ACTIB

ACTIB (Assessing Cognitive behavioural Therapy in Irritable Bowel): A randomized controlled trial of clinical and cost effectiveness of therapist delivered cognitive behavioural therapy and web-based self-management in irritable bowel syndrome

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LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CACE	Complier Average Causal treatment Effect
CBT	Cognitive Behavioural Therapy
CEACs	Cost-effectiveness acceptability curves
CI	Confidence Interval
CLRN	Comprehensive Local Research Network
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTU	Clinical Trials Unit
CRP	C Reactive Protein
DMEC	Data Monitoring and Ethics Committee
EQ5D	5 Item Euroquol Quality of Life Measure
FBC	Full Blood count
GCP	Good Clinical Practice
GI	Gastrointestinal
GSTT	Guy's and St Thomas' NHS foundation Trust
HADS	Hospital Anxiety and Depression Scale
HTA	Health Technology Assessment
ICH	International Conference for Harmonisation
IBS	Irritably Bowel Syndrome
IBS SSS	IBS Symptom Severity Score
ICERs	Incremental Cost Effectiveness Ratios
ICH GCP	International Conference on Harmonisation of Good Clinical Practice

ITT	Intention To Treat
LIBT	Low intensity web-based CBT programme
MAR	Missing At Random
NICE	National Institute for health and Clinical Excellence
NIHR	National Institute of Health Research
MIBS	Management of Irritable Bowel Syndrome
PCRN	Primary Care Research Network
QALYs	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RfPB	Research for Patient Benefit
ROME III	Diagnostic Questionnaire developed by the Rome Foundation for IBS
SCGC	Secondary Care Gastroenterology Clinics
SD	Standard Deviation
SGA	Subject Global Assessment of Relief
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAU	Treatment As Usual
TCBT	Therapist CBT
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UKCRC	United Kingdom Clinical Research Collaboration
WASAS	Work and Social Adjustment Scale

TRIAL SUMMARY

Background

IBS affects 10–22% of the UK population, with NHS costs over £200 million a year. Abdominal pain, bloating and altered bowel habit affect quality of life, social functioning and time off work. Current GP treatment relies on a positive diagnosis, reassurance, lifestyle advice and drug therapies, but many suffer ongoing symptoms.

CBT and self-management can be helpful, but poor availability in the NHS restricts its use. Further evidence on the clinical and cost-effectiveness of therapist CBT for IBS and low intensity alternatives will help in service planning and provision in the NHS.

Aims

To determine the clinical and cost-effectiveness of therapist delivered cognitive behavioural therapy and web-based CBT self-management in irritable bowel syndrome.

Plan of Investigation

495 participants with refractory IBS will be randomised to a high intensity therapist delivered CBT (TCBT) + Treatment as usual (TAU), or a low intensity web-based CBT programme (LIBT) + TAU or Treatment as usual alone.

The two CBT programmes will include the same content. However, TCBT will consist of six, 60 minute CBT sessions with a therapist over the telephone completed over 9 weeks at home and two 'booster' one-hour follow up phone calls at 4 and 8 months (8 hours therapist contact time).

LIBT will consist of access to a previously developed and piloted web-based CBT self-management programme (Regul8) and three 30 minute therapist telephone sessions completed over 9 weeks at home and two 'booster' 30 minute follow up phone calls at 4 and 8 months (2½ hours therapist contact time).

Clinical effectiveness will be assessed by examining the difference between arms in the IBS Symptom severity score (IBS SSS) and the work and social adjustment scale (WASAS) at 12 months from randomisation. Cost-effectiveness will combine measures of resource use with the IBS SSS at 12 months and QALYs.

Potential Impact

This trial will assess the clinical and cost-effectiveness of CBT for IBS in a well-designed rigorous study with a long term outcome. This will enable clinicians, patients and health service planners to make informed decisions regarding the management of IBS with CBT.

Summary for the Non-Expert

Irritable bowel syndrome (IBS) is a common chronic gastrointestinal (tummy) disorder that affects 10–22% of the UK population and costs the NHS over £200 million a year. Abdominal (tummy) pain, bloating and altered bowel habit (diarrhoea or constipation) affect quality of life, ability to enjoy social activities and time off work. Initial treatment relies on a positive diagnosis, reassurance, lifestyle advice, and drug therapies. However, many patients suffer on-going distressing symptoms.

