Long-term effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: follow-up of the CoBalT randomised controlled trial

Nicola J Wiles, Laura Thomas, Nicholas Turner, Kirsty Garfield, Daphne Kounali, John Campbell, David Kessler, Willem Kuyken, Glyn Lewis, Jill Morrison, Chris Williams, Tim J Peters, Sandra Hollinghurst

Summary

Background Cognitive behavioural therapy (CBT) is an effective treatment for people whose depression has not responded to antidepressants. However, the long-term outcome is unknown. In a long-term follow-up of the CoBalT trial, we examined the clinical and cost-effectiveness of cognitive behavioural therapy as an adjunct to usual care that included medication over 3–5 years in primary care patients with treatment-resistant depression.

Methods CoBalT was a randomised controlled trial done across 73 general practices in three UK centres. CoBalT recruited patients aged 18–75 years who had adhered to antidepressants for at least 6 weeks and had substantial depressive symptoms (Beck Depression Inventory [BDI-II] score ≥14 and met ICD-10 depression criteria). Participants were randomly assigned using a computer generated code, to receive either usual care or CBT in addition to usual care. Patients eligible for the long-term follow-up were those who had not withdrawn by the 12 month follow-up and had given their consent to being re-contacted. Those willing to participate were asked to return the postal questionnaire to the research team. One postal reminder was sent and non-responders were contacted by telephone to complete a brief questionnaire. Data were also collected from general practitioner notes. Follow-up took place at a variable interval after randomisation (3–5 years). The primary outcome was self-report of depressive symptoms assessed by BDI-II score (range 0–63), analysed by intention to treat. Cost-utility analysis compared health and social care costs with quality-adjusted life-years (QALYs). This study is registered with isrctn.com, number ISRCTN38231611.

Findings Between Nov 4, 2008, and Sept 30, 2010, 469 eligible participants were randomised into the CoBalT study. Of these, 248 individuals completed a long-term follow-up questionnaire and provided data for the primary outcome (136 in the intervention group *vs* 112 in the usual care group). At follow-up (median 45·5 months [IQR 42·5–51·1]), the intervention group had a mean BDI-II score of 19·2 (SD 13·8) compared with a mean BDI-II score of 23·4 (SD 13·2) for the usual care group (repeated measures analysis over the 46 months: difference in means –4·7 [95% CI –6·4 to –3·0, p<0·001]). Follow-up was, on average, 40 months after therapy ended. The average annual cost of trial CBT per participant was £343 (SD 129). The incremental cost-effectiveness ratio was £5374 per QALY gain. This represented a 92% probability of being cost effective at the National Institute for Health and Care Excellence QALY threshold of £20 000.

Interpretation CBT as an adjunct to usual care that includes antidepressants is clinically effective and cost effective over the long-term for individuals whose depression has not responded to pharmacotherapy. In view of this robust evidence of long-term effectiveness and the fact that the intervention represented good value-for-money, clinicians should discuss referral for CBT with all those for whom antidepressants are not effective.

Funding National Institute for Health Research Health Technology Assessment.

Introduction

Cognitive behavioural therapy (CBT) is an effective treatment for depression,[1,2] including for those who have not responded to antidepressants.[3] CBT teaches patients skills to help them better manage their mood, and so has the potential to result in benefit that is sustained beyond the end of therapy. However, little evidence of long-term effectiveness exists. Many trials report outcomes at the end of therapy[2] and although there is evidence that CBT is effective[3–8] and cost effective[9,10] in the medium term (6–12 months), many of these trials are small with sample sizes of fewer than 75 participants per group.[4–7] Trials of CBT in relapse prevention (with sample sizes of 40 followed up at 4 and 6 years[11,12] and 158 participants followed up at roughly 6 years[13]) suggest that CBT might be effective in the long-term. A 6-year follow-up of patients with residual depressive symptoms (not major depression) randomly assigned to CBT or usual care,[14] found that the difference in recurrence between groups persisted for 3 years.[13]

Data for long-term cost-effectiveness are sparse, yet the cost to health services and society is well recognised.[15,16] Resource use data were not collected in the long-term follow-ups of CBT for relapse prevention.[11–13] Other reports about the cost-effectiveness of CBT relate to different patient populations and briefer interventions.[17] In view of the chronic relapsing nature of depression, knowledge of long-term outcomes and cost-effectiveness is needed.[1]

Despite expansions in psychological services in the UK[18] and elsewhere, CBT is still a limited resource, often reserved for those with treatment-resistant depression who have not responded to antidepressants. The latter group represent a high proportion (>50%) of those treated with medication in primary care.[19] To inform decision making, evidence should be obtained to substantiate and quantify the potential for long-term benefit in this group.

