Therapist telephone-delivered CBT and web-based CBT compared with treatment as usual in refractory irritable bowel syndrome: the ACTIB three-arm RCT

Hazel Everitt,1* Sabine Landau,2 Paul Little,1 Felicity L Bishop,3 Gillian O’Reilly,1 Alice Sibelli,4 Rachel Holland,2 Stephanie Hughes,1 Sula Windgassen,4 Paul McCrone,5 Kim Goldsmith,2 Nicholas Coleman,6 Robert Logan,7 Trudie Chalder8 and Rona Moss-Morris4

1Primary Care and Population Sciences, University of Southampton, Southampton, UK
2Biostatistics, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, London, UK
3Centre for Applications of Health Psychology, University of Southampton, Southampton, UK
4Health Psychology Section, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, London, UK
5Institute of Psychiatry, Psychology & Neuroscience, King’s College London, London, UK
6Department of Gastroenterology, Southampton University Hospital, Southampton, UK
7Department of Gastroenterology, King’s College Hospital, London, UK
8Academic Department of Psychological Medicine, King’s College London, London, UK

*Corresponding author hae1@soton.ac.uk

Declared competing interests of authors: Paul Little was Programme Director of the Programme Grants for Applied Research (PGfAR) programme, Editor-in-Chief for the PGfAR journal and a member of the National Institute for Health Research (NIHR) Journals Library Editorial Group and the NIHR PGfAR expressions of interest – Health Technology Assessment Projects Remit Meeting. Trudie Chalder reports grants from Guy’s and St Thomas’ Charity. She was a faculty member at the Third International Conference on Functional (Psychogenic) Neurological Disorders, September 2017, Edinburgh, UK; a member of the Improving Access to Psychological Therapies (IAPT) Education and Training Evidence Review Group (2016); a member of the IAPT Outcomes and Informatics Meeting (2016–present); and the president of the British Association for Behavioural and Cognitive Psychotherapies (2012–15), for which she did not receive payment. She delivered workshops on medically unexplained symptoms during the conduct of the study (money paid into King’s College London for future research). Trudie Chalder has a patent for the background intellectual property (IP) of the manuals that were developed prior to the trial starting. The Trial Steering Committee Chairperson, Peter White, was a colleague of Trudie Chalder in the past but he has recently retired. Rona Moss-Morris reports personal fees from training in irritable bowel syndrome interventions for Central and North West
London NHS Foundation Trust and the University of East Anglia outside the submitted work. The patient manual is background IP developed by Rona Moss-Morris and Trudie Chalder in previous work. The therapist manual was developed for the Assessing Cognitive–behavioural Therapy in Irritable Bowel (ACTiB) trial. These manuals were made available only once the 12-month ACTiB follow-up was complete. Sabine Landau reports support via the Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King’s College London.

Published April 2019
DOI: 10.3310/hta23170

Scientific summary

The ACTiB three-arm RCT
Health Technology Assessment 2019; Vol. 23: No. 17
DOI: 10.3310/hta23170

NIHR Journals Library www.journalslibrary.nihr.ac.uk
Scientific summary

Background

Irritable bowel syndrome (IBS) is a common chronic gastrointestinal (GI) disorder affecting 10–22% of the UK population, with NHS costs of > £200M per year. Abdominal pain, bloating and altered bowel habits affect quality of life (QoL) and social functioning and can lead to time off work. Treatment relies on a positive diagnosis, reassurance, lifestyle advice and drug therapies. However, many patients suffer ongoing symptoms.

Face-to-face cognitive–behavioural therapy (CBT) has been shown to help IBS, reducing IBS symptoms and improving QoL measures, but NHS availability is poor and cost-effectiveness is uncertain. However, National Institute for Health and Care Excellence (NICE) guidance recommends CBT for patients with refractory IBS symptoms (i.e. ongoing symptoms after 12 months despite being offered appropriate medications and lifestyle advice) (NICE. Irritable Bowel Syndrome in Adults: Diagnosis and Management of Irritable Bowel Syndrome in Primary Care. Manchester: NICE; 2015).