Guidelines recommend Cognitive Behavioural Therapy (CBT) for patients with IBS who continue to have symptoms after 12 months. CBT is a therapeutic approach which centres on the interaction of bodily symptoms, thoughts, emotions and what people do to cope with their symptoms. However, access to this therapy is limited due to the cost and availability of therapists and there is uncertainty regarding how effective it is in reducing symptoms in the long term and its cost-effectiveness. One way to make CBT accessible to larger numbers of patients is to provide a less intense form of the therapy on the internet. We have developed a CBT-based website which could be accessed by patients countrywide. This low-intensity behavioural therapy (LIBT) has the potential to be more accessible, because it is less expensive and requires less therapist-time than traditional therapist-delivered CBT. However, there is a lack of high quality evidence on the clinical effectiveness and cost-effectiveness of these approaches.

The Therapist delivered CBT arm will have 6, 1 hour telephone CBT sessions with trained therapists over 9 weeks. Therapists will provide information about IBS, and use behavioural and cognitive techniques aimed at improving bowel habits, addressing unhelpful thoughts, reducing heightened attention to symptoms and preventing relapse. Patients will complete tasks to reinforce the sessions. Previous trials of Therapist CBT have shown that the positive effect of CBT on IBS diminishes with time as people can experience flare-ups of their condition, so we have added two booster CBT telephone sessions at 4 and 8 months to provide further support to manage relapse. The LIBT group will have access to the interactive, CBT based self-management website developed with substantial patient input in a previous study (MIBS). Participants undertake 8 sessions over 9 weeks at home, which include similar content to the therapist CBT, homework on online and weekly email reminders. In a feasibility study of the website, patients found it user friendly and accessible and it appeared to enhance maintenance of symptom improvement compared to control. They will also receive 3, 30 minute telephone support calls from a therapist and 2 booster telephone calls at 4 and 8 months. Several small trials of web-based CBT for IBS show promising results but indicate that some therapist input is necessary to encourage patients to engage with and work through a website. We will compare both therapies with 'treatment as usual' (TAU) – where patients continue with their current medications and GP or consultant care, but do not receive any psychological therapy.
This will be a multi-site trial. Participants will be recruited from London (by the research team at Kings) and the South coast of England (by the research team at Southampton). Hospital-based gastroenterology consultants and GPs will search their databases for patients with IBS and send out invitation letters. They will also recruit patients presenting to clinic or the surgery. People interested in participating will return a reply slip to the research team and be contacted by the study team who will assess them for eligibility screening to ensure they fulfil the entry criteria for the trial. Adults with IBS symptoms for at least 12 months that have

not improved with initial treatments will be eligible. They will have a simple blood test to exclude other conditions and then they will be randomly assigned to one of the 3 groups, therapist CBT, LIBT (the website), and treatment as usual (TAU). The main outcomes are IBS symptom severity and the work and social adjustment scale which measures people's ability to function and live their lives at 3, 6 & 12 months. We will also assess cost-effectiveness and wider benefits (e.g. quality of life and mood) as these provide important additional ways of assessing the impact of IBS on people's lives.

The trial will be conducted in full accordance with current guidelines for ethical research conduct. The research team has substantial experience in running trials and working with patients with IBS and thus are ideally placed to undertake this trial.

Main Research Question

What is the clinical and cost-effectiveness of cognitive behavioural therapy for patients with refractory irritable bowel syndrome?

Research Objectives

Primary Objectives:

1) Estimate the clinical effectiveness of therapist delivered CBT (TCBT) plus treatment as usual (TAU) for reducing the severity and impact of IBS symptoms compared to TAU alone at 12 months after randomisation.

2) Estimate the clinical effectiveness of a previously developed low intensity behavioural therapy (LIBT) plus TAU to TAU alone at 12 months after randomisation.

Secondary Objectives:

3) To compare the cost-effectiveness of TCBT and LIBT in comparison to TAU over the 12-month follow-up period.

4) To estimate 1) and 2) at 3 and 6 months after randomisation.