We report the long-term follow-up of the CoBalT trial. We aimed to examine whether CBT (in addition to usual care that included pharmacotherapy) was effective and cost effective in reducing depressive symptoms and improving quality of life over the long-term (3–5 years) compared with usual care alone in primary care patients with treatment-resistant depression.

Methods

Study design and participants
The design of the CoBalT trial has been previously described.[3] The CoBalT trial was a multicentre randomised controlled trial done across 73 general practices in three UK centres.[3,10,20] CoBalT recruited patients aged 18–75 years who had adhered to antidepressants for at least 6 weeks and had substantial depressive symptoms (Beck Depression Inventory[21] [BDI-II] score ≥14 and met the ICD-10 depression criteria).[3] This definition of treatment-resistant depression was inclusive and directly relevant to primary care.

Participants were randomly assigned to continue with usual care from their general practitioner, or to receive 12–18 sessions of CBT in addition to usual care. Randomisation was by means of a computer-generated code from a remote automated telephone randomisation service. Allocation was stratified by centre and minimised according to four factors (baseline BDI-II score, whether the general practice had a counsellor, previous treatment with antidepressants, and duration of depression at baseline). Therapists were representative of those working in NHS psychology services.[3] An independent assessor confirmed that therapy was delivered competently.[22] Participants and investigators were not masked to treatment assignment because of the nature of the intervention.

Patients eligible for long-term follow-up were those who had not withdrawn during the 12 month follow-up and had consented to be contacted about future research. Ethical approval for the follow-up study was given by the National Research Ethics Service Committee West Midlands, Edgbaston (reference number 13/WM/0149). Research governance approvals were obtained from the relevant local Research Ethics Committees and Clinical Commissioning Groups or Health Boards covering the three study sites (Bristol, Exeter, and Glasgow). The protocol is available online.

Procedures
General practices excluded individuals who had died, and those it was inappropriate to re-contact (eg, people who were terminally ill) from the list of potential participants. Participants were mailed an invitation letter, information leaflet, and questionnaire to collect data for the various outcomes. Those willing to participate were asked to return the completed questionnaire to the research team. One postal reminder was sent and non-responders contacted by telephone to complete a

For **expansions in psychological services elsewhere** see http://www.health.gov.au/mentalhealth-betteraccess

For **protocol** see http://www.bristol.ac.uk/psychiatry/research/resources

brief questionnaire, which included the Patient Health Questionnaire 9 (PHQ-9), questions about use of, and adherence to, antidepressants, and questions about use of health-care services. Follow-up took place at a variable interval after randomisation (3–5 years). Individuals who had moved were traced through the Health and Social Care Information Centre. Consent for tracing was obtained previously.

Outcomes

The primary outcome was self-report of depressive symptoms assessed by BDI-II score[21] (range 0–63). Secondary outcomes were response (≥50% reduction in depressive symptoms relative to baseline); remission (BDI-II score <10); quality of life (Short-Form health survey 12 [SF-12]);[23] and measures of depression (PHQ-9)[24] and anxiety (Generalised Anxiety Disorder assessment 7 [GAD-7])[25] used in psychological services. Data for the use of, and adherence to, antidepressants were collected and current comorbidities were ascertained. Data for health care used in primary and secondary care and complementary and alternative therapy were collected for the economic evaluation. Participants also completed the EQ-5D-5L (a standardised generic measure of health status used as part of the economic evaluation).[26] In a random sample of 50 participants from Bristol practices, data for primary care consultations and antidepressant medication since the 12 month follow-up were obtained to inform the economic evaluation.

Statistical analysis

A predefined analysis plan was agreed with the Trial Steering Committee. The primary outcome for the main trial was a binary response variable; for this follow-up, the primary outcome was specified as a continuous outcome (BDI-II score) to maximise power. The change in the specification of the primary outcome for the long-term follow-up was made at the time the request for additional funding was submitted to the funder (Nov 6, 2012).

