**Cognitive behavioural therapy (CBT) for irritable bowel syndrome (IBS): 24 month follow-up of ACTIB trial participants**

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**Summary**

**Background**

IBS is common, affecting 10-20% of the adult population with many people experiencing ongoing symptoms despite first line therapies. Cognitive behavioural therapy (CBT) is recommended in guidelines for refractory IBS but there is limited access to CBT for IBS and uncertainty whether benefits last in the longer term. ACTIB (Assessing Cognitive behavioural Therapy for IBS) was a large randomised controlled trial of two forms of CBT for patients with refractory IBS. ACTIB results showed, at 12 months, that both forms of CBT for IBS were significantly more effective than treatment as usual (TAU) at reducing IBS symptom severity and impact at 12 months in adults with refractory IBS.

This follow-up study aims to evaluate 24 month clinical outcomes of participants recruited to the ACTIB trial.

**Methods**

In the ACTIB three-arm randomised controlled trial, 558 adults with refractory IBS were randomly allocated to therapist-delivered telephone CBT (TCBT), web-based CBT with minimal therapist support (WCBT) or treatment as usual (TAU) and followed up for 12 months. Participants were adults with refractory IBS (clinically significant symptoms for ≥12 months despite first-line therapies), recruited by letter and opportunistically from 74 general practices and three gastroenterology centres in London and South of England between 1st May 2014 and 31st March 2016. Primary outcome measures were IBS Symptom Severity Score (IBS-SSS) and Work and Social Adjustment Scale (WSAS) Intention-to-treat (ITT) analyses with multiple imputation were undertaken. This study was a non-pre-specified naturalistic follow-up and analysis of ACTIB trial participants at 24 months.

**Findings**

24 months follow-up of outcomes was achieved for 57·9% (323/558) participants, (119/186 in the Telephone CBT arm, 99/185 in the Web CBT arm, 105 /187 in the treatment as usual arm). At 24 months compared to treatment as usual: IBS-SSS was 40·5 (95% CI 15·0 to 66·0) points lower (p=0·002) in the Telephone CBT arm and 12·9 (95% CI -12·9 to 38·8) points lower (p=0·325) in the Web CBT arm. WSAS was 3·1 (95% CI 1·3 to 4·9) points lower (p<0·001) in the Telephone CBT arm and 1·9 (95% CI 0·1 to 3·7) points lower (p=0·036) in the Web WCBT arm. A clinically significant IBS-SSS change (≧50 points), baseline to 24 months, occurred in 84/119 (70·6%) of participants in the Telephone CBT arm , 62/99 (62·6%) in the Web CBT arm and 48/105 (45·7%) in the treatment as usual arm.

There were no adverse no adverse events related to treatment.

**Interpretation**

At 24 month follow-up, sustained improvements in IBS were seen in both cognitive behavioural therapy arms compared to treatment as usual, though some previous gains were reduced compared to the 12 month outcomes. IBS-specific CBT has the potential to provide significant long-term improvement in IBS, achievable within a usual clinical setting. Increasing access to CBT for IBS could achieve long-term patient benefit.

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**Research In context**

**Evidence before this study**

We searched the PubMed, PsycInfo and Cochrane Library databases up to January 2019, without language restrictions for full papers reporting randomised controlled trials, systematic reviews, and meta-analyses with the search terms ‘irritable bowel syndrome’ and ‘cognitive behavioural therapy’. We excluded trials of adolescents, education, and group interventions.

Previous research evidence, including several RCTs, suggests that cognitive behaviour therapy is likely to be helpful for IBS in the short term. However, limitations of previous trials include small size, high dropout rates from therapy and lack of longer term follow up. The UK National Institute for Health and Care Excellence guideline for IBS, recommends offering CBT for people with refractory IBS but acknowledges that further research is needed. Currently there is limited access to CBT for IBS and many patients have no access to psychological therapies for IBS.

The ACTIB trial was, we believe, the largest study of CBT for IBS worldwide to date, recruiting 558 participants with 12 month follow up. Important clinically and statistically significant benefits in IBS symptoms and impact were found for both telephone-delivered and web-based CBT interventions compared to treatment as usual at 12 months.

**Added value of this study**

This follow-up study provides 24 month naturalistic follow up of the ACTIB participants. Participants received no further therapist input but both CBT intervention arms had sustained improvement in the primary and secondary ACTIB outcomes at 24 months.

This was achieved in a clinical setting with relatively modest amounts of therapist contact time.

**Implications of all the available evidence**

This longer follow up of a large RCT adds robust data to the evidence-base indicating that IBS-specific CBT has the potential to provide significant long-term improvement in IBS symptoms, functional impairment and mood and is achievable within a usual clinical setting. Both the higher intensity telephone therapist CBT and the web-based CBT with minimal therapist support can achieve significant clinically important improvements at 24 months. This trial reinforces NICE guidance, which relied on a limited evidence base, that CBT for IBS has the potential to benefit patients with refractory IBS and should be made more widely available for this patient group.