5) Assess whether TCBT and/or LIBT have a positive impact on relief of IBS symptoms, quality of life, enablement, anxiety and depression and health care usage and costs compared to TAU at 3, 6 and 12 months follow-up, and acceptability of the treatment.

Tertiary aims:

6) To investigate possible cognitive and behavioural mediators or processes of clinical improvement for both the CBT and LIBT.

7) To examine predictors and moderators of outcome.

Extisting Research

IBS is a common chronic gastrointestinal disorder that affects 10 – 22% of the UK population and costs the NHS over 200 million pounds a year (1, 2). Abdominal pain, bloating and altered bowel habit affect quality of life, social functioning and time off work (3, 4). Treatment relies on a positive diagnosis, reassurance, lifestyle advice and drug and psychological therapies. However, many patients suffer ongoing symptoms. There is a significant psychological aspect to IBS in many patients and psychological therapies, CBT, biofeedback and hypnotherapy can help (5), but availability of these treatments is limited.

Face to face Cognitive Behavioural Therapy (CBT) has been shown to be helpful for IBS, reducing symptom scores and improving QOL measures (5-7) but availability is poor in the NHS and CBT in this format was not shown to be cost effective in a Cochrane review (7). Additionally there are problems with limited concordance (7) with face to face therapy. For instance in the Kennedy trial (6), fewer than half of the participants were considered to have completed therapy by the end of the intervention and 41% were recorded as declining therapy or dropping out, often due to time issues such as work and child care commitments. However, NICE Guidance (8) recommends CBT for patients with refractory IBS symptoms (i.e.

ongoing symptoms after 12 months despite being offered appropriate medications and lifestyle advice)

Web-based CBT has been shown to be helpful for other long-term conditions e.g. depression (9), tinnitus (10), Muliple Sclerosis (11). Thus this could be a cost-effective way of providing help to those with IBS. Recent small pilot trials show promise for web-based CBT in IBS (12-14) but indicate some therapist input is needed. Web-based delivery has the advantage that it can be accessed at a time and place convenient to the participant, can be undertaken at a pace that suits each individuals circumstances and does not require extra travel time and costs.

NICE recommends the use of Computer CBT for depression, panic disorder and phobia in Primary Care (15). A computerised CBT programme for IBS has the potential to make CBT more widely available for IBS and at a low cost. The increasing availability of the Internet makes this a good medium to provide easily accessible patient information and self-management programmes. The majority of households in the U.K. now have web access. Currently 73% have access and this is increasing year on year. This is therefore an ideal time to assess and disseminate new web-based interventions. We have already developed a CBT website to support patients with IBS (Regul8) and trialled it among 135 patients with more than 90% follow-up in the NIHR-RfPB funded MIBS study (12). Even with this (underpowered) sample, and very minimal nurse input, Subjects Global Assessment of Relief (SGA) scores (i.e. relief from IBS symptoms) and their Enablement Scores (sense of control over their IBS) were significantly improved in the Regul8 groups compared to the non-website group.

Research Methods

Design 3 arm multicentre randomised controlled trial

Method 495 patients with refractory IBS will be individually randomised to therapist delivered CBT (TCBT) + Treatment as usual (TAU), or lower intensity web-based cognitive behavioural therapy programme (LIBT) (a previously developed self-management CBT website with low levels of therapist support) + TAU, or Treatment as usual (TAU) alone for 9 weeks with 12 month follow up.

Change in Sample Size in response to follow up rates

Follow up completion rates for 12m questionnaire are below the 80% expected in the sample size calculations at 18m into recruitment, and there is uncertainty what the final follow up rate will be. The trial statistician recalculated the sample size if follow up were to be 70%, not 80%, and calculated another 75 extra patients would be needed. The DOH agreed to fund excess treatments costs (Therapist time) for an additional 75 patients.

Re-calculation for 30% attrition

N = 119 per group before applying inflation and deflation factors

119 x 1.32 x 0.84 = 132 per group, as above

20% attrition: 132/(1 – 0.2) = 165 patients per group

30% attrition: 132/(1 – 0.3) = 189 patients per group

567 patients in total, so for an even group size we will aim for 570.

Setting Treatment will take place at participant's homes via telephone and internet. Therapists will be based at King's College London. Participants will be recruited from London and the South Coast of England from primary and secondary care.