Repeated measures analyses compared the groups as randomised by intention to treat, incorporating outcomes at 6 months, 12 months, and 3–5 years, adjusting for the original stratification and minimisation variables (study centre, baseline BDI-II score, whether the practice had a counsellor, previous treatment with antidepressants, and duration of their depressive episode at baseline) and baseline measurement of the outcome. These analyses used an extension to generalised estimating equations (Stata: xtqls command) using a Markov correlation structure to allow for the unequal spacing of measurements over time.[27] The summary effect measure represented the average difference in mean BDI-II scores between treatment groups over time. We formally assessed whether the treatment effects reported over 12 months were sustained or declined over the long term by introducing an interaction between time (in months since randomisation included as linear covariate) and treatment allocation in
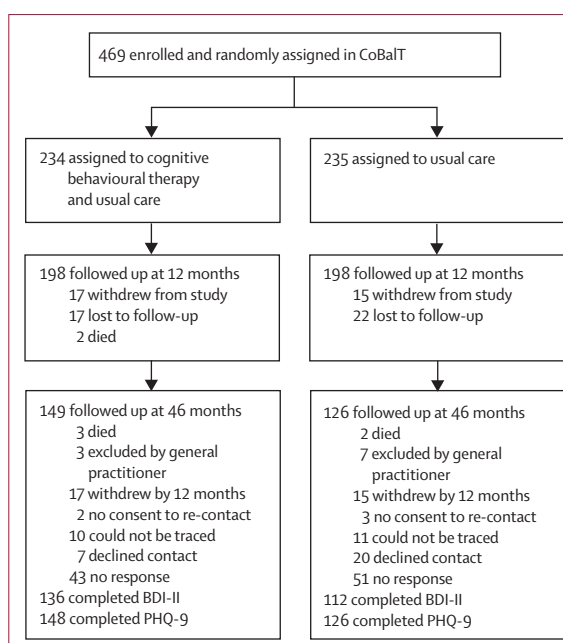

Figure 1: CoBalT trial profile extended to include long-term follow-up
BDI-II=Beck Depression Inventory score. PHQ-9=Patient Health Questionnaire 9.

the model. Similar regression models were used for analysis of the secondary outcomes. Differences in means, odds ratios, 95% CIs, and p values are reported.

Sensitivity analyses examined the effect of missing data using the multiple imputation by chained equation approach,[28] and linear random effect models,[29] modelling outcome trajectories jointly with the wave-specific probabilities of loss to follow-up.[30,31] We compared two alternative models for modelling loss to follow-up: (1) a model where loss to follow-up at each wave depended on the previous level of the patient's outcome (missing at random); and (2) where loss to follow-up depended on the current value of the outcome (informative drop-out or missing not at random; appendix, p 4).

The economic evaluation was done from the perspective of UK NHS and personal social services. We obtained information about patients' health care resource use for the past 6 months from the questionnaire. To estimate resource use during the whole follow-up period, we combined questionnaire data with resource use data from the main trial at an individual level and extrapolated. Estimates were refined using data for consultations and antidepressant medication collected for 50 patients for the whole period from general practitioner records. Resource use was valued at 2013 prices, using relevant unit costs (appendix p 2)[32–34] or inflated using the hospital and community health services index.[32] Costs and quality-adjusted life-years (QALYs) were discounted at 3·5%.[35]

EQ-5D-3L values collected during the trial were combined[26] with EQ-5D-5L values at long-term follow-up to estimate QALYs for the whole period. We adjusted for baseline EQ-5D scores to account for the difference in

For the **questions asked to collect data** see http://www.gp-patient.co.uk

See **Online** for appendix

	Intervention		Usual care		Adjusted difference in means at 46 months or adjusted odds ratio* (95% CI)	Repeated measures analyses			
	N	n (%) or mean (SD) at 46 months	N	n (%) or mean (SD) at 46 months		N	Adjusted difference in means or adjusted odds ratio* (95% CI)	p value	Effect size for continuous outcomes
Primary outcome									
BDI-II score	136	19·2 (13·8)	112	23·4 (13·2)	–3·6 (–6·6 to –0·6)	1062	–4·7 (–6·4 to –3·0)	<0·001	0·45
Secondary outcomes									
Response	136	59 (43%)	112	30 (27%)	2·09 (1·19 to 3·67)	1062	2·65 (1·97 to 3·55)	<0·001	..
Remission (BDI-II <10)	136	38 (28%)	112	20 (18%)	1·77 (0·93 to 3·39)	1062	2·49 (1·84 to 3·38)	<0·001	..
Percentage change in BDI-II score	136	–36·4% (42·3)	112	–21·0% (42·0)	–14·9% (–25·1 to –4·7)	1062	–18·2% (–23·7 to –12·6)	<0·001	..
PHQ-9	148	9·5 (7·1)	126	11·1 (6·3)	–1·6 (–3·0 to –0·1)	1470	–2·4 (–3·1 to –1·6)	<0·001	0·42
GAD-7	136	7·1 (5·9)	113	8·4 (5·5)	–1·1 (–2·4 to 0·2)	1064	–1·9 (–2·6 to –1·2)	<0·001	0·37
SF-12 mental subscale	132	38·7 (12·1)	110	34·6 (11·8)	3·5 (0·7 to 6·3)	1041	4·5 (2·8 to 6·2)	<0·001	0·49
SF-12 physical subscale	132	42·2 (13·8)	110	39·2 (13·5)	0·9 (–2·0 to 3·7)	1041	–0·3 (–1·6 to 1·0)	0·672	0·02

BDI-II=Beck Depression Inventory score. PHQ-9=Patient Health Questionnaire 9. GAD-7= Generalised Anxiety Disorder assessment 7. SF-12=Short-Form health survey 12. *The intention-to-treat analysis adjusted for baseline measure of outcome and the stratification (centre) and minimisation variables (baseline BDI-II score, previously prescribed antidepressants, whether the general practice had a counsellor, and duration of current episode of depression at baseline).