**INTRODUCTION**

Irritable Bowel Syndrome (IBS) is a common chronic gastrointestinal disorder affecting 10 to 20% of the population worldwide, with many people experiencing ongoing symptoms and incurring significant health costs.1, 2 Abdominal pain, bloating, and altered bowel habit affect quality of life, social functioning, and time off work.3 Currently, clinicians have few options to offer people with refractory IBS. The National Institute for Health and Clinical Excellence (NICE) Guidance 3 recommends CBT for patients with refractory IBS symptoms (i.e. ongoing symptoms after 12 months despite being offered appropriate medications and lifestyle advice). Published trials of CBT for IBS have reported promising results for CBT for IBS at 6 months post-randomisation follow-up 4, 5. However, there is still very limited access to CBT for IBS on the NHS and worldwide. Additionally and there is limited evidence regarding the longer-term outcomes after CBT for IBS, as highlighted in a Cochrane review 6.

ACTIB (Assessing cognitive behavioural therapy in IBS) was a parallel three arm, multicentre randomised controlled trial (RCT) of 2 modes of CBT designed specifically for IBS (telephone therapist-delivered CBT with a patient self-management manual (TCBT) and web-based CBT with minimal therapist support (WCBT)) compared to treatment as usual (TAU) alone, in adults with refractory irritable bowel syndrome (IBS) 7, 8. We believe it to be the largest RCT of CBT for IBS to date, and the only one to test effectiveness of therapist and web delivered CBT in the same trial. The ACTIB trial results showed that Telephone CBT and Web CBT were significantly more effective than treatment as usual (TAU) at reducing IBS symptom severity and impact at 12 months in adults with refractory IBS 8. This was achieved within the National Health Service (NHS) in the UK (CBT trained NHS therapists delivered the interventions).

The aim of the current study was to evaluate longer-term (24 month) clinical outcomes of the two ACTIB CBT for IBS interventions, (telephone therapist-delivered CBT (TCBT) and web-based CBT (WCBT)) compared to treatment as usual in adults with refractory IBS.

**METHODS**

**Study design and participants**

This study reports a naturalistic 24 month follow up of participants in the ACTIB (Assessing Cognitive behavioural Therapy for Irritable bowel Syndrome) trial. The ACTIB trial protocol 7 (<https://bmjopen.bmj.com/content/5/7/e008622>) and the 3, 6 and 12 month trial results 8 have previously been published.

ACTIB participants were people with refractory IBS who were randomly allocated to therapist-delivered telephone CBT (TCBT), web-based CBT with minimal therapist support (WCBT) or treatment as usual (TAU).

ACTIB Participants were recruited from 74 primary care general practice (GP) surgeries in the South East of England and London, and 3 secondary care gastroenterology outpatient clinics in two regions: Southampton (Southampton University Hospital) and London (Guy’s and St Thomas’ Hospital Trust, King’s College Hospital) between 1st May 2014 and 31st March 2016. 24 months data collection was completed by 31st May 2018.

ACTIB participants were eligible if they fulfilled criteria for refractory IBS, defined as fulfilling ROME III criteria for IBS 9; reported ongoing clinically significant symptoms on IBS symptom severity score (IBS-SSS) 10 i.e. ≧75; had been offered first line therapies (e.g. antispasmodics, antidepressants or fibre-based medications) and had IBS symptoms ≧12 months.

Medical exclusion criteria 7, 8 were unexplained rectal bleeding or weight loss, inflammatory bowel disease, coeliac disease, peptic ulcer disease, and colorectal carcinoma. Other exclusions were: patients <18 years, unable to participate in CBT due to speech or language difficulties, no access to an internet computer, received CBT in last 2 years, previous access to the online CBT for IBS intervention (Regul8) during the MIBS trial and currently participating in another IBS intervention trial.

Ethical approval was awarded by the NRES Committee South Central, Berkshire on 11th June 2013: reference number 13/SC/0206. Additional online informed consent was obtained from participants for 24 months follow up.

**Description of CBT interventions and Treatment as usual**

Two active interventions were assessed in the ACTIB study, therapist delivered telephone CBT (TCBT) with a detailed patient self-management manual and a low intensity web-based CBT (WCBT) – the Regul8 program developed in the MIBS trial 11, with some therapist support. All arms received treatment as usual (TAU), with control being TAU alone.

The core CBT content of the two treatment arms was similar, based on an empirical cognitive behavioural model of IBS 12 and versions of this model tested in previous smaller RCTs 13, 14. It consisted of education around the brain gut axis, behavioural techniques to improve bowel habits, developing stable healthy eating and exercise patterns, addressing unhelpful thoughts, managing stress and emotions, reducing symptom focussing, and preventing relapse. Treatments were standardised by provision of therapist training and therapist manuals. All therapists were available to work in both therapy arms (TCBT and WCBT) and with any participant regardless of recruitment centre.

Participants randomised to TCBT arm received a detailed self-management CBT manual including homework tasks and recording sheets and were offered six, one hour telephone sessions with a CBT therapist at week 1, 2, 3, 5, 7, 9 and homework tasks. They also received two one-hour booster sessions at 4 and 8 months (a total of 8 hours of therapist support).

WCBT participants received three 30 minute telephone therapy support calls at weeks 1, 3 and 5 and two 30-minute booster sessions at 4 and 8 months (2 ½ hours of therapist support).

TAU was defined as continuation of current medications, and usual GP or consultant follow-up with no psychological therapy. All GP sites or secondary care sites involved in the study received a copy of the NICE Guidance for IBS 3 to ensure all clinicians had standard best practice information on IBS management. They also received information to remind them of the guidelines, protocol guidance on prescribing psychological therapies and inclusion criteria. All participants received a standard information sheet on Lifestyle and Diet in IBS based on NICE guidance 3.