Web-based CBT (WCBT) has been shown to be helpful for other long-term conditions (e.g. depression) and has advantages; for example, it can be completed at a time, place and rate convenient to the participant, without extra travel time and costs. Small pilot trials showed that WCBT had promise for helping IBS but indicated that some therapist input is needed. We previously developed a CBT self-management website to support patients with IBS (Regul8) and trialled it among 135 patients in the National Institute for Health Research (NIHR) Research for Patient Benefit-funded Management of Irritable Bowel Syndrome (MIBS) feasibility study (Everitt H, Moss-Morris R, Sibelli A, Tapp L, Coleman N, Yardley L, et al. Management of irritable bowel syndrome in primary care: the results of an exploratory randomised controlled trial of mebeverine, methylcellulose, placebo and a self-management website. BMC Gastroenterol 2013;13:68).

This NIHR Health Technology Assessment (HTA) Assessing Cognitive–behavioural Therapy in Irritable Bowel (ACTIB) trial was in response to a commissioned call (HTA number 11/69/02) to assess the clinical effectiveness and cost-effectiveness of psychological interventions for patients with refractory IBS.

Objectives

To estimate the clinical effectiveness and cost-effectiveness of therapist telephone-delivered CBT (TCBT) and a web-based CBT (WCBT) compared with treatment as usual (TAU) in lessening IBS symptom severity and improving functioning at 3, 6 and 12 months after randomisation in adults with refractory IBS.

Methods


Design: three-arm multicentre randomised controlled trial

Adult patients with refractory IBS were individually randomised to TCBT, WCBT [a previously developed CBT website (Regul8) with low-level therapist support] or TAU with 12-month follow-up.
Setting: participants’ homes via telephone and internet
Therapists were based in the South London and Maudsley NHS Foundation Trust (SLAM). Participants were recruited from London and the south of England from primary and secondary care.

Inclusion criteria
Those meeting the inclusion criteria were adults (aged ≥ 18 years) with refractory IBS (defined as fulfilling the Rome III criteria for IBS: reporting ongoing clinically significant symptoms [i.e. an IBS Symptom Severity Score (IBS SSS) of ≥ 75], had been offered first-line therapies [e.g. antispasmodics, antidepressants or fibre-based medications] and had experienced continuing IBS symptoms for ≥ 12 months). Participants aged > 60 years were included only if they had received a consultant review in the previous 2 years to confirm that their symptoms were IBS related and to exclude other serious bowel conditions (there is an increased risk of bowel cancer in those aged > 60 years and clinical guidance suggests that further investigations are needed in this group).

Exclusion criteria
The exclusion criteria were having unexplained rectal bleeding or weight loss or a diagnosis of inflammatory bowel disease (IBD), coeliac disease, peptic ulcer disease or colorectal carcinoma. People were excluded if they were unable to participate in CBT because they had speech or language difficulties or had no access to an internet-enabled computer to be able to undertake the WCBT, or had received CBT for IBS in the past 2 years; also excluded were those who had previously had access to the Regu8 website or who were currently participating in an IBS/intervention trial.

Interventions
Two methods of delivering CBT were assessed: TCBT (total of 8 hours of telephone therapy contact time) and a lower-intensity WCBT (the Regu8 website) with 2.5 hours of therapist support.

The CBT content of the two treatments was the same, based on an empirical cognitive–behavioural model of IBS. It consisted of education, behavioural and cognitive techniques aimed at improving bowel habits, developing stable and healthy eating patterns, addressing unhelpful thoughts, managing stress, reducing symptom focusing and preventing relapse.

Participants randomised to the TCBT arm received a detailed CBT manual including homework. They received six 1-hour telephone sessions with a CBT therapist over 9 weeks and two 1-hour booster sessions at 4 and 8 months. Participants randomised to the WCBT arm received access to the Regu8 website and were advised to undertake the eight online weekly sessions and homework tasks. They received weekly automated e-mail reminders, three 30-minute telephone therapy support calls over 9 weeks and two 30-minute booster sessions at 4 and 8 months.

