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Extended Research Article

Integrated therapist and online cognitive behavioural therapy for depression in primary care: the INTERACT research programme, including the INTERACT RCT

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Abstract

Background: Cognitive–behavioural therapy is an effective treatment for depression. A key question is how to increase access. Engagement with cognitive–behavioural therapy-based computerised interventions is poor, and programmes are inflexible and impersonal. Innovative use of technology and integration of online materials could increase engagement and widen access.

Objectives: To develop and evaluate a novel approach to delivering cognitive–behavioural therapy for depression integrating therapist-led sessions and online cognitive–behavioural therapy materials.

Design and methods: The INTEgrated theRApist and online CbT for depression research programme comprised four work packages. The first developed the online therapy platform and materials, and training for therapists. This comprised a series of studies: a systematic review and network meta-analysis to compare the effectiveness of different types and components of cognitive–behavioural therapy; a Delphi study focused on the effective components of cognitive–behavioural therapy; a decision model to evaluate the cost-effectiveness of different formats of delivering cognitive–behavioural therapy; a survey of accredited cognitive–behavioural therapy therapists asking about their use and views of different resources used in cognitive–behavioural therapy; and iterative design work aimed at understanding the design requirements for the platform. The prototype platform was then evaluated in a pilot study, with subsequent final refinement. The second and third work packages evaluated the clinical and cost-effectiveness of the intervention compared with usual general practitioner care in a multicentre randomised controlled trial (with a parallel economic evaluation) over 12 months in primary care patients with depression. The fourth examined the intervention's acceptability through a nested qualitative study of patients, therapists and supervisors.

Setting: The randomised controlled trial was based in United Kingdom primary care in Bristol, London and York.

Participants: Patients aged ≥ 18 years experiencing depressive symptoms in primary care were eligible for the randomised controlled trial.

Interventions: In the randomised controlled trial, participants were individually randomised to: (1) integrated cognitive–behavioural therapy (in addition to usual general practitioner care); or (2) to continue with usual general practitioner care.

Main outcome measures: The primary outcome for the randomised controlled trial was depressive symptoms measured using the Beck Depression Inventory, version 2 at 6 months post randomisation. Secondary outcomes included response and remission (based on Beck Depression Inventory, version 2 score), depressive symptoms (Patient Health Questionnaire-9), anxiety symptoms (Generalised Anxiety Disorder-7), function (Work and Social Adjustment Scale), quality of life (EuroQol-5 Dimensions, five-level version), and costs of interventions and wider services.

Results: Work package 1: the network meta-analysis found no evidence of effect for any content components or combinations of components. There was uncertainty around estimates of cost-effectiveness for different treatment modalities and intensities. Effective components of cognitive–behavioural therapy were identified through the Delphi study, and resources used by therapists identified through a survey of United Kingdom cognitive–behavioural therapy practitioners. Key requirements of an online platform identified through iterative design work were: (1) overcoming depression-related barriers; (2) supporting engagement; (3) reinforcing learning and skill acquisition. In a pilot study with 18 primary care patients, patients said that the integrated approach made therapy more accessible. Therapists commented on the flexibility of the approach. Not all participants engaged with between-session tasks and some technical issues were experienced. Platform refinements were made prior to the randomised controlled trial.

Work package 2: overall, 451 patients were recruited to the INTEgrated theRApist and online CbT for depression randomised controlled trial. Participants were predominantly female (*n* = 313, 69%) and, on average, aged 39 years. The mean Beck Depression Inventory, version 2 score at baseline was 32.8, indicative of severe depression. Most had a history of depression (nearly half having had five or more prior episodes of depression), were taking antidepressants (70%) and the duration of the current episode of depression was ≥ 2 years for 51% of participants.

In the intervention group, 14 individuals (6.2%) had no therapy sessions and 137 participants (60.9%) completed therapy (received at least 9 sessions or reached an agreed end of therapy with their therapist in fewer than 9 sessions). Including the above 14 individuals, 88 (39.1%) either withdrew from therapy (*n* = 50) or were discharged for non-attendance (*n* = 38).

In total 334 patients (171 integrated cognitive–behavioural therapy; 163 usual care) were included in the primary analysis. The intervention group had a Beck Depression Inventory, version 2 score that was, on average, 4.4 points lower (less depressed) than the usual care group at 6 months [difference in means: −4.4 (95% confidence interval −7.0 to −1.9); *p* = 0.001]. In repeated-measures analyses using data from 6 and 12 months, individuals in the intervention group had a Beck Depression Inventory, version 2 score that was, on average, 3.8 points lower than those in the usual care group (95% confidence interval −6.1 to −1.5; *p* = 0.001). The intervention group had a twofold increased odds of response and remission, fewer symptoms of depression (Patient Health Questionnaire-9) and anxiety (Generalised Anxiety Disorder-7), and improved functioning (Work and Social Adjustment Scale).

Work package 3: the mean costs of integrated cognitive–behavioural therapy were £987 (standard error £14) per participant. The mean costs of usual care were estimated at £382 (standard error £57) in usual care group and £193 (standard error £42) in intervention group. In the primary analyses, costs from the National Health Service/Personal Social Services perspective were £753 (standard error £77) per participant in the usual care group and £1754 (standard error £127) in the intervention group, with adjusted incremental costs of £1009 (95% confidence interval £737 to £1286). The mean quality-adjusted life-years were 0.554 (standard error 0.017) in the usual care group and 0.597 (standard error 0.017) in the intervention group, with adjusted incremental quality-adjusted life-years at 0.033 (95% confidence interval −0.002 to 0.059). The incremental cost-effectiveness ratio was £30,576 per quality-adjusted life-year gain. Complete-case analysis from the National Health Service/Personal Social Services perspective showed a slightly more favourable picture with an incremental cost-effectiveness ratio at £22,421.

Work package 4: through interviews with trial participants and therapists, we found that the integrated approach helped patients manage their depression. Platform benefits included the opportunity to review transcripts and to support homework tasks. Typing allowed reflection and a focused discussion. Less could be covered than during an in-person session. Patients who did not complete therapy struggled with typing and found cognitive–behavioural therapy too demanding.

Limitations: In the trial, the 6-month follow-up rate was slightly below the original target.

Conclusions: Integrated cognitive–behavioural therapy is an effective and acceptable treatment for patients with depression. There was uncertainty around the cost-effectiveness of the intervention. This novel mode of delivery could increase the availability of cognitive–behavioural therapy and access for those who find it difficult to attend appointments in person.

Future work: To examine whether effects are sustained long term and to understand which aspects of the platform lead to improvements.

Study registration: This study is registered as ISRCTN14850613 (phase 2 pilot study) and ISRCTN13112900 (RCT).

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List of abbreviations

AE	adverse event
BABCP	British Association for Behavioural & Cognitive Psychotherapies
BDI-II	Beck Depression Inventory, version 2
BNSSG	Bristol, North Somerset and South Gloucestershire
CACE	complier-average causal effect
CBT	cognitive–behavioural therapy
CCA	complete-case analysis
CCBT	computerised cognitive–behavioural therapy
CEAC	cost-effectiveness acceptability curve
CEP	cost-effectiveness plane
CIS-R	Clinical Interview Schedule – Revised
CUA	cost–utility analysis
DMC	Data Monitoring Committee
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
F2F	face-to-face
GAD-7	Generalised Anxiety Disorder-7
GP	general practitioner
HRA	Health Research Authority
ICC	intraclass correlation coefficient
ICD-10	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision
ICER	incremental cost-effectiveness ratio
IM	instant messaging
INTERACT	INTEgrated theRApist and online CbT for depression
MAR	missing at random
MNAR	missing not at random
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	network meta-analysis
NNT	number needed to treat
OOP	out-of-pocket payment
PHQ-9	Patient Health Questionnaire-9 items
PPI	patient and public involvement
PSS	Personal Social Services
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
SAE	serious adverse event
TAU	treatment as usual
TSC	Trial Steering Committee
UC	usual care
WP	work package
WSAS	Work and Social Adjustment Scale

Plain language summary

There is a high demand for talking therapies such as cognitive–behavioural therapy for depression. Cognitive–behavioural therapy can be delivered by computers or online as written guidance that can be worked through with or without support. These computerised therapy packages are inexpensive and convenient but are not as effective or as engaging as having a therapist. They do not allow treatment to be tailored for the individual.

We built an online therapy platform. This combined live therapist sessions with online materials to help patients practise outside the sessions. In the first session, patients and therapists met by videocall. Thereafter, they communicated by typing during live online therapy sessions. We worked with stakeholders to develop integrated cognitive–behavioural therapy. Patients could receive between 9 and 12 sessions of therapy.

We evaluated integrated cognitive–behavioural therapy in three ways:

1. We recruited 451 patients with depression and randomly allocated them to either integrated cognitive–behavioural therapy or to continue with usual general practitioner care. Those allocated to therapy were less depressed and more likely to have recovered after 6 and 12 months. This means we can be confident that this is a clinically effective treatment.
2. We assessed whether integrated cognitive–behavioural therapy was good value for money. Although patients felt better, the treatment just failed to meet criteria for value for money. However, the average cost of integrated cognitive–behavioural therapy was similar to the cost of therapy in National Health Service talking therapy services.
3. In-depth interview study: we asked patients and therapists about the treatment. They found it acceptable. Patients who completed the therapy valued being able to talk to a therapist and had learnt skills to manage their depression. Reviewing the record of therapy sessions helped them complete homework tasks and track progress. While less could be covered in a session compared with in-person therapy, the slower pace allowed room for reflection. This also meant therapists used more focused questions. Some patients found it difficult to express themselves through typing.

Scientific summary

Some text in this section is reproduced from Tallon D, Thomas L, Brabyn S, Ching BCF, Hahn JS, Jude B, *et al.* Integrated therapist and online CBT for depression in primary care (INTERACT): study protocol for a multi-centre randomised controlled trial. *Trials* 2023;**24**:421. https://doi.org/10.1186/s13063-023-07396-9). This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The text below includes minor additions and formatting changes to the original text.

Background

Cognitive–behavioural therapy (CBT) is an effective treatment for depression and recommended by the National Institute for Health and Care Excellence (NICE). A key question for commissioners and healthcare providers is how to increase access.

Cognitive–behavioural therapy-based computerised CBT interventions form part of the stepped care pathway for depression but are not an alternative to high-intensity CBT as they lack flexibility and are impersonal.

Cognitive–behavioural therapy delivered online using instant messaging is clinically and cost-effective. Developing materials that are integrated with modern technologies yet permit the therapist to tailor treatment to the individual is critical. Ready access to such materials could facilitate engagement with tasks that take place outside therapy sessions and increase effectiveness.

In 2020–1, 90% of UK households had a home computer and 84% of over 16-year-olds private use of a smartphone. Innovative use of technological developments and integration of online materials into therapy offers the potential to increase engagement and widen access to populations that are difficult to reach (e.g. those who are disabled or have difficulty attending appointments for other reasons).

Our intervention integrates therapist-led sessions and online CBT materials in a novel approach to the treatment of depression.

Aims and objectives

The aim of the INTEgrated theRApist and online CbT for depression (INTERACT) programme was to develop [work package (WP) 1] and evaluate (WPs2–4) an integrated approach to delivering CBT for depression in primary care (integrated CBT).

The specific aims of the WPs are listed below.

Work package 1: intervention development

1. To identify clinical and cost-effective components of CBT to inform the development of the intervention.
2. To develop an online platform to support the delivery of integrated CBT.
3. To develop the online CBT materials.
4. To develop a training package for therapists.

Work package 2: randomised controlled trial

5. To examine the clinical effectiveness of an integrated approach to delivering CBT for depression over 12 months' follow-up.

Work package 3: economic evaluation

6. To examine the cost-effectiveness of the integrated CBT intervention.

Work package 4: qualitative evaluation

7. To explore patients', therapists' and supervisors' views and experiences of using an integrated approach to delivering CBT for depression.
8. To understand patients' reasons for completing or not completing integrated therapy.
9. To assess patients', therapists' and supervisors' views on how this novel approach affects the therapist-patient relationship.

Methods and results

Work package 1: intervention development

Systematic review and network meta-analysis of cognitive–behavioural therapy components

We conducted a systematic review of randomised controlled trials (RCTs) in adults with depression, which included a CBT intervention, to compare the effectiveness of different types of therapy, different components and combinations of components and aspects of delivery used in CBT for depression. Outcomes were pooled using standard and component-level network meta-analysis (NMA).

Among 91 studies included, there was strong evidence that CBT interventions resulted in a larger short-term decrease in depressive symptoms compared with treatment as usual (TAU). The standardised difference in mean change for face-to-face (F2F) CBT compared with TAU was −1.11 [95% credible interval −1.62 to −0.60]; for hybrid CBT was −1.06 (−2.05 to −0.08); and for multimedia CBT was −0.59 (−1.20 to 0.02). A wait list control was detrimental compared with TAU [0.72 (0.09 to 1.35)]. While multimedia and hybrid CBT may be as effective as F2F CBT, there was substantial uncertainty in the estimates of treatment effectiveness. We found no evidence of specific effects of any content components or combination of components.

Delphi Study on effective components of cognitive–behavioural therapy

We aimed to establish an expert consensus on the effective components of CBT for adults with depression. An international panel of CBT experts (n = 120) was invited to participate in an online survey. In round 1, experts rated the effectiveness of 35 items covering both content and process components of CBT. In a second round, experts rerated components to reach a consensus.

Of those invited, 32 participated in round 1 and 21 also provided data in round 2. Consensus was achieved in relation to nine content components (that facilitate behaviour change) and three process components (procedures for therapy delivery). Generic therapeutic competences comprised five of the nine content components. There was less agreement about the effectiveness of cognitive components of CBT.

Cost-effectiveness of different formats for delivery of cognitive–behavioural therapy for depression

We developed a decision model to evaluate the cost-effectiveness of F2F CBT, multimedia CBT and hybrid CBT, given in addition to TAU, in comparison with TAU alone. F2F and hybrid CBTs were modelled by treatment intensity defined by combinations of number and length of CBT sessions. The model covered an average treatment period of 4 months

with a 5-year follow-up period to extrapolate long-term cost-effectiveness. The model inputs were derived from our NMA and the literature. The primary outcome was quality-adjusted life-years (QALYs).

All CBT modes given in addition to TAU were more cost-effective than TAU alone. Probabilistic sensitivity analyses found that F2F CBT with intensities of six 30-minute sessions and sixteen 60-minute sessions had the highest probability of being cost-effective. However, neither option reached 50% probability of being most cost-effective (32.5% and 31.1%, respectively). There was substantial uncertainty around estimates.

Development of the online therapy platform

This comprised: (1) an iterative design stage, (2) a pilot study and (3) final refinement.

In phase 1, we held individual interviews, prototype testing sessions, platform walkthroughs and workshops with stakeholders aimed at understanding the design requirements for the platform. Feedback informed the intervention design.

Three requirements were identified for integrated CBT therapy platforms: (1) features to overcome depression-related barriers; (2) features that support engagement; and (3) that reinforce learning and support the acquisition and learning of new skills. Therapists highlighted the importance of collaborative working, and the impact of technology on therapists' workflow and workload, and its potential in supporting clients' engagement.

In phase 2, we conducted a pilot study to evaluate usability and user experience of the intervention. Patients with depression were recruited from primary care and offered a course of integrated therapy using the newly developed platform. Qualitative interviews were conducted with patients, including those who completed and withdrew from therapy.

Eighteen patients with depression were recruited from primary care. Of these, 10 completed therapy. Initial interviews were conducted with 13 patients (after 3–6 therapy sessions), and 9 'end of therapy' interviews were completed.

Patients appreciated the first session being F2F so they could meet their therapist and build rapport. Typing limited the amount discussed during online sessions, but some patients noted it aided focus and promoted reflection. Patients said that the integrated approach made therapy more accessible, but not all patients engaged with between-session tasks. Some found the worksheets too complex. Usage data showed that patients reviewed transcripts of the instant messaging therapy sessions and commented that these were a useful learning aid. Some technical issues were experienced that sometimes led to lower engagement.

Phase 3 involved final refinement of the platform following feedback from patients, therapists and wider stakeholders, and input from the multidisciplinary study team. Platform security was assessed.

Development of cognitive–behavioural therapy materials for the online platform

We conducted a survey of 3665 accredited UK CBT therapists asking about their use and views of resources commonly described in CBT manuals.

Overall, 994 individuals (27%) responded and a further 33 completed the questionnaire online. Over 85% of respondents used symptom measures, lists of problems/goals, activity schedules, behavioural activation diaries/plans, and case formulation worksheets 'frequently' or 'very frequently'.

Selection of platform materials was based on: therapist survey findings; the competency framework for CBT for depression; Delphi findings; and systematic review and NMA findings. Most worksheets were selected from resources already available and familiar to therapists.

Development of a training package for therapists

Training for the therapists employed for WP1.3 – phase 2 was developed and delivered with CBT experts in the research team and supported by the therapists' supervisor. Online training for the RCT included lectures covering the trial background, therapy protocol, managing risk, and role play.

Work package 2: randomised controlled trial

We conducted a pragmatic RCT of 451 patients with depression from 67 general practices in 3 UK sites. Patients aged ≥ 18 years, scoring ≥ 14 on the Beck Depression Inventory, version 2 (BDI-II) and who met *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10) criteria for depression were eligible. Patients were individually randomised to either integrated CBT [in addition to usual care (UC)] or to continue with usual general practitioner care (UC). The primary outcome was BDI-II score at 6 months post randomisation. Secondary outcomes included response and remission (based on BDI-II), other measures of depression and anxiety [Patient Health Questionnaire-9 items (PHQ-9)/Generalised Anxiety Disorder-7 (GAD-7)], function [Work and Social Adjustment Scale (WSAS)], EuroQol-5 Dimensions, five-level version, and costs of interventions and wider services at 6 and 12 months.

The primary analyses were of 334 patients (171 integrated CBT; 163 UC). Those in the intervention group had a BDI-II score that was, on average, 4.4 points lower (less depressed) than those in the UC group at 6 months {difference in means: −4.4 [95% confidence interval (CI) −7.0 to −1.9]; $p = 0.001$}. In repeated-measures analyses using data from 6 and 12 months, the intervention group had a BDI-II score that was, on average, 3.8 points lower than the UC group (95% CI −6.1 to −1.5, $p = 0.001$). The intervention group had a twofold increased odds of response (≥ 50% improvement in symptoms) and remission (BDI-II score < 10), fewer symptoms of depression (PHQ-9) and anxiety (GAD-7), and less functional impairment (WSAS).

Work package 3: economic evaluation

We assessed cost-effectiveness from three perspectives: NHS and Personal Social Services (PSS); participants and their informal carers; and societal. Costs were collected accordingly. The primary analysis was an incremental cost–utility analysis of integrated CBT over and above UC, over 12 months from an NHS and PSS perspective. The incremental cost-effectiveness ratio (ICER) was calculated by dividing incremental costs by incremental QALYs.

The mean costs of integrated CBT were £987 [standard error (SE) £14] per participant. The mean costs of UC were estimated at £382 (SE £57) in the UC group and £193 (SE £42) in the intervention group. In the primary analysis, costs from the NHS/PSS perspective were £753 (SE £77) per participant in the UC group and £1754 (SE £127) in the intervention group, with adjusted incremental costs of £1009 (95% CI £737 to £1286). The mean QALYs were 0.554 (SE 0.017) in the UC group and 0.597 (SE 0.017) in the intervention group, with adjusted incremental QALYs at 0.033 (95% CI −0.002 to 0.059). The ICER was £30,576 per QALY gain (probability of cost-effectiveness from £20,000 to £30,000: 13%–39%). Complete-case analysis (CCA) from NHS/PSS perspective showed a slightly more favourable picture with ICER at £22, 421 (probability of cost-effectiveness: 37%–66%).

Work package 4: qualitative evaluation

A qualitative study was nested within the main trial. We interviewed 30 patients (20 who received the intervention and 10 from UC), 9 therapists and 3 therapist supervisors. Data were analysed using thematic analysis.

The combination of one-to-one sessions with a therapist and having access to integrated online CBT resources enabled patients to better manage their depression. Benefits included the opportunity to review transcripts to clarify homework tasks and track progress in managing their depression. Those who completed therapy valued talking to a therapist and accessing CBT resources within a single platform. Those who did not complete therapy found it difficult to express themselves through typing and found the CBT approach too demanding. As typing limited what could be covered in a single session, therapists restricted the session agenda and asked more focused questions.

Conclusions

Developing an integrated approach to delivering cognitive–behavioural therapy

Based on the systematic review and NMA of trials of CBT interventions, we found no evidence of specific effects of any content components or combinations of components of CBT interventions to inform the platform development. Our decision model showed that there was uncertainty around estimates of cost-effectiveness for different treatment modalities and intensities limiting the extent to which this work could inform the intervention design.

Through our survey of CBT therapists, we identified the most frequently used resources. The Delphi study provided insight into the generic therapeutic competences that CBT experts agreed on. In the absence of evidence on the effective or cost-effective components of CBT from the earlier systematic review, NMA and decision model, the findings from the survey and Delphi study were used to map and identify the CBT resources required within our online platform that aligned with the CBT competences framework.

Iterative development of the online therapy platform resulted in a prototype platform that was acceptable to patients and therapists. Integrated CBT was provided to a small sample of depressed patients recruited from primary care.

Effectiveness, cost-effectiveness and acceptability of an integrated approach to delivering cognitive–behavioural therapy

Integrated CBT was effective in reducing depressive symptoms in primary care patients with depression. Benefits were also seen for the outcomes of response and remission in depressive symptoms, and symptoms of anxiety. Improvements were maintained over 12 months.

The intervention was not cost-effective based on the current thresholds used by NICE. However, the intervention cost included training costs that would be unlikely to be maintained at the same level if the intervention was rolled out in NHS services. Further, once trained, therapists could treat more patients (beyond the study sample) which would reduce the per-patient training cost and may make the longer-term cost–benefit more favourable.

The intervention was acceptable to patients and therapists. The qualitative study highlighted the importance of establishing patient and therapist goals and expectations about what can be achieved in CBT mediated by typing. Some patients are comfortable communicating via typing and are motivated to utilise online resources between sessions. Exploring the benefits and challenges of integrated CBT with patients will enable them to make an informed choice about referral for this novel therapy.

Implications for health care

The COVID-19 pandemic resulted in many services moving to remote delivery of therapy. There has also been a proliferation of mental health apps in recent years, but with little empirical evidence to support their use. The integrated approach that we have developed is of proven effectiveness. While the intervention was just above the upper limit in terms of accepted thresholds of value for money, the costs of training may be over-estimated compared to those incurred if this intervention was implemented within the NHS. Importantly, the approach was acceptable to patients and therapists and as such offers the potential to increase access for those who find it difficult to attend therapy appointments in person.

Recommendations for research

Future research needs to examine

The longer-term clinical and cost-effectiveness of integrated cognitive–behavioural therapy

Studies of in-person CBT have found that CBT is a clinically and cost-effective intervention over four years. Evidence is thus needed to quantify and substantiate the long-term gain for this integrated CBT approach.

