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Refractory depression – Cost-Effectiveness of Radically Open Dialectical Behaviour Therapy (RefraMED): findings of trial-based economic evaluation


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Abstract

Background
Refractory depression is a major contributor to the economic burden of depression. Radically Open Dialectical Behaviour Therapy (RO DBT) is an unevaluated new treatment targeting over-controlled personality, common in refractory depression, but it is not yet known whether the additional expense of RO DBT is good value for money.

Aim
To estimate the cost-effectiveness of RO DBT plus treatment as usual (TAU) compared with TAU alone in patients with refractory depression.

Methods
We undertook a cost-effectiveness analysis alongside a randomised trial evaluating RO DBT plus TAU versus TAU alone for refractory depression in three UK secondary care centres. Our economic evaluation, 12 months after randomisation, adopted the perspective of the UK National Health Service (NHS) and personal social services. It evaluated cost-effectiveness by comparing the net cost of RO DBT with the net gain in quality-adjusted life years, estimated using the EQ-5D-3L measure of health-related quality of life.

Results
The additional cost of RO DBT plus TAU compared to TAU alone was £7,048, which was associated with a difference of 0.032 QALYs, yielding an ICER of £220,250 per QALY. This ICER was well above the NICE upper threshold of £30,000 per QALY. A cost-effectiveness acceptability curve indicated that RO DBT had a zero probability of being cost-effective compared to TAU at the NICE £30,000 threshold.

Conclusion
In its current resource-intensive form, RO DBT was not a cost-effective use of resources in the UK NHS.

Declaration of interest
Six of the 16 authors have received royalties or fees for RO DBT.

Word count 250
Introduction
The economic burden of depression is substantial. The total cost of adult depression across England in 2007 was more than £7.5 billion, including £1.6 billion for health and social care and £5.8 billion for loss of earnings. Many of these costs are due to refractory depression or treatment-resistant depression. For example, Crown found that depression-related costs for treatment-resistant inpatients were 19 times greater than those of other inpatients, and the costs for treatment-resistant outpatients were 2.5 times greater than other outpatients. This paper evaluates the cost-effectiveness of Radically Open Dialectical Behaviour Therapy (RO DBT), a new treatment targeting over-controlled personality, common in refractory depression.

Methods
Design
The Refractory depression – Mechanisms & Efficacy of Radically Open Dialectical Behaviour Therapy (RefraMED) study included a three-centre parallel-group randomised trial which compared RO DBT plus treatment as usual (TAU) with TAU alone and an integrated economic evaluation. We assessed participants at baseline and 7, 12 and 18-months after randomisation; the primary endpoint of the trial was 12-months after randomisation.

Participants
Patients were eligible for the RefraMED trial if they: were 18 years or older; had an IQ more than 70; spoke English well enough to participate; had a current diagnosis of major depressive disorder in the Structured Clinical Interview for Diagnostic and Statistical Manual-IV Axis I (SCID-I); were suffering from refractory depression, defined below as chronic depression lasting at least two years or recurrent depression with at least two previous episodes; and had a Hamilton Rating Scale for Depression (HRSD) score of at least 15. and had not responded to an adequate dose of antidepressant medication (ADM) for at least six weeks in their current episode.

Definitions of refractory depression vary across studies. For example, Berlim and Turecki (2007) found more than ten different descriptive terms for treatment-resistant refractory major depression. In the present study, we define ‘refractory depression’ as either chronic depression (depression lasting at least two years) or treatment-resistant depression (depression that does not respond to adequate intervention, which we operationalised as two or more previous episodes of depression).

In the present study we define refractory depression as either chronic depression, that is depression lasting at least 2 years, or treatment-resistant depression, that is recurrent depression (which we
operationalised as two or more previous episodes) which has not responded to an adequate dose of anti-depressant medication (ADM) for at least 6 weeks in the current episode.

Interventions

Treatment as usual (TAU)

All participants received TAU, including prescribed antidepressant medication (ADM) or psychotherapy. In addition, control patients could access any treatment offered by the NHS or privately, except standard DBT.

Radically Open Dialectical Behaviour Therapy (RO DBT)

RO DBT is a trans-diagnostic therapy designed to address a spectrum of disorders that are difficult to treat, notably chronic depression. It differs from other psychotherapies, notably by encouraging social bonding through emotional expression and ‘social signalling’, defined as any behaviour that an individual performs in the presence of another person, regardless of intention or awareness. At the time of the trial RO DBT comprised 29 weekly individual therapy sessions each lasting an hour and 27 skills training classes each lasting 2.5 hours. Though they continued to receive ADM as prescribed, we strongly discouraged them from seeking additional psychotherapy during RO DBT. Further information on RO DBT is contained in the clinical paper.