Trained CBT therapists provided the TCBT sessions for both therapy arms. Each therapist received 2 days’ training and a therapy manual. Post training, therapists received monthly supervision with an experienced therapist. Treatment fidelity was assessed using audio-recordings of therapy sessions.

Treatment as usual
Patients in all three arms received TAU, with the control arm being TAU alone. TAU was defined as continuation of current medications and usual general practitioner (GP) or consultant follow-up with no psychological therapy for IBS. All GPs or consultants received a copy of the NICE guidance for IBS to ensure that all clinicians had the standard best practice information on IBS management. All participants received a standard information sheet on lifestyle and diet related to IBS, which was based on the NICE guidance. TAU-only participants had access to the WCBT website at the end of the trial follow-up period, but without therapist support.
Recruitment
Participants were recruited from general practice surgeries and gastroenterology clinics in two regions [Southampton and London (Guy’s and St Thomas’ NHS Foundation Trust, and King’s College Hospital)]. Primary care patients were identified by searching GPs’ lists for those with a diagnosis of IBS and by opportunistically recruiting patients presenting with IBS. An invitation letter was sent, including a patient information sheet and a reply slip to be returned to the research team. In secondary care, when available, clinic lists were also searched for patients with a diagnosis of IBS and potential participants were invited by letter. However, most recruitment was opportunistic during gastroenterology clinics. Advertisements were placed in relevant general practice and GI clinics and on NHS websites.

Study procedures
The study team undertook initial telephone screening for eligibility. Any patient indicating that they might have a ‘red flag’ symptom (i.e. unexplained weight loss or rectal bleeding) was referred back to their GP for further assessment.

Those eligible after telephone screening completed online consent and were invited for screening blood tests at their general practice surgery or hospital clinic for full blood count, C-reactive protein and tissue transglutaminase (as recommended in NICE guidelines). If the blood test results were within normal limits, the participant was invited to complete baseline questionnaires and be randomised.

Randomisation
Randomisation was carried out by an independent randomisation service at King’s College London Clinical Trials Unit (CTU), which was accessed by study sites via a web-based system. Randomisation was at the level of the individual, using block randomisation with randomly varying block sizes, stratified by recruitment centre (Southampton general practices, Southampton secondary care, London general practices, London secondary care).

Blinding participants to therapy was not possible and the research assistants responsible for allocating patients to therapists could not be blinded. However, the principal investigators and statisticians remained blinded.

The baseline measures included outcome measures, sociodemographic details, current medication, medical history and medications, duration of IBS symptoms and previous or current psychiatric diagnoses.

The outcome measures were completed by participants at baseline and at 3, 6 and 12 months after randomisation.

Primary outcomes
The IBS SSS measures the severity and duration of abdominal pain, abdominal distension/tightness, bowel habit and QoL (score of 0–500).

The Work and Social Adjustment Scale (WSAS) measures the effect of IBS on people’s ability to work and manage at home, participate in social and private leisure activities and maintain relationships.

Secondary outcome measures
The Subject’s Global Assessment (SGA) of relief measures responses to treatment and the Patient Enablement Questionnaire (PEQ) assesses any change in participants’ ability to cope with their illness and life after treatment. Mood was measured by the Hospital Anxiety and Depression Scale (HADS). The Client Service Receipt Inventory (CSRI) and EuroQol-5 Dimensions (EQ-5D) were used to gather information on use of health services and health-related QoL, respectively.

Adherence to therapy was measured by the number of telephone sessions and/or web sessions. Compliance was defined as patients randomised to WCBT completing at least four web sessions and one or more of the
telephone support calls. For patients randomised to TCBT, compliance was defined as completing at least four of the initial telephone CBT sessions.

Patients’ GP notes were reviewed at 12 months to assess GP and other consultations in the year prior to entering the study and in the 12 months since study entry.