Which aspects of the platform led to improvements in depression

This may enable refinement of the intervention to increase benefits.

Study registration

This study is registered as ISRCTN14850613 (phase 2 pilot study) and ISRCTN13112900 (RCT).

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Synopsis

Background

Some text in this section is reproduced from Tallon *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The text below includes minor additions and formatting changes to the original text. The paragraph starting 'Innovative use of technological developments' was originally written by INTERACT coauthors as part of our INTEgrated theRApist and online CbT for depression (INTERACT) NHS REC application form for the therapist survey and Delphi study; this wording was subsequently published on the Health Research Authority (HRA) website.[2]

Depression is one of the leading causes of disability worldwide.[3] Ways to increase the availability of effective treatments are needed to reduce the unsustainability of current spending on health care.

National Institute for Health and Care Excellence (NICE) depression guidelines advocate psychological therapies for those with severe or chronic depression or who have not responded to initial treatments.[4] The importance of patient preference is highlighted, with a meta-analysis demonstrating a threefold preference for psychological over pharmacological interventions.[5] Many patients are willing to take antidepressants, but medication is not always effective; only half respond after the prescribed course.[6]

Cognitive–behavioural therapy (CBT) is an effective treatment for depression. Substantial investment in the NHS Talking Therapies (for anxiety and depression) programme (www.england.nhs.uk/mental-health/adults/nhs-talking-therapies/) (formerly, the Improving Access to Psychological Therapies services)[7] has increased provision of brief, low-intensity interventions in England. Such low-intensity interventions are a key part of the stepped care model of treatment[4] and are particularly appropriate for patients with less severe/complex depression. Although NHS Talking Therapies has increased the provision of high-intensity CBT (16–20 sessions), demand greatly exceeds supply. The lack of availability of CBT has implications for patient choice and clinical outcomes.

Therefore, a key question for commissioners and healthcare providers is how to increase access to high-intensity CBT without delay and without greatly increasing costs. The Chief Medical Officer's annual report on mental health published in 2013 argued there was a need for pragmatic clinical trials to evaluate new technologies, including online interventions.[8]

The growth in CBT-based computerised interventions (CCBT) (e.g. MoodGym, Beating the Blues, Silvercloud) is an example of attempts to increase the efficiency of delivery in health care through the use of technology. Some CCBT packages have been endorsed by NICE.[9] However, current UK evidence does not support the idea that CCBT materials alone can be an alternative to high-intensity CBT.[10] Adherence to CCBT without support is poor and, in the absence of therapist support, effects are modest and short-term.[11] As Helgadóttir (p. 246)[12] argues, the lack of flexibility in these programmes is 'theoretically problematic, and inconsistent with the emphasis on individual formulations that is the crux of traditional CBT'.

Nonetheless, CBT is particularly suited to the integration of computer and mobile technology with a therapist led approach. Exercises that take place outside the psychotherapeutic session are an important part of CBT and adherence to these can increase effectiveness.[13] Working online with specially adapted interactive materials can be supported by timely reminders using mobile devices and wider use of digital media such as 'apps' that can be used to target emotions, thoughts and behaviours, and may improve adherence and engagement.[14] Such Behavioural Intervention Technologies[15] are low cost and can be integrated into daily life in a responsive and personalised way.

We had previously shown that delivering CBT online using instant messaging (IM) is clinically[16] and cost-effective.[17] However, therapy via IM alone is limited as it does not support the practice of CBT (e.g. thought records and other

homework). Technological advancements make it possible to reduce therapist time and incorporate online materials as an integral part of therapy. One 'proof of concept' study (n = 15) suggests that an integrated or 'blended' approach is acceptable.[18] Developing materials that are integrated with modern technologies, yet permit the therapist to tailor treatment to the individual, is critical and aligns with the CBT competencies framework[19] and the idea of 'meta-competences' whereby the therapist adapts CBT to each patient's needs.

Access to the internet and use of mobile devices (smart phones/tablets) has greatly increased over the last 15 years. At the outset of this programme of work in 2016, 75% of UK households were online, 92% of UK adults owned a mobile phone, 51% a smart phone and 24% a tablet.[20] Since then, smartphone use has increased to more than 80% of the UK population[21] and these developments are mirrored in other countries, including low- and middle-income countries. Interventions that incorporate online resources accessed via mobile devices may reach more effectively into people's lives, allowing more immediate recording of thoughts and experiences. Mobile devices may also enable discreet completion of worksheets (such as thought diaries) thereby addressing concerns about the risk of 'getting caught' completing homework tasks in public.[22] Use of such devices may therefore increase engagement with CBT 'homework' which is an important mediator of outcome.[13,23] Engendering a sense of control and ownership are necessary to maximise engagement, and require collaboration with experts in human–computer interaction[24] to develop platforms and materials that meet modern users' expectations.

Experience-based design methods emphasise the importance of engaging users in the design and development of a new intervention.[25] Previous reviews have focused on the uptake and acceptability of low-intensity CCBT.[26,27] A recent meta-synthesis found that 'absence of the self' was prominent in reports of user experience of CCBT.[28] An integrated approach where the therapist adapts the CBT to the individual's needs will address such concerns.

Innovative use of technological developments and integration of online materials into therapy could offer increased engagement, reduce costs and widen access to populations that are difficult to reach (e.g. those who are disabled or have difficulty attending appointments for other reasons), while maintaining the effectiveness of CBT delivered by high-intensity therapists.[2] Moreover, such platforms could be extended, as recommended by others,[29] through the development of additional online materials as 'bolt-ons' to enhance utility within NHS services by addressing the needs of service users with a range of mental health problems or long-term conditions, further increasing utility and efficiency in terms of service provision.

At the start of our programme in 2016, there were no registered trials (http://apps.who.int/trialsearch/) integrating online materials with therapist led CBT for depression. An EU project (E-COMPARED: 2013–8: www.e-compared.eu/) of 'blended care' [face-to-face (F2F) CBT and self-help] for depression had some similarities, but in our model therapist, contact took place in real-time via IM rather than in person, and online materials were an integral part of therapy. Since 2016, no other trials have examined an integrated approach to delivering CBT.

Our intervention integrating therapist and online materials is a novel method of delivering CBT. It blends high-intensity therapy with innovative use of technology and aims to maintain the effectiveness of in-person CBT. The intervention was developed in collaboration with NHS service providers, ensuring it is fit for clinical purpose, and, if clinically and cost-effective, this model of integrated CBT could easily be introduced into existing psychological services, increasing access to, and equity of, CBT provision.

The INTEgrated theRApist and online CbT for depression programme

Aims and objectives

The aim of this National Institute for Health and Care Research (NIHR) programme was to develop and evaluate a novel approach to delivering CBT for adults with depression in primary care that integrates online CBT materials with input from an accredited CBT therapist (or 'integrated CBT'). The specific objectives were:

	Workstream
1. To identify clinical and cost-effective components of CBT to inform the development of the intervention	1
2. To develop an online platform to support the delivery of integrated CBT	1
3. To develop the online CBT materials	1
4. To develop an online training package for therapists	1
5. To examine the clinical and cost-effectiveness of an integrated approach to delivering CBT for depression over 12 months' follow-up	2 and 3
6. To explore patients', therapists' and supervisors' views and experiences of using an integrated approach to delivering CBT for depression	4
7. To understand patients' reasons for completing or not completing therapy	4
8. To assess patients', therapists' and supervisors' views on how this novel approach affects the therapist-patient relationship	4

Overview of programme

Figure 1 provides an overview of the INTERACT programme and the four work packages (WPs), and *Table 1* summarises the programme's aims, workstreams and outputs to date. *Table 2* summarises changes made to the programme since the original grant application.

Our intervention development phase (WP1) was conducted between April 2016 and December 2019. The systematic review and network meta-analysis (NMA), Delphi study of CBT experts and therapist survey aimed to evaluate the most clinically and cost-effective components of CBT for depression, and informed early designs of the integrated CBT intervention and platform. We then used iterative research methods with stakeholders to design, pilot and refine our novel intervention. Security testing of the final platform took place in September 2020.

Once the intervention had been finalised, we commenced the evaluation of its clinical and cost-effectiveness, and acceptability [WPs2–4: randomised controlled trial (RCT); parallel economic evaluation and nested qualitative study]. Ethical approvals were in place by January 2020. However, the start of trial recruitment was delayed by 6 months (from June 2020 to December 2020) by the COVID-19 pandemic. The last data collection from patient general practice records took place in June 2024. As each WP used different methodology, we have reported the methods and results of each WP separately.

Work package 1: developing the intervention

The aim of this WP was to identify optimal combinations of CBT components and develop an innovative approach to delivering CBT. The focus was to provide a solution to demand on mental health services, by reducing therapist time, increasing availability and introducing online materials as an integral part of therapy, without compromising the efficacy of treatment.

The main objectives of this WP were to:

1. Identify the clinical (WP1.1) and cost-effective (WP1.2) components of CBT to inform the development of the intervention.
2. Develop an online platform to support the delivery of Integrated CBT (WP1.3); the online materials and a training package for therapists (WP1.4).

Work package 1.1: identifying the clinically effective components of cognitive–behavioural therapy

Aim

To identify clinically effective components of CBT to inform the development of the integrated CBT intervention.

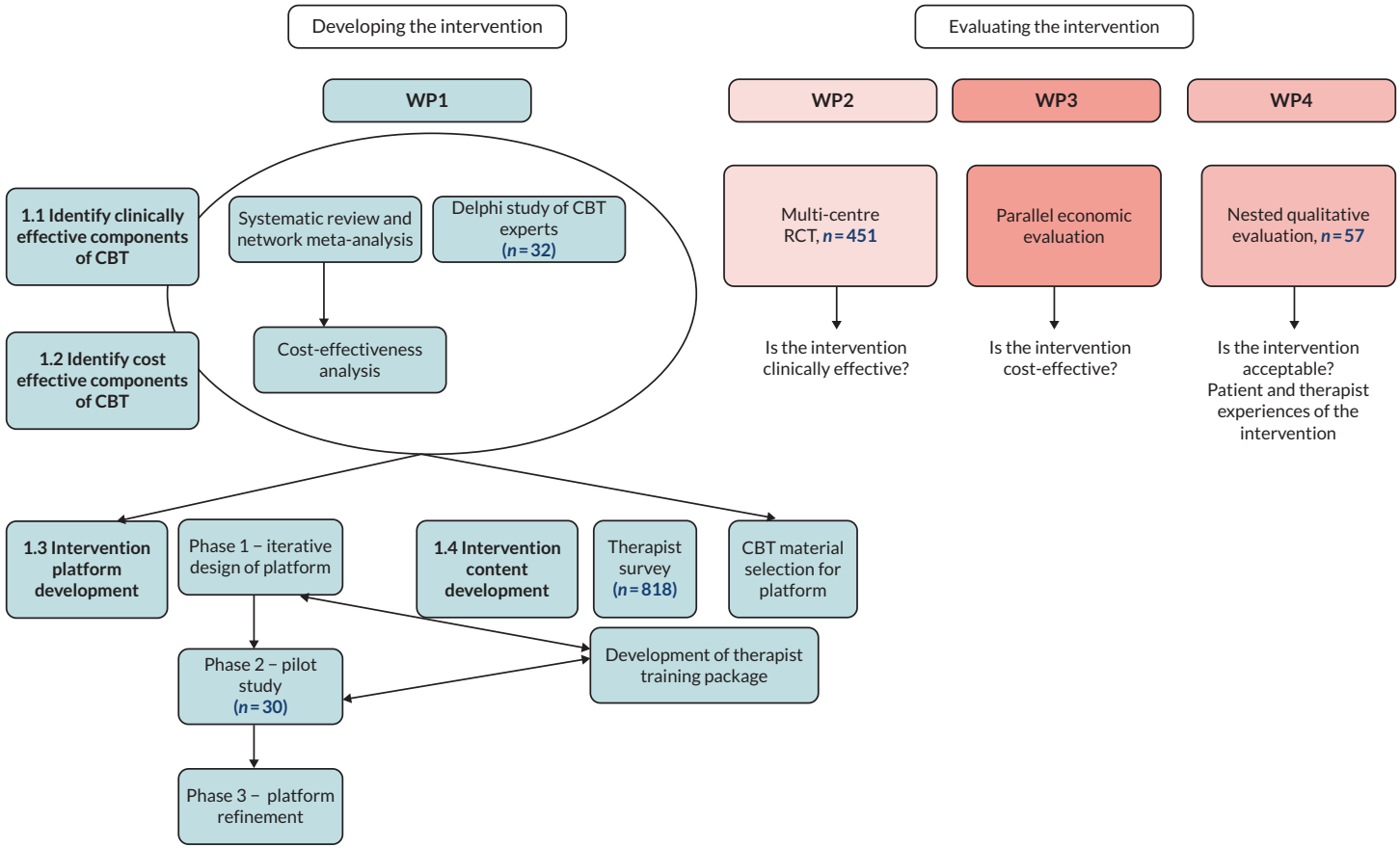

FIGURE 1 The INTERACT research pathway diagram.

TABLE 1 Overview of programme aims, workstreams and outputs

Programme objectives	Research activity	Programme outputs
WP1.1: to identify the clinically effective components of CBT	Systematic reviews	Davies[30] Davies[31]
	NMA	López-López[32]
	Delphi study on effective components of CBT	Taylor[33]
WP1.2: to identify the cost-effective components of CBT	Cost-effectiveness decision model	Wu[34]
WP1.3: to develop the online therapy platform	Phase 1: iterative design stage Phase 2: usability and user experience evaluation, including a pilot study Phase 3: final refinement of platform	Stawarz[35] Stawarz[36] Stawarz[37] Stawarz[38]
WP1.4: to develop the content of the intervention content and a training package for CBT therapists	Therapist survey	Tallon[39]
		Integrated CBT intervention, including an online therapy platform with integrated online CBT resources, a treatment manual for therapists, and therapist training package
WP2: to conduct a full-scale RCT of integrated CBT + UC vs. UC alone	Multicentre RCT to assess the clinical effectiveness, cost-effectiveness and acceptability of integrated CBT	Tallon (protocol)[1] MacNeill (statistical analysis plan)[40] Tallon (clinical effectiveness)[41]
WP3: to examine the cost-effectiveness of the integrated CBT intervention	Parallel economic evaluation	Li (health economics analysis plan)[42]
WP4: to conduct a qualitative evaluation of patients' and therapists' views of the integrated CBT intervention	Nested qualitative study	Fox[43] Fox[44]

This WP comprised two pieces of work: (1) building a data set for a NMA to identify effective and acceptable components of CBT; and (2) a modified Delphi study to identify the most effective components of CBT through a consensus approach.

Part 1: systematic review and network meta-analysis

Aim

We aimed to compare the effectiveness of different types of therapy, different components and combinations of components and aspects of delivery used in CBT interventions.

Methods

We undertook a systematic review of RCTs in adults with a primary diagnosis of depression where the effectiveness of a CBT intervention was compared with treatment as usual (TAU), no treatment, a wait list, psychological/attention placebo and/or another CBT intervention. We included RCTs comparing F2F CBT with computerised CBT, online CBT (with or without an interactive element), and other partial/full remote access provision (such as telephone support and text reminders).

Outcomes were pooled using standard (intervention-level) and component-level NMA. NMA is a form of meta-regression that enables the simultaneous comparison of multiple interventions in a single analysis. It allows all pairwise relative effects to be estimated from a connected network, even when no direct evidence is available, while respecting the randomised structure of the evidence. Interventions were classified based on the type of therapy and mode of delivery for our primary analysis. In addition, more advanced component-level models were fitted to examine the effectiveness of each content component or combination of components.

TABLE 2 Changes to the programme

1.	Change from F2F initial therapy session to a videocall (2020) In our research proposal, we originally had specified that the first therapy session would take place in person. However, the COVID-19 pandemic necessitated switching to a remote mode of delivery via videocall for the first session (together with remotely conducted fieldwork for general practice and participant recruitment). Subsequent therapy sessions were conducted online via IM using the INTERACT therapy platform as planned. Following relaxations of restrictions, and discussion with our independent Programme Steering and Data Monitoring Committees in June/July 2021, we decided to continue with a video-call appointment for the first therapy session given the wider use of remote appointments within the NHS and the fact that 66 participants had already been randomised, of whom 25 had started therapy by this point
2	Changes to trial questionnaire measures (2020) Because research visits needed to be conducted remotely, rather than in person due to the COVID-19 pandemic, we shortened some of the baseline and follow-up questionnaire assessments to reduce the burden on participants. The SF-12[45] questionnaire was replaced with the Work and Social Adjustment Scale.[46] The Dysfunctional Attitudes Scale 2nd short version (DAS-SF_2)[47] and meta-cognitive awareness questionnaire (MAQ)[48] (that were originally included as potential mediators) were also removed from the baseline and 6- and 12-month questionnaires to further reduce burden
3.	Optional, linked functional magnetic resonance imaging (fMRI) study in Bristol (2020) During the conduct of the INTERACT RCT, participants from the Bristol site were given the option of taking part in a linked brain imaging study that would involve attending one fMRI scan 6 months after randomisation. The fMRI research team screened 99 Bristol participants for eligibility, and of these, 41 were eligible and scanned. This supplementary scanning study was funded by the NIHR Bristol Biomedical Research Centre and will be reported separately to the INTERACT programme
4.	Internal pilot extended from 6 to 9 months (2020) We originally planned a 6-month internal pilot to ensure that we were able to recruit to the RCT and engage participants with the intervention. However, there was considerable uncertainty about recruiting from primary care after the COVID-19 pandemic lockdown, given pressures on the NHS. While we expected an increase in recruitment over the initial months, we anticipated that it would take longer to reach a steady state. There was also potential for disruption in the event of further COVID-19 surges or local lockdowns. Therefore, we extended the length of the pilot from 6 to 9 months to be confident in our recruitment projections. We retained the original progression criteria to judge success, with an emphasis on the emerging recruitment trajectory
5.	Exit (feedback) questionnaires and interviews (2022) Questions were added to the 12-month questionnaire to ask participants about their reasons for taking part in the study, and regarding their experience of participating. We were interested to see how reasons for participation compared with previous depression trials, and to hear views on participating in a trial which has been conducted remotely. We planned to conduct some in-depth qualitative interviews with a sample of participants
6.	Recruitment extended (2022) Initial recruitment in two sites was slower than anticipated due to difficulties recruiting CBT therapists to deliver the intervention, and because local Clinical Research Network (CRN) and practice staff were prioritising urgent public health studies. At the other site, both CBT therapists left their posts sequentially in 2021, which reduced capacity to deliver the intervention and restricted recruitment for 4 months. Due to these cumulative delays, RCT recruitment was extended by 9 months to 31 May 2023

SF-12, Short Form questionnaire-12 items.

Key findings

In total, 91 studies were included in our review. There was strong evidence that CBT interventions resulted in a larger short-term decrease in depressive symptoms compared with TAU. The standardised difference in mean change for F2F CBT compared with TAU was −1.11 (95% credible interval −1.62 to −0.60); for hybrid CBT was −1.06 (−2.05 to −0.08); and for multimedia CBT was −0.59 (−1.20 to 0.02). In contrast, there was evidence that wait list increased depressive symptoms compared with TAU [0.72 (0.09 to 1.35)]. While multimedia and hybrid CBT may be as effective as F2F CBT, there was substantial uncertainty in the estimates of treatment effectiveness. We found no evidence of specific effects of any content components or combinations of components.

Limitations

Our efforts were hampered by inconsistent reporting of interventions. Some studies provided sufficient detail about the CBT intervention(s) evaluated to enable coding of components, while many others referred to a therapy treatment manual and only included a brief description. It is possible that some interventions included additional components that were not reported and that some of the reported components may not have been received by all study participants.

Related publications

The systematic review and NMA was reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses-NMA guidelines.[49]

López-López JA, Davies SR, Caldwell DM, Churchill R, Peters TJ, Tallon D, *et al.* The process and delivery of CBT for depression in adults: a systematic review and network meta-analysis. *Psychol Med* 2019;**49**:1937–47. https://doi.org/10.1017/S003329171900120X

The Cochrane protocol for the systematic review and network meta-analysis on the process and delivery of CBT is accessible at the following URL: www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013140/epdf/full

Davies SR, Caldwell DM, López-López JA, Dawson S, Wiles N, Kessler D, *et al*. The process and delivery of cognitive behavioural therapy (CBT) for depression in adults: a network meta-analysis. *Cochrane Database Sys Rev* 2018;**10**:CD013140. https://doi.org/10.1002/14651858.CD013140

The Cochrane protocol for the systematic review on multimedia-delivered CBT versus face-to-face CBT is accessible at the following URL: www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013184/full

Davies SR, Caldwell DM, Dawson S, Sampson SJ, Welton NJ, Wiles N, *et al*. Multimedia-delivered cognitive behavioural therapy versus face-to-face cognitive behavioural therapy for depression in adults. *Cochrane Database Sys Rev* 2018;**11**:CD013184. https://doi.org/10.1002/14651858.CD013184

Part 2: modified Delphi survey of cognitive–behavioural therapy experts

Aim

We aimed to establish an expert consensus on the effective components of CBT for adults with depression.

Methods

An international panel of CBT experts (n = 120) was invited to take part via an online survey. In round 1, experts were asked to rate the components of CBT that were most effective in bringing about clinically helpful change. Experts were provided with a list of 35 items covering both content (that facilitate behaviour change) and process components (procedures for the delivery of therapy) of CBT on a 9-point Likert scale from 1 (not at all effective) to 9 (very effective). Suggestions for additional components could be given. We followed the quality criteria proposed by Diamond *et al.*[50] in conducting the study. This included specifying a priori our definition of consensus and the choice to stop data collection after two rounds. A priori rules were used to identify components carried forward to a second round, in which experts were asked to rerate components in light of feedback on the (first round) scores of other experts, with the final consensus items identified from the second round.

Key findings

Of the 120 CBT experts invited to participate, 32 participated in round 1 and 21 also provided data in round 2. Consensus was achieved in relation to nine content components (that facilitate behaviour change, e.g. self-monitoring and thought restructuring) and three process components (procedures for delivery of therapy, e.g. mode of delivery, number of sessions, support between sessions). The content components were: ensuring understanding; developing and maintaining a good therapeutic alliance; explaining the rationale for CBT; eliciting feedback; identifying and challenging avoidant behaviour; activity monitoring; undertaking an initial assessment; methods to prevent relapse; and homework assignments. Process components were: ensuring therapist competence; scheduling CBT sessions flexibly; and scheduling sessions for 45–60 minutes' duration. Generic therapeutic competences (rather than items specific to CBT) comprised five of the nine content components. There was less agreement about the effectiveness of the cognitive components of CBT. The latter may reflect a greater emphasis on the behavioural aspects of CBT, aligning with the low-intensity treatments offered by NHS talking therapy services, but this warrants further research.