Table 1: **Intention-to-treat analyses of primary and secondary outcomes over 46 months**

scores between groups at baseline. As the follow-up period varied between 3 and 5 years, average annual values of costs and QALYS were derived to ensure comparability. An incremental cost-effectiveness ratio was estimated and uncertainty captured with non-parametric bootstrapping. A cost-effectiveness acceptability curve was plotted to indicate the probability of the intervention being cost effective at different values of willingness to pay. Net monetary benefit statistics were estimated for the thresholds of £20000 and £30000 per QALY. Additional sensitivity analyses were done to test the robustness of our assumptions in terms of grade of therapist, often band 7 in Improving Access to Psychological Therapies services instead of 8a as in the trial, without using general practice note data to adjust resource use, and imputing missing values. Statistical analyses were done with Stata version 13.1. This trial is registered with isrctn.com, number ISRCTN38231611.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
469 participants were randomly assigned in CoBalT, 32 withdrew from the study by 12 months, two individuals died, and five did not consent to future contact.[3] Thus, 430 individuals were eligible to participate in the long-term follow-up. Of these, a further three individuals died between the 12 month and 46 month follow-up (one in the intervention group and two in the usual care group),

ten were excluded by their general practitioner, and 21 could not be traced. Hence, 396 individuals were invited to participate between Sept 1, 2013, and April 14, 2014, in which time 275 individuals had completed a questionnaire. 27 individuals declined to participate and 94 did not respond. Long-term follow-up data were available for 59% of the original 469 participants randomly assigned. The median time from randomisation to long-term follow-up questionnaire completion was 45·5 months (IQR 42·5–51·1), which was, on average, 39·7 months (SD 5·2) after the end of therapy for those who had had at least 12 sessions of CBT (n=105). 149 (64%) participants were followed up in the intervention group compared with 126 (54%) in the usual care group (figure 1). Of these, 136 participants in the intervention group and 112 participants in the usual care group completed the BDI-II questionnaire and 148 participants in the intervention group and 126 participants in the usual care group completed the PHQ-9 questionnaire.

At trial entry, most participants had severe (mean baseline BDI-II score 30·9 [SD 9·8]) and chronic depression (duration ≥2 years, n=162 [59%]).[3] 66 participants (24%) met ICD-10 criteria for severe depression.[3] Physical and psychological comorbidity were common.[3] 205 (75%) had a secondary diagnosis of an anxiety disorder. At the long-term follow-up, 199 (80%) participants reported at least one long-term health condition (of 249 participants who completed the full-length questionnaire). 115 reported musculoskeletal problems, 53 reported high blood pressure, 48 reported asthma or chest problems, and 34 reported diabetes.

Participants in the intervention group had a BDI-II score that was, on average, 3·6 points lower (less depressed, 95% CI –6·6 to –0·6) at 46 months than those
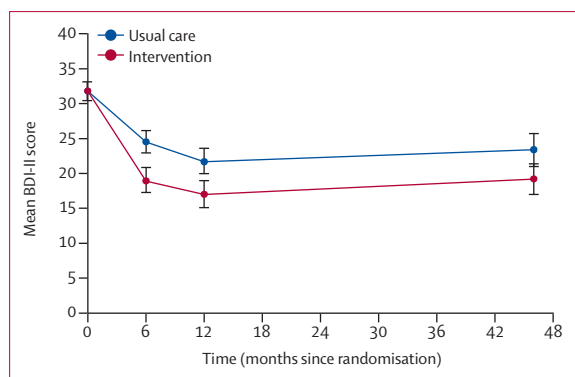
Figure 2: **Mean BDI-II scores for the intervention and usual care groups at 6, 12, and 46 months**
Error bars represent SD. BDI-II=Beck Depression Inventory score.

	Intervention (n=116)	Usual care (n=98)
All primary care	£412 (570)	£472 (809)
Antidepressants	£64 (97)	£87 (168)
Hospital care	£50 (294)	£37 (186)
Personal social services	£17 (112)	£9 (49)
National health service and personal social services total	£542 (912)	£604 (904·15)
Cost of cognitive behavioural therapy	£343 (129)	..
Total cost	£885 (937·92)	£604 (904·15)
QALYs	0·596 (0·17)	0·544 (0·20)
Incremental cost (95% CI)	£281 (32–531)	..
Incremental benefit, QALY gain (95% CI)	0·052 (0·003–0·102)	..
Incremental cost-effectiveness ratio, cost per QALY gain	£5374	..
Median net monetary benefit (probability net monetary benefit>0)	..	..
Willingness to pay=£20 000 per QALY	782 (0·92)	..
Willingness to pay=£30 000 per QALY	1317 (0·95)	..

Data are mean (SD), unless otherwise specified. Mean annual cost and benefit per participant are only presented for complete cases. QALY=Quality-adjusted life-year.

Table 2: **Cost-utility analysis from a National Health Service and personal social services perspective**

in the usual care group (table 1). In repeated measures analyses, using data from 6, 12, and 46 months (figure 2, appendix, p 3), individuals in the intervention group had a mean BDI-II score that was, on average, 4·7 points lower (–6·4 to –3·0) over the 46 months compared with those in the usual care group (table 1). This equated to an effect size of 0·45 using the baseline SD for BDI-II (pooled). Mean BDI-II scores at 46 months for the usual care group were similar to scores at 6 and 12 months (figure 2, appendix, p 3).[3] Although the intervention effect decreased slightly across the timepoints, there was no statistical evidence of an interaction between treatment allocation and time (p=0·29).

A beneficial effect of the intervention was found for all secondary outcomes except the SF-12 physical health subscale (table 1). Individuals in the intervention group had nearly a three-fold increased odds of response over the 46 months compared with those in the usual care group. Those in the intervention group were also more likely to experience remission (BDI-II score <10), a reduction in anxiety (GAD-7), and greater improvement on the SF-12 mental health subscale over the 46 months compared with those in the usual care group (table 1). There was no statistical evidence that the effect of the intervention varied over time (interactions between treatment allocation and time: p>0·11). Inclusion of a quadratic term for time made no difference to the findings. The results of sensitivity analyses to examine the robustness of the findings to varying assumptions about missing data identified either slightly smaller or larger effects, albeit consistent with the results using all available data (appendix, p 5).

197 (72%) participants reported taking antidepressants for the time since the 12 month follow-up, but sustained use of antidepressants was lower in the intervention group than in the usual care group (101 [68%] in the intervention group *vs* 96 [76%] in the usual care group). The intervention group were less likely to be taking antidepressants at 46 months (120 in the intervention group [81%] *vs* 107 [85%] in the usual care group;

difference –4·4% [95% CI –13·3 to 4·5]), but the percentage who adhered to their medication was slightly higher in the intervention group (111 [93%] of 120) compared with the usual care group (96 [90%] of 107); difference 2·8% [–4·7 to 10·2]). However, the 95% surrounding these differences included the null. Only five participants had used a computerised or internet-based CBT package since the 12 month follow-up (appendix, p 9). 34 (27%) participants in the usual care group and 31 (21%) in the intervention group had received counselling or talking therapy since the 12 month follow-up (appendix, p 9). However, only 17 individuals had received cognitive therapy, and only five had received 12 sessions.

The economic evaluation using complete-case data included 116 (50%) of 234 participants in the intervention group and 98 (42%) of 235 participants in the usual care group. Average annual NHS and personal social service resource use was similar between the two groups (appendix, p 10), emulating the 1 year follow-up result.[10] The results from the base case cost-utility analysis are presented in table 2. The mean annual cost per participant of the intervention was £343. NHS and personal social service costs were slightly higher in the usual care group (£604 *vs* £542), resulting in an annual incremental cost of £281 (95% CI £32–£531). Mean annualised QALYs were higher in the intervention group (0·596 *vs* 0·544), representing better health-related quality of life over the whole period. The incremental cost-effectiveness ratio was £5374. At a societal willingness to pay of £20 000 per QALY, the net monetary benefit per patient per year was £782, with a probability of 0·92 of being cost effective (figure 3). Results remained robust throughout sensitivity analyses (appendix, p 11). If therapists were employed at grade 7, the incremental
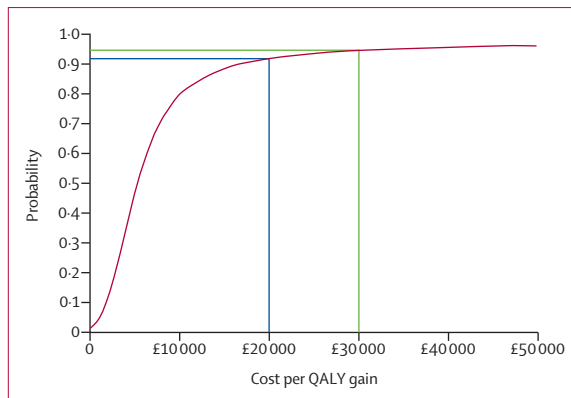
Figure 3: Cost-effectiveness acceptability curve showing the probability that the intervention is cost effective at different levels of willingness to pay
QALY=quality-adjusted life-year.

cost-effectiveness ratio decreased to £4622. Without using general practitioner note data to adjust resource use, the incremental cost-effectiveness ratio increased slightly to £5982. With all missing data imputed, the incremental cost-effectiveness ratio increased to £6890. The probability of the intervention being cost effective ranged from 0·92 to 0·94 at a societal willingness to pay of £20 000 per QALY (appendix, p 11).

Discussion

CBT as an adjunct to usual care was an effective treatment for primary care patients with treatment-resistant depression over the long-term, and represented good value for money. The intervention reduced depressive symptoms and improved quality of life over an average of 46 months. This was, on average, 40 months after the end of therapy. A long-term benefit was also seen in terms of remission of symptoms. In view of the fact that, at baseline, most CoBalT participants had severe and chronic depression, with physical or psychological comorbidity, or both, these results are noteworthy and have clear implications for clinical practice.

To our knowledge, this study is the first to show long-term effectiveness of CBT as an adjunct to pharmaco-therapy for primary care patients with treatment-resistant depression. Previous systematic reviews[36,37] underlined the absence of high quality evidence in this area. Earlier trials were small (with sample sizes of less than 100 participants per group) with only short-term outcomes (8–20 weeks).[36] Previous findings from the CoBalT trial were the first evidence of sustained effectiveness at 12 months.[3] Other studies reporting outcomes 6–12 months after the end of CBT are small (with sample sizes of less than 75 participants per group),[4–7] with one exception,[8] and long-term outcome data (4–6 years) relate to CBT for relapse prevention.[11–13] Other psychological therapies might be as effective as CBT in the short-to-medium term,[38] but no evidence of long-term effectiveness exists.

The health-care costs of individuals with treatment-resistant depression are larger than for many other groups.[39,40] However, we previously showed that CBT was a cost-effective treatment for patients with treatment-resistant depression over a 12 month period.[10] Present findings represent the first evidence of long-term cost-effectiveness. The cost difference between groups was driven by the initial cost of therapy, as health-care costs were very similar for the duration and no top-up sessions were offered. The benefit, in terms of health-related quality of life, was sustained over time, and therefore achieved at no additional cost. This finding reinforces our conclusion at 12 months that investing in CBT services for these patients represents an efficient use of health-care resources. Although lost productivity was not investigated in the long-term follow-up and a difference between groups was not evident at 12 months,[10] the sustained effect might affect paid and non-paid activities as well as wider societal benefits, such as the wellbeing of families.

Our study had several strengths and limitations. The sample size of this study was large and it was set in UK primary care. Although participants in the intervention group were more likely to be followed up at 46 months, in sensitivity analyses, no evidence existed that missing data had biased the findings for either the clinical or the cost-effectiveness analyses. In terms of costs, for the various sensitivity analyses, the estimated incremental cost-effectiveness ratio remained well below the £20 000 per QALY threshold used by the National Institute for Health and Care Excellence.

Limited resources meant that the long-term follow-up data were collected by postal questionnaire rather than self-completion of a questionnaire at a face-to-face appointment with a researcher (as at the 6 and 12 month follow-ups). This difference probably affected the response rate achieved, although as stated above, there was no evidence of bias because of missing data. Importantly, collection of the same outcome measures as the original trial enabled comparison of data in the long-term. Only a small number of patients received CBT after the end of the trial (12 months); therefore, contamination did not affect the findings. The proportion taking long-term antidepressants was also similar between groups. We aimed to reduce patient reporting bias by validating self-report data with patient notes, which resulted in slightly higher estimates of NHS and personal social services costs, implying patients had under-reported their health-care use. However, the difference was small, as shown by sensitivity analyses, and there was no apparent difference between the two groups, allowing us to be confident in our estimations of resource use for the whole period.

More than 50% of primary care patients with depression do not respond to antidepressants.[19] Our findings provide robust evidence for the effectiveness of CBT given as an adjunct to usual care that includes

medication in reducing depressive symptoms and improving quality of life over the long term. The effects observed were substantial and represented good value for money. As most of the CoBalT participants had severe and chronic depression, with physical or psychological comorbidity, or both, these results should offer hope for this population of difficult-to-treat patients. Clinicians need to discuss referral for CBT with all those for whom antidepressants are not effective.

Inequity in provision of mental and physical health care has been recognised internationally. From January, 2014, the Affordable Care Act mandated coverage for mental health care in all US insurance plans, and waiting time targets for mental health services were introduced in England in April, 2015. Initiatives to improve provision of psychological treatments have mainly focused on increasing low-intensity interventions such as computerised CBT packages and guided self-help for which there is little evidence of long-term effectiveness. Recent figures from Improving Access to Psychological Therapies services[41] in England show that most patients receive substantially less than the 12–18 sessions of high-intensity CBT delivered in CoBalT and, in similar services elsewhere, the number of CBT sessions is restricted. Translation of these findings into patient benefit will need increased investment and innovation. CBT has been shown to be of benefit in many different health-care systems, and can be delivered online in real-time.[8] The challenge that remains is how best to use technology to increase efficiency in the delivery of CBT while maintaining these long-term benefits. Only by doing so will we be able to improve outcomes for a condition that leads to substantial disability in developed countries.

Contributors
NJW, JC, DKe, WK, GL, JM, CW, TJP, and SH were responsible for securing additional funding for the follow-up study and drafting the original protocol. NJW as chief investigator had overall responsibility for the management of the follow-up study which was done from Bristol. All authors (with the exception of NT and DKo) contributed to refinement of the study protocol. LT was the study co-ordinator and, with KG, collected data from general practitioner records. NJW, SH, and TJP drafted the analysis plan. NT did the data cleaning and analyses of the clinical outcomes (under the supervision of NJW and TJP) and contributed to the interpretation of the data. KG did the data cleaning and analyses of the cost-effectiveness data (under the supervision of SH) and contributed to the interpretation of the data. DKo did missing at random or missing not at random sensitivity analyses and contributed to the interpretation of the data. NJW wrote the first draft of the manuscript incorporating the methods (LT), the results and discussion of the economic evaluation (KG and SH), and sensitivity analyses (DKo). All authors contributed to and approved the final manuscript.

Declaration of interests
CW is the author of a range of CBT-based resources that address anxiety, depression, and other disorders. These resources are available commercially as books, computerised CBT products, and classes. CW receives royalties, and is shareholder and director of a company (Five Areas Ltd) that commercialises these resources. CW's wife is also a shareholder and company secretary in Five Areas Ltd. WK is the co-author of the 2009 CBT book Collaborative Case Conceptualization, and receives royalties from its sales. All other authors declare no competing interests.

References
1 Butler AC, Chapman JE, Forman EM, Beck AT. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clin Psychol Rev* 2006; **26:** 17–31.

2 DeRubeis RJ, Hollon SD, Amsterdam JD, et al. Cognitive therapy *vs* medications in the treatment of moderate to severe depression. *Arch Gen Psychiatry* 2005; **62:** 409–16.

3 Wiles N, Thomas L, Abel A, et al. Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial. *Lancet* 2013; **381:** 375–84.

4 Miller IW, Norman WH, Keitner GI. Cognitive-behavioural treatment of depressed inpatients: six- and twelve- month follow-up. *Am J Psychiatry* 1989; **146:** 1274–79.

5 Kovacs M, Rush AJ, Beck AT, Hollon SD. Depressed outpatients treated with cognitive therapy or pharmacotherapy. *Arch Gen Psychiatry* 1981; **38:** 33–39.

6 Simons AD, Murphy GE, Levine JL, Wetzel RD. Cognitive therapy and pharmacotherapy for depression. *Arch Gen Psychiatry* 1986; **43:** 43–48.

7 Hollon SD, DeRubeis RJ, Shelton RC, et al. Prevention of relapse following cognitive therapy vs medications in moderate to severe depression. *Arch Gen Psychiatry* 2005; **62:** 417–22.

8 Kessler D, Lewis G, Kaur S, et al. Therapist-delivered internet psychotherapy for depression in primary care: a randomised controlled trial. *Lancet* 2009; **374:** 628–34.

9 Hollinghurst S, Peters TJ, Kaur S, Wiles N, Lewis G. Cost-effectiveness of therapist-delivered online cognitive-behavioural therapy for depression: randomised controlled trial. *Br J Psychiatry* 2010; **197:** 297–304.

10 Hollinghurst S, Carroll FE, Abel A, et al. Cost-effectiveness of cognitive-behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: economic evaluation of the CoBalT Trial. *Br J Psychiatry* 2014; **204:** 69–76.

11 Fava GA, Grandi S, Zielezny M, Rafanelli C, Canestrari R. Four-year outcome for cognitive behavioural treatment of residual symptoms in major depression. *Am J Psychiatry* 1996; **153:** 945–47.

12 Fava GA, Rafanelli C, Grandi S, Canestrari R, Morphy MA. Six-year outcome for cognitive behavioral treatment of residual symptoms in major depression. *Am J Psychiatry* 1998; **155:** 1443–45.

13 Paykel ES, Scott J, Cornwall PL, et al. Duration of relapse prevention after cognitive therapy in residual depression: follow-up of controlled trial. *Psychol Med* 2005; **35:** 59–68.

14 Paykel ES, Scott J, Teasdale JD, et al. Prevention of relapse in residual depression by cognitive therapy: a controlled trial. *Arch Gen Psychiatry* 1999; **56:** 829–35.

15 Wang PS, Simon G, Kessler RC. The economic burden of depression and the cost-effectiveness of treatment. *Int J Methods Psychiatr Res* 2003; **12:** 22–33.

16 Olchanski N, McInnis Myers M, Halseth M, et al. The economic burden of treatment-resistant depression. *Clin Ther* 2013; **35:** 512–22.

17 Durham RC, Chambers JA, Power KG, et al. Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland. *Health Technol Assess* 2005; **9:** 1–174.

18 Department of Health. Talking therapies: a four-year plan of action. London: Department of Health, 2011.

19 Thomas L, Kessler D, Campbell J, et al. Prevalence of treatment-resistant depression in primary care: cross-sectional data. *Br J Gen Pract* 2013; **63:** e852–58.

For the **Affordable Care Act** see https://www.congress.gov/bill/111th-congress/house-bill/3590

For **waiting time targets** see https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/361648/mental-health-access.pdf

For **initiatives to improve psychological treatment** see http://www.iapt.nhs.uk

For **CBT session restriction** see http://www.psychology.org.au/news/news_updates/archives/#6Dec2012

20 Thomas LJ, Abel A, Ridgway N, et al. Cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment resistant depression in primary care: the CoBalT randomised controlled trial protocol. *Control Clin Trials* 2012; **33:** 312–19.

21 Beck AT, Steer RA, Brown GK. Beck Depression Inventory—second edition: manual. San Antonio: The Psychological Corporation, 1996.

22 Blackburn IM, James IA, Milne DL, et al. The revised cognitive therapy scale (CTS-R): psychometric properties. *Behav Cogn Psychother* 2001; **29:** 431–46.

23 Jenkinson C, Layte R. Development and testing of the UK SF-12 (short form health survey). *J Health Serv Res Pol* 1997; **2:** 14–18.

24 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; **16:** 606–13.

25 Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder. The GAD-7. *Arch Intern Med* 2006; **166:** 1092–97.

26 van Hout B, Janssen MF, You-Shan F, et al. Interim Scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012; **15:** 708–15.

27 Shults J, Ratcliffe SJ, Leonard M. Improved generalized estimating equation analysis via xtqls for quasi-least squares in Stata. *Stata J* 2007; **7:** 147–66.

28 van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med* 1999; **18:** 681–94.

29 Molenberghs G, Kenward MG. Missing data in clinical studies. Chichester: John Wiley & Sons, 2007.

30 Diggle P. Dealing with missing values in longitudinal studies. In: Everitt DE, Dunn G, eds. Statistical analysis of medical data: new developments. London: Arnold, 1998: 203–27.

31 Diggle P. An approach to the analysis of repeated measurements. *Biometrics* 1998; **44:** 959–71.

32 Curtis L. Unit costs of health and social care 2013. Canterbury: PSSRU, University of Kent, 2013.

33 Department of Health. NHS Reference Costs. London: Department of Health, 2013.

34 Health & Social Care Information Centre. Prescription cost analysis England 2013. London: Health and Social Care Information Centre, 2014.

35 National Institute for Health and Clinical Excellence. Guide to the Methods of Technology Appraisal. London: Department of Health, 2008.

36 Trivedi RB, Nieuwsma JA, Williams JW. Examination of the utility of psychotherapy for patients with treatment resistant depression: a systematic review. *J Gen Intern Med* 2011; **26:** 643–50.

37 Perez-Wehbe AI, Perestelo-Perez L, Bethencourt-Perez JM, Cuellar-Pompa L, Penate-Castro W. Treatment-resistant depression: A systematic review of systematic reviews. *Intern J Clin Health Psychol* 2014; **14:** 145–55.

38 Driessen E, Van HL, Don FJ, et al. The efficacy of cognitive-behavioral therapy and psychodynamic therapy in the outpatient treatment of major depression: a randomized clinical trial. *Am J Psychiatry* 2013; **170:** 1041–50.

39 Fostick L, Silberman A, Beckman M, Spivak B, Amital D. The economic impact of depression: resistance or severity? *Eur Neuropsychopharmacol* 2010; **20:** 671–75.

40 Gibson TB, Jing Y, Smith Carls G, et al. Cost burden of treatment resistance in patients with depression. *Am J Manag Care* 2010; **16:** 370–77.

41 Health and Social Care Information Centre. Psychological therapies, annual report on the use of IAPT services: England—2013/14 experimental statistics. London: Health and Social Care Information Centre, 2014.