Target population

Inclusion Criteria: Adults (18yrs and over) with refractory IBS (clinically significant symptoms defined by a IBS-SSS i.e. >75), fulfilling ROME III criteria and who have been offered first-line therapies (eg anti-spasmodics, anti-depressants or fibre based medications) but still have continuing IBS symptoms for 12 months or more. Potential participants over 60 yrs will only be included if they have had a consultant review in the previous two years to confirm that their symptoms are related to IBS and that other serious bowel conditions have been excluded. This is because NICE guidelines (8) advise that a new change in bowel habit in over 60 years should have further investigations, as there is an increased risk of bowel cancer in the over 60 years age group.

Exclusion criteria: Unexplained rectal bleeding or weight loss, diagnosis of inflammatory bowel disease, coeliac disease, peptic ulcer disease or colorectal carcinoma. Unable to participate in CBT due to speech or language difficulties. No access to an internet computer to be able to undertake the LIBT. Has received CBT for IBS in the last two years. Has had previous access to the MIBS website. Is currently participating in an IBS/intervention trial.

Withdrawal criteria: Participants will be withdrawn from the trial if there are any concerns regarding informed consent. Participant can also withdraw if they choose without giving a reason. If a participant withdraws consent for research follow-up during the trial, the trial team should be informed. The information on the event will be collected in the Drop-out Report Form.

Planned Interventions

Two health technologies are being assessed in this study: Therapist CBT (TCBT) and the low intensity web-based CBT programme (LIBT) – the Regul8 website with some therapist support.

The CBT content of the two treatments is the same and is based on an empirical cognitive behavioural model of IBS (16, 17). The model specifies that factors such as stress and/or gastric infection trigger the symptoms of IBS, which are then maintained by patients' cognitive, behavioural and emotional responses to the symptoms. For instance, if a patient becomes anxious (emotion) about the symptoms, believes he/she has no control over them (cognitions) and responds by avoiding social situations (behaviour), this can increase anxiety and maintain symptoms through the link between a heightened autonomic nervous system and the enteric nervous system. This model was used to structure the content of the therapy sessions in our Regul8 website for the MIBS pilot study (12) which in turn drew from two efficacious IBS RCTs conducted by members of our research team, a nurse-delivered CBT trial (6) and a trial of a more minimal CBT based self-management programme (17). The therapy consists of education, behavioural and cognitive techniques, aimed at improving bowel habits,

developing stable, healthy eating patterns, addressing unhelpful thoughts, managing stress, reducing symptom focussing and preventing relapse. A summary of the sessions and related homework tasks are presented in the table below.

Table: Summary of the Self-Management Sessions included in the Regul8 website and the TCBT patient manual

Session 1. Understanding your IBS	Rationale for self-management which includes the following explanations: 1. Possible causes of IBS and illustrative physiology of the digestive system together with the functional changes that occur in the gut as a result of IBS. 2. How the autonomic nervous system ("fight-or-flight" stress system) may interact with the enteric nervous system
Session 2. Assessing your symptoms	Self-assessment of the interaction between thoughts, feeling and behaviours and how these can impact on stress levels and gut symptoms. Development of a personal model of IBS which incorporates these elements. Homework: Daily diaries of the severity and experience of IBS symptoms in conjunction with stress levels and eating routines/behaviours
Session 3. Managing Symptoms and Eating	Review of the symptom diary Behavioural management of the symptoms of diarrhoea and constipation, and common myths in this area are discussed. Goal setting is explained. The importance of healthy, regular eating and not being overly focused on elimination is covered. Homework: Goal setting for managing symptoms and regular/healthy eating. Goal setting, monitoring and evaluation continue weekly throughout the programme.
Session 4. Exercise and Activity	Importance of exercise in symptom management is covered Identifying activity patterns such as resting too much in response to symptoms or an all-or-nothing style of activity is addressed. Homework: Goal setting for regular exercise and managing unhelpful activity patterns if relevant.
Session 5. Identifying your thought patterns	Identifying unhelpful thought (negative automatic thoughts) in relation to high personal expectations and IBS symptoms is introduced. Link between these thoughts, feelings, behaviours and symptoms is reinforced. Homework: Goal setting plus daily thought records of unhelpful thoughts related to personal expectations and patterns of over activity.
Session 6. Alternative thoughts	The steps for coming up with alternatives to unhelpful thoughts are covered together with personal examples. Homework: Goal setting plus daily thought records including coming up with realistic alternative thoughts.
Session 7. Learning to Relax, Improving Sleep, Managing Stress and Emotions	Basic stress management and sleep hygiene are discussed. Diaphragmatic breathing, progressive muscle relaxation and guided imagery relaxation are presented in video and audio formats. Identifying common positive and negative emotions and the participant's current ways of dealing with these. New strategies to facilitate expression of emotion as well as coping with negative or difficult emotions are discussed Homework: Goal setting for stress management, good sleep habits and emotional processing.
Session 8. Managing flare-ups and the future	The probability of flare-ups is discussed and patients are encouraged to develop achievable, long term goals and to continue to employ the skills they have learnt throughout the manual to manage flare-ups and ongoing symptoms.