Economic perspective

The economic perspective was that of the UK National Health Service (NHS) and personal social services, as preferred by the UK National Institute for Health and Care Excellence (NICE). We also explored the addition of productivity losses resulting from time off work due to illness, in sensitivity analysis.

Method of economic evaluation

The primary method of economic evaluation was cost-utility analysis with effects measured in quality-adjusted life years (QALYs), as preferred by NICE. We also undertook a cost-effectiveness analysis with effects measured in depressive symptoms, the primary outcome of the RefraMED trial.

Outcomes

For our primary economic evaluation, we estimated QALYs using the EQ-5D-3L measure of health-related quality of life. The EQ-5D-3L is a generic, preference-based measure for describing and valuing health-related quality of life. It rates health in five domains – mobility, self-care, usual
activities, pain or discomfort, and anxiety or depression. The health states described in the EQ-5D-3L were assigned a utility weight or score using responses from a representative sample of adults in the UK. These weights were applied to the time between interviews and QALYs calculated using the area under the curve approach. The EQ-5D has been validated in economic evaluations for common mental health disorders. For our secondary economic evaluation, effects were measured in terms of depression using the HRSD, which was the primary clinical outcome of the RefraMED trial.

Resource use
We collected resource use data using a version of the Adult Service Use Schedule (AD-SUS) designed for depressed populations. Research assessors completed this in interview with participants and recorded all use of hospital and community-based health and personal social care. For medications, we asked participants to report prescribed antidepressants, antipsychotics, sleeping tablets and painkillers. To avoid unblinding research assessors, participants reported their use of all talking therapies on a separate self-reported questionnaire. We collected information about time off work due to illness alongside the AD-SUS using the productivity questions from the World Health Organisation Health and Work Performance Questionnaire (HPQ). We asked participants to complete the AD-SUS and HPQ at baseline, to cover the previous six months, and at the 7, 12 and 18-month interviews to cover the time since the previous interview, thus covering the full period from baseline to final follow-up. We abstracted information on RO DBT resource use, including the number of individual and group sessions attended by each participant, from therapy records.

Unit costs
With the exception of RO DBT, we estimated mean costs of health and social services for each group by multiplying patients’ reported use by unit costs from national sources. All unit costs, summarised in Table S1 in the online supplement, were for the financial year 2014-15, uprated where necessary using the Hospital and Community Health Services Index. We based medication costs on the median dose of the most common category of drug (e.g. antidepressant, antipsychotic) reported by participants. We used participant-reported start and finish dates to estimate duration of their time using that drug, assuming full compliance. We estimated the costs of depression-related absenteeism and presenteeism for patients in paid employment using the human capital approach based on the national gross average wage.
We estimated RO DBT costs using the micro-costing approach developed by the Personal Social Services Research Unit (PSSRU) at the University of Kent.\textsuperscript{21} We costed individual sessions from the average therapist Agenda for Change salary bands, including employer’s costs (national insurance and pension contributions) and overhead costs (buildings, utilities, management and administration) from national sources.\textsuperscript{16,22} We weighted salary costs to cover time away from clients using information from 16 RO DBT therapists on the time they spent running RO DBT therapy sessions and on other activities, which suggested a direct to non-direct ratio of 1:0.91. Individual sessions on average lasted 60 minutes. Table S2 in the online supplement details our method of valuing therapist time.

We costed RO DBT group sessions on the basis that they were closed to other participants and went ahead irrespective of how many participants attended.\textsuperscript{23} We allocated the total cost of each group session across all participants invited to attend, whether or not they did attend. Group sessions lasted 2.5 hours on average. The number of therapists running groups varied by group size. Groups larger than three clients were typically run by two therapists. The valuation of the cost of these group sessions is summarised in Table S3 in the online supplement.

We did not include DBT-specific training costs because equivalent costs for the control group could not be easily identified and costed, making comparison difficult. In clinical practice, therapists undertake a wide range of training as part of professional development. So it is reasonable to assume that RO DBT training, if rolled out, would form part of this professional development in the same way as therapists receive training in other therapies like CBT. Similarly, we excluded the cost of participants who failed to attend RO DBT individual sessions from analysis given the absence of equivalent data for the control group. Only when comparing two specific therapies is it possible to record and cost non-attendance from both groups. In this study TAU varied; thus, participants reported attendances with therapists and other health professionals, but not non-attendance. Furthermore we assumed that therapists would undertake other work activities during the time freed by non-attendances, thus reducing the cost of those non-attendances, potentially to zero.

**Statistical analysis**

**Costs and outcomes**

We initially present descriptive data on costs and outcomes adjusted for baseline differences in costs and relevant outcomes plus pre-specified clinical predictors as outlined in the accompanying clinical paper.\textsuperscript{9} We adjusted cost-effectiveness analyses for the same pre-specified clinical predictors and
baseline values of the variables of interest (costs, EQ-5D-3L or HRSD). We analysed cost differences by t-tests with confidence intervals around adjusted mean differences estimated using non-parametric bootstrapping to reflect non-normality of cost data.\textsuperscript{24} We imputed missing cost, QALY and HRSD data using ‘multiple imputation using chained equations’ (MICE) under the assumption that these data were missing at random.\textsuperscript{25} We set the number of multiply imputed data sets (m) to be equal to the fraction of incomplete service use information (30%; m=30) at the 12-month follow-up as recommended by White and colleagues.\textsuperscript{25} Multiple imputation reports the sensitivity of results to missing data and the assumption that the data were missing at random. There is evidence that multiple imputation provides less biased estimates of costs and effects than complete case analysis unless data are missing not at random.\textsuperscript{25} We set the number of bootstrap replications to 1,000 for each of the 30 multiply imputed data sets (30,000 bootstrap replications) \textsuperscript{26}

\textit{Cost-effectiveness analysis}

We conducted the pre-specified primary cost-effectiveness analysis after 12 months, as with the clinical analyses. We assessed cost-effectiveness by estimating incremental cost-effectiveness ratios which divide the difference in costs between two interventions by the difference in outcomes.\textsuperscript{27} We did not conduct a power calculation for the cost-effectiveness analysis because these are problematic due to the large variability in resource use and cost measures, and the complexity of forecasting the joint distribution of the difference in costs and benefits between treatment arms. Instead we followed recommendations to take a decision-making approach and focus on estimating cost and QALY differences, and estimating the likelihood that RO DBT is cost-effective compared to TAU, given the data available.\textsuperscript{28} We generated the joint distribution of incremental mean costs and effects for RO DBT relative to TAU using non-parametric bootstrapping to explore the probability that one of the groups is the better choice given NICE’s ‘willingness-to-pay’ threshold of £20,000 to £30,000 per QALY. We characterised uncertainty around the cost and effectiveness estimates by cost-effectiveness acceptability curves.\textsuperscript{29}

\textit{Sensitivity analysis}

We conducted five sensitivity analyses to explore the impact of variations in methods and assumptions on the relative cost-effectiveness of RO DBT and TAU:

1. A complete case analysis for comparison with the results using multiple imputation for missing data.
2. A broader economic perspective, additionally including the cost of absenteeism from work, given that depression is known to have a substantial impact on employment.\textsuperscript{30}
3. Adjustment of the cost of RO DBT group sessions to address the fact that group session attendance was particularly low and thus costs particularly high relative to the cost of groups reported in similar studies. On the assumption that group attendance is unlikely to be as low in routine NHS services, we replaced the estimated cost of the RO DBT groups with the national cost applied to participants reporting group therapy attendances (£14 rather than £99).

4. Analysis of cost-effectiveness after 18 months to explore over a longer period of time the impact of RO DBT relative to TAU.

5. Analysis of cost-effectiveness using cost per point difference in the primary clinical outcome, the HRSD, as the measure of effect.

**Ethical approval and conduct**

Before starting the trial we gained approval from the Hampshire Research Ethics Committee (National Research Ethics Service [NRES] reference 11/SC/0146) and the Research Governance Department of the University of Southampton, the Sponsor of this trial. We asked trial participants for consent on three occasions: oral before telephone screening; signed before baseline assessment; and signed before randomisation.

**Patient and public inclusion**

The NIHR Mental Health Research Network and ‘Involve’, the national advisory group on public engagement, helped us to recruit service users – two to the Trial Steering Group (TSC) and two to the Trial Management Group (TMG). They contributed to developing patient information leaflets, managing the trial, and disseminating its findings.