Information was collected on any changes in IBS treatments/management during the study and numbers of GP and consultant consultations were recorded for all three arms.

After the 12-month follow-up assessments TAU alone participants were given access to the Regul8 website (but with no therapy support) via an email link, the WCBT participants also had ongoing access to the Regul8 website. TCBT participants were not given access to Regul8 but were able to continue to use their CBT manuals. Neither CBT group were offered further therapist support. Thus, the last contact with a trial therapist in TCBT and WCBT was approximately 16 months prior to the 24 month follow up. Participants were free to seek CBT through any available means for IBS or any other condition.

**Therapy Procedures**

Thirteen CBT trained therapists, 10 (77%) female, with a mean age 42 years (range 34 to 52) based at South London and Maudsley NHS Trust (SLAM) provided the telephone CBT sessions for both therapy arms. Six therapists were clinical psychologists (46%) and 7 (54%) cognitive behavioural psychotherapists with a median of 7 years (range 4 to 24) experience. All sessions were audio-recorded for supervision and treatment fidelity purposes. Each therapist received a therapist manual, two days training and post-training supervision. Supervision was conducted in 90-minute fortnightly group sessions in the first half of the trial, then monthly.

Treatment fidelity was further assessed at the end of trial by two independent experienced CBT therapists using audio-recordings of therapy sessions.

**Role of Funding Source**

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

The corresponding author had full access to all of the data and the final responsibility to submit for publication.

**Outcomes**

Outcome measures were completed on-line by participants at 24 months (or a paper-copy was posted or telephone follow-up undertaken as described in the protocol for the 12 month follow up) 7.

24 month data was collected on the two co-primary outcomes from the ACTIB trial 8: IBS Symptom Severity Score (IBS-SSS) 10 and the Work and Social Adjustment Scale (WSAS) 14 , which measures impact on life including ability to work, manage at home and participate in social activities.

Data was also collected on the ACTIB trial secondary outcome measures: Hospital Anxiety and Depression Scale (HADS) 15, measuring mood as a total distress score; Patient Enablement Questionnaire (PEQ) 16, measuring people’s ability to cope with their illness and life after treatment; Subject’s Global Assessment of Relief (SGA) 17 which assessed IBS symptom relief in a scale of 1-5.

Participants were also asked whether they had sought CBT for IBS, CBT for any other condition or had used the WCBT (Regul8 website) between 12 and 24 month follow-up.

**Statistical analysis**

The statistical analysis of the 24 month outcomes followed the analysis approach used to evaluate the 3, 6 and 12 month outcomes. Details can be found in the published primary trial publication and online materials 8. The analysis of the 24 month data was not pre-specified in the original trial protocol as the original trial funding only covered the follow-up to 12 months. We sought an extension to the original trial from our funders and the ethics committee to undertake 24 month follow-up and participants were re-consented to collect 24 month data.

Briefly, an intention-to-treat approach was used for all 24 month outcomes. For each outcome we compared the CBT arms (TCBT or WCBT) with the TAU arm to assess treatment effectiveness. Modelling of continuous variables relied on normal assumptions for error terms and treatment effects were quantified by trial arm differences (and standardised differences). The PEQ measure was reclassified as a binary variable with a score of ≥6 considered a “responder” to facilitate modelling within a logistic regression framework and treatment effects quantified by odds ratios (ORs).

Formal trial arm comparisons were carried out by multiple imputation (MI) using the flexible

Multivariate Imputation by Chained equations (MICE) approach with 100 imputations. 18 This was necessary because non-adherence with treatment was found to be predictive of missing primary outcomes at 12 months in the CBT arms. We also previously assessed whether baseline variables were predictive of outcome missingness and identified baseline IBS symptom severity score and index of multiple deprivation (IMD)19 as further possible predictors. The linear regression or logistic regression analysis models of the MI procedure included the respective outcome variable as the dependent variable and trial arm (two dummy variables indicating the TCBT and WCBT arms), baseline values of the outcome (if available) and randomisation stratifier (dummy variables for centres) as explanatory variables. Since both TCBT and WCBT involved therapists delivering the intervention possible therapist effects on 24 months outcomes were assessed empirically using the same methods as in the primary trial paper 8. Therapist effects were not detected at the liberal 10% alpha level and so therapist effects were not included in any of the 24 months analysis models. For each outcome variable the imputation model of the MI procedure included (i) all variables of the analysis model, (ii) measures of the outcome variable at other assessment time points including baseline and (iii) known predictors of missingness (binary adherence variables for each of TCBT and WCBT, baseline IBS-SSS and IMD).

Per-protocol analyses was used to estimate the efficacy of TCBT and WCBT respectively in terms of the original primary outcomes. The analyses for IBS-SSS and WSAS at 24 months were repeated after restricting the sample to those trial participants who: (i) adhered with randomised treatment offer during the 12 months trial period (adherence to therapy was defined as: WCBT completing ≥4 website sessions and one or more telephone support calls; TCBT completing ≥4 of the initial telephone CBT sessions 7, 8). (ii) did not access any form of CBT during the 12 to 24 naturalistic follow-up period and (iii) provided 24 month outcome data (complete case approach, no imputation). Respective linear regression analyses were adjusted for known baseline predictors of missingness at 12 months (IMD and IBS-SSS).