**Sample size**

A 35-point difference between therapy groups and TAU on the IBS SSS at 12 months was regarded as clinically significant (assuming a 15-point placebo response in the TAU arm in the trial). Assuming a within-group IBS SSS standard deviation (SD) of 76 (MIBS pilot study), this equates to an effect size of 0.46. To achieve 90% power at a 2.5% significance level (adjusting for two primary outcomes) required 119 subjects per group. This sample size was increased by an inflation factor of 1.32 to take account of therapist effects, decreased by a deflation factor of 0.84 assuming that baseline values are predictive of post-treatment values (correlation 0.4) and further inflated (factor 1.25) for attrition of < 20%. The final sample size was 165 patients per group, or 495 patients in total. For WSAS, this would be sufficient to detect a clinically important difference between WCBT (or TCBT) and TAU.

**Statistical analysis**

The Trial Steering Committee (TSC) approved the statistical analysis plan. All analyses followed the intention-to-treat principle. Group differences for IBS SSS and WSAS were assessed using a mixed linear regression model for repeated measurements. The mixed models accounted for missing outcome data under the missing-at-random assumption. Secondary outcomes were analysed similarly (as appropriate for continuous or dichotomous outcomes).

**Economic evaluation**

A health service and societal perspective was used. Service use was measured with a service receipt schedule at baseline and at each follow-up. Societal costs were calculated by including family care costs and lost work costs. Cost-effectiveness was assessed by combining the cost data with the IBS SSS and WSAS score at 12-month follow-up and quality-adjusted life-years (QALYs) (generated from the EuroQol-5 dimensions, five-level version). Sensitivity analyses were conducted by varying the therapy costs and imputing missing cost and QALY data.

**Results**

In total, 558 (38.4%) out of the 1452 patients screened for eligibility were recruited between May 2014 and March 2016: 186 were randomised to TCBT, 185 to WCBT and 186 to TAU. The most common reasons for exclusion at screening were not having refractory IBS (defined as an IBS SSS of ≥ 75), being > 60 years of age and not having had recent consultant review and not having been offered first-line therapies. Over-recruitment from the original sample size was undertaken (within the original recruitment time frame) to compensate for a lower follow-up rate than had been allowed for in the original sample size calculation. Follow-up rates of 76.5% at 3 months (427/558), 72.9% at 6 months (407/558) and 70.3% at 12 months (392/558) were achieved. The 1-year follow-up was completed in April 2017.

The proportion of female participants was 75.8% (423/558). The mean age of participants was 43.1 years (SD 13.2 years) and the median time since diagnosis was 7.4 years (range 0.3–64.6 years); 10.2% of participants had seen a GI consultant. Their mean IBS SSS was 265 (SD 95.5), indicating moderately severe IBS, and the baseline mean WSAS score was 12.5, suggesting significant, but not severe, functional impairment. The median time from the start of symptoms to diagnosis was 3.0 years (range 0.0–47.0 years); 30.3% of participants (169/558) reported having received treatment for anxiety and 39.4% (220/558) reported having received treatment for depression. The mean baseline HADS anxiety score was 10.7 (SD 4.2) and the mean baseline HADS depression score was 5.7 (SD 3.7). This suggests that participants were more
anxious than depressed at baseline but that, overall, there was no significant mental health comorbidity. Baseline characteristics were well balanced between the groups, indicating that randomisation had been successful.

Mean IBS SSS were 61.6 (95% CI 89.5 to 33.8) lower ($p < 0.001$) in the TCBT arm and 35.2 (95% CI –12.6 to 57.9) lower ($p = 0.002$) in the WCBT arm than in the TAU arm (mean IBS SSS of 205.6 at 12 months) at 12 months. The mean WSAS score in TAU arm was 10.8 at 12 months and was 3.5 (95% CI 5.1 to 1.9) lower ($p < 0.001$) in the TCBT arm and 3.0 (95% CI 4.6 to 1.3) lower ($p = 0.001$) in the WCBT arm.