**Data availability**

All non-confidential data reported in our manuscripts are available from the Figshare database (figshare.com), a secure online public repository for research data. Syntax for key analyses is available from Dr Ben Whalley of Plymouth University.

**Role of the funding source**

The Efficacy & Mechanism Evaluation (EME) Programme, funded by the MRC and administered by the National Institute for Health Research (NIHR), funded this trial by grant 09/150/12. The NIHR was responsible only for monitoring the progress of the trial, notably by appointing the independent members of the Trial Steering and Data Monitoring & Ethics Committees. Thus, the grant holders
were responsible for: study design; collecting, analysing, and interpreting data; writing this paper; and deciding to submit it for publication.

Results

Participants
We randomised 250 eligible patients, 162 (65%) to RO DBT and 88 to control. Recruitment started in Dorset in March 2012 with an internal pilot. Recruitment in Hampshire and North Wales started in September 2012. Recruitment at all three centres continued until April 2015. Of the full sample of 250, 164 (64%) were female; 138 (55%) were aged between 35 and 55; 232 (97% of 238 responders) were ‘white’; 106 (42%) reported being in a stable relationship; and 82 (34% of 241 responders) had a University qualification. Ninety-two participants (37%) reported a first depressive episode before the age of 16; 179 (84% of 213 responders) were chronically rather than recurrently depressed; and 191 (82% of 234 responders) had previously received psychotherapy. In addition, 79% of the sample met criteria for a comorbid personality disorder. Full details of the flow participants through the RefraMED trial and their baseline demographic and clinical characteristics are contained in the accompanying clinical paper.9

Missing data
At 12-month follow-up, full service-use data were available for the entire follow-up period for 125 participants in the RO DBT group (77%) and 61 in the TAU group (69%). This is compared to complete data in the RO DBT group for 118 (73%) at 7 months and for 101 (62%) at 18 months and in the TAU group for 61 (69%) at 7 months and for 51 (58%) at 18 months. There were no statistically significant differences between groups in the proportion of missing data (X²=0.25, p=0.61). Missing resource use items in completed questionnaires were assumed to indicate no service use and were given a zero value.

Resource use
Resource use over the follow-up period is summarized in Table S4 in supplementary online material. Participants enrolled in the RO DBT group attended an average of 22.8 individual RO DBT sessions (median 26) and 19.3 group RO DBT sessions (median 22.5). In addition, they attended an average of 3.4 sessions of other types of talking therapy. Participants in the TAU group attended an average of 9.1 sessions of various talking therapies. The use of all other health and social care services, including medications, was broadly similar between the two groups, suggesting that group allocation did not have a substantial impact on the intensity of other service use. Days reported off work and unproductive working hours were also similar between the two groups.
**Costs**

Table 1 summarises health and social care costs from the NHS and personal social services perspective over the six months prior to trial entry and over the 12 and 18-month follow-up periods. Disaggregated costs are based on complete case data as data imputation was conducted at the aggregate level. The cost of all health and social care services used over the six months prior to trial entry were lower in RO DBT compared with TAU, but the difference was not significant (mean difference -£1,029, bootstrap 95% CI -£2,465 to £407 p=0.160). Excluding the cost of RO DBT, the cost of all health and social care services used was lower over the 12-month follow-up period in the RO DBT group compared to the control group (adjusted mean difference £-909, bootstrap 95% CI -£1,799 to -£19 p=0.045) and also at the 18-month follow-up period (adjusted mean difference of -£901, bootstrap 95% CI, -£2,755 to £952 p=0.340). The RO DBT intervention cost approximately £5,000 per person, including the cost of both individual and group sessions, resulting in total costs that were significantly higher in the RO DBT group compared with TAU over both the 12-month follow-up period (adjusted mean difference £4,566, bootstrap 95% CI £3,691 to £5,440 p<0.001) and the 18-month follow up period (adjusted mean difference £4,463, bootstrap 95% CI £2,915 to £6,011 p<0.001).

Table 1 about here

**Outcomes**

Mean EQ-5D-3L scores and QALYs are presented in Table 2, together with unadjusted differences and differences after adjustment and imputation for missing data. EQ-5D-3L scores improved in both groups over the 18-month follow-up. Over the 7 and 12-month follow-up periods, EQ-5D-3L scores and QALYs were slightly higher in the RO DBT group compared with the TAU group, but over 18-months of follow-up, they were slightly higher in the TAU group. Differences were small and non-significant at all follow-up points.