All analyses were carried out in Stata version14.2.This study is registered as an International Standard Randomised Controlled Trial Number ISRCTN44427879

**Patient and public involvement (PPI)**

A PPI representative participated in the trial management group and was included in all phases of trial design, including planning recruitment and recruitment materials. They had been a participant in the MIBS feasibility study 11 and thus were able to provide first-hand insight into the burden of the intervention and the time required to participate in the research. The CBT interventions were developed with PPI input.11 The independent trial steering committee included another PPI member.

**RESULTS**

323/558 (57·9%) of the patients randomised as part of the ACTIB trial provided 24 months follow up data (64·0%, 53·5% and 56·1% of patients within Telephone CBT (TCBT), Web-based CBT (WCBT) and Treatment as usual (TAU) arms respectively) compared to 70·1% at 12 months (391/558). The mean follow-up time was 638 days SD 217, median 730 days (IQR 730 to 730).

24 month data collection took place between 1st March 2016 and 31st May 2018.

Table 1 provides descriptive summaries for outcome measures at 12 and 24 months. Results of the formal comparisons of the outcomes between the CBT arms (TCBT or WCBT) and the TAU arm are provided in Table 2. Comparisons at 12 months have been presented previously8; the results shown Table 2 differ slightly from those presented previously as they could exploit the extra information provided by the 24 months outcomes.

Compared to TAU (IBS Symptom Severity Score (IBS-SSS) score 198 at 24 months), IBS-SSS scores were 40·5 (95% CI (15·0 to 66·0)) points lower (p<0·002) in TCBT and 12·9 (95% CI -12·9 to 38·8) points lower (p=0·325) in WCBT at 24 months. Thus, based on ITT analysis a statistically significant difference in IBS-SSS was sustained at 24 months for the TCBT arm but not the WCBT arm when compared to TAU. In terms of IBS-SSS responders, i.e. participants who had a clinically significant change in IBS-SSS (≧50 point) from baseline to 24 months, the percentages who were responders in the three trial arms were: 84/119 (70·6%) in the TCBT arm, 62/99 (62·6%) in WCBT and 48/105 (45·7%) in TAU.

Table 3 and Figure 1 show predicted IBS-SSS means for each trial arm and assessment time point. The predicted means are derived from the multiply imputed data and adjusted for missing data biases, and thus allow us to compare means over time. They show that our findings may be explained by the TCBT and WCBT arms losing some previous benefits between 12 months and 24 months, while TAU arm participants appeared to continue to improve on IBS-SSS. At 24 months, IBS SSS in both the TCBT and WCBT arms had deteriorated by 14·1 and 14·9 points respectively compared to 12 months follow up, whereas the TAU arm had improved by 7·6 points. For the WCBT arm where the estimated arm difference at 12 months was 35·4, the deterioration in the WCBT scores and the improvement in the TAU arm mean that the difference was no longer statistically significant.

For the Work and social Adjustment Scale (WSAS) both TCBT and WCBT maintained statistically significant improvements compared to TAU at 24 months. WSAS score 9·7 in TAU at 24 months and was 3·1 (95% CI 1·3 to 4·9) points lower (p<0·001) in TCBT and 1·9 (95% CI 0·1 to 3·7) points lower (p=0·036) in WCBT. Figure 2 and Table 3 show that WSAS mean remained relatively stable from 12 to 24 months.

Further ACTIB outcome measures showed significant improvement in both therapy arms compared to TAU at 24 months (Table 3). For the Hospital anxiety and depression scale (HADS) differences were also maintained: TCBT to TAU 3·1 points reduction (95% CI 1·6 to 4·7) p<0·001 and WCBT to TAU 2·7 points reduction (95% CI 1·0 to 4·4) p=0·002. For Patient enablement (PEQ) responders the effects remained large: TCBT to TAU OR 8·3 (95% CI 4·2 to 16·4) p<0·001, WCBT to TAU OR 3·3 (95% CI 1·8 to 6·0) p=0·001. Unfortunately, for subjects’ global improvement of symptoms (SGA) there was a problem with data collection at 24 months and very few participants completed this outcome measure (Table 1). Thus, numbers were too small to be formally analysed.

Additional CBT treatments during naturalistic follow up was assessed. Table 4 shows that the numbers of participants seeking any form of CBT between 12 and 24 months was low, 8·6% of the participants sought CBT in some form for any condition (8·1%, 7·0%, 10·7% in arms TCBT, WCBT and TAU respectively); 1·4% sought IBS-specific CBT (1·6% in TCBT arm, 0·5% in WCBT and 2·1% in TAU). There were no significant differences between the trial arms in the proportions of participants seeking CBT in the 12-24 months period (Fisher’s exact test, TCBT vs TAU p=0·48, WCBT vs TAU p=0·27). Only 10 participants from the TAU arm accessed Regul8 (5·4%) despite all TAU participants being sent an access link at 12 months. The percentages of participants deviating from the treatment allocated to them in the trial for any reason are shown in the final column of Table 4.

Assessment of longer-term efficacy of WCBT and TCBT was also assessed. For IBS-SSS at 24 months efficacy as quantified by the per-protocol analysis was -50·0 points (CI from -75·5 to -24·5, p<0·001) for TCBT compared with TAU and -51·5 points (CI from -79·0 to -23·9, p<0·001) for WCBT compared with TAU. For WSAS at 24 months the reduction for TCBT was -4·1 points (CI from -5·9 to -2·2, p<0·001) compared with TAU and for WCBT -3·7 points (CI from -5·7 to -1·7, p<0·001) compared with TAU. We estimate that the efficacy of the CBT treatments was higher than their effectiveness, in particular for the WCBT arm which was subject to higher rates of non-adherence with therapy (Table 4). For TCBT compared to TAU this was an additional improvement in scores of -9·5 for IBS-SSS and -1·0 for WSAS, and for WCBT the equivalent improvement in scores for compliers was -38·6 for IBS-SSS and -1·8 for WSAS. However, these efficacy results should be treated with care as they are based on the complete cases at 24 months only and subject to selection bias, while the MI effectiveness analyses are able to adjust for further variables driving the missing data generating process.

Data on adverse events was recorded. At the end of the year following the trial, participants were asked to report any adverse events in months 12 to 24. A total of 41 adverse events were reported (11, 15 and 15 in TCBT, WCBT and TAU arms respectively). Of these, 8 were reported as gastro-intestinal related (2 TCBT, 4 WCBT, 2 TAU) and 5 were psychological (2 TCBT, 0 WCBT and 3 TAU) and 6 (1TCBT, 2 WCBT and 3 TAU) were musculoskeletal. No adverse events were reported as related to the intervention.

**DISCUSSION**

Compared to the Treatment as usual (TAU) arm, both Telephone (TCBT) and Web-based (WCBT) intervention arms showed sustained improvements in outcomes at 24 months. However, these were reduced in magnitude at 24 months compared to 12 months. Despite this, the ITT analysis showed that at 24 months both CBT arms reported significantly less impact of IBS on life than the TAU arm, and the TCBT arm reported significantly greater reductions in IBS-SSS. A clinically significant change in IBS symptoms (IBS-SSS change ≧50 point between baseline to 24 months, occurred in 70·6% of those in the Telephone CBT arm, 62·6% in the web-based CBT arm compared with 45·7% in the TAU arm. In terms of other outcomes, reductions in total anxiety and depression and patient enablement gains (ability to cope with their illness) in the CBT arms remained strong at 24 months.

The complete case per protocol analysis indicated that those who adhered with the CBT interventions (as defined in our protocol 7) and did not seek additional CBT treatments in the 12-24 months period maintained significant gains in both IBS-SSS and WSAS at 24 months in both the CBT arms. The difference in the intention to treat and per-protocol analysis was particularly marked for the WCBT group. This may be owing to CBT adherence rates in WCBT being somewhat lower (69% for WCBT compared to 84% for TCBT). Differential adherence between the WCBT and TCBT arms may also explain some of the differences seen in the outcome measures between the CBT arms in the intention to treat analysis.

This study’s strengths include follow-up of a well-powered rigorously conducted RCT with broad inclusion. The IBS specific CBT was based on an explicit theoretical model 12, 20 informing the detailed patient and therapy manuals and the web-based CBT (Regul8). Therapists were experienced in delivering CBT, and trained and supervised to deliver IBS specific CBT. Trial interventions had good treatment fidelity 8 and were delivered by NHS therapists in an NHS setting. We believe this is the first large scale trial of CBT for IBS to publish 24 months follow up data. This longer-term follow-up provides both patients and clinicians with valuable information that the benefits of CBT for IBS are sustained.

Limitations include the potential for lack of external validity as people with IBS unwilling to consider undertaking CBT for IBS are unlikely to have participated in the trial. However, we believe that the sample was broadly representative of people with IBS, as the age and gender was similar between those invited to participate in the ACTIB trial and those randomised, though ethnic diversity was limited. Follow up rates were 57·9% at 24 months compared to 70·3% at 12 months. Thus, there is potential for 24 months outcomes analyses to be affected by missing data biases. To mitigate against this multiple imputation, accommodating all observed predictors of missingness, was used.

The 12 month results from ACTIB 8 and previous research has shown face-to-face and telephone delivered CBT to be beneficial for IBS 6, 13, 14 particularly immediately after completing treatment. However, a Cochrane review 6 concluded that it was unclear whether the effects were maintained longer-term. Other large published trials of CBT for IBS report 6 months post-randomisation follow-up 4, 5. For instance, a recently published three-arm RCT (n=436) compared face-to- face CBT for IBS with home-based CBT (minimal contact cognitive behavioural therapy (MC-CBT)) using self-study materials, and IBS education alone (EDU).5 This showed promising results for low-intensity CBT for IBS. Improvement was reported at 2 weeks in both their CBT arms compared with EDU, and on gastroenterologist (but not patient) ratings at 6 months on the clinical global impressions improvement scale. However, there follow-up was limited to 6-months, participants were only recruited from tertiary centres, and at no time point did they show significantly greater improvements for CBT on IBS-SSS. ACTIB 24 month follow-up showed improvements in IBS-SSS and global symptoms (SGA).

We believe we are the first large scale trial of CBT for IBS to publish 24 months follow up data. The gains maintained at 24 months are despite having no further ACTIB trial therapist input since month 8 (i.e. 16 months prior to 24 month outcome measures were recorded). Most of the therapy contact was in the first 3 months (two booster sessions were offered at 6 and 8 months) and the overall maximum dose of therapy was 8 hours for the TCBT and 2·5 hours for WBCT. In the NHS, therapist delivered CBT is typically offered as between 5-20 sessions, so even the higher intensity CBT is at the lower end of the typical therapy dose.