Secondary outcomes also showed significant improvement in the therapy arms. For SGA of relief, 84.8% of participants were responders in the TCBT arm at 12 months, compared with 41.7% in the TAU arm (odds ratio (OR) 6.1, 95% CI 2.5 to 15.0; $p < 0.001$) and 75.0% in the WCBT arm (OR 3.6, 95% CI 2.0 to 6.3; $p < 0.001$). For the PEQ, 78.3% of participants were responders in the TCBT arm, compared with 23.5% in the TAU arm (OR 9.3, 95% CI 4.5 to 19.3; $p < 0.001$) and 54.8% in the WCBT arm (OR 3.5, 95% CI 2.0 to 5.9; $p < 0.001$). For HADS, compared with the TAU arm [mean HADS score 16.4 (SD 6.9) at 12 months], scores were 2.8 (95% CI 4.1 to 1.5) lower ($p < 0.001$) in the TCBT arm and 2.3 (95% CI 3.7 to 1.0) lower ($p < 0.001$) in the WCBT arm at 12 months.

There was no evidence that the interventions had an impact on the use or cost of other health-care services. Health service costs during the follow-up period were £956 higher for TCBT than for TAU (bootstrapped 95% CI £601 to £1435) and £224 higher for WCBT than for TAU (bootstrapped 95% CI –£11 to £448). TCBT produced 0.0429 more QALYs and WCBT produced 0.0290 more QALYs than TAU. The incremental cost-effectiveness ratio for TCBT compared with TAU was £22,284 and for WCBT compared with TAU was £7724; the ratios after imputation were £29,000 and £19,593, respectively.

In a nested qualitative study, 52 participants (17 or 18 from each trial arm) were interviewed at 3 months and 42 participants were interviewed again at 12 months. This highlighted an increased capacity to cope with symptoms, negative emotions and other challenges of daily life in the CBT arms. It also suggested that therapists are important in supporting patients to engage with CBT and to make sense of the therapy and their IBS. Patients valued having therapist support available alongside the Regul8 website and this may have helped enhance their engagement and outcomes.

**Conclusions**

This is believed to be the largest trial of CBT for IBS worldwide. It recruited from primary and secondary care sites in the UK. Both CBT arms showed significant improvements in IBS outcome measures compared with TAU at 12 months. WCBT had a lower cost per QALY than TCBT. Therapist input was found to be important in supporting web-based CBT. This large, rigorously conducted randomised controlled trial indicates that these CBT interventions can provide sustained improvements in IBS symptoms at an acceptable cost.

**Trial registration**

This trial is registered as ISRCTN44427879.

**Funding**

Funding for this study was provided by the HTA programme of the National Institute for Health Research (NIHR). The University of Southampton sponsored this study. Funding was received from the NIHR HTA Board and the NIHR Clinical Research Network and support was received from the NIHR Clinical Research Network.
Criteria for inclusion in the Health Technology Assessment journal

Reports are published in Health Technology Assessment (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 11/69/02. The contractual start date was in September 2013. The draft report began editorial review in January 2018 and was accepted for publication in June 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

© Queen’s Printer and Controller of HMSO 2019. This work was produced by Everitt et al. under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).
NIHR Journals Library Editor-in-Chief

Professor Ken Stein  Professor of Public Health, University of Exeter Medical School, UK

NIHR Journals Library Editors

Professor John Powell  Chair of HTA and EME Editorial Board and Editor-in-Chief of HTA and EME journals. Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK, and Honorary Professor, University of Manchester, and Senior Clinical Researcher and Associate Professor, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK

Professor Andrée Le May  Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals) and Editor-in-Chief of HS&DR, PGfAR, PHR journals

Professor Matthias Beck  Professor of Management, Cork University Business School, Department of Management and Marketing, University College Cork, Ireland

Dr Tessa Crilly  Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin  Senior Scientific Advisor, Wessex Institute, UK

Dr Peter Davidson  Consultant Advisor, Wessex Institute, University of Southampton, UK

Ms Tara Lamont  Director, NIHR Dissemination Centre, UK

Dr Catriona McDaid  Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire  Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads  Professor of Wellbeing Research, University of Winchester, UK

Professor John Norrie  Chair in Medical Statistics, University of Edinburgh, UK

Professor James Raftery  Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma  Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts  Professor of Child Health Research, UCL Great Ormond Street Institute of Child Health, UK

Professor Jonathan Ross  Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks  Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Ken Stein  Professor of Public Health, University of Exeter Medical School, UK

Professor Jim Thornton  Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Professor Martin Underwood  Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK

Please visit the website for a list of editors: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk