & Bowman, J. (2015). Mechanisms of change: Exploratory outcomes from a randomised controlled trial of acceptance and commitment therapy for anxious adolescents. *Journal of Contextual Behavioral Science, 4,* 56–67.

Terrill, A. L., Hartoonian, N., Beier, M., Salem, R., & Alschuler, K. (2015). The 7-item generalized anxiety disorder scale as a tool for measuring generalized anxiety in multiple sclerosis. *International Journal of MS C*are, 17(2), 49-56.

Thomas, P. W., Thomas, S., Hillier, C., Galvin, K., & Baker, R. (2006). Psychological interventions for multiple sclerosis. *Cochrane Database of Systematic Reviews,* CD004431.

Torneke, N. (2010). *Learning RFT: An introduction to relational frame theory and its clinical application*. Oakland, CA: New Harbinger Publications.

Vøllestad, J., Nielsen, M. B., & Nielsen, G. H. (2012). Mindfulness-and acceptance-based interventions for anxiety disorders: A systematic review and meta-analysis. *British Journal of Clinical Psychology, 51*, 239–260.

Walters, S. J., & Brazier, J. E. (2005). Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Quality of Life Research, 14,* 1523–1532.

Wolgast, M. (2014). What does the acceptance and action questionnaire (AAQ-II) really measure? *Behavior Therapy, 45,* 831–839.

Wolitzky-Taylor, K. B., Arch, J. J., Rosenfield, D., & Craske, M. G. (2012). Moderators and non-specific predictors of treatment outcome for anxiety disorders: A comparison of cognitive behavioral therapy to acceptance and commitment therapy. *Journal of Consulting and Clinical Psychology, 80*, 786.

Yuen, E. K., Herbert, J. D., Forman, E. M., Goetter, E. M., Juarascio, A. S., Rabin, S., … Bouchard, S. (2013). Acceptance based behavior therapy for social anxiety disorder through videoconferencing. *Journal of Anxiety Disorders, 27*, 389–397.

Zettle, R. D. (2012). Acceptance and commitment therapy (ACT) vs. systematic desensitization in treatment of mathematics anxiety. *The Psychological Record, 53,* 3.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67*, 361–370.

Appendices

Appendix A: Ethics Approval Letter

NHS
Health Research Authority
NRES Committee East Midlands - Nottingham 1
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839428

03 December 2014

Dr Thomas Schroder
Associate Professor in Clinical Psychology
University of Nottingham
Division of Psychiatry and Applied Psychology
Jubilee Campus
University of Nottingham

Dear Dr Schroder

Study title:	**A Feasibility Randomized Control Trial of Telephone-supported Acceptance and Commitment Therapy for Low Mood in Multiple Sclerosis**
REC reference:	**14/EM/1228**
Protocol number:	**14094**
IRAS project ID:	**156887**

Thank you for your letter of 3 December responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Ms Penelope Gregory, NRESCommittee.EastMidlands-Nottingham1@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of Sponsor Insurance]	1.0	22 September 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of Sponsor Insurance]	1	30 July 2014
GP/consultant information sheets or letters [Letter to GP]	1.0	19 September 2014
Interview schedules or topic guides for participants [Telephone Interview Guide]	1.0	19 September 2014
IRAS Checklist XML [Checklist_02102014]		02 October 2014
IRAS Checklist XML [Checklist_01122014]		01 December 2014
IRAS Checklist XML [Checklist_02122014]		02 December 2014
IRAS Checklist XML [Checklist_03122014]		03 December 2014
Letter from sponsor [Sponsor Letter]	1.0	22 September 2014
Letters of invitation to participant [Letter of invitation to participate]	1.0	19 September 2014
Non-validated questionnaire [Demographic Information Questionnaire]	1.0	19 September 2014
Other [Supervisor CV]	1.0	02 October 2014
Participant consent form [Consent Form]	2.0	28 November 2014
Participant information sheet (PIS) [Participant Information Sheet]	4.0	03 December 2014
REC Application Form [REC_Form_02102014]		02 October 2014
Research protocol or project proposal [Protocol]	2.0	28 November 2014
Summary CV for Chief Investigator (CI) [Summary CV for CI]	1.0	19 September 2014
Summary CV for student [Student CV]	1.0	19 September 2014
Summary CV for supervisor (student research) [Supervisor CV]	1.0	19 September 2014
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Protocol Flowchart]	1.0	22 September 2014
Validated questionnaire [HADS Screening Questionnaire]	1.0	19 September 2014
Validated questionnaire [GAD7]	1.0	19 September 2014
Validated questionnaire [PHQ9]	1.0	19 September 2014
Validated questionnaire [EQ5D]	1.0	19 September 2014
Validated questionnaire [MSIS]	1.0	19 September 2014
Validated questionnaire [AAQII]	1.0	19 September 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

14/EM/1228	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely



Dr Carl Edwards
Chair

Email:NRESCommittee.EastMidlands-Nottingham1@nhs.net

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: *Miss Angela Stone, University of Nottingham*
Miss Charlotte Davies, Nottingham University Hospitals NHS Trust

Appendix B: Participant Information Sheet

(Final Version 3.0: 01.12.14)

Title of Study: A Feasibility Randomised Control Trial of Telephone-Supported Acceptance & Commitment Therapy for Low Mood in Multiple Sclerosis

Name of Researchers: Barnaby Proctor, Dr Roshan das Nair, Dr Nima Moghaddam

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Ask us if there is anything that is not clear.

What is the purpose of the study?
The purpose of the study is to assess the practicalities of completing a randomised control trial on the effectiveness of a telephone-supported self-help psychological intervention with patients with Multiple Sclerosis (MS) and low mood.

Why have I been invited?
You are being invited to take part because you have MS and have been assessed/ will be assessed for low mood. We are inviting over 25 participants like you to take part.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights or your usual medical care.

What will happen to me if I take part?
If you take part in the study then you will be randomly allocated to either a group where you are given a self-help book to complete or you just continue to have treatment as usual. The way your allocation is decided by someone at the clinic who will pick an envelope at random which will state “self-help” or “usual care”; this is so it is fair to everyone. If it is decided that you receive the self-help book you will be posted a self-help manual called “Get out of your Mind and into your Life. The book will be divided into 8 sections and each week you will be encouraged to read one section and complete the activities. Participants in this group will also receive 8 weekly telephone calls from a Trainee Clinical Psychologist who is managing the project. It is expected that the calls would last up to 30 minutes. We can be flexible with the time of the call. All phone calls will be recorded and only shared within the research team. You will not need to pay for the phone calls. Some anonymised direct quotes may be published in the write-up of the study.

We will request all participants to fill out questionnaires on three separate occasions. These can be done online or can be posted to you to fill out by hand, along with a stamped return envelope to post back. The questionnaires will ask you about your

mood, the impact of MS, your coping styles, your overall health and the health resources you use.

After you have completed the book or receiving usual care, you may be selected to be interviewed on the phone about how you have found being involved in the trial. You can decide whether you want to be interviewed or not. The interview is to get feedback on the study and how it might be improved in the future. All participants will be involved in the study for 6-7 months. Participants who were allocated to not receive the book will be offered a copy of the book after the full study has finished.

Expenses and payments
Participants will not be paid to participate in the study. Participants do not need to travel anywhere for any part of the study; the study can be completed from home. You will not need to pay for phone calls.

What are the possible disadvantages and risks of taking part?
A possible disadvantage of taking part in the study is that it will require some of your time to complete the questionnaires and if you also have the self-help manual this will also require your time and effort. If you have the self-help manual you will be asked to expose yourself to feelings and thoughts, which may be distressing. However it is through doing this work that we believe the self-help manual may improve mood.

If you feel you are becoming distressed or may require additional support during your enrolment in the trial, you will be able to receive face-to-face psychological support from clinical psychologists based within the MS Service at QMC. You could self-referrals or refer through member of the study team will be accepted.

What are the possible benefits of taking part?
We cannot promise the study will help you but the information we get from this study may help other people that people with MS and low mood receive support in the future.

What happens when the research study stops?
The results will be written up as part of studies towards a Doctorate in Clinical Psychology at University of Nottingham. It will also be submitted for publication in a scientific journal. If you would like a copy of our report prepared for the general public, let us know and we will send you a copy at the end of the study.

What if there is a problem?
If you have a concern about any aspect of this study, you can ask to speak to the researchers who will do their best to answer your questions. Alternatively, you can contact the NHS Patient Liaison and Advice Service (PALS) at the QMC by calling 0800 183 0204.