Limitations
There is no standard definition of 'consensus' and hence our definition was arbitrary, but a lower threshold may not have reflected a consensus. The results may have been different had a different group of experts taken part. However, the Delphi technique aims to recruit a small subset of those who can provide in-depth expertise rather than a representative sample.

Related publications
The accepted author manuscript for the modified Delphi survey is available at the following URL: https://research-information.bris.ac.uk/ws/portalfiles/portal/203250524/2019_07_04_Delphi_paper_revised2_clean_with_figure1.pdf

Taylor A, Tallon D, Kessler D, Peters TJ, Shafran R, Williams C, Wiles N. An expert consensus on the most effective components of cognitive behavioural therapy for adults with depression: a modified Delphi study. *Cogn Behav Ther* 2019;**49**:242–55. https://doi.org/10.1080/16506073.2019.1641146

Work package 1.2: identifying the cost-effective components of cognitive–behavioural therapy

Aim
To evaluate the cost-effectiveness of various components and combinations of CBT in depression in order to inform the development of the intervention.

Methods
This evaluation utilised the systematic review and NMA data set compiled in WP1.1. We developed a decision model to evaluate the cost-effectiveness of different CBT delivery formats that varied in terms of modes/intensities F2F CBT, multimedia CBT and hybrid CBT given in addition to TAU, in comparison with TAU alone for treating depression.

Key findings
All CBT delivery modes given in addition to TAU were found to be more cost-effective than TAU alone. Probabilistic sensitivity analyses found that F2F CBT with intensities of six 30-minute sessions and sixteen 60-minute sessions had the highest probability of being cost-effective. However, neither option reached a 50% probability of being most cost-effective (32.5% and 31.1%, respectively).

Limitations
There was substantial uncertainty around the estimates derived.

Related publications
The paper reporting the decision-analytic model evaluating the cost-effectiveness of different CBT delivery modes and variations in intensity is available at: https://doi.org/10.1016/j.jval.2020.07.008

Wu Q, Li J, Parrott S, López-López JA, Davies SR, Caldwell DM, *et al*. The cost effectiveness of different formats for delivery of cognitive behavioural therapy for depression: a systematic review based economic model. *Value Health* 2020;**23**:1662–70. https://doi.org/10.1016/j.jval.2020.07.008

Links between work packages 1.1 and 1.2 and other work packages
To optimise the design of new approaches to delivering CBT and improve the efficiency of treatment, it is important to understand the 'active ingredients'. The NMA and Delphi survey were complementary pieces of work that highlighted the challenges in understanding such factors.

The findings of the NMA were encouraging as they suggested that hybrid interventions that combine online treatment and therapist contact, such as INTERACT, might be as effective as F2F (in-person) CBT, although these results should be interpreted with caution given the sparse data. However, there was little robust evidence as to the relative effectiveness of specific components or combinations of components. The NMA also found that wait list had a detrimental effect

on outcome, and this informed our design of the multicentre RCT in WP2. The consensus on the importance of the provision of resources found in the Delphi study, especially those that supported the generic therapeutic competences and behavioural modification, informed the design of the platform and materials to be included.

Without robust new evidence regarding potential cost-effectiveness, we followed our original plans to ensure that the platform encouraged and supported between session work, and reduced the total number of therapy sessions (compared with F2F CBT) with the aim of increasing the intervention's cost-effectiveness (WP3).

Work package 1.3: development of the online therapy platform

Aim

To develop an IT platform to support the use of online materials for integrated CBT that would be evaluated in the RCT (WP2).

This work consisted of three main stages: the development of the platform (phase 1); the evaluation with primary care patients with depression (phase 2); and further refinements (phase 3).

Phase 1: iterative design

Aim

1. To explore patients' and therapists' views and expectations on using an integrated approach to delivering CBT for depression and to establish design requirements.
2. To evaluate the usability and acceptability of prototypes and further inform the platform design.

Methods

Four user-centred design studies were conducted that aimed at understanding the requirements for the technical platform. Data on general requirements for an online integrated therapy platform were gathered from design workshops with people who had completed CBT in the past (n = 12) and individual interviews with CBT therapists (n = 12). More detailed design requirements were explored through prototype testing with people who had received CBT in the past (n = 7) and role-play sessions with CBT therapists (n = 5). All research activities were recorded with participant consent and transcribed. Affinity mapping was used to identify key themes from workshops, prototype testing sessions and role plays. A thematic approach was used to analyse transcripts of individual interviews. In addition, as part of usability testing and role-play sessions, we collected participants' feedback on their experience using the standardised System Usability Scale[51,52] which asks about subjective experience of using the system, including its perceived effectiveness and efficiency, and users' satisfaction. Additional work was also conducted to identify factors that support user engagement, including a review of mental well-being apps[35] and an online survey of app users to evaluate user feedback on mental health apps.[36]

Key findings from phase 1

Three key requirements were identified for integrated CBT therapy platforms: (1) features to overcome depression-related barriers; (2) features that support engagement; and (3) features that reinforce learning and support the acquisition and learning of new skills. Therapists highlighted the importance of collaborative working, the impact of technology on therapists' workflow and workload, and potential of technology in supporting clients' engagement with therapy. A list of 12 design considerations for the development of an integrated therapy platform was outlined.

These considerations focused on: strengthening the therapeutic relationship; personalising treatment; supporting learning; enhancing engagement and accountability; and adapting to the workload, schedules and expectations of therapists. F2F sessions help build rapport and trust, while online sessions are well-suited for supporting skills

development. Therapists and patients should collaborate on exercises, such as worksheets, with therapy records and resources available for ongoing use. Flexibility and personalisation are important, allowing therapists to tailor exercises and worksheets to individual patient needs, and offering the option to modify materials as necessary. A balance between therapist-led and patient-led approaches is crucial, with clear expectations for patients alongside opportunities for independent exploration of relevant resources. Engagement is fostered by making patient commitments explicit, enabling progress tracking, and providing personalised feedback from therapists, supported by automated feedback where appropriate. Finally, therapists' workloads and boundaries must be considered, with guidance on between-session contact and a clear approach to risk management that avoids overburdening therapists outside of sessions.

Limitations

A relatively small number of participants were involved in the study. Others may hold different views. However, the number of participants was comparable with other user-centred design studies and this methodology has been shown to provide design guidelines that are generalisable.

Related publications

The paper reporting the user-centred design studies is available at: https://mental.jmir.org/2020/9/e15972

Stawarz K, Preist C, Tallon D, Wiles N, Kessler D, Turner K, *et al*. Design considerations for the integrated delivery of cognitive behavioral therapy for depression: user-centered design study. *JMIR Mental Health* 2020;**7.** https://doi.org/10.2196/15972

Additional work was conducted to identify factors that support user engagement, including a review of mental well-being apps and an online survey of app users to evaluate user feedback on mental health apps.

Stawarz K, Preist C, Tallon D, Wiles N, Coyle D. User experience of CBT apps for depression: an analysis of app functionality and user reviews. *J Med Internet Res* 2018;**20**:e10120. https://doi.org/10.2196/10120

Stawarz K, Preist C, Coyle D. Use of smartphone apps, social media and online resources to support mental health and wellbeing: an online survey. *JMIR Ment Health* 2019;**6**:e12546. https://doi.org/10.2196/12546

Phase 2: usability and user experience evaluation

Aim

The aim of this evaluation was to explore primary care patients' and CBT therapists' views and experiences of the platform developed during WP1.3 phase 1 (iterative design) to ensure the online platform and CBT materials are acceptable to patients and therapists; and to identify areas for improvement prior to the main trial.

Methods

This evaluation comprised three strands of work that ran in parallel:

1. a longitudinal evaluation study with patients with depression recruited from primary care;
2. participatory design work with therapists providing CBT and their clinical supervisor;
3. usability testing sessions with people who had received CBT in the past.

We conducted an 11-month pilot study, in which 18 patients with depression were recruited from primary care and offered a course of treatment (up to nine 1-hour sessions of CBT) delivered by therapists trained in using the newly developed therapy platform. Therapy was delivered by three CBT therapists who also had a co-design role, providing substantial feedback on design and usability issues, and the therapist training package.

The first session of therapy was delivered in person at the patient's general practitioner (GP) surgery, with subsequent sessions held online using IM in the therapy platform. Up to three shorter 'check-in' sessions to facilitate engagement and/or to review between session tasks (maximum 20 minutes) could be scheduled between regular therapy sessions as part of the 9 hours' contact time.

Patients were interviewed twice: first over the telephone after three to six sessions of therapy to gather their initial views on the platform and online materials, and again (in-person) after completing therapy (or withdrawal or discharge) to explore their views and experiences of receiving integrated CBT. With participant consent, we also collected usage statistics for their engagement with the platform, including the number of times they logged in, worksheets completed and shared with the therapist, homework tasks set and completed, and their access to session notes and transcripts.

Initial interviews with therapists took place shortly after starting to use the platform, and further interviews were conducted after the end of therapy, along with a focus group for therapists and their supervisor to inform final revisions to the platform prior to the main trial.

Data collection and analysis (of individual patient interviews) proceeded in parallel to enable analytical insights from earlier interviews to shape later data collection. Data were analysed thematically. Affinity mapping was used to analyse data from therapist debriefing sessions, design sessions and the final focus group. A task-oriented analysis of usability testing sessions was conducted to identify the most common and serious issues that need to be addressed. Usage statistics were aggregated to identify the most commonly used (and 'underused') features and materials. These data, together with feedback provided by users (patients and therapists) via the platform feedback mechanism, allowed identification of areas that required further improvements and/or clarifications and addressed on a case-by-case basis following review and discussion within the research team.

In addition, we recruited eight patients who had had CBT in the past from local psychological services. These patients had a single usability testing session (approximately 1 hour) with a researcher during which time they were asked to use platform's features (e.g. share a worksheet, look at session preparation questions) and to talk aloud while completing tasks.

This phase of development also included completion of a thorough information security risk (privacy impact) assessment, which was approved by the University of Bristol Information Security Manager, and the preparation of detailed documents to evidence the system readiness to 'go live'. The platform also underwent extensive, independent security testing. The privacy impact assessment was reviewed prior to the main RCT and updated in September 2021.

Key findings from phase 2

A total of 18 patients with depression were recruited from primary care. Of these, 10 completed therapy; 1 withdrew before the start of therapy; 4 withdrew during therapy and 3 were discharged for non-attendance. Initial interviews were conducted with 13 patients (after 3–6 therapy sessions), and 9 'end of therapy' interviews were completed.

Interview findings suggested that patients appreciated the first session being F2F so they could meet their therapist and build rapport, making subsequent online contact by IM easier. Typing limited the amount discussed during online sessions, but some patients noted it aided focus and promoted reflection. Some patients said that the integrated approach made therapy more accessible, but not all participants engaged with the between-session tasks (often due to time constraints). Some found the worksheets too complex. Usage data showed that patients reviewed transcripts, and patients commented that these were a useful aid to learning. Some technical issues were experienced using the platform, and sometimes these led to lower engagement.

Therapists echoed patients' comments regarding the importance of an initial F2F meeting in establishing the therapeutic relationship and the lack of nonverbal cues when communicating online. Therapists commented on the challenges of being able to cover less material when typing compared with meeting clients in person. They raised concerns related to managing risk that may require flexibility in terms of mode of contact for vulnerable patients and flexibility in terms of the number of sessions offered.

Therapists were unsure as to how best to use the short 'check-in' sessions and one did not use them at all. However, therapists commented on the flexibility and accessibility of an integrated approach, and valued access to the library of resources that could be shared with clients to support therapy.

Usability testing sessions provided additional feedback that informed platform development and contributed to improving usability of the platform.

Limitations

Most of the patients interviewed had completed therapy, and therefore, there is a potential bias in terms of the views represented. However, patients who completed therapy expressed a range of views regarding the acceptability of the integrated approach. Most participants were female, and while there was some diversity in terms of socioeconomic status, all participants were White. A more diverse group of participants should be included in future research.

Related publications

The paper reporting the findings from the work piloting the delivery of integrated CBT using the INTERACT therapy platform in 17 patients with depression from primary care is available at: https://dl.acm.org/doi/pdf/10.1145/3313831.3376510

Stawarz K, Preist C, Tallon D, Thomas L, Turner K, Wiles N, *et al*. Integrating the Digital and the Traditional to Deliver Therapy for Depression: Lessons from a Pragmatic Study. CHI Conference paper; 2020. https://dl.acm.org/doi/pdf/10.1145/3313831.3376510

Phase 3: refinement and development of the final platform

Aim

To refine and develop the final online therapy platform for use in the main RCT (WP2).

Methods

The process of refining the platform began in tandem with phase 2. This was an iterative process led by the researcher with expertise in human-computer interaction. It involved the incorporation of feedback from patients, therapists and wider stakeholders, input from our patient and public involvement (PPI) representative at monthly team meetings, as well as regular meetings between the programme leads, human–computer interaction researchers and software developers. Feedback was assimilated into a list of 'tickets' that each outlined a proposed modification or new functionality to the online therapy platform. These 'tickets' were prioritised through discussion between the programme leads, human–computer interaction researchers and software developers based on the importance and/or frequency with which an issue had been raised by patients and/or therapists, and the time and resources available within the project. An external assessment of the security of the platform was completed prior to the start of recruitment to the main trial to ensure system readiness.

Key findings

Data from the phase 2 patient and therapist interviews informed the final changes and adjustments to the platform and enabled the development of a system that was user-friendly. Key changes included: (1) adding a typing indicator to the IM feature of our platform in order to improve the communication process during online therapy sessions; (2) redesigning the structure of the library of resources to make it easier for therapists to find and share resources with patients; (3) simplifying the way resources were displayed to patients; (4) removing functionality for brief 'check-in' sessions; and (5) integrating a telephony system within the therapy platform. In addition, in response to therapist feedback, the therapy protocol was revised in terms of the number of sessions offered (to permit (up to) an additional three sessions if clinically indicated) to provide flexibility for managing risk and/or patient complexity.

Limitations

Budgetary constraints limited the incorporation of all suggestions from stakeholders with regards to platform design and functionality. However, feedback was prioritised to ensure that critical changes were implemented. There were several features that we would have included if additional time and resources had been available. These included functionality for uploading images, having a whiteboard to enable drawing during therapy session, and the ability for the therapist and patient to be able to edit worksheets simultaneously. These would have made the platform and therapy more interactive.

Links to other work packages

The online therapy platform that was developed in this WP1.3 was then evaluated in the RCT (WP2), parallel economic evaluation (WP3), and nested qualitative study (WP4). The original plan was for the first therapy session to take place in-person F2F. However, due to the COVID-19 pandemic, this was switched to a videocall.

Work package 1.4: intervention content development

Aim

This WP aimed to: (1) identify the resources used by CBT therapists to support Beckian CBT for depression and (2) to develop and pilot an online training package for CBT therapists that covers use of the online materials and technical aspects of the INTERACT therapy platform.

Part 1: selection of materials for inclusion in the platform

Therapist survey

Aim

To identify materials commonly used by therapists delivering individual CBT with patients who have depression, and to identify those materials perceived as most effective in bringing about clinically helpful change.

Methods

Questionnaires were sent to 3665 British Association for Behavioural and Cognitive Psychotherapies (BABCP) accredited UK CBT therapists asking about their use of resources described in CBT manuals, and their views on the effectiveness of such resources.

Key findings

Of 3665 approached by post/e-mail, 994 individuals (27%) responded, with a further 33 completing the questionnaire via the study website. Most respondents (80%; *n* = 818/1027) were BABCP accredited CBT therapists who deliver one-to-one therapy. Over 85% of respondents used symptom measures, lists of problems/goals, activity schedules, behavioural activation diaries/plans, and case formulation worksheets 'frequently' or 'very frequently'. Resources that were regarded as the most effective in bringing about change were: activity schedules, behavioural activation diaries/plans, case formulation worksheets, thought records and resources to support identification of conditional beliefs.

Limitations

The low response rate may have introduced bias. However, there was no evidence of differences in resource use, or ratings of effectiveness, between those who responded to the initial invitation or subsequent reminders.

Final selection of cognitive–behavioural therapy materials

The selection of materials to be incorporated into the platform was based on consideration of four sources of information:

1. the competences framework for the delivery of CBT for depression which describes the activities that need to be brought together in order to carry out CBT effectively;[19]
2. the findings from the therapist survey (outlined above);
3. the consensus regarding the effective components of CBT from the Delphi study (WP1.1);
4. the findings from the systematic review/NMA (WP1.1), which identified that social skills training was a component of treatment for depression in previous research and hence we included a specific worksheet on this in the platform.

Materials were divided into three categories: psychoeducational materials, worksheets for completion by patients, and short animations. Worksheets were adapted for the platform to be interactive and usable online. Psychoeducational materials and worksheets came mainly from four sources used by CBT therapists: (1) Psychology Tools (www.psychologytools.com/); (2) GetSelfHelp (www.getselfhelp.co.uk/); (3) Centre for Clinical Interventions (www.cci.health.wa.gov.au/); and (4) the Five Areas® Approach/Living Life to the Full Approach (www.llttf.com/). Worksheets were identified for each of the core competences for CBT for depression. A wide variety of materials was incorporated to

allow therapists more choice and flexibility to tailor treatment for the individual. A series of animations were created by the research team in collaboration with a graphic designer. These were designed as brief (< 2 minutes) introductions to key topics in CBT.

Links to other work packages

Through the therapist survey, we learnt that therapists use a wide range of CBT materials in their practice. This was reflected in the materials that we added to the platform. We also learnt about the sources from which they draw their materials and gained appropriate permissions to use such materials, so that therapists would be working with materials with which they were familiar. We discovered that therapists used these materials both within the session with the patient and recommended them for use outside the session, and this was reflected in the platform design. In addition, we developed 16 brief animations designed to introduce patients to the platform, provide psychoeducation, and support patients in their work outside therapy sessions. The animations were voiced and subtitled, and their content drew on available worksheets and other materials, and on the research outlined above.

Related publications

The accepted author manuscript for the paper reporting the findings of the therapist survey is available at: https://research-information.bris.ac.uk/ws/portalfiles/portal/173757515/Submitted_manuscript_proof_23_10_2018.pdf

Tallon D, McClay CA, Kessler D, Lewis G, Peters TJ, Shafran R, *et al*. Materials used to support cognitive behavioural therapy for depression: a survey of therapists' clinical practice and views. *Cogn Behav Ther* 2019;**48**:463–81. https://doi.org/10.1080/16506073.2018.1541927

Part 2: development and implementation of a training package for therapists

Aim

To develop an online training package for therapists.

Methods

Training for the therapists employed for WP1.3 – phase 2 was developed and delivered with CBT experts in the research team and supported by the therapist's supervisor. The emphasis of the training was on the use of the platform and delivery of Beckian CBT in the online context. Therapists were provided with a therapist manual and platform user guide, and undertook self-directed learning and familiarisation with the platform and embedded materials (worksheets, psychoeducational sheets and videos). Therapists attended 1.5 days of formal in-person training and undertook a series of individually tailored training sessions, including role play, with members of the research team. The training was streamlined and delivered with a therapist who joined the team part-way through the phase 2 work. This informed the development of an online training package for the main trial.

Key findings

Final revisions to the training manual were made for the RCT with emphasis on: (1) making clear the differences between delivering CBT F2F and delivering therapy using the INTERACT therapy platform; (2) when/how to incorporate the telephone into online sessions where IM is the main mode of communication); and (3) time management. Refinements were made to the platform user guides (for patients and therapists) and relevant standard operating procedures were prepared for the RCT.

Links to other work packages

In the main trial, therapists were employed 1 month prior to the start of providing therapy in order to familiarise themselves with the trial and therapy platform. For the first two therapists, training was delivered online in real-time ('live') via videoconferencing. These sessions formed the basis for the development of an online training package (accessed via a password-protected page on the INTERACT website) for all other therapists. Online training comprised a mixture of asynchronous materials (e.g. recorded lectures covering background to the trial, therapy protocol, using the INTERACT therapy platform, managing risk and research procedures). There was the opportunity to ask questions about each week's material during a live online question and answer session with the INTERACT study leads and other members of the research team. Therapists also gained hands-on practice in using the platform in role play sessions (with research team members playing the role of the 'client').

Work package 2: randomised controlled trial

Full details of the trial are provided in *Appendix 1*. The full protocol[1] and WP results[41] have been published.

Aim

The aim of this WP was to evaluate the clinical effectiveness of an integrated approach to delivering CBT in reducing depressive symptoms and improving quality of life (QoL) over 12 months [compared with usual care (UC)] for primary care patients with depression, in an individually randomised pragmatic trial.

Methods

We used broad and pragmatic inclusion criteria to recruit individuals with depression from primary care. Eligible patients were those who were aged 18 or over, scored ≥ 14 on the Beck Depression Inventory, version 2 (BDI-II)[53] and met *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10) criteria for a depressive episode.[54,55] We recruited participants from 67 general practices in areas surrounding the 3 trial sites: Bristol, London and York. Participants were identified either via a search of practice electronic records or by direct referral from their GP. Those who agreed to contact via either recruitment method were telephoned by a researcher and asked a few screening questions. Those who met the screening criteria were invited to an appointment with a researcher (baseline assessment) to explain the trial, undertake the baseline assessment, establish eligibility and obtain written informed consent. Most participants were e-mailed a link to an online consent form, and completed this using their own smartphone, tablet or computer during their baseline appointment. If they were unable to complete this electronically (e.g. due to technical issues), they were posted a consent form to complete on paper and post back to the researcher. Participants were sent a copy of their completed consent form. If eligible, participants were randomised to one of two groups: usual GP care or integrated CBT (in addition to usual GP care). Randomisation was by means of a computer-generated code from an automated, remote randomisation service, stratified by study centre and minimised on gender, current antidepressant use and depression (BDI-II) severity.

Key features of the Integrated CBT intervention are illustrated in *Figure 2*. Integrated CBT comprised nine therapist-led sessions, with (up to) a further three sessions where clinically appropriate. The first session took place by videocall (90 minutes) with subsequent 50-minute therapy sessions taking place online via IM (typing) within the INTERACT therapy platform. Therapists and patients could use a collaborative workspace to view, edit and discuss CBT resources (worksheets, information sheets, brief videos) within the platform. Therapists could agree tasks (e.g. worksheets) with the patient for them to complete between therapy sessions. Patients could access transcripts of their online IM therapy sessions.

The library of resources within the platform covered: avoidance; behavioural activation; assumptions, rules and beliefs; formulation; general psychoeducation; goal setting; problem solving; relapse prevention; risk; sleep; working with thoughts; and a small number of resources related to anxiety. Additional information on the origin of the resources is given earlier in *Final selection of cognitive–behavioural therapy materials*.

The intervention was delivered by nine part-time CBT therapists, accredited as CBT practitioners by the BABCP. Therapists received training in use of the platform and provided standard Beckian CBT.[56]

All participants were followed up at 3, 6, 9 and 12 months post randomisation.