Currently clinicians have few options to offer people with refractory IBS, particularly in primary care. This study shows that IBS-specific CBT has the potential to provide significant improvement in IBS impact and symptom severity with ongoing benefits at 24 months. Offering both WCBT and TCBT in NHS services such as IAPT (Improving Access to Psychological Therapy) could allow many patients to gain significant benefits with WCBT with minimal therapist input whilst allowing a ‘step-up’ approach to TCBT for those needing more support.

We are planning a future publication on the cost effectiveness of the telephone and web-based CBT for IBS interventions and also on whether there are identifiable moderators and mediators that would indicate who is most likely to benefit from CBT for IBS. Further research is needed to assess whether telephone and web-based CBT can be widely disseminated in a non-trial clinical settings.

**CONCLUSION**

This study reinforces NICE guidance 3, that patients with refractory IBS should be offered CBT for IBS, which is currently poorly available. Our results show that both telephone therapist-delivered and web-based CBT for IBS can provide long-term benefits.

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**ACTIB trial group:** Trial Steering Committee (independent members) - Peter White (Chair), Else Guthrie, Qasim Aziz and Tom Sensky. Data Monitoring and Ethics Committee (DMEC) (independent members) - Astrid Fletcher (Chair), Charlotte Feinmann. and Ronan O'Carroll. Patient and public involvement (PPI) member on TSC and DMEC - Jill Durnell. Trial management group PPI member - Kate Riley.

**Contributors**

The principal investigators (HE, RMM and TC) and the other co-investigators PMc, PL, SL, FB, KG, RL, NC) designed the study and obtained funding. The protocol was further developed by the Trial Management Group and agreed by the Trial Steering Committee and Data Monitoring and Ethics Committee. The Trial Management Group, chaired by HE, included all the authors of this paper and Jill Durnell and Kate Riley, the PPI representatives. RH and SL carried out the statistical analyses of the longer term follow up study. The Regul8 website was previously developed in the MIBS NIHR RfPB funded study and was managed and updated for this study by SH and AS. TC and RMM developed the therapy protocols and treatment manuals, and trained and supervised the trial therapists. RMM led the website arm and TC the therapist arm. The CBT therapists were Suzanne Roche, Mary Burgess, Barbara Bowman, Natalia Fainblum, Fabio Simao, David McCormack, Caroline Stokes, Antonia Dittner, Claire Willis, Jerome Tierney. Independent assessors of therapy fidelity – Alison Griffiths and Sarah Lack.

The chief investigator was HE and the trial manager was GO. SH, AS and SW were the research assistants. HE led primary care recruitment.NC and RL were clinic expert advisors and led secondary care recruitment at Southampton and London respectively. All authors contributed to this manuscript and approved it prior to submission.

**Competing Interests**

PL was director of PGfAR and a member of the Journals Library Board. RMM reports personal fees from training in IBS intervention for Central and North west London NHS Foundation Trust and University of East Anglia, outside the submitted work

TC reports grants from Guy’s and St Thomas’ Charity.  She was a Faculty member, 3rd International Conference on Functional (Psychogenic) Neurological Disorders, Sept 2017, Edinburgh , Member of the IAPT Education and Training  ERG (2016-),  Member of the IAPT Outcomes and Informatics Meeting (2016-),  President of the British Association of Behavioural and Cognitive Psychotherapies (2012-2015) for which she did not receive payment. Workshops were delivered on medically unexplained symptoms, during the conduct of the study (money paid into KCL for future research). TC has a patent Background IP - manuals were developed prior to trial starting. SL and KG report grants from NIHR. The TSC Chair, PW, was a colleague of TC in the past but he has recently retired. RMM reports personal fees from training in IBS intervention for Central and northwest London NHS Foundation Trust and University of East Anglia, outside the submitted work. Since this study was completed, she has received payment for consultancy to Mahana Therapeutics. Since this study was completed and the paper submitted, a private company has signed a licence agreement with King’s College London with the view to bringing the Regul8 website product to the NHS and other international markets. RMM, HE, TC, AS, GOR will be beneficiaries of this licence through contracts with their respective Universities. The CBT patient and therapist manual used in the telephone CBT arm are freely available on the National Improving Access to Psychological Therapies (IAPT) for LTC/MUS website as part of evidenced based resources for IAPT. The patient manual is background IP developed by CI's RMM and TC in previous work. The therapist manual was developed for the ACTIB trial. These manuals were only made available once the 12 month ACTIB follow up was complete. None for FB, RH, SL, SH, SW, PMc, NC, RL.

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The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All named authors, commented on drafts, and approved the ﬁnal report. Members of the writing group had responsibility for submitting the report, and HE had ﬁnal responsibility for the decision to submit for publication.

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

**Transparency**

The lead author HE affirms that is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

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**Data sharing statement**

Lead Author (HE) can be contacted on hae1@soton.ac.uk regarding data sharing requests.

Individual participant data that underlie the results reported in this article, may be available after de-identification to researchers who provide a methodologically sound proposal and whose proposed use of the data has been approved by an independent review committee. To gain access, data requestors will need to sign a data access agreement

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**Table 1 Descriptive summaries for outcome measures at 24 months follow-up**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **TCBT**N=186 | **WCBT**N=185 | **TAU**N=187 | **All**N=558 |
|  | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N |
| **IBS-SSS** |  |  |  |  |  |  |  |  |  |  |  |  |
| Baseline | 272·3 | 95·5 | 186 | 264·2 | 99·3 | 185 | 258·5 | 91·6 | 187 | 265·0 | 95·5 | 558 |
| 12 months | 139·0 | 94·8 | 136 | 163·0 | 108·8 | 124 | 205·6 | 100·5 | 131 | 168·9 | 104·8 | 391 |
| 24 months | 164·4 | 94·9 | 119 | 167·6 | 107·5 | 99 | 197·9 | 98·6 | 105 | 176·3 | 100·9 | 323 |
| **WSAS** |  |  |  |  |  |  |  |  |  |  |  |  |
| Baseline | 12·3 | 8·8 | 186 | 13·0 | 9·3 | 185 | 12·4 | 7·4 | 187 | 12·5 | 8·5 | 558 |
| 12 months | 6·0 | 7·5 | 138 | 7·4 | 7·7 | 124 | 10·8 | 9·3 | 132 | 8·1 | 8·5 | 394 |
| 24 months | 6·1 | 7·6 | 118 | 7·3 | 8·0 | 99 | 9·7 | 8·5 | 105 | 7·6 | 8·1 | 322 |
| **HADS distress** |  |  |  |  |  |  |  |  |  |  |  |  |
| Baseline | 16·1 | 6·9 | 186 | 17·0 | 7·3 | 185 | 16·0 | 6·4 | 187 | 16·4 | 6·9 | 558 |
| 12 months | 12·2 | 6·5 | 120 | 12·7 | 7·4 | 117 | 15·0 | 7·2 | 113 | 13·3 | 7·1 | 350 |
| 24 months | 12·1 | 6·4 | 118 | 12·2 | 7·6 | 98 | 15·1 | 6·6 | 103 | 13·1 | 7·0 | 319 |
|  | Non- responder (%) | Res- ponder (%) | N | Non-responder (%) | Res-ponder (%) | N | Non-responder (%) | Res-ponder (%) | N | Non-responder (%) | Res- ponder (%) | N |
| **PEQ responders\*** |  |  |  |  |  |  |  |  |  |  |  |  |
| 12 months | 30 (21·7) | 108 (78·3) | 138 | 56 (45·2) | 68 (54·8) | 124 | 101 (76·5) | 31 (23·5) | 132 | 187 (47·5) | 207 (52·5) | 394 |
| 24 months | 25 (21·0)  | 94 (79·0) | 119 | 38 (38·4) | 61 (61·6) | 99 | 75 (72·8) | 28 (27·2) | 103 | 138 (43·0) | 183 (57·0) | 321 |
| **SGA responders\*\*** |  |  |  |  |  |  |  |  |  |  |  |  |
| 12 months | 21 (15·2) | 117 (84·8) | 138 | 31 (25·0) | 93 (75·0) | 124 | 77 (58·3) | 55 (41·7) | 132 | 129 (32·7) | 265 (67·3) | 394 |
| 24 months\* | 5 (11·1) | 40 (88·9) | 45 | 17 (48·6) | 18 (51·4) | 44 | 22 (50·0) | 22 (50·0) | 44 | 44 (35·5) | 80 (64·5) | 124 |

\*PEQ: responders are defined as those getting a score of 6 or more. PEQ is not recorded at baseline.

\*\*SGA responders are defined as those getting a score of between 1 and 3. SGA is not recorded at baseline. SGA was only recorded at 24 months for those participants who completed the outcome measures by paper questionnaire.

**Table 2 Formal comparisons between therapy arms and TAU\***

|  |  |  |
| --- | --- | --- |
|  | **TCBT vs TAU** | **WCBT vs TAU** |
| Estimated difference | 95% CI | Test (degrees of freedom) p-value | Standar-dised difference \*\* | Estimated difference | 95% CI | Test (degrees of freedom) p-value | Standar-dised difference\*\* |
| **IBS-SSS** |  |  |  |  |  |  |  |  |
| 12 months | -62·3 | (-90·0, -34·6) | t(1981)= -4·4 p<0·001 | 0·65 | -35·4 | (-58·4, -12·3) | t(251)= -3·0 p=0·003 | 0·37 |
| 24 months | -40·5 | (-66·0, -15·0) | t(185)= -3·1p=0·002 | 0·42 | -12·9 | (-38·8, 12·9) | t(178)= -1·0p=0·325 | 0·14 |
| **WSAS** |  |  |  |  |  |  |  |  |
| 12 months | -3·5 | (-5·2, -1·8) | t(257)= -4·2 p<0·001 | 0·41 | -2·9 | (-4·5, -1·3) | t(287)= -3·5 p<0·001 | 0·34 |
| 24 months | -3·1 | (-4·9, -1·3) | t(211)= -3·4 p<0·001 | 0·36 | -1·9 | (-3·7, -0·1) | t(213)= -2·1 p=0·036 | 0·22 |
| **HADS** |  |  |  |  |  |  |  |  |
| 12 months | -2·8 | (-4·1, -1·4) | t(211)= -4·0 p<0·001 | 0·40 | -2·2 | (-3·4, -0·9) | t(268)= -3·4 p=0·001 | 0·32 |
| 24 months | -3·1 | (-4·7, -1·6) | t(184)= -4·0 p<0·001 | 0·46 | -2·7 | (-4·4, -1·0) | t(142)= -3·1p=0·002 | 0·39 |
| **PEQ respon-ders** | Estimated OR | 95% CI | Test (degrees of freedom), p-value |  | Estimated OR | 95% CI | Test (degrees of freedom), p-value |  |
| 12 months\*\*\* | 9·4 | (4·5, 19·7) | t(2510)=5·9 p<0·001 |  | 3·6 | (2·1, 6·0) | t(775)=4·7 p<0·001 |  |
| 24 months | 8·3 | (4·2, 16·4) | t(359)=6·1 p<0·001 |  | 3·3 | (1·8, 6·0) | t(467)=3·9 p<0·001 |  |

\*All inferences were derived by multiple imputation as described in the Methods section. Each model used k=100 imputations.