Will my taking part in the study be kept confidential?
If you decide to take part, some parts of your medial record will be examined by the study team. They may also be looked at by authorised people who monitor studies to make sure they are being carried out correctly. The information looked at will be kept confidential amongst the research team.

All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the hospital be anonymised and will have a unique code will be used so that you cannot be recognised from it.

All research data will be kept securely for 7 years, then erased. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

Written work about the study that is submitted for publication in a scientific journal will contain no participant identifying information.

What will happen if I don't want to carry on with the study?
Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. Withdrawing from the study will not have an impact on any future care. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

Involvement of the General Practitioner/Family doctor (GP)
Your GP or a member of your Neurology team will be notified of your participation.

What will happen to the results of the research study?
The results of the study will be written up as part of Clinical Psychology doctorate at the University of Nottingham. It is also intended that the results will also be published in a journal.

Who is organising and funding the research?
This research is being organised and funded by the University of Nottingham

Who has reviewed the study?
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Nottingham Research Ethics Committee 1.

Further information and contact details
Researcher: Barnaby Proctor, Trainee Clinical Psychologist, under the supervision of Dr Roshan das Nair.
Email: lwxbjp@nottingham.ac.uk or roshan.nair@nottingham.ac.uk
Address: Doctorate in Clinical Psychology, Institute of Work, Health & Organisations, International House, Jubilee Campus, Wollaton Road, Nottingham, NG8 1BB.

Other contact
You can contact the Chief Investigator, Thomas Schroeder, who is not directly involved in the study, for independent advice. Email: lwzts@exmail.nottingham.ac.uk

Appendix C: Consent Form

(Final Version 3.0: 14.01.15)

Title of Study: A Feasibility Randomised Control Trial of Telephone-Supported Acceptance & Commitment Therapy for Low Mood in Multiple Sclerosis

REC Ref: 14/EM/1228

Name of Researchers: Barnaby Proctor, Dr Nikos Evaneglou, Dr Roshan das Nair, Dr Nima Moghaddam

Name of Participant:

1. I confirm that I have read and understand the information sheet version number 1.0 dated 08/09/2014 for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis.

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential.

4. I understand and agree that if I was to have Acceptance & Commitment Therapy I will need to complete a self-help book and have weekly telephone support.

5. I understand and agree to these weekly telephone calls being recorded for

research purposes. Direct quotes may be anonymously published in the study write-up.

6. I agree to my GP/Neurology clinician confirming my diagnosis and being informed of my participation in this study.

7. I agree to take part in the above study.

_____ _____ _____

Name of Participant Date Signature

_____ _____ _____

Name of Person taking consent Date Signature

_____ _____ _____

Appendix D: Telephone Support Call Guide

Participant Name: Date:

1. Have you read chapter X?

2. If so, how did you find it? If not, what got in the way?

3. Was there anything you would like to clarify with me?

4. What did you like?

5. What did you not like?

6. Did you do the exercises? If so how did you find them? If not, why not?

7. Is there anything you would like to discuss in relation to chapter X?

8. Have you any questions on it? Or any questions relating to the process of the study?

9. Set up time of call for next week.

Appendix E: Feasibility Interview Schedule

Participant Name: Date:

Intervention/Control/Intervention then withdrew (Circle one)

Only to "Intervention, then withdrew" group:

1. You already explained to Barnie that you no longer wanted to take part in the study, but could we ask you once more why you decided to no longer take part?

All three groups:

2. How did you find the recruitment process?
3. How did you find the randomisation process?
4. How did you find completing the online and postal measures?
5. What kind of usual care did you receive?
6. Have you read any other self-help books? Have you been to any mindfulness groups, have you taken part in meditation groups recently?
6. What changes to the study (if any) would you recommend?

Intervention group only.

7. What did you think of the self-help manual?
8. What did you think of the telephone support?
9. What changes, if any, have you noticed in yourself since you started the intervention

[If changes present:]

* What do you attribute these changes to?
* Do you think these changes would have happened without the intervention?

10. What did you find most helpful?
11. What did you find least helpful?
12. Have there been any things (e.g., in your current/recent life situation) that have made it difficult for you to make use of the book/support calls?
13. Do you think other people with MS would find the book and the phone support helpful?

Appendix F: An example of a transcript of a feasibility interview arranged into the predefined framework of feasibility

Feasibility subcategory	Question(s) in telephone interview	Participant X
Recruitment	How did you find the recruitment process?	It was fine. It was easy enough. I emailed Barnie, as saw an ad on the MS newsletter. The information I received was clear enough
Randomisation	How did you find the randomisation process?	It was fine. Didn't find a problem with anything. It was fair.
Measures	How did you find completing the online and postal measures?	They were easy enough. Clear and simple and easy to read. I think they captured the right kind of things. Didn't actually take that long to complete, so happy.
Treatment as usual	What constitutes "Treatment as Usual" for you?	No other support whilst enrolled in study. No psychological therapies after diagnosis. I am on some antidepressants. Citalopram? Daily. Started last December. No other self-help books. Went yesterday to join a mindfulness group, heard about it through MS neuro team.
Future study feasibility	What changes to the study (if any) would you recommend?	No I don't think so. Maybe the book; I couldn't concentrate on it.
Acceptability	Why did you no longer want to take part?	At the time I wasn't feeling very well and I didn't even get round to looking at the book properly and I didn't feel it was fair to let him down. The illness was related to my MS.
Self-help text	What did you think of the self-help manual?	Language was fine. It was the length of each chapter that was my problem. Too much to read per week. Better if it was possible to spread out over a longer period. E.g. a month for two chapters.
Telephone support	What did you think of the telephone support?	Not really had any. He rang to see how I was getting on. Then I emailed him to say I couldn't do what was asked.
Evaluation	What did you find most/least helpful of intervention?	Didn't get far enough. Can't honestly remember, my memory is diabolical.
Acceptability	Do you think others would find the book and the phone support helpful?	I think so yeah. If you find the right people who are willing to take the time out and read it.
Change processes	Other things going on in life? Changes in you?	Not really.

Appendix G: Service-Use Questionnaire

We would like to know a little about any contacts with the health services listed below in the last 3 months that were due to your MS.

General practice and community nursing services

Number of times you saw a GP at the surgery.

Number of times you saw a GP at your home.

Number of times you spoke to a GP on the telephone.

Number of times you saw a nurse at the surgery.

Number of times you saw a nurse at your home.

Number of times you saw a counsellor at the surgery.

Number of contacts with anyone else from the surgery.

If applicable, who was this additonal contact with?

Hospital and Community Services

Number of times you saw a neurologist at the hospital.

Number of times you saw a MS nurse in the hospital.

Number of times you saw a MS nurse at your home.

Therapy Services

Number of contacts with a hospital based physiotherapist.

Number of contacts with a community based physiotherapist.

Number of contacts with a hospital based occupational therapist.

Number of contacts with community based occupational therapist.

Number of contacts with a psychologist (not including recruitment to this study).

Number of contacts with a pharmacist.

Number of times you contacted the NHS 111 service.

Social Services

Number of times you saw a social worker.

Number of times you saw a home help.

Number of times you saw a care assistant.

Number of times you visited a Day Centre.

Number of contacts with anyone else from Social Services.
If applicable, who was this additional contact with?
If applicable, please list any home adaptions or equipment you have had provided by Social Services.

Other Services

Number of times you attended a Day Hospital.
Number of times you went to a hospital clinic.
If applicable, which clinic(s) did you attend?
Number of nights you spent on a hospital ward.
Number of contacts with anyone else from the hospital.
If applicable, who did you see from the hospital?

Medication

Are you on any medication, for MS or any other complaints or illnesses? This includes any current medications to help manage your mood, if applicable.
Please list any medications below.

Have you started and/or stopped any medication in the last 3 months?
Medications started within the last 3 months.
Medications stopped within the last 3 months.

Are you suffering from any other complaints or illnesses besides your multiple sclerosis?
If YES, please list any serious illnesses followed by the year of diagnosis. For example, "Type 2 Diabetes, 2002".

Appendix H. Example search strategy

Example of the search strategy employed by the review with the EMBASE database

1. multiple sclerosis.mp
2. Multiple Sclerosis (subject heading)
3. 1 or 2
4. tele$.mp
5. phone.mp
6. Telemedicine/ or Telecommunication/ or teleconsultation (subject headings)
7. 4 or 5 or 6
8. RCT
9. randomi*ed
10. Controlled Clinical Trial (subject heading)
11. 8 or 9 or 10
12. 3 and 7 and 11

Poster