There are two key differences between the therapy trial arms:

1. The amount of therapist contact time/intensity of the intervention – TCBT participants will receive a total of 8 hours of therapy contact time compared to 2.5 hours in LIBT. The TCBT telephone sessions will be more formulation driven and although based on the content of the sessions/chapters of the patient manual, order and extent to which these are covered will be individualised.

2. The use of a CBT self-management manual in the TCBT arm versus access to an interactive website in the LIBT arm.

Participants randomised to TCBT will be contacted by one of the therapist team to organise the therapist telephone sessions and will be sent a detailed CBT manual including homework sessions to support the sessions. The TCBT arm will have six one hour telephone sessions with a CBT therapist at week 1, 2, 3, 5, 7, 9 and homework tasks. They will also receive two one hour booster sessions at 4 and 8 months.

Participants randomised to the LIBT arm will be provided with log in access to Regul8, an interactive, tailored CBT self-management website developed with substantial patient input in MIBS trial (12). They will be advised to start working through the 8 online weekly sessions and homework tasks and will receive weekly automated email reminders. In addition, they will receive three, brief 30 minute telephone therapy support calls at weeks 1, 3 and 5 and two, 30 minute booster sessions at 4 and 8 months. The telephone CBT sessions for the LIBT arm are undertaken whilst they are working through the website self-management programme to help them engage them with the CBT programme. Partcipants will also be able to email the therapist regarding queries about the website programme during the study. It is important to have some therapist input in the web self-management programme arm as several small trials of web-based (13, 14) or manual-based (17) CBT for IBS have shown promising results but indicated that therapist input is important to maintain participant engagement. Qualitative interviews with participants from the MIBS (12) study also highlighted the benefit of the telephone support session in improving patient understanding.

In both therapy arms, medical questions will not be addressed by the therapists and participants will be advised to seek medical advice if they have medical queries.

'Booster' sessions are included in both arms to discuss any setbacks and to reinforce positive symptoms management. Telephone CBT sessions rather than face to face are proposed for this study, as they have similar efficacy, improve accessibility, are efficient, less costly and could be readily delivered across the NHS from a centralised service. Face to face therapy has a significant drop out rate (6), often due to time issues such as work and child care commitments.

All telephone therapy sessions will be audio recorded for the purpose of assessing treatment fidelity. These will be used for supervision during the study and a percentage of the audio recordings (10%) will be analysed once the trial has ended by two independent clinicians, who will be masked to allocated treatment. At least two sessions for every therapist, (when available) and for therapy type will be rated in terms of adherence to the manual or web based approach (7-point Likert scale). The therapeutic alliance between

therapist and participant will also be rated on a 7-point Likert scale used in a previous large RCT of treatments for chronic fatigue syndrome (18).

Secure website pass-wording will ensure non-contamination of treatments. Patients in the TCBT arm will also be requested not to share their manual with others. Therapy manuals will be compiled for all the therapy sessions in both arms. Regular supervision will ensure that the therapists stick to the protocols in each arm. The manual will include instructions for the optimum setting for the telephone calls i.e. a quiet environment without interruptions.