\*\*Differences were standardised by dividing by the baseline SD for IBS-SS (95·5), WSAS (8·8) and HADS (6·9) respectively.

\*\*\*The 12 months model included therapist effects in the TCBT arm. Thus these effects are conditioned on therapist.

**Table 3: Predicted change in mean outcomes between 12 and 24 months**

*Predictions are derived from the models fitted at 12 or 24 months using MI. Predictions are for sample average values of baseline variables (IBS-SSS =265, WSAS = 12·5, HADS distress = 16·4) and for the site from which most participants were recruited which was “Southampton GPs”)*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome | **Trial arm** | **12 months****Predicted mean (95% CI)** | **24 months****Predicted mean (95% CI)** | **Predicted change over long-term follow-up period** |
| **IBS SSS** | TCBT | 146·9 (122·7, 171·0) | 161·0 (140·2, 181·9) | +14·1 |
| WCBT | 173·7 (155·3, 192·2) | 188·6 (169·9, 207·2) | +14·9 |
| TAU | 209·1 (192·5, 225·8) | 201·5 (182·7, 220·3) | -7·6 |
| **WSAS** | TCBT | 7·2 (6·0, 8·5) | 7·0 (5·6, 8·4) | -0·2 |
| WCBT | 7·8 (6·6, 9·1) | 8·2 (6·9, 9·5) | +0·4 |
| TAU | 10·7 (9·5, 11·9) | 10·1 (8·8, 11·4) | -0·6 |
| **HADS** | TCBT | 12·5 (11·4, 13·5) | 12·5 (11·3, 13·8) | +0·0 |
| WCBT | 13·0 (12·1, 14·0) | 13·0 (11·7, 14·3) | +0·0 |
| TAU | 15·2 (14·2, 16·2) | 15·7 (14·5, 16·8) | +0·5 |
|  |  | **12 months****Log\_odds (95% CI)****[odds (95% CI]** | **24 months****Log\_odds (95% CI)****[odds (95% CI]** |  |
| **PEQ** log-odds scale[odds scale] | TCBT | 1·08 (0·41, 1·75) \*[2·68 (1·37, 2.95] \* | 1·11 (0·55, 1·66)[3·02 (1·73, 5·28)] | Difference in log odds = +0·03 |
| WCBT | 0·11 (-0·29, 0·51)[1·02 (0·52, 1·12)] | 0·18 (-0·24, 0·60)[1·20 (0·79, 1·82)] | Difference in log odds = +0·07 |
| TAU | -1·16 (-1·59, -0·72)[0·29 (0·15, 0·31)] | -1·01 (-1·47, -0·55)[0·36 (0·23, 0·58)] | Difference in log odds = +0·15 |

\* For the TCBT arm at the 12 month time period, therapist effects were found to be significant and were included in the model. The (log-)odds presented here are conditional effects (conditioned on therapist in the TCBT arm).

**Table 4: Additional CBT treatments sought during naturalistic follow-up**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total participants | 12-24 months post trial follow-up period  | Trial period (0-12 months)  | Whole observation period (0-24 months) |
| Any CBT sought incl. Regul8(N / %) | CBT for IBS sought(N / %)\* | CBT for other condition sought(N / %)\* | Regul8 used(N / %)\* | Non-adherence with allocated treatment (N / %) | Participants not receiving treatment allocated in ACTIB trial or receiving some form of CBT in the follow-up period (N / %) |
| TCBT | 186 | 15 / 8·1 | 3 / 1·6 | 13 / 7·0 | 0 / 0·0 | 29 / 15·6 | 43 / 23·1 |
| WCBT | 185 | 13 / 7·0 | 1 / 0·5 | 12 / 6·5 | 0 / 0·0 | 57 / 30·8 | 68 / 36·8 |
| TAU | 187 | 20 / 10·7 | 4 / 2·1 | 12 / 6·4 | 10 / 5·4 | 0 / 0·0 | 20 / 10·7 |
| All | 558 | 48 / 8·6 | 8 / 1·4 | 37 / 6·6 | 10 / 1·8 | 86 / 15·4 | 131 / 23·5 |

\*These treatments are not mutually exclusive. Participants were free to seek treatment for any or all categories.

**Figure 1: Predicted IBS-SSS means by assessment time point and trial arm**

*Predictions are derived made from respective analysis models fitted by MI with baseline set to the sample average value (IBS-SSS =265) and for the site from which most participants were recruited (“Southampton GPs”)*



**Figure 2: Predicted WSAS means by assessment time point and trial arm**

*Predictions are derived from the respective analysis models fitted by MI with baseline set to the sample average value (WSAS = 12·5) and for the site from which most participants were recruited (“Southampton GPs”)*