Primary comparative analyses between the two randomised groups were conducted according to the groups 'as randomised', without imputing missing values. Linear regression was used to compare the primary (continuous) outcome (BDI-II score) at 6 months between randomised groups, adjusting for the study centre, baseline BDI-II score and the other two minimisation variables. Similar regression models were used for secondary outcomes. The effect of the intervention on outcomes over 12 months was summarised using repeated-measures models, with an interaction between treatment and time to formally test whether effects varied with time.

Additional sensitivity analyses were used to examine the effect of: (1) missing data; (2) any baseline imbalances in prognostic factors; (3) number of treatment sessions attended; (4) potential clustering by therapist[57] and (5) timing of

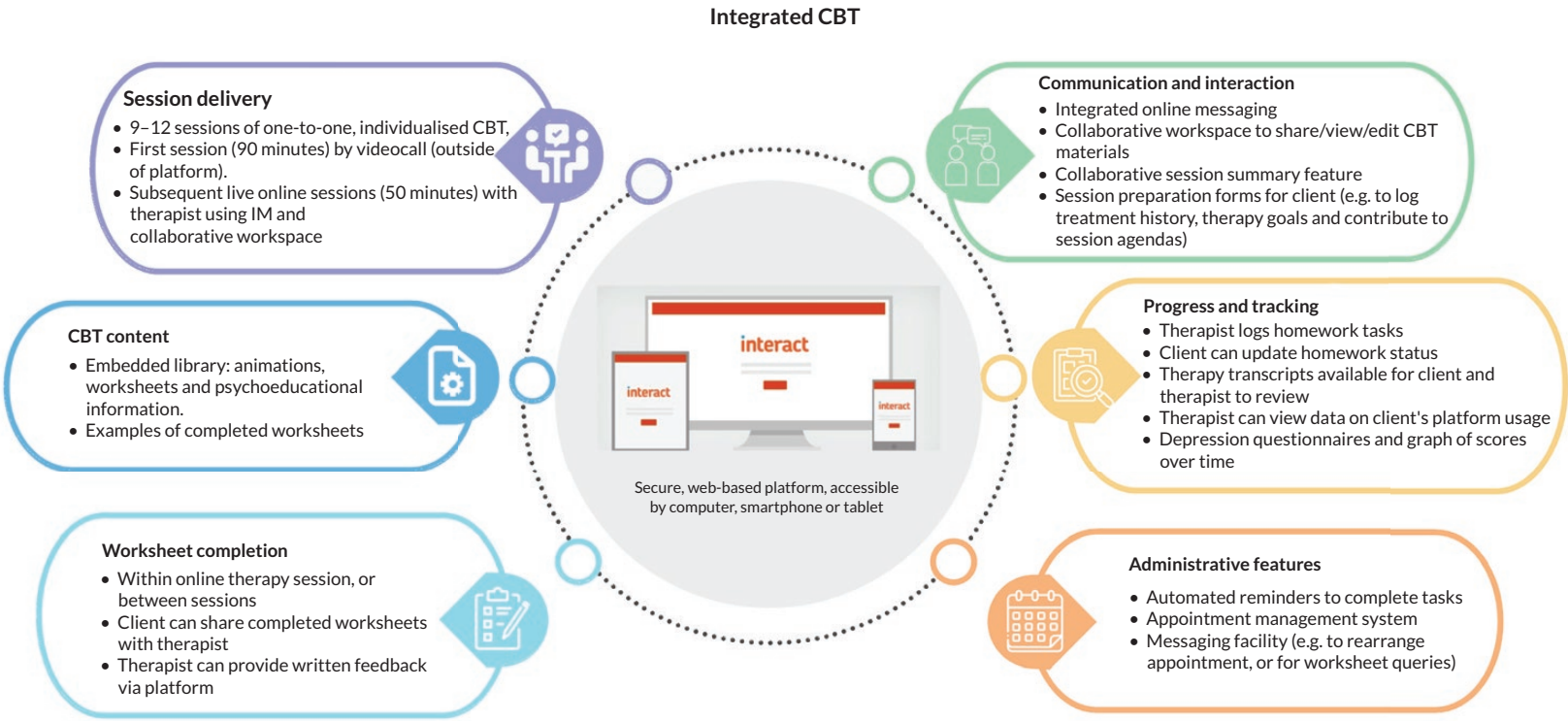

FIGURE 2 Key features of integrated CBT.

questionnaire completion. Complier-average-causal effect (CACE) analyses were conducted to estimate the treatment effect among compliers. A priori specified subgroup analyses explored the potential for differential treatment effects based on chronicity and severity of depression, and personality difficulties.[58]

Key findings

From 12,182 letters of invitation and 381 direct referrals, 1455 patients agreed to being contacted by the research team (see *Appendix 1*, *Figure 4*). In total, 761 individuals were identified as potentially eligible at telephone screen and agreed to attend a baseline assessment. Of these, 451 patients were eligible and randomised to receive either integrated CBT (n = 225) or to continue with usual GP care (n = 226). Three hundred and forty-six (77%) were followed up at 3 months (*Figure 3*), 334 (74%) at 6 months, 328 (73%) at 9 months and 327 (73%) at 12 months.

Participants were predominantly female (n = 313, 69%) and, on average, aged 39 years (see *Appendix 1*, *Table 3*). The mean BDI-II score at baseline was 32.8, indicative of severe depression. Most had a history of depression (with nearly half having had 5 or more prior episodes of depression), were taking antidepressants (70%) and the duration of the current episode of depression was ≥ 2 years for 51% of participants (see *Appendix 1*, *Table 3*).

Fourteen individuals (6.2%) had no therapy sessions. A total of 137 participants (60.9%) completed therapy (defined as receiving at least 9 sessions or reaching an agreed end with their therapist in fewer than 9 sessions) and 88 (39.1%) either withdrew from therapy or were discharged for repeated non-attendance. The mean duration of the intervention from randomisation was 3.2 months [standard deviation (SD) 1.6] (for n = 211 who had ≥ 1 session). Participants received a median of 8 therapy sessions [interquartile range (IQR): 3–10], with a slightly higher figure for those who completed therapy [median: 9 (IQR: 9–11)]. A total of 152 participants (67.6%) received at least 6 sessions of integrated CBT or reached an agreed end in < 6 sessions (CACE definition).

Those assigned to the intervention logged into the INTERACT therapy platform a median of 28 times (IQR: 12–42) with a median of 10 resources (worksheets/information sheets) shared by the therapist to their client, and 5 practice at home tasks (homework) agreed. Use of the platform was higher among the CACE sample [median (IQR) number of logins: 37 (27–49.5); number of resources shared: 13 (9.5–17); and number of homework tasks set: 9 (4–13)].

Those in the intervention group had a BDI-II score that was, on average, 4.4 points lower (less depressed) than those in the UC group at 6 months {difference in means: −4.4 [95% confidence interval (CI) −7.0 to −1.9] p = 0.001}. This equated to an effect size of 0.43 (using baseline pooled SD). Adjustment for baseline imbalances slightly increased the between-group difference, but adjustment for actual time to follow-up had no effect (see *Appendix 1*, *Table 4*).

Individuals in the intervention group had nearly a threefold increased odds of meeting criteria for response [odds ratio (OR): 2.78 (95% CI 1.63 to 4.74) p < 0.001] and remission (BDI-II score < 10) [OR: 2.74 (1.46, 5.15) p = 0.001] at 6 months, equating to a number needed to treat (NNT) of 6 (95% CI 4 to 11) and 8 (95% CI 5 to 19). The difference in mean proportional change in depressive symptoms on the BDI-II was −14.6% (see *Appendix 1*, *Table 7*). In other words, individuals in the intervention group had experienced (on average) a 15% greater reduction in depressive symptoms (relative to baseline) compared with those in the UC group. There were beneficial effects of the intervention in terms of other secondary outcomes. The intervention group had fewer depressive symptoms on the Patient Health Questionnaire-9 (PHQ-9), fewer symptoms of anxiety [Generalised Anxiety Disorder-7 (GAD-7)] and less impairment in terms of functioning at 6 months (see *Appendix 1*, *Tables 8–10*).

There was little evidence of clustering of outcomes by therapist [intraclass correlation coefficient (ICC): < 0.0001] and, commensurate with this, the results from a fully heteroscedastic model that accounted for clustering by therapist [difference in means: −4.4 (95% CI −6.9 to −1.9)] were identical to the results of the primary analysis.

For the a priori subgroup analyses, there was no evidence that personality difficulties (p-value for interaction: 0.47), depression severity (BDI-II score: p = 0.22) or chronicity of symptoms (p = 0.77) had any effect on the difference between the intervention and UC group at 6 months.

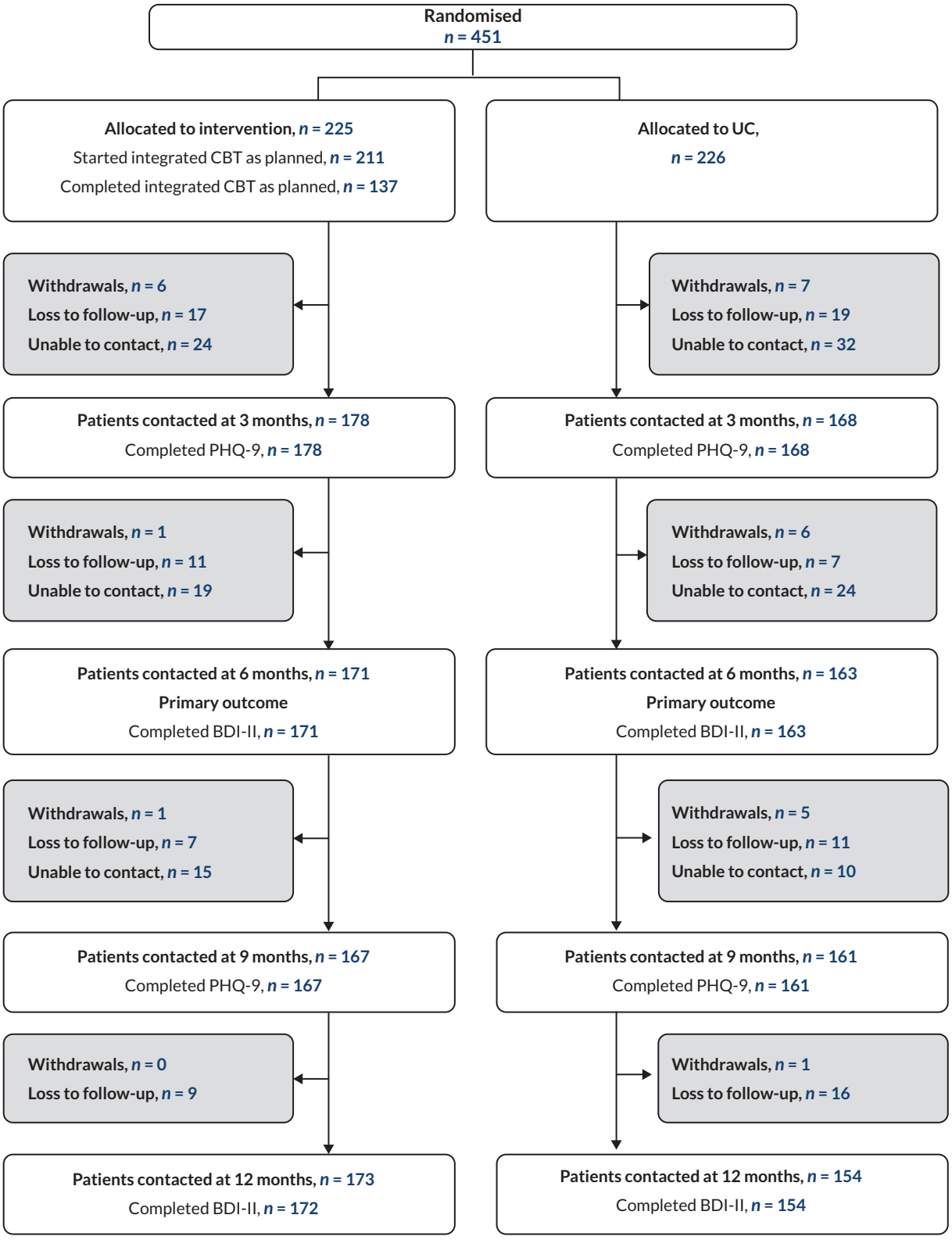

FIGURE 3 INTEgrated theRApist and online CbT for depression Consolidated Standards of Reporting Trials flow diagram.

In repeated-measures analyses using data from 6 and 12 months, individuals in the intervention group had a BDI-II score that was, on average, 3.8 points lower than those in the UC group [see *Appendix 1*, *Table 11*: difference in means: −3.8 (−6.1, −1.5) $p = 0.001$]. In repeated-measures analyses, the intervention group also had a twofold increased odds of response and remission, and benefits in terms of reductions in PHQ-9 and GAD-7 scores and function [Work and Social Adjustment Scale (WSAS)] (see *Appendix 1*, *Tables 5–10*). There was little evidence that the effects varied over time (*p*-values for interactions ranged from 0.12 to 0.96).

The results of CACE analyses [difference in means: −5.8 (95% CI −9.1 to −2.6) $p < 0.001$] showed that the effect of the intervention was larger among who completed treatment as intended (see *Appendix 1*, *Table 12*).

The results following the imputation of missing data were consistent with those of the primary analysis (see *Appendix 1*, *Table 13*). Other scenarios for missing data were also considered (see *Appendix 1*, *Table 13*) that represent extremes in the pattern of missingness.

In terms of receipt of other treatments (outside of the trial), by 6 months, 13/324 (4.0%) of participants had received computerised CBT [intervention group: $n = 2/166$ (1.2%); UC group: $n = 11/158$ (7.0%); median number of sessions was 7 (6, 8) and 4 (3, 9), respectively]. By 6 months, 74 individuals [intervention: $n = 24/168$ (14.3%); UC: $n = 50/161$ (31.1%)] had received another talking therapy outside the trial. Of these, 15 individuals had received high-intensity individual CBT [intervention group: $n = 5/168$ (3.0%), median number of sessions: 10 (IQR: 8–12); UC group: $n = 10/160$ (6.3%), median number of sessions: 10 (7, 11)]. At 6 months, 64.9% ($n = 216$) of participants [107 of 170 (62.9%) intervention group; 109 of 163 (66.9%) UC group] were taking antidepressant medication [difference: −3.9% (95% CI −14.2% to 6.3%)].

There were 54 adverse events (AEs) and 14 serious adverse events (SAEs) during the study (see *Appendix 1*, *Tables 14–17*). There were a higher number of AEs in the intervention group, possibly due to more frequent contact. No SAEs were definitely/probably related to the intervention.

Limitations

The follow-up rate at 6 months was slightly below the original retention target (74% vs. target 80%). Some imbalances in baseline characteristics between randomised groups were identified but there was no evidence that adjustment for these impacted on the conclusions drawn. Results imputing missing data were consistent with the findings of the primary analysis.

Links to other work packages

The INTERACT trial evaluated the clinical effectiveness of the integrated approach to delivering CBT that was developed in the first part of the programme (WP1). The cost-effectiveness and acceptability of the intervention were evaluated in WP3 and WP4, respectively.

Related publications

Work package 2 is reported in full in Tallon *et al.*[41]

Work package 3: cost-effectiveness evaluation

Full details of the cost-effectiveness evaluation are given in *Appendix 2*.

Aim

The aim of this WP was to establish the cost-effectiveness of integrated CBT in reducing depressive symptoms and improving QoL over and above UC over 12 months for primary care patients with depression.

Methods

Costs of integrated CBT included costs of training, post-training supervision, intervention sessions, and operating and maintaining the INTERACT platform. The costs of staff were estimated by multiplying the time they spent by their

respective hourly costs (salary + oncosts + overheads + capital). The costs of operating and maintaining the INTERACT platform was estimated based on information provided by the University of Bristol Research information technology team where it was hosted during the study. These were extracted from study records.

Usual care included psychological services, including packages of CCBT, counselling or talking therapy provided by NHS, and prescriptions of antidepressant medication. Prescription of antidepressant medication and GP consultation were extracted from GP records for 12 months post randomisation. Use of UC and other healthcare services for mental health, and costs from wider perspectives were collected at 6 and 12 months post randomisation, as part of the self-reported questionnaire. All monetary outcomes were presented in Great British pounds 2022–3.

The effectiveness measure was quality-adjusted life-years (QALYs), derived from EuroQol-5 Dimensions, five-level version (EQ-5D-5L).[59] It was administered at baseline, 6 and 12 months. The response to EQ-5D-5L was converted to utilities using a mapping approach, following the recommendation by NICE.[60,61] The utilities were then used to derive QALYs following area under the curve approach.[62]

The primary analysis was an incremental cost–utility analysis (CUA) from an NHS and Personal Social Services (PSS) perspective.[60] The costs comprised costs of integrated CBT and UC, primary, community, secondary health care, and social services for mental health.

Incremental costs and incremental QALYs were estimated using generalised linear regression, costs with the gamma family and log link while QALYs with the default family and link. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental costs by incremental QALYs, when both were positive. Uncertainty surrounding the point estimate was assessed using non-parametric bootstrap resampling technique.[63] A cost-effectiveness plane (CEP) and cost-effectiveness acceptability curves (CEACs)[64] were constructed based on the bootstrap iterations to illustrate the uncertainty of conclusion of cost-effectiveness of integrated CBT over and above UC. The conclusion was drawn against the maximum acceptable ICER thresholds at £20,000–30,000 per QALY gain recommended by NICE.[60]

Secondary analyses followed the methods used in the primary analysis but were undertaken from the participants' and informal carers' perspective and societal perspective, respectively. The costs from the participants' and informal carers' perspective comprised participants' payments in relation to treatments and remedies for mental health, and lost income of participants and/or their informal carers due to participants' mental health conditions. The costs from the societal perspective comprised both the costs from a NHS and PSS perspective and from the patient and informal carer perspective; and costs of treatments or therapies provided by entities other than NHS, free of charge or at a nominal price to participants, informal carer's allowance, paid leave and extra costs to arrange for cover for participants. However, as there were no recommended maximum ICER thresholds for these two perspectives, the results are presented without reference to thresholds.

Primary and secondary analyses were undertaken using a multiple imputed data set, following Rubin's rule.[65] Multiple imputation with chained equation was used to handle missing data.

Sensitivity analyses were conducted using complete-case analyses (CCAs) from three perspectives, considering those who had complete data on all variables. To examine the missing at random (MAR) assumption, a set of sensitivity analyses using pattern mixture modelling[60] was also undertaken. The missing not at random (MNAR) assumptions were those who had missing values at follow-ups and were either in need of more healthcare services or experienced worse health, or both conditions at the same time.

Key findings

The mean costs of integrated CBT were estimated at £987 [standard error (SE) £14] per participant (see *Appendix 2*, *Table 18*). The mean costs of UC were estimated at £382 (SE £57) in the UC group and £193 (SE £42) in the integrated CBT group (see *Appendix 2*, *Table 19*).

The costs from NHS/PSS perspective were £753 (SE £77) per participant in the UC group and £1754 (SE £127) in the integrated CBT group, with adjusted incremental costs at £1009 (95% CI £737 to £1286) (see *Appendix 2*, *Table 19*). The

mean QALYs were 0.554 (SE 0.017) in the UC group and 0.597 (SE 0.017) in the integrated CBT group, with adjusted incremental QALYs at 0.033 (95% CI −0.002 to 0.059). The ICER was £30,576 per QALY gain (probability of cost-effectiveness from £20,000 to £30,000 : 13–39%) (see *Appendix 2*, *Table 19* and *Figure 5b*).

Complete-case analysis from NHS/PSS perspective included 109 participants in the UC group and 103 participants in the integrated CBT group. It showed a slightly more favourable picture with an ICER at £22,421 (probability of cost-effectiveness from £20,000 to £30,000 : 37–66%) (see *Appendix 2*, *Table 19* and *Figure 5d*).

The mean out-of-pocket payments (OOPs) and lost income were £808 (SE £190) in the UC group and £1127 (SE £318) in the integrated CBT group (see *Appendix 2*, *Table 20*). The mean societal costs were £2734 (SE £439) in the UC group and £3890 (SE £475) in the integrated CBT group. The incremental costs from the perspective of participants and informal carers and from a societal perspective were £179 (95% CI −£249 to £680) and £1259 (95% CI £164 to £2099), respectively (see *Appendix 2*, *Table 20*). With incremental QALYs the same, the ICER from the participants' and informal carers' perspective was £5424 per QALY gain (probability of cost-effectiveness reaching 50% at approximately £7000 per QALY gain) and from a societal perspective £38,152 per QALY gain (probability of cost-effectiveness reaching 50% at approximately £38,400 per QALY gain) (see *Appendix 2*, *Table 20* and *Figure 6a* and *6c*).

The MNAR sensitivity analyses found no significant impact on the conclusions. Excluding seven participants identified post hoc as outliers in costs, OOPs, lost income or non-NHS benefits (see *Appendix 2*, *Table 21*), while reduced ICERs from the three perspectives, did not impact on the conclusions already drawn.

Limitations

Missing data (in terms of resource use) was an issue. While CCAs showed lower ICERs than those estimated from imputed data, it should be noted that fewer than half of participants were included in the CCAs.

Links to other work packages

The evaluation of cost-effectiveness was conducted alongside the trial that evaluated the clinical effectiveness of the integrated approach to delivering CBT (WP2) and the nested qualitative study that evaluated the acceptability of the intervention (WP4).

Work package 4: qualitative evaluation

Aim

The aims of the nested qualitative study were to:

(1) explore patients', therapists' and supervisors' views and experiences of using an integrated approach to delivering CBT;
(2) understand patients' reasons for completing or not completing treatment;
(3) assess patients', therapists' and supervisors' views on how this novel approach affected the therapist-patient relationship.

Methods

Semistructured interviews were held with 30 trial participants (n = 20 intervention; n = 10 UC) after they had completed their primary trial outcome measures at 6 months post randomisation. These patients were purposively sampled across the trial sites to achieve maximum variation in relation to age, gender, depression severity, treatment response, adherence to treatment and therapeutic alliance. Twelve of those interviewed in the intervention arm had completed therapy (defined as having at least nine sessions of therapy or reaching an agreed end) and eight had not.

Interviews were conducted with all trial therapists (n = 9) and their clinical supervisors (n = 3) towards the end of their involvement in the trial.