Table 2 about here

**Cost-effectiveness**

The base case 12-month additional cost of RO DBT plus TAU compared to TAU alone was £7,048, which was associated with a difference of 0.032 QALYs, yielding an ICER of £220,250 per QALY. This ICER was well above the NICE upper threshold of £30,000 per QALY.
The cost-effectiveness plane shown in Figure 1 illustrates the scatterplot of 30,000 bootstrapped cost and effectiveness pairs for RO DBT versus TAU from the perspective of NHS and personal social services at the primary 12-month endpoint. All scatter points lie above the x-axis, illustrating that total health and social care costs are higher for the RO DBT group than the TAU group in all cases. The majority of scatter points fall in the North-East quadrant where RO DBT is more effective than TAU but also more costly. Uncertainty around the ICER was explored in a cost-effectiveness acceptability curve (CEAC) shown in Figure 2. This illustrates that RO DBT in its current format has zero probability of being cost-effective compared with TAU at the NICE willingness to pay threshold of £30,000.

Figure 1 about here

Figure 2 about here

Sensitivity analyses
We based the primary economic analysis on a cost-utility analysis conducted at the 12-month follow-up point, from the perspective of NHS and personal social services with imputation of missing data. Table S5 in the online supplement summarises how variation in methods and assumptions affected the ICERs. In sensitivity analyses 1 to 4 (complete case, inclusion of productivity losses, reduction in the cost of RO DBT group sessions and analysis at the 18-month follow-up point), with all other factors being equal to the base-case, RO DBT remained cost-in-effective compared with TAU, with costs per QALY all well above the NICE threshold of £30,000 per QALY. For illustration, replication of the analysis at the 18-month follow-up is reported in Figures S1 and S2 in the online supplement. The results were very similar to the 12-month follow-up point, with all replications in the scatter plot (Figure S1) falling above the threshold willingness to pay of £30,000 per QALY and the CEAC (Figure S2) indicating a zero probability that RO-DBT was cost-effective compared to TAU. In the final scenario, we undertook a cost-effectiveness analysis using the primary clinical outcome as the measure of effect (the HRSD), with all other factors being equal to the base case analysis. This yielded an ICER of £7,048 per unit improvement on the HRSD. Figure S3 in the online supplement illustrates the scatterplot of 30,000 bootstrapped cost and effectiveness pairs for RO DBT versus TAU based on differences in HRSD score using the £1,000 per HRSD point threshold proposed by Romeo and colleagues. The results were also very similar to the cost-utility analysis with all replications falling above the threshold willingness to pay and the CEAC indicating a zero probability that RO DBT was cost-effective compared with TAU (Figure S4 in the online supplement).
Discussion

Our clinical report indicated that RO DBT achieved moderate but not statistically significant improvement in depressive symptoms in a highly problematic treatment group. This economic analysis adds important information about whether the moderate gains might still be a worthwhile use of scarce NHS resources. RO DBT with TAU was not cost-effective compared with TAU alone in the treatment of patients with refractory depression, either from the perspective of the NHS and personal social services or when productivity losses were included. RO DBT is a resource-intensive intervention which does not achieve sufficient gains in outcomes or savings in the use of other health and social services to justify the additional cost of the intervention over the cost of TAU. Cost-ineffectiveness was driven by the high amount of contact time in RO DBT, some of which may have been an artefact of the rigour of a clinical trial. Whether such an intensive service would be made available in routine mental health services in the UK NHS is debatable.

This is the first economic evaluation of RO DBT for depression and one of very few studies to explore the economic implications of a DBT-informed approach for over-controlled disorders. Previous economic evaluations have focused on standard-DBT for borderline personality disorder (BPD). One economic study alongside a randomised trial compared standard DBT with treatment as usual for self-harming patients with BPD. Though it focused on the cost of the intervention and other health and social care and did not include a formal cost-effectiveness analysis, it is a useful comparator. The mean costs of health and social care over 12 months by the BPD population (intervention group about £2,500 per patient; control group about £3,400) were similar to those of our depressed population (intervention group about £2,200; control group about £3,500). The cost of standard DBT (£3,200 per patient) was lower than the cost of RO DBT in the current study (£5,000) but still substantially higher than that of therapies provided by the UK NHS, like CBT. The authors concluded that standard DBT was effective in reducing self-harm in patients with borderline personality disorder, but acknowledged that this would incur higher costs.

The remaining four economic evaluations were all part of a systematic review and preliminary economic evaluation of evidence for psychological therapies for BPD. They used clinical data from four randomised trials of standard DBT for BPD, and cost data from the trials where available and other published sources where necessary. Two evaluations suggested that standard DBT dominated the comparison arm (TAU in one study, client-centred therapy in the other), achieving better
outcomes at a lower cost per patient. The third evaluation found slightly higher costs but better outcomes in parasuicides avoided for standard DBT compared with TAU. The final evaluation found that standard DBT was more costly than TAU but delivered only moderate gains in outcomes (parasuicide events avoided and QALYs) at an ICER considerably above the NICE threshold. All these analyses showed considerable uncertainty because they analysed between 20 and 44 patients. Furthermore, they relied heavily on assumptions and data outside the original trials, since none of them included economic data. The authors concluded that the findings do not support the cost-effectiveness of standard DBT, though it has the potential to be cost-effective for BPD.

In comparison, the RefraMED economic evaluation provides rigorous economic evidence about RO DBT in the NHS using NICE criteria established for clinical disorders. Interestingly, when it comes to treatment recommendations for personality disorders, NICE is equivocal about cost estimates. Despite costs for outpatient DBT far exceeding recommended thresholds, NICE still recommends DBT for treatment of borderline personality disorder in the NHS. As noted by NICE, costing parameters for the treatment of personality disorders have yet to be identified and broad consensus has been repeatedly noted for a change in how we measure and pay for mental healthcare in the NHS—especially when it comes to treating chronic mental health problems. The high rates of comorbid personality disorder in RefraMED (79%) suggest that cost considerations for our trial and other similar trials of chronic depression—may be best understood when evaluated similarly.

The interpretation of our economic results is subject to some important limitations. First, in terms of generalisability, there are a range of definitions of refractory depression and treatment-resistant depression which should be taken into account when considering the generalisability of our findings. Second, our economic findings may also have limited generalisability outside NHS mental health services in England and Wales. Third, the study fell short of the target recruitment (250/276, 91%) and full follow-up for the economic evaluation were only available for 74% (186/250) of the sample, consequently the study was underpowered with respect to the pre-planned target effect size.

In summary, our results suggest that RO DBT in its current form is not cost-effective relative to usual treatment according to NICE criteria. Hence research should address how to refine RO DBT to maintain the present gains but at lower cost for longer. There are many ways of adjusting the delivery of RO DBT to reduce costs, and future work must address the effectiveness and cost-effectiveness of these amended manuals. For example, we could taper treatment by reducing the
frequency of sessions after an initial intensive period or adopt a stepped approach offering group sessions initially and individual sessions only to those who fail to respond. Indeed small studies of RO DBT skills training classes alone have reported promising improvements in effectiveness.\textsuperscript{35,36} Another important avenue of future research will be the development and evaluation of a RO DBT support programme on mobile phones or the web. Several participants suggested that this would helpful during active treatment and thereafter. Further exploratory analyses of the RefraMED dataset will be critical in developing a shorter version of the skills programme that could be used in NHS settings with limited funding.

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Authors’ contributions

All authors contributed to writing and reviewing this paper.

- Sarah Byford (Professor of Health Economics) contributed to the design of the study and managed the economic evaluation.
- Rampaul Chamba (Patient and Public Representative) contributed to managing the study and to patient and public engagement.
• Susan Clarke (Visiting Professor, Consultant Clinical Psychologist; Principal Investigator and Clinical Lead for Dorset until 2014) contributed to the design of the study and clinical methods, supervised therapists and research assistants, and delivered therapy.

• Roelie Hempel (Senior Research Fellow) contributed to the design of the study and acted as Trial Manager throughout the study.

• David Kingdon (Professor of Mental Health Care Delivery; Site Principal Investigator) contributed to the design of the study, and supervised research assistants.

• Thomas Lynch (Emeritus Professor of Clinical Psychology; Chief Investigator) developed Radically Open Dialectical Behaviour Therapy and contributed to all aspects of the design and management of the study.

• Heather O’Mahen (Senior Lecturer in Clinical Psychology; Assessment Lead) trained clinical assessors, provided clinical supervision to research assistants, supported follow-up assessments, managed the study, and conducted reliability analyses.

• Bob Remington (Emeritus Professor in Psychology) contributed to writing the grant proposal and managing the study.

• Sophie Rushbrook (Consultant Clinical Psychologist, Clinical Lead for Dorset site) supervised therapists and delivered therapy.

• Ian Russell (Professor of Clinical Trials) was trial methodologist and contributed to the design and management of the study.

• James Shearer (Lecturer in Health Economics) undertook economic analyses.

• Maggie Stanton (Consultant Clinical Psychologist; Clinical Lead for Hampshire site) supervised therapists and delivered therapy.

• Michaela Swales (Consultant Clinical Psychologist; Reader in Clinical Psychology; Site Principal Investigator for North Wales site) supervised therapists and research assistants, and delivered therapy.

• Alan Watkins (Associate Professor of e-Trials Research) designed and managed the randomisation service, drafted the statistical analysis plan and reviewed its implementation, and contributed to validating data.

• Ben Whalley (Lecturer in Psychology) contributed to the design of the study and writing the grant proposal, and undertook data analyses.

Authors’ competing interests
• Sarah Byford declares no competing interests.
• Rampaul Chamba declares no competing interests.
• Paul Clarke declares no competing interests.
• Susan Clarke declares no competing interests.
• Roelie Hempel is co-owner and director of Radically Open Ltd, the RO DBT training and dissemination company.
• David Kingdon reports grants outside the submitted work from NIHR.
• Thomas Lynch receives royalties from New Harbinger Publishing for sales of RO DBT treatment manuals, speaking fees from Radically Open Ltd, and a grant outside the submitted work from the Medical Research Council. He was co-director of Radically Open Ltd between November 2014 and May 2015 and is married to Erica Smith-Lynch, the principal shareholder and one of two directors of Radically Open Ltd.
• Heather O’Mahen reports personal fees outside the submitted work from the Charlie Waller Institute and Improving Access to Psychological Therapy.
• Bob Remington declares no competing interests.
• Sophie Rushbrook provides RO DBT supervision through her company S C Rushbrook Ltd.
• Ian Russell reports grants outside the submitted work from NIHR and Health & Care Research Wales.
• James Shearer declares no competing interests.
• Maggie Stanton reports personal fees outside the submitted work from British Isles DBT Training, Stanton Psychological Services Ltd, and Taylor & Francis.
• Michaela Swales reports personal fees outside the submitted work from British Isles DBT Training, Guilford Press, Oxford University Press, and Taylor & Francis.
• Alan Watkins declares no competing interests.
• Ben Whalley was co-director of Radically Open Ltd between November 2014 and February 2015.
References


### Table 1. Disaggregated mean costs by group at baseline, 12 months and 18 months

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<th></th>
<th>RO DBT Mean (SD)</th>
<th>TAU Mean (SD)</th>
<th>Mean difference*</th>
<th>95% CI*</th>
<th>p*</th>
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</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>N=162</td>
<td>N=88</td>
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<tr>
<td>Talking therapy</td>
<td>£364 (£795)</td>
<td>£692 (£1,112)</td>
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<tr>
<td>Hospital services</td>
<td>£1,305 (£4,280)</td>
<td>£1,968 (£5,140)</td>
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<tr>
<td>Community services</td>
<td>£713 (£733)</td>
<td>£755 (£852)</td>
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<tr>
<td>Medications</td>
<td>£17 (£12)</td>
<td>£19 (£11)</td>
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</tr>
<tr>
<td>Total NHS/PSS costs</td>
<td>£2,397 (£4,418)</td>
<td>£3,426 (£5,812)</td>
<td>-£1,029</td>
<td>-£2,463 to £407</td>
<td>0.160</td>
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<tr>
<td>Absenteeism</td>
<td>£3,821 (£5,563)</td>
<td>£4,648 (£6,277)</td>
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<tr>
<td>Presenteeism</td>
<td>£3,382 (£1,749)</td>
<td>£2,676 (£2,771)</td>
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<tr>
<td>Total societal costs</td>
<td>£9,600 (£6,469)</td>
<td>£10,750 (£8,354)</td>
<td>-£1,830</td>
<td>-£3763 to £104</td>
<td>0.064</td>
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<td><strong>Baseline to month 12</strong></td>
<td>N=125</td>
<td>N=61</td>
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<tr>
<td>RO DBT individual</td>
<td>£3,095 (£1,095)</td>
<td>0 (0)</td>
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<tr>
<td>RO DBT groups</td>
<td>£1,910 (£817)</td>
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<tr>
<td>Total RO DBT</td>
<td>£5,005 (£1,809)</td>
<td>0 (0)</td>
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<tr>
<td>Talking therapy</td>
<td>£256 (£137)</td>
<td>£1,317 (£2,388)</td>
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<tr>
<td>Hospital services</td>
<td>£934 (£1,803)</td>
<td>£1,216 (£2,400)</td>
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<td>Community services</td>
<td>£986 (£1,527)</td>
<td>£966 (£1,411)</td>
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<tr>
<td>Medications</td>
<td>£29 (£18)</td>
<td>£35 (£20)</td>
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<tr>
<td>Total NHS+PSS costs</td>
<td>£7,210 (£3,343)</td>
<td>£3,534 (£4,240)</td>
<td>£4,566</td>
<td>£3,691 to £5,440</td>
<td>&lt;0.001</td>
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<tr>
<td>Absenteeism</td>
<td>£2,415 (£5,248)</td>
<td>£4,063 (£9,145)</td>
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## RO DBT vs TAU

<table>
<thead>
<tr>
<th>Category</th>
<th>RO DBT Mean (SD)</th>
<th>TAU Mean (SD)</th>
<th>Mean difference*</th>
<th>95% CI*</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenteeism</td>
<td>£5,641 (£2,662)</td>
<td>£4,827 (£2,419)</td>
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<tr>
<td>Total societal costs</td>
<td>£15,266 (£5,072)</td>
<td>£12,424 (£6,764)</td>
<td>£2,657</td>
<td>£1,217 to £4,098</td>
<td>&lt;0.001</td>
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<tr>
<td>Baseline to month 18</td>
<td>N=101</td>
<td>N=51</td>
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<tr>
<td>Talking therapy</td>
<td>£501 (£253)</td>
<td>£1,633 (£1,561)</td>
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<td>Hospital services</td>
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<tr>
<td>Community services</td>
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<tr>
<td>Medications</td>
<td>£45 (£46)</td>
<td>£55 (£48)</td>
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<tr>
<td>Total NHS/PSS costs</td>
<td>£8,389 (£4,357)</td>
<td>£5,099 (£7,677)</td>
<td>£4,463</td>
<td>£2,915 to £6,011</td>
<td>&lt;0.001</td>
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<tr>
<td>Absenteeism</td>
<td>£4,050 (£9,616)</td>
<td>£5,833 (£13,224)</td>
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<td>Presenteeism</td>
<td>£7,634 (£6,925)</td>
<td>£7,718 (£7,818)</td>
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<tr>
<td>Total societal costs</td>
<td>£20,073 (£6,967)</td>
<td>£18,650 (£12,262)</td>
<td>£1,062</td>
<td>-£1,762 to £3,886</td>
<td>0.461</td>
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</tbody>
</table>

*All analyses adjusted and bootstrapped; PSS=personal social services
Table 2. EQ-5D Scores and QALYs at baseline, 12- and 18-Month Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>RO DBT</th>
<th>TAU</th>
<th>Mean difference*</th>
<th>95% CI*</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<tr>
<td>Baseline EQ-5D</td>
<td>0.422 (0.291)</td>
<td>0.395 (0.329)</td>
<td>-</td>
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<tr>
<td>12-month EQ-5D</td>
<td>0.552 (0.339)</td>
<td>0.547 (0.307)</td>
<td>0.008</td>
<td>-0.074 to 0.090</td>
<td>0.847</td>
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<tr>
<td>18-month EQ-5D</td>
<td>0.564 (0.311)</td>
<td>0.596 (0.309)</td>
<td>0.005</td>
<td>-0.087 to 0.091</td>
<td>0.096</td>
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<tr>
<td>12-month QALYs</td>
<td>0.534 (0.315)</td>
<td>0.496 (0.349)</td>
<td>0.032</td>
<td>-0.029 to 0.093</td>
<td>0.297</td>
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<tr>
<td>18-month QALYs</td>
<td>0.702 (0.067)</td>
<td>0.763 (0.453)</td>
<td>0.023</td>
<td>-0.074 to 0.114</td>
<td>0.677</td>
</tr>
</tbody>
</table>

*All analyses adjusted, imputed and bootstrapped*
Figure 1 Scatter plot of differences in costs versus differences in QALYs for RO DBT versus TAU after 12-months from perspective of NHS and personal social services.
Figure 2 Cost-effectiveness acceptability curve for QALYs showing the probability that RO DBT is cost-effective compared with TAU after 12-months from perspective of NHS and personal social services.