Interviews were held remotely by telephone or videocall. Topic guides were developed for each group (patients, therapists and supervisors) but included similar questions to facilitate triangulation of accounts. All interviews were

audio-recorded, transcribed, anonymised and analysed using an inductive thematic approach.[67] A coding frame was then developed and applied to all transcripts. NVivo software (QSR International, Warrington, UK) was used to facilitate electronic coding and data retrieval. Data from the three groups were analysed separately before findings were triangulated to identify areas of commonality and differences across them. Data collection and analysis preceded in parallel. The final number of interviews conducted was guided by information power.[68]

Key findings

Integrated CBT – that combined therapist-led sessions with CBT resources within an online platform – was acceptable for primary care patients with depression. Patients who completed therapy valued being able to talk to a therapist and access resources within a single platform and had learnt skills to better manage their depression. The ability to review transcripts of IM therapy sessions assisted with completion of homework tasks and allowed patients to track their progress. Typing allowed reflection but less could be covered in one session, compared with an in-person therapy session. This meant therapists set expectations regarding the session agenda and used more focused questions to ensure benefit. Therapists believed that delivering therapy this way was a useful initial first step to enable people to learn CBT skills. Patients who did not complete therapy found the CBT approach too structured or, between session tasks, too onerous. Many also found therapy by IM challenging – they found it difficult to express themselves through typing, were confused by overlapping messages and frustrated by the time taken waiting for a reply. Individuals in the UC group were disappointed not to get the intervention but described a range of ways that they managed their depression, such as medication and lifestyle changes. Many were glad to have participated in the trial, to support research about managing depression.

Limitations

The views of those interviewed (patients, therapists and supervisors) may not be representative of those outside the trial context. Because the intervention was being assessed within a trial context, therapists had less flexibility in how it could be used and were limited in the CBT resources they could share.

Related publications

The paper reporting the results of the nested qualitative study is available at: https://doi.org/10.1111/hex.70002

Fox F, Wiles N, Kessler D, Tallon D, Thomas L, Williams C, *et al*. Patients' and therapists' views of integrated online CBT for depression. *Health Expect* 2004;**27**:e70002.

Links to other work packages

The nested qualitative study was part of the evaluation of the integrated approach to delivering CBT. It was conducted alongside the randomised trial and economic evaluation that evaluated the clinical and cost-effectiveness of the intervention (WP2 and WP3, respectively). The findings from all three WPs have been brought together in the conclusions from the programme.

Involvement of patients and/or the public

Patients, service users and members of the public were involved in the design and management of this research and advised on dissemination activities.

Intervention development

Prior to undertaking the RCT, we conducted substantial pilot work to gather stakeholder feedback on the trial intervention. For example, the first phase of intervention development focused on user-centred design and included design workshops and prototype testing sessions with 18 people who had received CBT for depression in the past, and qualitative interviews and CBT role-play sessions with 12 CBT therapists experienced in the treatment of depression.

Next, the phase 2 study gathered detailed feedback from 18 primary care patients who received the intervention as part of the pilot study, and from the therapists and supervisor who delivered this treatment. This work was pivotal in informing the final design of the intervention evaluated in the RCT.

Patient and public involvement advice on remote research protocols

Due to the pandemic, we needed to redesign the trial protocol so that we could deliver the trial remotely. It was important for us to understand whether remote research procedures, such as e-consent, video-call assessments, online surveys, and holding the first therapy 'F2F' via videocall (instead of in-person) would be acceptable to potential participants. In August/September 2020, we conducted seven in-depth PPI interviews with people who have taken part in previous trials, to ask for their input on these changes. These interviews were very helpful in reassuring us that these methods would be acceptable (and perhaps even beneficial) to potential participants. Furthermore, there were many helpful suggestions on how we could offer more flexibility to participants and improve their experience of the remote assessments. For example, we were advised to: consider offering further support for people who might struggle to use online tools; minimise participants' anxiety by being clear about what taking part in the trial would involve; offer breaks during the remote appointment; and provide the flexibility for participants to do some tasks independently if this makes them feel more comfortable. We incorporated these suggestions into our protocols.

Patient and public involvement advisors

The INTERACT Programme Management Group included a PPI member (Paul Lanham), who was also a service user representative co-applicant, and member of the management group responsible for developing the intervention and the trial. The Independent Steering Committee included two PPI members. More recently, we have established a PPI group comprising people who have taken part in previous depression trials.

Patient and public involvement advisors provided ongoing input into design and management of the programme. They also provided valuable feedback on the patient information sheet, invitation letter, consent form and newsletters for trial participants.

Dissemination

We have published a summary of the results of the therapist survey in the BABCP members' magazine, 'CBT Today' in order to reach professional stakeholder groups, and the therapist survey participants (most of whom are BABCP members).

We also circulated the results of the Delphi study to the survey participants. We have circulated the results of the pilot study to participants who indicated they wished to receive this. Similarly, we plan to send a summary of results to the RCT participants and to the GP practices involved in recruitment activities. We also aim to disseminate findings through relevant community organisations. We will seek advice from our service user co-applicant and PPI group with regards to our dissemination strategy. A PPI advisor (Paul Lanham) has coauthored several INTERACT manuscripts.

Future plans

We will ask our PPI group to advise us on the planned results newsletters for INTERACT trial participants and to provide input into the design of future depression studies.

Climate, health and sustainability

Who is the INTEgrated theRApist and online CbT for depression platform for?

In the past, psychotherapies such as CBT have been delivered in person. In 2003, the first 'computer therapy programme for anxiety and depression', Beating the Blues, was tested in the UK.[69] Since then, there has been a rapid growth in online therapies, and it is likely that this will continue. However, lack of flexibility and resultant poor levels of adherence to computerised psychotherapy has been a barrier to clinical effectiveness. INTERACT offers the personalisation and responsiveness of in-person CBT and delivers comparable health benefits. The platform is clinically effective and acceptable for patients with depression. There are benefits in terms of accessibility for patients and convenience for both therapist and patient, which may improve the reach of therapies for those who find travel difficult or cannot manage office hours. There is also evidence that even without specific materials for the management of anxiety disorder, patients who undertook the therapy were less anxious at the primary outcome time point. The platform could therefore be expanded to support treatment of other disorders, such as anxiety.

Climate and sustainability and relevance to the health service

Both therapists and patients can work from home and the reduction in travel to sessions could result in lower carbon emissions, as could less printing of materials provided by therapists to patients. The environmental impact of delivering the service itself, from an energy and resource perspective based on scoping attributional footprint data from the University of Bristol Computer Science department, is likely to be significantly less than these gains. The platform was designed for use in psychological services, such as NHS talking therapies. It can be adapted to local needs and practices.

Plans for implementation

We have held discussions with the Research Manager at the Bristol, North Somerset and South Gloucestershire Integrated Care Board (BNSSG ICB) who hosted the programme. We agreed the next steps would be to discuss licensing issues for the software with our Sponsor, the University of Bristol, if the platform is to be rolled out to existing providers. We will also approach Health Innovation Networks (previously Academic Health Science Networks) who can link us with decision-makers in different parts of the country.

Equality, diversity and inclusion

Language and terminology

The development of the platform was an iterative process, including a longitudinal evaluation study involving patients with depression recruited from primary care, participatory design work with therapists providing CBT and their clinical supervisor and usability testing sessions with people who had received CBT in the past. Patient and GP-facing materials in the trial were reviewed by our PPI colleagues. The platform was designed from the first to be accessible and understandable.

Participant representation, recruitment and retention

Our inclusion criteria for participants from primary care were as broad as possible. All participants were aged 18 years or over and had depression. We excluded those who were under psychiatric care, had a current history of alcohol or substance abuse, had dementia, bipolar disorder or psychotic illness. We did not exclude participants with psychiatric comorbidity. In some of our previous primary care mental health trials (of both psychotherapy and medication), we have not been successful in recruiting from an ethnically diverse population; our average proportion of non-White participants was < 5% in three recent trials. We improved on this for the INTERACT trial where the proportion of non-White participants was 15%, in part by recruiting from a centre with a diverse population. We also had more ethnic diversity among the therapists providing the intervention, which may have had an impact on retention for ethnic minority participants. There were two important limitations to our capacity to be inclusive in this study. The first is that we were not able to include those unable to read or write in English. We did not have capacity within the time frame of the study to provide both translations for the online materials and employ therapists (and researchers) who could work in other languages. However, one of the strengths of an online CBT platform such as INTERACT is that it has the flexibility to provide access to non-English-speaking therapists for non-English speakers if the intervention is adapted for wider use. In addition, there is the flexibility to incorporate additional content and/or materials to meet different cultural needs. The second issue is more complex. It has been argued that there is a 'digital divide' between those who have reliable internet access and the necessary hardware, and those who do not. This divide worsens with increasing levels of deprivation and age. It is, therefore, likely that there is a selection bias in studies of online treatments, and this is borne out by data from our previous work. The participants in INTERACT have relatively high levels of educational attainment and employment, similar to an earlier study of online CBT (IPCRESS)[16] and higher compared with a study of in-person CBT for treatment-resistant depression (CoBalT).[70] It may be that increasing access to and familiarity with online interventions in the population will gradually lessen this divide over time.

Reflections on what was and what was not successful in the programme

Our efforts to identify the clinically effective components of CBT through our systematic review and NMA to inform the development of the intervention were hampered by the limited reporting of the components of interventions. Similarly, our ability to identify the cost-effectiveness of different modes of delivering CBT and variations in intensity

was limited by a high level of uncertainty around estimates. Nonetheless, we used data derived from other aspects of the programme – the Delphi study on effective components of CBT, the therapist survey which identified commonly used resources to support CBT alongside the competency framework for CBT for depression – to inform the selection of materials for inclusion in the platform. Extensive iterative design work with stakeholders (patients and therapists) enabled us to develop an online therapy platform that enabled the delivery of integrated CBT and that we were able to evaluate in a large RCT set in UK primary care. Importantly, we found that this integrated approach to delivering CBT was acceptable to both patients and therapists.

Due to the COVID-19 pandemic, we had to adapt our trial processes and procedures to enable the INTERACT RCT to proceed. This was a substantial amount of work. All research appointments with participants were subsequently conducted remotely (either by videocall or telephone). The first therapy appointment changed from being held in person to taking place by videocall. Implementing these changes enabled us to successfully deliver the RCT. We recruited 451 patients and followed up 73% of participants for 12 months. The latter follow-up rate was lower than our original target (80%); however, results of analyses imputing missing data were consistent with the findings of the primary analyses. Encouragingly, engagement with the integrated CBT approach was similar to engagement with in-person therapy, and much higher than low-intensity CBT interventions.

The eligibility criteria for the INTERACT RCT were deliberately broad and included those experiencing a new episode of depression, as well as those with more chronic depression or who had not responded to initial treatments. These are all groups for whom NICE advocate psychological treatment. It is noteworthy that INTERACT participants were not dissimilar in terms of their disease severity and chronicity to participants in a primary care trial of treatment-resistant depression (CoBalT).[70] In INTERACT, on average participants had moderate to severe depression. While just 19% of INTERACT participants had experienced their current depressive episode for < 6 months, 51% had a current episode lasting more than 2 years. Many (27%) had previously been referred to a psychiatrist (CoBalT: 40%), and 70% were taking antidepressants. This contextual information is key in terms of thinking about the population to whom the results of this trial can be generalised.

It was surprising that, while the intervention was clinically effective, the intervention was not cost-effective given prior evidence of cost-effectiveness of other CBT interventions for depression in similar populations.[17,71] The incremental QALY gain for INTERACT was 0.033, similar to that seen in an earlier trial of IM therapy (0.027),[17] but smaller than the incremental QALY gain (0.053) in a trial of in-person CBT for patients with treatment-resistant depression.[71] Costs have risen over the 10–15 years since these earlier studies were conducted [mean cost of CBT per participant: IPCRESS, 2009 (mean 8 sessions): £493;[17] CoBalT, 2013 (median 12 sessions): £910[71] compared with INTERACT (median 8 sessions): £987], but the threshold used by NICE for assessing cost-effectiveness has remained the same.

The intervention costs for INTERACT included training costs. However, it is likely that therapists had more time to familiarise themselves with the platform than would be the case if the intervention were to be rolled out within NHS talking therapy services. In addition, in a service, these fixed costs would also be spread across a larger number of patients as the number of patients treated by an individual therapist would not be constrained by the trial recruitment target. Together, these factors would likely lead to a reduction in the per-patient costs of training.

Conclusions from the whole programme

We successfully developed an online therapy platform that integrates therapist-led sessions with online CBT materials and offers a novel approach to delivering therapy.

Integrated CBT was effective in reducing depressive symptoms in primary care patients with depression. Benefits were also seen for the more stringent outcomes of response and remission, and in terms of symptoms of anxiety and improved function. Improvements were maintained over 12 months. Benefits were likely to be clinically important.

Engagement with the integrated CBT approach was similar to engagement with in-person therapy and substantially higher than low-intensity CBT interventions. In qualitative interviews, we found that many of the reasons that patients

did not complete therapy were similar to those for in-person CBT. However, aspects of the typed message exchange (e.g. overlapping messages or delays in replies) were confusing or frustrating for some patients. Although less could be covered in a typed session (compared with in-person therapy), the ability to reflect, review transcripts of sessions and have access to resources that enabled patients to learn skills to manage their depression were important. Crucially, the model of integrated CBT enables the therapist to tailor treatment to the individual in line with the idea of meta-competences set out in the CBT competences framework.

Based on the current threshold used by NICE for decision-making, the integrated CBT approach would not be considered cost-effective from the perspective of the NHS/PSS, but the estimate was only just over the upper threshold. Training costs are one component of the intervention costs. These costs would be unlikely to be maintained at the same level if the intervention was rolled out within the NHS. Moreover, once trained, therapists would be likely to treat more patients than was the case within the trial context, which would reduce the per-patient training cost and may make the cost–benefit more favourable in the longer term.

There are no official acceptable thresholds for ICERs from participants' and their carers' perspective and from a societal perspective. Such thresholds would need to be determined by the relevant stakeholders independently in order to draw conclusions regarding the cost-effectiveness of the intervention from a wider perspective. Stakeholders may have disparate objectives in terms of outcomes, and hence QALYs might not be the outcome of interest. The analysis of interventions which impact upon wider stakeholders pose a challenge in health economic evaluation. Future evaluations may strive to impose weights upon outcomes to different interests and raises the discussion about the value of output created in different sectors and to different socioeconomic groups.

Recommendations for future research

Given the often chronic nature of depression, future research needs to examine the longer-term clinical and cost-effectiveness from the perspective of the healthcare provider and wider society in general. CBT is an educational approach; hence, those in the intervention group may be better equipped to manage their depression in the longer term. Studies of in-person CBT have found that CBT is a clinically and cost-effective intervention over 4 years.[72] Evidence is thus needed to quantify and substantiate the potential for long-term gain using this integrated approach, including the potential for economies of scale such as spreading training costs over time more efficiently. If clinically and cost-effective over the long term, this would have important implications for the management of depression.

In addition, future research needs to examine which aspects of the platform led to improvements in depression. This may enable refinement of the intervention to increase benefits.

Implications for practice (and any lessons learnt)

More and more people have access to the internet and their own personal devices that would enable them to engage in therapy online. The COVID-19 pandemic and social distancing requirements resulted in many services moving to remote delivery of therapy, either by telephone or videocall. This switch to remote therapy has persisted post COVID. There has also been a proliferation of mental health apps (including those based on CBT). However, there is little empirical evidence to support the use of many of these. The integrated CBT approach that we have developed was acceptable to patients and clinically effective. While there was some uncertainty around its cost-effectiveness, this novel mode of delivery has the potential to increase the availability of CBT and increase access for those who find it difficult to attend appointments in person.

Additional information

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Mike Jones: Software.

Kieren Pitts: Software.

Tessa Alexander: Software.

Josh Jones: Software.

David James: Software.

Other contributions

Paul Lanham: PPI representative.

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The INTERACT Programme Steering Group (PSG) [who also acted as the Trial Steering Committee (TSC) for the main RCT] and Data Monitoring Committee (DMC) have provided invaluable support and guidance throughout the programme. The PSC was chaired by André Tylee (until July 2021), Sandra Eldridge (July–October 2021) and Ed Watkins (from October 2021), and included Shaun Lawson, Philip Pallmann (from November 2021), Michael Moore (from May 2021), Mark Tucker, Vivien Lindow (until January 2021), and Marta Sawinska (from April 2021). DMC members were: David Kingdon (Chair), Chris Burton and Nikki Totton.

We are grateful to our research programme administrators, Vivien Jones and Fiona Reid.

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This study was designed and delivered in collaboration with the Bristol Trials Centre, a UKCRC-registered clinical trials unit. This study was also supported by the National Institute for Health and Care Research Bristol Biomedical Research Centre. Supplementary funding was provided by the NIHR School for Primary Care Research (SPCR - 2014-10043 Award: L).

Study data were collected and managed using REDCap[73] hosted at the University of Bristol.

All research at Great Ormond Street Hospital NHS Foundation Trust and UCL Great Ormond Street Institute of Child Health is made possible by the NIHR Great Ormond Street Hospital Biomedical Research Centre.

Data-sharing statement

We encourage and will facilitate data-sharing with 'bona fide' researchers. In the first instance, all data requests should be submitted to the coleads, Nicola Wiles and David Kessler, for consideration. Access to anonymised data may be granted following review.

Data from the INTERACT RCT (underpinning the clinical and cost-effectiveness analyses) will be made available as a controlled data set managed by the University of Bristol's Research Data Repository (https://data.bris.ac.uk/data). To gain access, data requestors will need to apply for access at www.bristol.ac.uk/staff/researchers/data/accessing-research-data/. Data release will be contingent on a signed data access agreement. This agreement limits use of data to non-commercial research only. Requests for any other purposes must be negotiated separately.

Ethics statement

Informing the development of online CBT Materials for an integrated approach to delivering CBT (INTERACT therapist survey and Delphi study)

Approved by the Faculty of Health Sciences Research Ethics Committee (FREC reference: 31642) at the University of Bristol (29/2/16) and the HRA (8/3/16), (IRAS ID: 198271).

Designing and developing integrated therapist and online CBT for depression (INTERACT phase 1)

Approved by the South West – Frenchay NHS Research Ethics Committee (REC) (24/3/17) and HRA (3/4/17), (IRAS ID: 221433; REC reference: 17/SW/0058).

The pilot evaluation of an online platform for delivering integrated high-intensity cognitive–behavioural therapy for depression (INTERACT phase 2)

Approved by the South West – Central Bristol NHS Research Ethics Committee (15/11/17) and HRA (17/11/17), (IRAS ID: 235168; REC reference: 17/SW/0243).

Multicentre randomised controlled trial of integrated therapist and online CBT for depression in primary care (INTERACT RCT)

The RCT (including the nested qualitative and cost-effectiveness studies) was approved by the South West – Frenchay Research Ethics Committee (20/3/19), (REC reference 19/SW/0038, IRAS ID: 257620) and HRA (15/5/19).

Information governance statement

The University of Bristol is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, the University of Bristol is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights, and the contact details for our Data Protection Officer here: www.bristol.ac.uk/secretary/data-protection/gdpr/data-protection-officer/.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJNW3912.

Primary conflicts of interest: Debbie Tallon, Laura Thomas, Sally Brabyn, Jinshuo Li: salaries funded by INTERACT NIHR PGfAR grant (RP-PG-0514-20012) to institution.

Deborah M Caldwell: Committee member of NIHR HTA Prioritisation Committee – Social Care – 1/5/24 – 31/5/27 (non-financial interest).

Simon Gilbody: HTA Post-Funding Committee teleconference (2017–20), HTA Funding Committee Policy Group (2017–22), HTA Commissioning Committee (2016–20).

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Stephanie MacNeill**:** HTA General Committee – 11 August 2020 (ongoing).

Irwin Nazareth: receipt of research grant awards from NIHR, UKRI and Wellcome Trust. PRIMENT CTU funded by NIHR 2021. Paid for attending grant panel meetings in London Barts Charity and Eire for HRB panel meetings. Chair of the Drug Safety Monitoring committee for the APRIL RCT led by the LSHTM. On the advisory board of the CRUK core funded CTU at QMUL.

Steve Parrott: NIHR i4i: RESTART-PD grant NIHR206530; NIHR GHR (RIGHT): SCIMITAR–SA Trial grant NIHR205601; NIHR HTA: PORTRAIT grant NIHR159676; NIHR HTA: HAMLET grant NIHR157343; YORQUIT grant from Yorkshire Cancer Research (YCR); NIHR PHR Advance D trial grant NIHR154546; NIHR HTA: (SCOOTT) trial grant NIHR154694; Police drug diversion grant from Cabinet Office; TB-Diabetes grant from the Higher Education Commission NIHR RfPB: (PAMHOP) grant NIHR203484; NIHR PHR: (SCeTCH) grant NIHR132158.

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Nicky J Welton: NIHR grant to institution.

Chris Williams: Five Areas Ltd (employed), and for which, CW is Director and shareholder, has provided licence agreement to use materials in the INTERACT platform. Payments made to Five Areas Ltd for Chris Williams's time on INTERACT project. Other grants/contracts via Five Areas Ltd (research, CBT resources, training contracts – multiple). Five Areas Limited markets the worksheets and related training materials and receives licence fees. Research grants University of Aberdeen, University of Helsinki and more. Five Areas Ltd: Royalty for sales of the worksheets and related resources (books/classes, online resources) in Canada via the Canadian Mental Health Association. Royal College of Psychiatrists: workshops × 2 annually. NHS Greater Glasgow and Clyde: eating disorders teaching session annually. University of Exeter Nurture U. DMEC Chair; University of Manchester EQUITy PSC Chair; University of Central Lancashire COMMITS TSC Chair (all personal capacity/University of Glasgow). Adviser Anxiety UK: personal capacity/University of Glasgow. Stock options: Five Areas Ltd (trading company), Five Areas Resources Ltd (holding company).

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Copyright and credit statement

Publications

Work package 1: intervention development

Davies SR, Caldwell DM, López-López JA, Dawson S, Wiles N, Kessler D, *et al.* The process and delivery of cognitive behavioural therapy (CBT) for depression in adults: a network meta-analysis. *Cochrane Database Syst Rev* 2018;**10**:CD013140. https://doi.org/10.1002/14651858.CD013140

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Materials used to support cognitive behavioural therapy for depression: a survey of therapists' clinical practice and views. *CBT Today*, May 2019. *Short summary of results published in the BABCP Members' magazine, CBT Today, May 2019 (p21).*

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Author accepted manuscript available at: https://research-information.bris.ac.uk/ws/portalfiles/portal/203250524/2019_07_04_Delphi_paper_revised2_clean_with_figure1.pdf

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Wu Q, Li J, Parrott S, López-López JA, Davies SR, Caldwell DM, *et al.* Cost-effectiveness of different formats for delivery of cognitive behavioural therapy for depression: a systematic review based economic model. *Value Health* 2020;**23**:1662–70. https://doi.org/10.1016/j.jval.2020.07.008

Work package 2: randomised controlled trial

Tallon D, Thomas L, Brabyn S, Ching BCF, Hahn JS, Jude B, *et al.* Integrated therapist and online CBT for depression in primary care (INTERACT): study protocol for a multi-centre randomised controlled trial. *Trials* 2023;**24**:421. https://doi.org/10.1186/s13063-023-07396-9

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Work package 3: economic evaluation

Li J, Wu Q, Parrott S, Tallon D, Wiles NJ. Multi-centre randomised controlled trial of integrated therapist and online CBT for depression in primary care (INTERACT RCT): Health Economics Analysis Plan. 2024. https://research-information.bris.ac.uk/ws/portalfiles/portal/397633247/INTERACT_RCT_HEAP_v1.0_20240104_signed_-Signatures_redacted.pdf

Work package 4: qualitative evaluation

Fox F, Wiles N, Kessler D, Tallon D, Thomas L, Williams C, *et al.* Patients' and therapists' views of integrated online CBT for depression. *Health Expect* 2024;**27**:e70002. https://doi.org/10.1111/hex.70002

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Conference presentations

López-López JA, Davies S, Caldwell D, Churchill R, Tallon D, Dawson S, *et al. Using Network Meta-analysis to Identify Effective Components of Complex Mental Health Interventions*. Oral presentation at Research Synthesis 2019, Dubrovnik, 29 May 2019.

López-López JA, Davies S, Caldwell D, Churchill R, Tallon D, Dawson S, *et al. Are All CBT Interventions for Depression Equally Effective? A Component Level Network Meta-analysis*. Oral presentation at Annual Meeting of the Society for Research Synthesis Methodology, Bristol, 18 July 2018.

Taylor A, Hollon S, Kessler D, Peters T, Tallon D, Shafran R, *et al. Expert Consensus on the Clinically Effective Components of CBT: A Delphi Study*. Poster presentation at the 24th International Symposium on Current Issues and Controversies in Psychiatry, Barcelona, 20–22 April 2017.

Taylor A, Hollon S, Kessler D, Peters T, Tallon D, Shafran R, *et al. Expert Consensus on the Clinically Effective Components of CBT: A Delphi Study*. Poster presentation at the 45th BABCP Annual Conference, Manchester, 25–28 July 2017.

Stawarz K, Preist C, Tallon D, Wiles N, Coyle D. *User Experience of CBT Apps for Depression: An Analysis of App Functionality and User Reviews*. Invited presentation at the third Symposium on Computing and Mental Health, CHI 2018: Conference on Human Factors in Computing Systems, Montreal, Canada, 21–26 April 2018.

Stawarz K. *Designing a Platform for Delivering Integrated Therapy for Depression: Challenges and … More Challenges*. Invited presentation at Glasgow Active Minds Conference, Glasgow, 18 July 2018.

Fox F, Tallon D, Jude B, Lanham P, Shafran R, Williams C, *et al. Patients' Reasons for Declining a Trial Evaluating Integrated Online Cognitive Behavioural Therapy for Depression*. SAPC Primary Care Mental Health Conference, Bristol, 16 May 2023.

Additional dissemination activities

Katarzyna Stawarz invited to attend a panel discussion on Ethical Web Design at Bath Digital Festival, 25 October 2018. Discussion included the mental health apps review, challenges of working with vulnerable users, and experiences of usability testing in INTERACT.

The results of the Delphi survey were sent to the Delphi participants (October 2019).

Stawarz K, Preist C, Tallon D, Thomas L, Turner K, Wiles N, *et al. Integrating the Digital and the Traditional to Deliver Therapy for Depression: Lessons from a Pragmatic Study*. Invited presentation at the Irish CHI 2020 online event, 12 June 2020.

Stawarz K. *Integrating the Digital and the Traditional to Deliver Therapy for Depression: A User-Centred Design Study*. Invited presentation at the UCLIC Research Seminar, 25 November 2020.

Nicola Wiles presented an overview of the INTERACT RCT and linked fMRI imaging study at a NIHR Clinical Research Network event, Bristol, 5 March 2020.

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Appendix 1 Randomised controlled trial (work package 2)

The trial protocol has been published and is available at: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-023-07396-9

Tallon D, Thomas L, Brabyn S, Ching BCF, Hahn JS, Jude B, *et al*. Integrated therapist and online CBT for depression in primary care (INTERACT): study protocol for a multi-centre randomised controlled trial. *Trials* 2023;**24**:421. https://doi.org/10.1186/s13063-023-07396-9

The trial statistical analysis plan is available at: https://research-information.bris.ac.uk/ws/portalfiles/portal/397633546/INTERACT_SAP_v1.pdf

MacNeill SJ, Wiles NJ, Peters TJ. *Multi-centre Randomised Controlled Trial of Integrated Therapist and Online CBT for Depression in Primary Care (INTERACT): Statistical Analysis Plan*. Bristol, UK: University of Bristol; 2024:40.

The RCT (clinical effectiveness) results have been published and are available at: https://doi.org.10.1016/j.lanprc.2026.100164

The (clinical) RCT **background** was described in the main synopsis.

Objective: to establish the clinical effectiveness of an integrated approach to delivering CBT in reducing depressive symptoms and improving QoL over 12 months (compared with UC) for primary care patients with depression.

Methods: INTERACT was a pragmatic multicentre RCT with two parallel groups. We recruited participants from 67 general practices in areas surrounding the 3 trial sites: Bristol, London (UCL) and York. The full protocol has been published.[1] Ethical approval was granted by the South West – Frenchay Research Ethics Committee (REC reference 19/SW/0038, IRAS ID: 257620) and HRA.

Eligibility criteria

Eligible participants were those: aged 18 or over; scoring ≥ 14 on the BDI-II;[53] and who met ICD-10 criteria for depression [assessed using the Clinical Interview Schedule – Revised version (CIS-R)].[54,55] Excluded were those: with alcohol or substance dependency in the past year; bipolar disorder; schizophrenia; psychosis; dementia; currently under (or referred for) psychiatric care for depression; who could not complete questionnaires unaided or would require an interpreter; currently receiving CBT or other psychotherapy; who had received high-intensity CBT in past four years; taking part in another intervention trial; not willing or able to receive CBT via computer/laptop/smartphone.

Participant identification

Participants were identified either via a search of practice electronic records or by direct referral from the GP. Those who agreed to contact were telephoned by a researcher and asked several screening questions. Those who met the screening criteria were invited to a baseline assessment with a researcher to explain the trial, establish eligibility and obtain written informed consent. Most participants were e-mailed a link to an online consent form (e-consent), and completed this using their own smartphone, tablet or computer during their baseline appointment. If they were unable to complete this electronically (e.g. due to technical issues), they were posted a consent form to complete on paper and post back to the researcher. Each participant was sent a copy of their completed consent form.

Randomisation

Eligible participants were randomised to one of two groups: usual GP care (UC) or integrated CBT (in addition to usual GP care). Randomisation was by means of a computer-generated code from an automated, remote randomisation service that was developed by the Bristol Trials Centre. Use of this randomisation service ensured that allocation was concealed from the study team. Study researchers enrolled participants and accessed the randomisation service by telephone or online in order to obtain the treatment allocation for each participant. Allocation was stratified by centre and minimised on gender, current antidepressant use, and baseline BDI-II score. Given the nature of the intervention, it was not possible to blind participants, GPs, CBT therapists or researchers to the treatment allocation. One person randomised to UC received the intervention in error.

Trial intervention and comparator

There were no restrictions on the treatment options for those randomised to continue with UC from their GP.

Integrated CBT comprised nine therapist-led sessions, with (up to) a further three sessions where appropriate. The first session took place by videocall (90 minutes) with subsequent 50-minute therapy sessions taking place online via IM (typing) within the INTERACT therapy platform. (For a summary of the key features of integrated CBT, see *Figure 2*.) All sessions were provided to participants individually. Therapists and patients could use a collaborative workspace to view, edit and discuss CBT resources (worksheets, information sheets, videos) within the platform. They could agree tasks for the patient to complete between therapy sessions. Patients could access transcripts of their online (IM) sessions.

We recruited BABCP-accredited CBT therapists with experience comparable to high-intensity therapists within NHS Talking Therapy services. Therapists received training in use of the platform and provided standard Beckian CBT.[56]

The intervention was delivered by nine part-time therapists in three sites. Fidelity to the CBT model was assessed[74] in a random sample of IM transcripts by two independent raters; both were BABCP-accredited therapists and experienced CBT assessors, working within NHS Talking Therapy Services.

Follow-up schedule

Participants were followed up at 3, 6, 9 and 12 months post randomisation. Follow-ups at 3 and 9 months were (mostly) by telephone, whereas follow-ups at 6 and 12 months were (mostly) by telephone or videocall. In order to maximise follow-up completion, researchers offered flexibility with regard to questionnaire completion methods. Participants were able to complete questionnaires independently (e.g. by post or online) if they preferred this. If participants did not complete questionnaires, researchers made attempts to recontact them and/or sent reminder questionnaires. If participants still did not respond at 6 or 12 months, they were posted a much shorter version of the questionnaire in order to facilitate minimum data collection. A £10 shopping voucher was offered for each of the 3-, 6- and 12-month follow-ups. Study newsletters were also posted periodically to participants to encourage retention and engagement with the study.

Outcomes

The primary outcome was the score on the BDI-II at 6 months, measured as a continuous variable.

Secondary outcomes included response (≥ 50% reduction in BDI-II score relative to baseline), remission (BDI-II score< 10), percentage reduction in depressive symptoms on the BDI-II, measures of depression and anxiety used in NHS Talking Therapy services (PHQ-9[75] and GAD-7[76]), and function (WSAS)[46], all measured at 6 months, with these outcomes and the BDI-II continuous score at 12 months. In addition, QoL (EQ-5D-5L[77]), use of medication, healthcare

and wider services, and other costs were recorded at 6 and 12 months to inform the economic evaluation (see *Appendix 2*).

Safety reporting

The study team logged any AEs spontaneously reported by participants to researchers or INTERACT therapists, and any reported as part of routine follow-up data collection, for example, data on mental health-related accident and emergency visits and hospital admissions were collected as part of the 6- and 12-month follow-up questionnaires. All AE reports were reviewed for causality, expectedness and seriousness by a clinical PI who was not blind to treatment allocation. Data on AEs were shared with the TMG, DMEC and TSC groups. University Hospitals Bristol and Weston NHS Foundation Trust reviewed all SAE reports on behalf of the sponsor.

Justification of sample size

The sample size calculation was based on 173 participants in each group, providing 90% power to detect a difference of 0.35 SDs (approx. 4–5 points) on the BDI-II at a two-sided 5% significance level. Allowing for 20% attrition at 6 months, our recruitment target was 434 patients. There was a 9-month internal pilot to ensure that we could recruit as planned and that participants were engaging with the intervention.

Statistical analysis

Analysis and reporting was in accordance with recognised standards[78] and followed a pre-defined analysis plan[40] agreed with the independent TSC. Analyses were conducted in Stata® 18.0 (StataCorp LP, College Station, TX, USA).

Primary comparative analyses between the two randomised groups were conducted according to the group to which the participants were randomised, without imputing missing values. Descriptive statistics were used to identify any marked imbalances in baseline characteristics. Linear regression was used to compare the primary (continuous) outcome (BDI-II score) at 6 months between randomised groups, adjusting for the study centre, baseline BDI-II score, and the other two minimisation variables. Similar regression models were used for secondary outcomes. The effect of the intervention on outcomes over 12 months was summarised using repeated-measures models, with an interaction between treatment and time to formally test whether effects varied with time. Regression coefficients (or odds ratios), with 95%CI and *p*-values were reported.

Sensitivity analyses were used to examine the effect of: (1) missing data; (2) baseline imbalances in prognostic factors; (3) number of treatment sessions attended; (4) potential clustering by therapist using a fully heteroscedastic model;[57] and (5) timing of questionnaire completion. CACE analyses were conducted to estimate the treatment effect among compliers (those who had received at least 6 sessions of CBT or reached an agreed end in < 6 sessions). A priori specified subgroup analyses explored the potential for differential treatment effects based on chronicity and severity of depression, and personality difficulties.[58]

Results

The trial opened to recruitment on 8 December 2020, with the first referral on 29 December 2020 and the first invitation mail out conducted on 28 January 2021. The final participant was randomised on 27 April 2023 (after the recruitment target had been met). Follow-up data were collected between 7 April 2021 and 26 April 2024.

From 12,182 letters of invitation and 381 direct referrals, 1455 patients agreed to being contacted by the research team (see *Figure 4*). In total, 761 individuals were identified as potentially eligible at telephone screen and agreed to attend a baseline assessment. Of these, 451 (59%) were eligible and randomised to receive either integrated CBT

(*n* = 225) or to continue with usual GP care (*n* = 226). 346 (77%) were followed up at 3 months, 334 (74%) at 6 months, 328 (73%) at 9 months and 327 (73%) at 12 months (see *Figure 3*).

Participants were predominantly female (*n* = 313, 69%) and, on average, aged 39 years (see *Table 3*). The mean BDI-II score at baseline was 32.8, indicative of severe depression. Most had a history of depression (nearly half having had five or more prior episodes of depression), were taking antidepressants (70%) and the duration of the current episode of depression was ≥ 2 years for 51% of participants (see *Table 3*). While the two groups had similar characteristics at baseline, there was some evidence of imbalances. Those in the intervention group were more likely to be single, have experienced five or more prior episodes of depression, report current suicidal ideation and to report less financial strain ('living comfortably/doing all right').

The number of patients per therapist ranged from 10 (4.4%) to 36 (16.0%). Based on a random sample of 50 transcripts, the mean CTS-R scale rating (adjusted for caseload) was 28.4 (95% CI 26.8 to 30.0) for rater 1 and 32.3 (95% CI 30.1 to 34.4) rater 2.

Fourteen individuals (6.2%) had no therapy sessions. One hundred and thirty-seven participants (60.9%) completed therapy (received at least 9 sessions or reached an agreed end of therapy with their therapists in fewer than 9 sessions) and 88 (39.1%) either withdrew from therapy or were discharged for repeated non-attendance. The mean duration of the intervention from randomisation was 3.2 months (SD 1.6) (for *n* = 211 who had ≥ 1 session). On average (median), participants received 8 therapy sessions (IQR: 3–10). One hundred and fifty-two participants (67.6%) received at least 6 sessions of CBT or reached an agreed end in < 6 sessions (CACE definition).

Those assigned to the intervention logged into the INTERACT therapy platform, on average (median), 28 times (IQR: 12–42). On average, 10 resources (worksheets/information sheets) were shared by the therapist to their client and 5 practice at home (homework) tasks were agreed. Use of the platform was higher among the CACE sample [median (IQR) number of logins: 37 (27, 49.5); number of resources shared: 13 (9.5, 17); and number of homework tasks set: 9 (4, 13)].

Those in the intervention group had a BDI-II score that was, on average, 4.4 points lower (less depressed) than those in the UC group at 6 months (see *Table 4*). This equated to an effect size of 0.43 (using baseline pooled SD). Adjustment for baseline imbalances slightly increased the between-group difference (see *Table 4*) difference in means: −4.9 (95% CI −7.6 to −2.2), but adjustment for actual time to follow-up had no effect (see *Table 4*).

Individuals in the intervention group had nearly a threefold increased odds of meeting criteria for response and remission (BDI-II score< 10) at 6 months (see *Tables 5* and *6*), equating to a NNT of 6 (95% CI 4 to 11) and 8 (95% CI 5 to 19). The difference in mean proportional change in depressive symptoms on the BDI-II was −14.6% (see *Table 7*). In other words, individuals in the intervention group had experienced (on average) a 15% greater reduction in depressive symptoms (relative to baseline) compared with those in the UC group). There were other beneficial effects. The intervention group had fewer depressive symptoms on the PHQ-9 (see *Table 8*), fewer symptoms of anxiety (GAD-7) (see *Table 9*) and less impairment in terms of functioning (WSAS) (see *Table 10*).

There was little evidence of clustering of outcomes by therapist (ICC: < 0.0001). Results from a fully heteroscedastic model that accounted for clustering by therapist [difference in means: −4.4 (95% CI −6.9 to −1.9)] were identical to the results of the primary analysis.

For the a priori subgroup analyses, there was no evidence that personality difficulties (*p*-value for interaction: 0.47), depression severity (BDI-II score: *p* = 0.22) or chronicity of symptoms (*p* = 0.77) had any effect on the difference between the intervention and UC group at 6 months.

In repeated-measures analyses: using data from 6 and 12 months, individuals in the intervention group had a BDI-II score that was, on average, 3.8 points lower than those in the UC group (see *Table 11*). The intervention group also had a twofold increased odds of response and remission and benefits in terms of reductions in PHQ-9 and GAD-7 scores

and function (see *Tables 5–10*). There was little evidence that the effects varied over time (*p*-values for interactions ranged from 0.12 to 0.96).

The results of CACE analyses showed that the effect of the intervention was larger among who completed treatment as intended (see *Table 12*).

The results imputing missing data were consistent with the findings of the primary analysis (see *Table 13*). Other scenarios for missing data were also considered that represented more extreme patterns of missingness (see *Table 13*).

In terms of receipt of other treatments (outside of the trial), by 6 months, 13/324 (4.0%) of participants had received computerised CBT [intervention group: *n* = 2/166 (1.2%); UC group: *n* = 11/158 (7.0%); median (IQR) number of sessions was 7 (6–8) and 4 (3–9), respectively. By 6 months, 74 individuals [intervention: *n* = 24/168 (14.3%); UC *n* = 50/161 (31.1%)] had received another talking therapy outside the trial. Of these, 15 individuals had received high-intensity individual CBT [intervention group: *n* = 5/168 (3.0%), median number of sessions: 10 (IQR: 8–12); UC group: *n* = 10/160 (6.3%), median number of sessions: 10 (7–11)]. At 6 months, 64.9% (*n* = 216) of participants (107 of 170 (62.9%) intervention group; 109 of 163 (66.9%) UC group) were taking antidepressant medication [difference: −3.9% (95% CI −14.2% to 6.3%)].

There were 54 AEs and 14 SAEs during the study (see *Tables 14–17*). Of the 68 reported AEs, 35 were considered by the clinical lead to be related to mental health. The relatedness and expectedness of these AEs are detailed in *Tables 16* and *17*. There were a higher number of AEs in the intervention group. Three AEs were rated as definitely or probably related to the intervention, and one was probably related to study participation. All four were mental health related (increased anxiety/depression, risk of self-harm). No SAEs were definitely/probably related to the intervention. There were no participant deaths during the trial period.

Discussion

Integrated CBT was effective in reducing depressive symptoms in primary care patients with depression. Benefit was also seen in terms of the outcomes of response and remission in depressive symptoms, improved function and symptoms of anxiety. Improvements were maintained over 12 months. Benefits were likely to be clinically important (based on prior evidence that a minimum clinically important difference is a 20% (relative) improvement in depressive symptoms or 3.5–4.4 points on the BDI-II).[79]

Adverse events were more common in the intervention group, possibly due to more frequent contact. The three AEs that were considered to be (definitely/probably) related to the intervention were all mental health related. The number of serious AEs was small, and none were directly attributable to the intervention.

Strengths and limitations

This large study recruited from primary care where most patients with depression are managed. Participants represented a heterogeneous group. While many had severe and chronic depression and had been taking antidepressant medication for more than 12 months, 19% were experiencing their first or second episode of depression. The population recruited were more diverse than in our previous primary care depression trials of psychotherapy.[16,70] Thus, results should have greater external validity.

The recruitment target was achieved and although the final follow-up rate at 6 months was slightly below the original target, retention was good (74% vs. target 80%). Some imbalances in baseline characteristics between randomised groups were identified but there was no evidence that adjustment for these impacted on the conclusions. Only a small number of individuals received high-intensity individual CBT outside the trial by 6 months.

Therapists were representative of those working in NHS talking therapy services and hence the results should be generalisable. An independent evaluation of therapist competence found mean CTS-R ratings below the traditional cut-point for competence (score ≥ 36). However, scores were in line with mean scores in an earlier trial of IM therapy.[16]

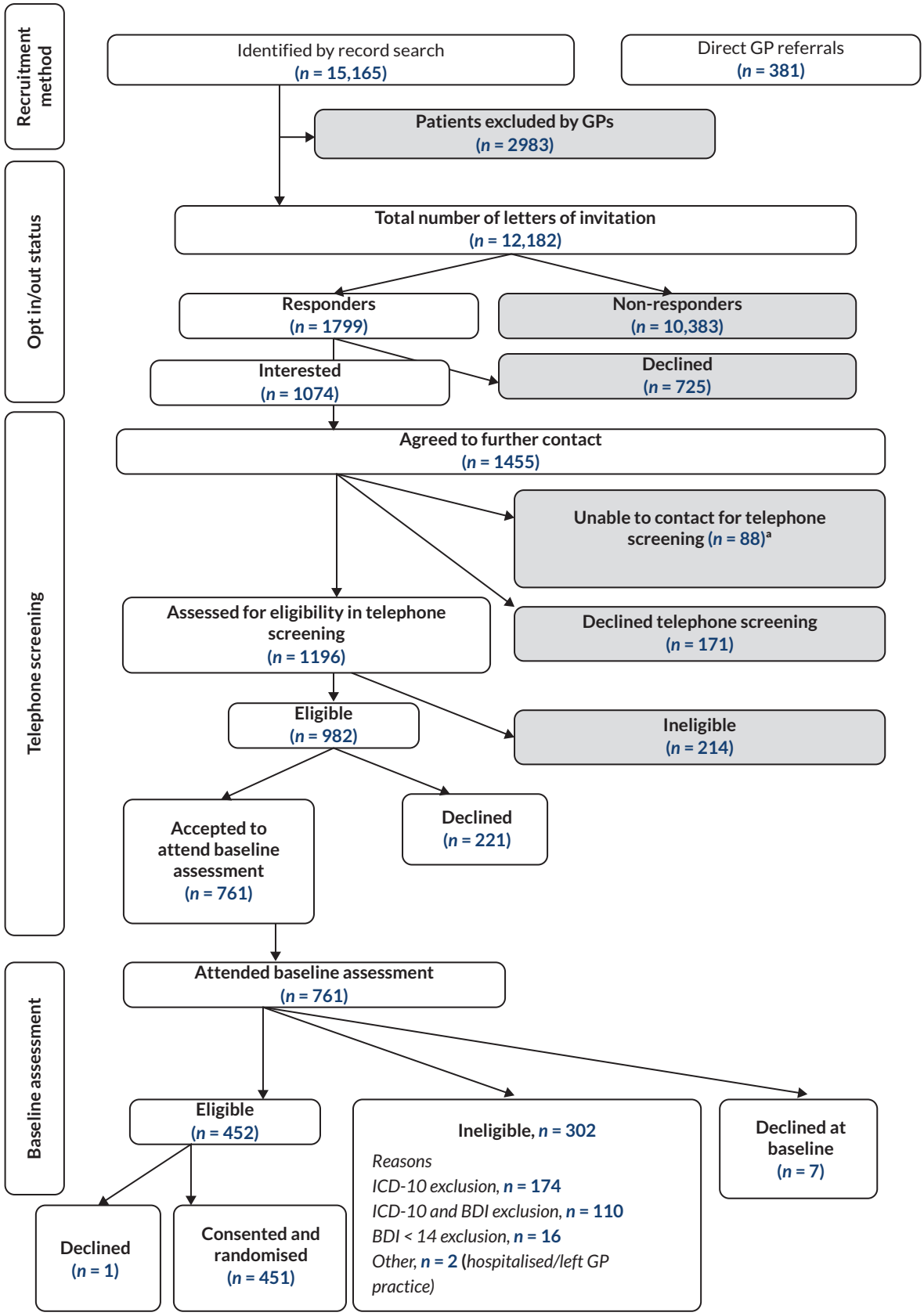

FIGURE 4 Flow of participants: recruitment pathway. a, Incudes seven who replied too late.

Comparison with other literature

No previous studies have integrated the use of online CBT materials with therapist-led CBT for depression. Recently, Haun *et al.*[80] evaluated the effectiveness of five sessions of therapy delivered by videocall and found a small reduction [effect size: 0.21 (95% CI 0.03 to 0.39)] in symptoms of depression and anxiety at 6 months compared with UC. Others have proposed 'blended care'[81] that combines individual in-person CBT sessions (*n* = 10) with a course of online treatment modules (*n* = 9). In this blended care, the online materials are not an integral part of the therapist-led sessions. Hence, the integrated approach evaluated in this trial represents a novel approach to delivering CBT enabling therapists to tailor treatment to the individual.

Engagement with the integrated CBT approach was similar to engagement with in-person therapy (61% vs. 68%),[70] and substantially higher than low-intensity CBT interventions (e.g. telephone facilitated CBT: 30% completed at least 3 sessions;[10] internet delivered CBT: 41% completed course[82]).

Implications and future research

Integrated CBT is an effective treatment for primary care patients with depression. It has the potential to increase the availability of CBT and increase access for those who find it difficult to attend appointments in person (e.g. those in full-time employment, with caring responsibilities, living in more remote areas, social anxiety). Future research needs to examine which aspects of the platform led to improvements and to understand whether the effects are sustained long term.

TABLE 3 Baseline comparability of randomised groups

	Intervention (*n* = 225)	UC (*n* = 226)	Total (*n* = 451)
Stratification variable: centre n (%)			
Bristol	139 (61.8)	139 (61.5)	278 (61.6)
London	49 (21.8)	50 (22.1)	99 (22.0)
York	37 (16.4)	37 (16.4)	74 (16.4)
Minimisation variables			
Female: *n* (%)	157 (69.8)	156 (69.0)	313 (69.4)
Baseline BDI-II score: n (%)			
≤ 25	60 (26.7)	62 (27.4)	122 (27.1)
26–35	82 (36.4)	83 (36.7)	165 (36.6)
≥ 36	83 (36.9)	81 (35.8)	164 (36.4)
Currently taking antidepressants: *n* (%)	157 (69.8)	157 (69.5)	314 (69.6)
Sociodemographic variables			
Age (years): mean (SD)	39.0 (15.9)	39.5 (14.0)	39.3 (14.9)
Self-reported gender: n (%)			
Male	65 (28.9)	70 (31.0)	135 (29.9)
Female	157 (69.8)	156 (69.0)	313 (69.4)

continued

TABLE 3 Baseline comparability of randomised groups (*continued*)

	Intervention (*n* = 225)	UC (*n* = 226)	Total (*n* = 451)
Other	3 (1.3)	0 (0)	3 (0.7)
Ethnic group: n (%)			
White	194 (86.2)	187 (82.7)	381 (84.5)
Marital status: n (%)			
Married/living as married	78 (34.7)	98 (43.4)	176 (39.0)
Single	123 (54.7)	100 (44.2)	223 (49.4)
Separated/widowed/divorced	24 (10.7)	28 (12.4)	52 (11.5)
Employment status: n (%)			
In paid employment (full/part-time)	134 (59.6)	129 (57.1)	263 (58.3)
Student	31 (13.8)	27 (11.9)	58 (12.9)
Not in employment	30 (13.3)	34 (15.0)	64 (14.2)
Unemployment due to ill health	30 (13.3)	36 (15.9)	66 (14.6)
Educational attainment: n (%)			
A-level, higher grade or above	178 (79.1)	174 (77.0)	352 (78.0)
GCSE, standard grade or equivalent	38 (16.9)	38 (16.8)	76 (16.9)
No formal qualifications	9 (4.0)	14 (6.2)	23 (5.1)
Housing: n (%)			
Home owner	78 (34.7)	91 (40.3)	169 (37.5)
Tenant or living with relative/friend	141 (62.7)	127 (56.2)	268 (59.4)
Hostel/care home, homeless or other	6 (2.7)	8 (3.5)	14 (3.1)
Financial well-being: n (%)			
Living comfortably/doing all right	107 (47.6)	95 (42.0)	202 (44.8)
Just about getting by	64 (28.4)	78 (34.5)	142 (31.5)
Finding it difficult/very difficult to make ends meet	54 (24.0)	53 (23.5)	107 (23.7)
IT literacy: I am confident using computers; n (%)			
Strongly agree	145 (64.4)	134 (59.3)	279 (61.9)
Agree	63 (28.0)	69 (30.5)	132 (29.3)
Neither agree nor disagree	11 (4.9)	13 (5.8)	24 (5.3)
Disagree	5 (2.2)	8 (3.5)	13 (2.9)
Strongly disagree	1 (0.4)	2 (0.9)	3 (0.7)
Alcohol consumption			
AUDIT-PC score: median (IQR)	3 (1–5)	3 (1–5)	3 (1–5)
Number of life events in the past 6 months: mean (SD)	1.4 (1.3)	1.5 (1.4)	1.5 (1.3)
Social support score: mean (SD)	11.8 (3.9)	12.4 (3.6)	12.1 (3.7)
Long-standing illness or disability; n (%)			
Any	143 (63.6)	146 (64.6)	289 (64.1)
Alzheimer's disease/dementia	0 (0)	0 (0)	0 (0)

TABLE 3 Baseline comparability of randomised groups (*continued*)

	Intervention (*n* = 225)	UC (*n* = 226)	Total (*n* = 451)
Angina/long-term heart problem	6 (2.7)	4 (1.8)	10 (2.2)
Arthritis/long-term joint problem	19 (8.4)	19 (8.4)	38 (8.4)
Asthma/long-term chest problem	25 (11.1)	24 (10.6)	49 (10.9)
Blindness/severe visual impairment	3 (1.3)	1 (0.4)	4 (0.9)
Cancer in the last 5 years	3 (1.3)	2 (0.9)	5 (1.1)
Deafness/severe hearing impairment	4 (1.8)	8 (3.5)	12 (2.7)
Diabetes	14 (6.2)	7 (3.1)	21 (4.7)
Epilepsy	2 (0.9)	1 (0.4)	3 (0.7)
High blood pressure	19 (8.4)	14 (6.2)	33 (7.3)
Kidney or liver disease	4 (1.8)	4 (1.8)	8 (1.8)
Learning difficulty	5 (2.2)	10 (4.4)	15 (3.3)
Long-term back problem	25 (11.1)	29 (12.8)	54 (12.0)
Long-term mental health problem	86 (38.2)	82 (36.3)	168 (37.3)
Long-term neurological problem	10 (4.4)	7 (3.1)	17 (3.8)
Another long-term condition	38 (16.9)	37 (16.4)	75 (16.6)
None of the above	13 (5.8)	13 (5.8)	26 (5.8)
Prefer not to say	0 (0)	1 (0.4)	1 (0.2)
Work and social adjustment score (WSAS); mean (SD)	26.3 (7.7)	26.3 (7.3)	26.3 (7.5)
Standardised assessment of personality scale (SAPAS); mean (SD)	4.2 (1.8)	4.3 (1.8)	4.3 (1.8)
Post-traumatic stress			
Ever experienced a traumatic event; *n* (%)	106 (47.1)	108 (47.8)	214 (47.5)
PC-PTSD-5 score; n (%)			
0	7 (6.6)	7 (6.5)	14 (6.5)
1	7 (6.6)	5 (4.6)	12 (5.6)
2	10 (9.4)	7 (6.5)	17 (7.9)
3	21 (19.8)	17 (15.7)	38 (17.8)
4	22 (20.8)	28 (25.9)	50 (23.4)
5	39 (36.8)	44 (40.7)	83 (38.8)
BFI neuroticism score; mean (SD)	4.0 (0.6)	3.9 (0.7)	3.9 (0.6)
Measures of depression			
Duration of current episode: n (%)			
Between 2 weeks and 6 months	40 (17.8)	46 (20.4)	86 (19.1)
Between 6 months and 1 year	37 (16.4)	31 (13.7)	68 (15.1)
Between 1 and 2 years	35 (15.6)	32 (14.2)	67 (14.9)
Between 2 and 5 years	49 (21.8)	54 (23.9)	103 (22.8)

continued

TABLE 3 Baseline comparability of randomised groups (*continued*)

	Intervention (*n* = 225)	UC (*n* = 226)	Total (*n* = 451)
More than 5 years	64 (28.4)	63 (27.9)	127 (28.2)
Suffered depression in the past: *n* (%)	198 (88.0)	188 (83.2)	386 (85.6)
Number of prior episodes of depression: n (%)			
0–1	40 (17.8)	47 (20.8)	87 (19.3)
2–4	70 (31.1)	78 (34.5)	148 (32.8)
≥ 5	115 (51.1)	101 (44.7)	216 (47.9)
Family history of depression: n (%)	167 (74.2)	175 (77.4)	342 (75.8)
Previous referral to a psychiatrist for depression: n (%)	64 (28.4)	59 (26.1)	123 (27.3)
Among those currently taking antidepressants – length of current course[a] of antidepressants: n (%)			
< 6 weeks	24 (15.3)	18 (11.5)	42 (13.4)
6 weeks–3 months	12 (7.6)	22 (14.0)	34 (10.8)
3–6 months	20 (12.7)	24 (15.3)	44 (14.0)
6–12 months	36 (22.9)	25 (15.9)	61 (19.4)
> 12 months	63 (40.1)	66 (42.0)	129 (41.1)
Missing data	2 (1.3)	2 (1.3)	4 (1.3)
Among those currently taking antidepressants – adherence to antidepressants in past 6 weeks at baseline: n (%)			
I have taken my tablets every day	98 (62.4)	103 (65.6)	201 (64.0)
I have taken my tablets nearly every day	49 (31.2)	48 (30.6)	97 (30.9)
I have taken more than half my tablets	5 (3.2)	3 (1.9)	8 (2.5)
I have taken less than half my tablets	4 (2.5)	3 (1.9)	7 (2.2)
I have hardly taken any of my tablets	0 (0)	0 (0)	0 (0)
I have not taken any of my tablets	1 (0.6)	0 (0)	1 (0.3)
ICD-10 primary diagnosis: n (%)			
Mild	35 (15.6)	24 (10.6)	59 (13.1)
Moderate	101 (44.9)	113 (50.0)	214 (47.5)
Severe	89 (39.6)	89 (39.4)	178 (39.5)
Secondary psychiatric diagnosis according to the CIS-R: n (%)			
0. No diagnosis identified	1 (0.4)	1 (0.4)	2 (0.4)
1. Mixed anxiety and depressive disorder (mild)	22 (9.8)	18 (8.0)	40 (8.9)
2. GAD (mild)	4 (1.8)	8 (3.5)	12 (2.7)
3. Mixed anxiety and depressive disorder	31 (13.8)	31 (13.7)	62 (13.7)
4. Specific (isolated) phobia	8 (3.6)	8 (3.5)	16 (3.5)
5. Social phobia	8 (3.6)	4 (1.8)	12 (2.7)
6. Agoraphobia	7 (3.1)	6 (2.7)	13 (2.9)
7. GAD	102 (45.3)	107 (47.3)	209 (46.3)
8. Panic disorder	42 (18.7)	43 (19.0)	85 (18.8)

TABLE 3 Baseline comparability of randomised groups (*continued*)

	Intervention (*n* = 225)	UC (*n* = 226)	Total (*n* = 451)
BDI-II score: mean (SD)	32.6 (10.4)	32.9 (10.3)	32.8 (10.3)
GAD-7 score: mean (SD)	12.7 (5.0)	13.0 (5.1)	12.8 (5.0)
PHQ-9 score: mean (SD)	17.2 (5.4)	17.3 (5.1)	17.2 (5.2)
EQ-5D-5L score: mean (SD)	*n* = 222 0.522 (0.262)	*n* = 226 0.504 (0.262)	*n* = 448 0.513 (0.262)
CIS-R score: mean (SD)	30.6 (9.2)	31.5 (9.3)	31.0 (9.3)
Suicidal ideation (CIS-R thoughts/plans): *n* (%)	92 (40.9)	80 (35.4)	172 (38.1)

AUDIT-PC, Alcohol Use Disorders Identification Test – Primary Care; BFI, Big Five Personality Inventory; PC-PTSD-5, Primary Care Post-Traumatic Stress Screen - 5.
a If participant reported taking more than one antidepressant, this is the duration for the first listed antidepressant.

Note
Where data are incomplete for some variables, the numbers with information available are listed here.
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TABLE 4 Primary outcome: mean and difference in mean BDI-II scores at 6 months

Randomisation groups	*n*	Mean	SD	Difference in means[a]	95% CI	*p*-value
Intervention	171	22.5	14.4	−4.4	−7.0 to −1.9	0.001
UC	163	27.4	14.0			
Analysis adjusted for [a] and variables imbalanced at baseline (marital status, financial well-being, number of prior episodes of depression, and suicidal ideation)				−4.9	−7.6 to −2.2	< 0.001
Analysis adjusted for [a] and the timing of the return of the follow-up questionnaire				−4.4	−7.0 to −1.9	0.001

a Adjusted for baseline BDI-II (numeric) and the stratification and other minimisation variables.

TABLE 5 Percentage and OR of 'response to treatment' (improvement of at least 50% in BDI-II score compared with baseline) at 6 and 12 months

	Follow-up					
	6 months			12 months		
Randomisation groups	*N*	*n*[a]	%	*N*	*n*[a]	%
Intervention	171	59	34.5	172	66	38.4
UC	163	26	16.0	154	37	24.0
Regression analysis						
	N	OR[b]	95% CI		*p*-value	
6-month follow-up	334	2.78	1.63 to 4.74		0.0001	
12-month follow-up	326	1.94	1.20 to 3.16		0.0067	
Repeated measures	660	2.22	1.45 to 3.41		0.0003	
Treatment–time interaction					0.24	

a Number of patients reporting an improvement of at least 50% in BDI-II score compared with baseline (*n*) as a percentage of the total number (*N*) in the group.
b Adjusted for baseline BDI-II score and the stratification and other minimisation variables.

TABLE 6 Percentage and OR of 'remission of symptoms' (BDI-II of < 10) at 6 and 12 months

	Follow-up					
	6 months			12 months		
Randomisation groups	*N*	*n*[a]	%	*N*	*n*[a]	%
Intervention	171	41	24.0	172	48	27.9
UC	163	17	10.4	154	22	14.3
Regression analysis						
	N	OR[b]	95% CI		*p*-value	
6-month follow-up	334	2.74	1.46 to 5.15		0.0012	
12-month follow-up	326	2.36	1.32 to 4.23		0.0030	
Repeated measures	660	2.40	1.43 to 4.02		0.0009	
Treatment–time interaction					0.6649	

a Number of patients reporting a BDI-II of < 10 (*n*) as a percentage of the total number (*N*) in the group.
b Adjusted for baseline BDI-II score and the stratification and other minimisation variables.

TABLE 7 Proportional change in depressive symptoms on the BDI-II at 6 and 12 months

Randomisation groups	*n*	Mean	SD	Difference in means[a]	95% CI	*p*-value
Proportional change between 6 months and baseline						
Intervention	171	−31.4	(38.2)	−14.6	−22.7 to −6.6	0.0004
UC	163	−16.8	(36.5)			
Proportional change between 12 months and baseline						
Intervention	172	−33.3	43.7	−12.2	−21.3 to −3.09	0.0079
UC	154	−21.6	39.0			
Repeated-measures analysis	660			−13.0	−20.4 to −5.6	0.0006
Treatment–time interaction						0.28

a Adjusted for baseline BDI-II score and the stratification and other minimisation variables.

TABLE 8 Means and differences in mean PHQ-9 scores at 6 and 12 months

	3 months			6 months			9 months			12 months		
Randomisation groups	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Intervention	178	11.5	6.3	169	10.4	6.3	167	10.3	6.6	171	10.1	6.8
UC	168	13.6	6.0	161	12.6	6.7	161	12.6	6.9	153	12.3	6.9
Regression analyses												
	N	Difference in means[a]		95% CI			*p*-value					
6-month follow-up	330	−2.0		−3.2 to −0.8			0.0012					
12-month follow-up	324	−2.0		−3.3 to −0.6			0.0035					
Repeated measures using 3, 6, 9 and 12 months	1328	−2.1		−3.0 to −1.2			< 0.0001					
Treatment–time interaction							0.96					

a Adjusted for baseline PHQ-9 score and the stratification and other minimisation variables.

TABLE 9 Means and differences in mean GAD-7 scores at 6 and 12 months

	3 months			6 months			9 months			12 months		
Randomisation groups	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**
Intervention	177	9.4	5.5	168	8.1	5.4	167	8.2	5.7	171	8.0	5.9
UC	167	11.4	5.5	161	10.0	6.0	161	10.4	5.9	153	9.7	6.0
Regression analyses												
	N	**Difference in means[a]**		**95% CI**			***p*-value**					
6-month follow-up	329	−1.7		−2.7 to −0.7			0.0013					
12-month follow-up	324	−1.6		−2.7 to −0.4			0.0071					
Repeated measures using 3, 6, 9 and 12 months	1325	−1.9		−2.7 to −1.1			< 0.0001					
Treatment–time interaction							0.82					

a Adjusted for baseline GAD-7 score and the stratification and other minimisation variables.

TABLE 10 Means and differences in mean WSAS scores at 6 and 12 months

Randomisation groups	***n***	**Mean**	**SD**	**Difference in means[a]**	**95% CI**	***p*-value**
6 months						
Intervention	166	19.2	11.3	−2.1	−4.2 to −0.03	0.044
UC	160	21.1	11.3			
12 months						
Intervention	170	18.8	11.9	−2.1	−4.3 to 0.1	0.061
UC	153	20.7	11.3			
Repeated measures using 6 and 12 months	649			−1.9	−3.8 to −0.1	0.040
Treatment–time interaction						0.93

a Adjusted for baseline WSAS score and the stratification and other minimisation variables.

TABLE 11 Means and differences in mean BDI-II scores at 12 months and repeated-measures analysis

Randomisation groups	***n***	**Mean**	**SD**	**Difference in means[a]**	**95% CI**	***p*-value**
Intervention	172	21.6	15.4	−3.3	−6.1 to −0.6	0.0174
UC	154	25.2	13.4			
Total *N*	326	23.3	14.6			
Repeated measures	660			−3.8	−6.1 to −1.5	0.0014
Treatment–time interaction						0.12

a Adjusted for baseline BDI-II score and the stratification and other minimisation variables.

TABLE 12 Comparison of results from 'as randomised' and CACE analyses for the primary outcome of BDI-II score at 6 months

	n	Difference in means[a]	95% CI	*p*-value
Primary analysis of groups as randomised	334	−4.4	−7.0 to −1.9	0.001
CACE – attending at least 6 sessions or reaching a jointly agreed end to therapy	334	−5.8	−9.1 to −2.6	< 0.001
CACE – attending at least 6 sessions or reaching a jointly agreed end to therapy (incorporating endogenous variables associated with adherence)	334	−6.2	−9.4 to −3.0	< 0.001

a Adjusted for baseline BDI-II score, stratification and other minimisation variables.

TABLE 13 Comparison of results of 'as randomised' analysis of complete cases with the analysis where missing data were imputed using 'better-' and 'worse-' case scenarios and multiple imputation for primary outcome of BDI-II score at 6 months

	n	Difference in means[a]	95% CI	*p*-value
Complete case	334	−4.4	−7.0 to −1.9	0.001
Better-case scenario				
Assuming 1 SD shift from mean	451	−12.1	−14.4 to −9.7	< 0.001
Assuming 0.5 SD shift from mean	451	−8.4	−10.5 to −6.4	< 0.001
Worse-case scenario				
Assuming 1 SD shift from mean	451	2.5	0.2 to 4.7	0.028
Assuming 0.5 SD shift from mean	451	−1.1	−3.2 to 0.9	0.265
Multiple imputation	451	−4.6	−7.1 to −2.0	0.001

a Adjusted for baseline BDI-II score, stratification and other minimisation variables.

TABLE 14 Relatedness of all reported AEs and SAEs to study intervention/procedures

	Related		Unrelated		
	Intervention	UC	Intervention	UC	Total
AE	5 possibly related 1 probably related 2 definitely related	2 possibly related 1 probably related	21 not related 4 unlikely related	15 not related 2 unlikely related	54[a]
SAE	1 possibly related	0	9 not related 2 unlikely related	1 not related 1 unlikely related	14

a One UC AE (accident and emergency attendance for a physical health reason) was unable to be rated as participant did not provide any details.

TABLE 15 Expectedness of all reported AEs and SAEs to study intervention/procedures

	Expected		Unexpected		
	Intervention	UC	Intervention	UC	Total
AE	13	3	20	17	54[a]
SAE	2	1	10	1	14

a One UC AE (accident and emergency attendance for a physical health reason) was unable to be rated as participant did not provide any details.

TABLE 16 Relatedness of 'mental health-related' AEs by group (*n* = 35)

	Related		Unrelated		
	Intervention	**UC**	**Intervention**	**UC**	**Total**
AE	4 possibly related 1 probably related 2 definitely related	2 possibly related 1 probably related	7 not related 4 unlikely related	7 not related 2 unlikely related	30
SAE	1 possibly related	0	1 not related 2 unlikely related	0 not related 1 unlikely related	5

TABLE 17 Expectedness of 'mental health-related' AEs by group (*n* = 35)

	Expected		Unexpected		
	Intervention	**UC**	**Intervention**	**UC**	**Total**
AE	11	3	7	9	30
SAE	2	1	2	0	5

Appendix 2 Economic evaluation (work package 3)

The trial health economics analysis plan is available here: https://research-information.bris.ac.uk/ws/portalfiles/portal/397633247/INTERACT_RCT_HEAP_v1.0_20240104_signed_-Signatures_redacted.pdf

Li J, Wu Q, Parrott S, Tallon D, Wiles NJ. *Multi-centre Randomised Controlled Trial of Integrated Therapist and Online CBT for Depression in Primary Care (INTERACT RCT): Health Economics Analysis Plan*. Bristol, UK: University of Bristol; 2024.

Aim

The aim of the economic evaluation was to establish the cost-effectiveness of an integrated approach to delivering CBT in reducing depressive symptoms and improving QoL over and above UC over 12 months for primary care patients with depression.

Methods

We assessed cost-effectiveness from three perspectives: the NHS and PSS perspective; participants' and/or their informal carers' perspective; and finally a societal perspective. The costs were collected in line with these perspectives.

The effectiveness measure for all three perspectives was QALYs, derived from EQ-5D-5L.[59] It was administered at baseline and 6 and 12 months post randomisation. Following the recommendation by NICE,[60] the mapping approach was used to execute the conversion from domains to utilities.[61] Using area under the curve approach,[62] the utilities at the three time points were used to derive QALYs.

The costs from the NHS and PSS perspective comprised costs of the integrated CBT (intervention) and UC (comparator), primary, community, secondary health care, and social services for mental health.

The costs from the patients' and informal carers' perspective comprised payments for treatments and remedies for mental health, spending on journeys to receive care, and lost income of participants and/or their informal carers due to participants' mental health conditions.

The costs from the societal perspective comprised both costs from the NHS and PSS perspective and from the patient and informal carer perspective, and benefits received. Benefits included treatments or therapies provided by entities other than NHS, free of charge or at a nominal price to participants, informal carer's allowance, paid leave and extra costs to arrange for cover for participants.

Costs of integrated CBT included costs of training and ongoing (weekly) supervision, and costs of delivery. The costs of staff were estimated by multiplying the time they spent by their respective hourly costs (salary + oncosts + overheads + capital). The costs of operating and maintaining the INTERACT platform was estimated based on information provided by the University of Bristol Research information technology team where it was hosted during the study.

Usual care included psychological services, including packages of computerised CBT (CCBT), counselling or talking therapy provided by NHS, and prescriptions of antidepressant medication. It should be noted that both groups received UC.

Except for costs of integrated CBT, prescribed antidepressants and primary health care, all other costs, OOPs, and benefits were estimated based on quantities of use collected via self-reported questionnaire at baseline and 6 and 12 months post randomisation. Costs of integrated CBT were estimated based on the research team records. Costs of prescribed antidepressants and primary health care were estimated based on data from participants' GP records over

12 months. A set of national average unit costs of the services was compiled from published secondary sources of the year 2022–3[83–94] and applied to the quantities collected to estimate the costs.

Missing values at baseline assessment were imputed by the mean of the measure of the pooled sample of both groups.[95] Missing data on measures at follow-ups were handled using multiple imputation with chained equation method by allocation, following Rubin's rule and assuming MAR.[65,66] The number of imputed data sets was set as approximately the highest percentage figure of the missing data.[95]

All analyses were carried out following the principle of analysing participants in the group to which they were (randomly) allocated. All monetary outcomes were presented in Great British pounds 2022–3. Data that were not available in 2022–3 prices, was inflated. Discounting was not undertaken as the costs and outcomes covered a period of 1 year only.

Excel was used for data compilation of intervention costs and data from GP records. The resulting data set was merged with data from the CRF and analysed using Stata MP18.0. Analysis and reporting were conducted in accordance with recognised standards[96] and followed a pre-defined analysis plan.[42]

The primary analysis was an incremental CUA of integrated CBT over and above UC over 12 months from an NHS and PSS perspective.[60] Both incremental costs and incremental QALYs were estimated using linear regression. The ICER was calculated by dividing the incremental costs by incremental QALYs, when both were positive. Uncertainty around the point estimate was assessed using non-parametric bootstrap resampling technique.[63] A CEP CEACs[64] were constructed based on the bootstrap iterations to illustrate the uncertainty of conclusion of cost-effectiveness of integrated CBT over and above UC.

Secondary analyses followed the methods used in the primary analysis but were undertaken from the participants' and informal carers' perspective and from the societal perspective, respectively. However, as there were no recommended maximum ICER thresholds for these two perspectives, the results were described but not compared with any thresholds.

Complete-case analyses from three perspectives were undertaken following the same approach of the base case analyses on those who had complete data on all variables involved, respectively. To examine the MAR assumption, sensitivity analyses were carried out using pattern mixture modelling[66] assuming those who had missing values at follow-ups either were in need of more healthcare services or experienced worse health, or both at the same time. A post hoc sensitivity analysis was undertaken excluding outliers identified during the analysis process.

Results

Nine therapists were trained, and eight trainers were involved in training. Excluding research-related training, training time was estimated at 5.6 working days for each therapist. In most cases, training was held online (asynchronous and synchronous content) with materials provided digitally. In total, 339 weekly group supervision sessions were held, lasting 1–1.25 hours each. Delivery of integrated CBT sessions included attended sessions and DNA/rescheduling/cancellations. The maintenance and operation of the INTERACT platform (August 2022–May 2023) involved basic maintenance, operating system end of life mitigations, development framework upgrade and user interface upgrades. *Table 18* presents the breakdown of costs of integrated CBT. The mean costs were estimated as £987 (SD £212) per participant.

Table 19 presents the results of primary analysis and CCA from the NHS/PSS perspective. Less than half of participants in both groups were included in the CCA. The highest percentage of missing data was 45% for participants' lost income. For data concerning the NHS/PSS perspective, the missing data level was around 30%.

The adjusted incremental costs were similar in primary analysis (£1009) and CCAs (£1040). Mean QALYs were similar in the UC group in primary and CCAs, but higher in the integrated CBT group in CCA compared with the primary analysis, resulting in a larger adjusted incremental QALYs in CCA (0.046) compared to primary

analysis (0.033) (see *Table 19*). The ICER was, therefore, higher (£30,576 per QALY gain) for the primary analysis compared with the CCA (£22,421).

Figure 5 illustrates the uncertainty surrounding the estimated ICERs and conclusion of cost-effective. For the primary analysis, the probability of cost-effectiveness was 13–39% using £20,000–30,000 thresholds (see *Figure 5b*) whereas CCA results had higher probability of integrated CBT being cost-effective (probability: 37–66%) (see *Figure 5d*).

Table 20 presents the results of secondary cost-effectiveness analyses. *Figure 6* illustrates the corresponding uncertainty. CCAs from the participants' and their carers' perspective and from the societal perspective only included a total of 161 participants and 119 participants, respectively. The incremental OOPs and lost income became negative and incremental societal costs were smaller in the CCA compared with their respective estimates from imputed data while the incremental QALYs were larger, resulting in more preferable ICERs for the CCA (less costly but more effective and £10,416 per QALY gain) than estimated from imputed data (£5424 and £38,152) (see *Table 20*).

Pattern mixture modelling (exploring the MAR assumption) showed that the incremental costs decreased with the increasing imputed costs while the incremental QALYs increased with the reduction of imputed utilities. The resulting ICERs from NHS/PSS perspective ranged from £27,027 per QALY gain to £29,588 per QALY gain.

Post hoc sensitivity analysis

During analysis, a few outliers were identified for seven participants (see *Table 21*). Excluding these seven participants reduced incremental costs from all three perspectives but did not materially affect the derived ICERs in terms of either the NHS/PPS or societal perspective. While the ICER for the participant and carer perspective was substantially reduced (£5424 to £1903), it did not impact on the conclusions already drawn.

Discussion

The costliest component of integrated CBT was session delivery, followed by post-training supervision. The two components accounted for 80% of costs of integrated CBT. Incremental costs of integrated CBT over and above UC were mostly attributed by costs of integrated CBT. EQ-5D-5L utilities in the integrated CBT group were consistently higher than those in the UC group, even at baseline. The ICER from NHS/PSS perspective was just over £30,000 per QALY gain. By current acceptable thresholds as recommended by NICE,[60] integrated CBT would not be considered cost-effective over and above UC.

There are no official acceptable thresholds for ICERs from participants' and their carers' perspective and from societal perspective. These would need to be determined by relevant stakeholders independently. However, participants and their carers would need to be willing to pay more than £7000 per QALY gain to reach a higher than 50% probability of cost-effective. Similarly, society would need to be willing to bear more than £38,400 per QALY gain to achieve an over 50% probability of cost-effectiveness.

Strengths and limitations

This economic evaluation was part of a large multicentre RCT which recruited to target and achieved a good follow-up rate. Missing data (in terms of resource use) was an issue. Our primary analysis in terms of the NHS/PSS perspective relied upon the imputed data set. However, we had complete data of costs of integrated CBT for all participants which comprised the key component of the costs.

From the NHS/PSS perspective, the fixed costs of training were included. These represent costs that would be unlikely to be maintained at the same level if the intervention were to be rolled out within talking therapy services. Training of

1 day may be more realistic. Moreover, those who received training could proceed to treat more patients beyond the study sample size, thus further reducing the per-patient cost of training in the longer term.

There were more missing data in terms of the costs from the participants and their carers, and the social perspective (over 10% more). This meant that there was greater uncertainty around estimates of cost-effectiveness from these perspectives. Furthermore, from a societal perspective, multiple stakeholders were involved, such as employers, charities, social care agencies. QALYs might not be an outcome of interest from their respective perspective.

Implications and future research

The intervention would not be considered cost-effective based on current thresholds used by NICE. However, the cost–benefit of the intervention may be more favourable if training is optimised to be delivered over a shorter period. The results presented are restricted to the 12-month follow-up period of the trial. However, given the often chronic nature of depression, it would be valuable to examine the long-term clinical and cost-effectiveness from the perspective of the healthcare provider and society in general. CBT is an educational approach and hence those in the intervention group may be better equipped to manage their depression beyond the 12 months of this trial. Studies of in-person CBT for patients with treatment-resistant depression have found that CBT is a clinically and cost-effective treatment over 4 years.[72] Evidence is thus needed to substantiate and quantify any long-term gain for this novel integrated approach.

TABLE 18 Breakdown of costs of integrated CBT (*n* = 225)

Cost items	Costs (2022–3)
Training in use of the platform and integrated approach	
Costs of trainers	£9182
Costs of therapists	£23,672
Total	£32,854
Per participant	£146
Ongoing supervision	
Costs of supervisors	£25,638
Costs of therapists	£51,042
Total	£76,680
Per participant	£341
Integrated CBT delivery	
Costs of sessions per participant	£412 (SD £212)
Costs of platform per participant	£88
Costs of integrated CBT per participant	**£987 (SD £212)**

TABLE 19 Cost-effectiveness analysis from NHS/PSS perspective: results from primary analysis and CCA

	Primary analysis		CCA	
	UC (*n* = 226)	Integrated CBT (*n* = 225)	UC (*n* = 109)	Integrated CBT (*n* = 103)
Costs, mean (SE)				
Integrated CBT	–	£987 (£14)	–	£1051 (£17)
UC	£382 (£57)	£193 (£42)	£390 (£80)	£163 (£49)
Healthcare and social services	£371 (£38)	£574 (£118)	£418 (£61)	£623 (£191)
Total NHS/PSS costs	£753 (£77)	£1754 (£127)	£808 (£115)	£1837 (£199)
EQ-5D-5L utility, mean (SE)				
Baseline	0.504 (0.017)	0.523 (0.017)	0.510 (0.024)	0.557 (0.024)
6 months	0.574 (0.021)	0.618 (0.022)	0.562 (0.026)	0.652 (0.027)
12 months	0.564 (0.022)	0.630 (0.022)	0.577 (0.028)	0.666 (0.028)
QALYs	0.554 (0.017)	0.597 (0.017)	0.553 (0.023)	0.632 (0.023)
Incremental estimates adjusted for baseline covariats,[a] mean (95% CI)				
Incremental costs	£1009 (£737 to 1286)		£1040 (£722 to 1462)	
Incremental QALYs	0.033 (−0.002 to 0.059)		0.046 (0.002 to 0.089)	
ICER, mean (probability of cost-effective)				
ICER	£30,576 (from £20,000 to £30,000 : 13–39%, see *Figure 5a* and *b*)		£22,421 (from £20,000 to £30,000 : 37–66%, see *Figure 5c* and *d*)	

a Baseline covariates included stratification (centre) and minimisation (gender, current antidepressant use, and BDI-II tertiles) variables, age and previous psychiatry referral. Incremental QALYs were further adjusted by index value at baseline.

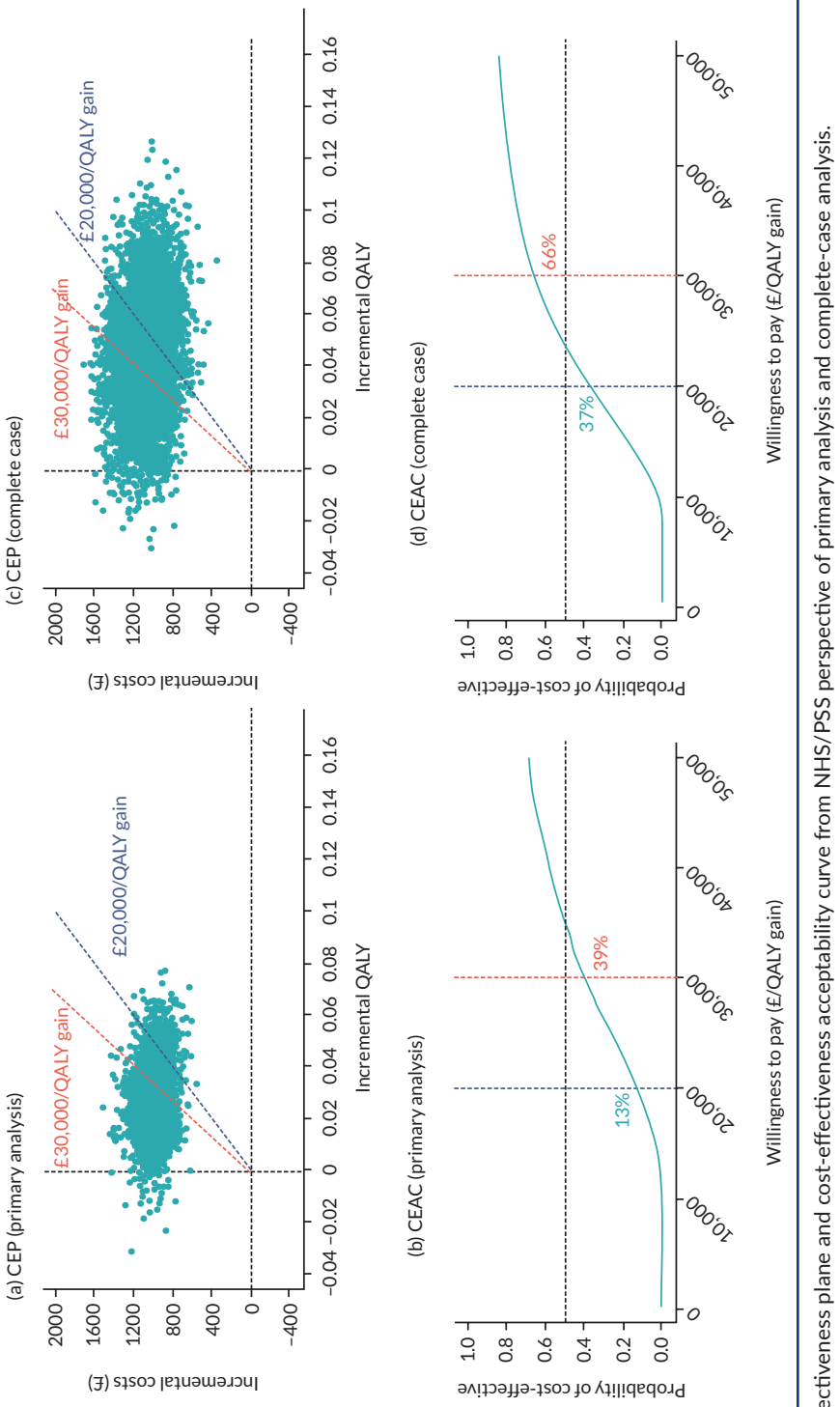

FIGURE 5 Cost-effectiveness plane and cost-effectiveness acceptability curve from NHS/PSS perspective of primary analysis and complete-case analysis.

TABLE 20 Secondary cost-effectiveness analyses: from participants' and their carers' perspective and from societal perspective

	Primary analysis		CCA	
From participants' and their carers' perspective				
	UC (*n* = 226)	**Integrated CBT (*n* = 225)**	**UC (*n* = 73)**	**Integrated CBT (*n* = 88)**
OOPs and lost income, mean (SE)				
OOP for UC	£110 (£22)	£62 (£20)	£120 (£37)	£85 (£43)
OOP for healthcare and social services	£45 (£16)	£39 (£13)	£40 (£15)	£24 (£9)
Participants' lost income				
6 months	£336 (£118)	£339 (£125)	£501 (£265)	£425 (£241)
12 months	£101 (£52)	£418 (£180)	£68 (£45)	£473 (£322)
Carers' lost income				
6 months	£60 (£31)	£73 (£30)	£20 (£12)	£60 (£38)
12 months	£157 (£127)	£196 (£112)	£26 (£17)	£15 (£11)
Total OOPs and lost income	*£808 (£190)*	*£1127 (£318)*	*£775 (£273)*	*£1083 (£550)*
QALYs, mean (SE)				
QALYs	0.554 (0.017)	0.597 (0.017)	0.594 (0.027)	0.684 (0.018)
Incremental estimates adjusted for baseline covariates[a], mean (95% CI)				
Incremental OOPs and lost income	£179 (−£249 to £680)		−£172 (−£566 to £340)	
Incremental QALYs	0.033 (−0.002 to 0.059)		0.065 (0.018 to 0.112)	
ICER				
	£5424 (see *Figure 6a*)		Less costly but more effective (see *Figure 6b*)	
From societal perspective				
	UC (*n* = 226)	**Integrated CBT (*n* = 225)**	**UC (*n* = 58)**	**Integrated CBT (*n* = 61)**
Non-NHS costs, mean (SE)				
UC	£390 (£63)	£150 (£34)	£386 (£103)	£49 (£24)
Other benefits	£813 (£308)	£890 (£292)	£383 (£119)	£737 (£313)
Total non-NHS costs	*£1203 (£317)*	*£1039 (£296)*	£769 (£151)	£786 (£326)
Total NHS/PSS costs	*£753 (£77)*	*£1754 (£127)*	*£837 (£160)*	*£1674 (£136)*
Total OOPs and lost income	*£808 (£190)*	*£1127 (£318)*	*£597 (£160)*	*£1137 (£777)*
Total societal costs	*£2734 (£439)*	*£3890 (£475)*	*£2173 (£298)*	*£3570 (£884)*
QALYs, mean (SE)				
QALYs	*0.554 (0.017)*	*0.597 (0.017)*	*0.567 (0.030)*	*0.704 (0.020)*
Incremental estimates adjusted for baseline covariates,[a] mean (95% CI)				
Incremental societal costs	£1259 (£164 to £2099)		£1071 (£32 to £2401)	
Incremental QALYs	0.033 (−0.002 to 0.059)		0.103 (0.041 to 0.160)	
ICER				
	£38,152 (see *Figure 6c*)		£10,416 (see *Figure 6d*)	

a Baseline covariates included stratification (centre) and minimisation variables (gender, current use of antidepressant and BDI-II tertiles), and age, history of depression and employment status. Incremental QALYs were adjusted by stratification and minimisation variables, age, previous psychiatry referral and index value at baseline.

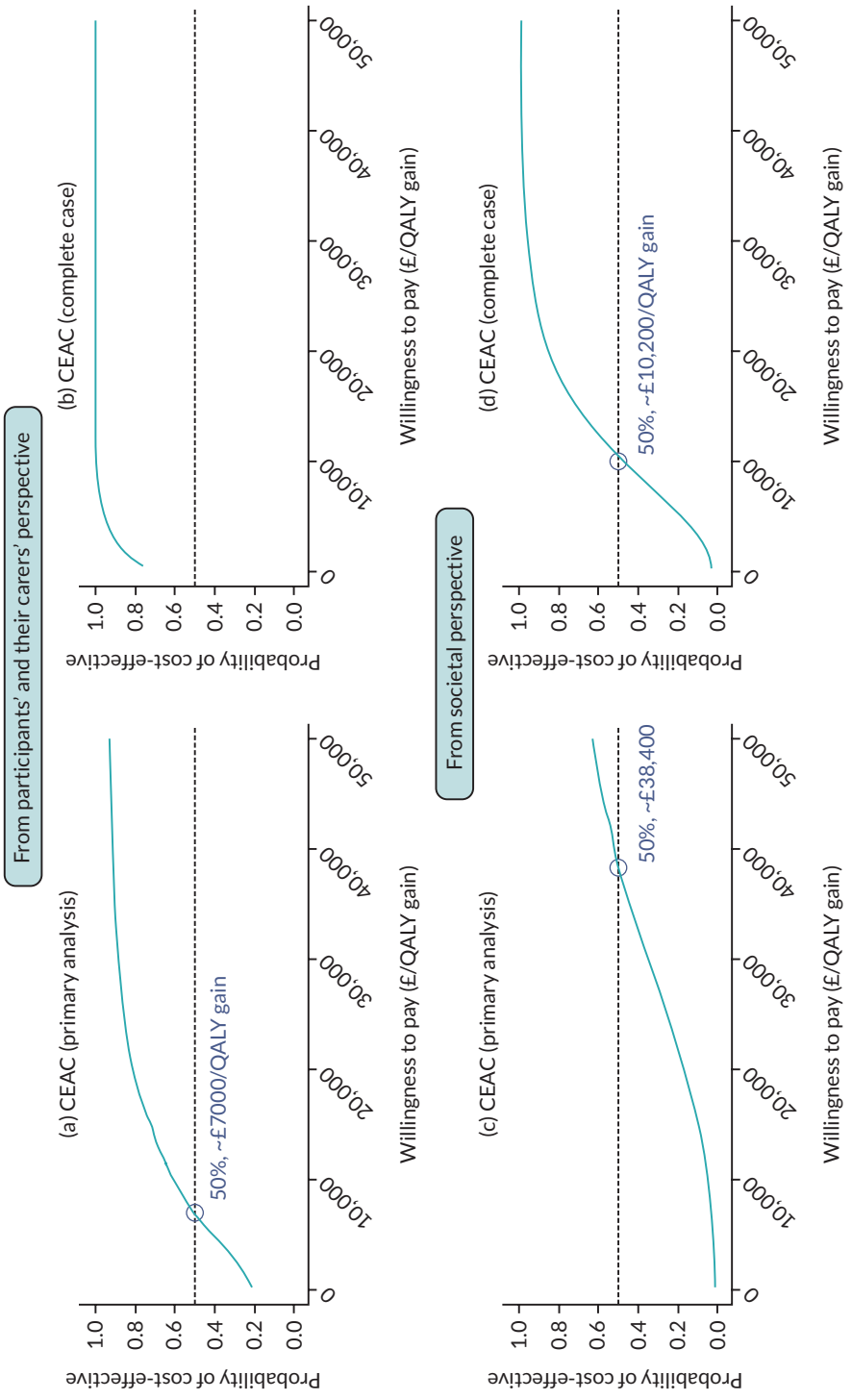

FIGURE 6 Cost-effectiveness acceptability curve from participants' and carers' perspective and from societal perspective based on primary analysis and CCA.

TABLE 21 Seven participants identified as outliers

Outliers	Allocation	Outlying measure	Outlying value (£)	Maximum values among rest participants in both groups (£)
1	Integrated CBT	NHS/PSS costs	18,337	5573
2	Integrated CBT	OOPs	3520	1957
3	UC	OOPs	4576	
4	Integrated CBT	Lost income	47,000	21,000
5	UC	Non-NHS benefits	36,395	
6	UC	Non-NHS benefits	46,224	15,763
7	Integrated CBT	Non-NHS benefits	53,017	

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