Therapists

Ten CBT trained therapists working two sessions a week (or equivalent) will provide the telephone CBT sessions for both the TCBT and LIBT arms of the study. The therapists will receive training in the two protocols before recruitment starts. They will also receive fortnightly supervision in the first half of the trial then monthly in the second half from RMM, TC and additional accredited supervisors employed on the study to ensure quality of therapy and adherence to protocol. Regular supervision is part of good clinical practice in CBT. All sessions will be audio recorded to record length and number of phone sessions and to check treatment fidelity throughout and at the end of the trial.

Treatment as Usual (TAU)

Patients in all three arms will receive TAU, with the control arm being TAU alone. TAU is defined as continuation of current medications, and usual GP or consultant follow-up with no psychological therapy. All GPs or consultants involved in the study will receive a copy of the NICE Guidance for IBS at the start of the study to ensure all clinicians have standard best practice information on IBS management. They will also receive a Deskside reminder to remind them of the guidelines, protocol guidance on prescribing psychological therapies and inclusion criteria. All participants will receive a standard information sheet on Lifestyle and Diet in IBS based on the NICE guidance. Information will be collected on any changes in IBS treatments/ management during the study and numbers of GP and consultant consultations will be recorded for all three arms.

The TAU alone participants will have access to the LIBT website at the end of the trial follow-up period.

Ethical issues

The trial will be conducted in full accordance with current guidelines for ethical research conduct. The study will be performed subject to Research Ethics Committee (REC) approval, including any provisions of Site Specific Assessment (SSA), and local Research and Development (R&D) approval.

The potential benefit to participants from the interventions in this study is a greater understanding of the IBS, an improved ability to manage their condition and possibly reduced symptom severity or impact on their life from their IBS. This may lead to societal benefits such as a reduction in work days lost and reduced use of NHS resources. The risks of undertaking CBT are minimal, undertaking the sessions will require a time commitment on behalf of the participant and focussing on their IBS symptoms could temporarily worsen the symptoms in the short term. The CBT is provided alongside usual care so the participants will still have

access to all usual NHS services. Participants will be fully informed of the trial procedures before entering the study via a Patient Information Sheet and any questions will be answered by the research team prior to signing the on-line consent form.

Study documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All source documents will be retained for a period of 10 years following the end of the study in line with the University of Southampton guidelines. The end of the trial is defined by the closure of the trial database.

Fair access to the study:

Participants need to have web access, which could exclude some people who would otherwise like to take part. However, three quarters of households have web access, this figure is rapidly increasing, and those without home access could use public computers (e.g. local library).

Participants aged over 60 years must have had a consultant review to exclude other serious causes of their bowel symptoms in the last two years because colorectal cancer is more common in the over 60s and guidelines recommend that changes in bowel habit in this group require hospital tests beyond the scope of this trial.

To maximise recruitment and to ensure that motivated patients are not excluded from treatments that may help, participants in the TAU alone group will be given access to the Regul8 website at the end of the trial.

Recruitment

Patients will be recruited from secondary and primary care.

We plan to recruit 495 participants over 22 months (23 randomised /month) from GP surgeries in 2 regions (Southampton and London) and Secondary Care Gastroenterology Clinics in 2 regions (Southampton (UHS ± 500 IBS pts/yr) and London (GSTT, King's College Hospital and GSST ± 1000 IBS pts/yr)).

Primary care patients will be identified by searching general practitioners lists for those with a diagnosis of IBS and by opportunistic recruitment of patients presenting with symptoms consistent with IBS. We will utilise the English Primary Care network (PCRN) to aid recruitment and retention of GP practices. We will include practices with urban and rural settings and with a range of socio-demographic characteristics. GP practices willing to participate in the study will search their list for adult patients aged 18 years and over with a diagnosis of IBS. Potential participants will be contacted by letter (sent by the GP surgery) informing them about the trial and inviting them to take part. The GPs will check the lists of patients to be contacted prior to the invite letters being sent out to ensure that it is appropriate to contact them. The mailing will include the ACTIB patient information sheet. Participants who are interested in participating in the study will return a reply slip with their contact details in a prepaid response envelope to the research team. GPs will also be able to opportunistically provide information about the trial to potential recruits during their GP surgeries. Thus, if a patient with IBS attends a GP consultation, GPs will give them the patient information sheet regarding the trial and the reply slip and envelope.

Assuming 30 to 80 patients with a computer diagnosis of IBS per GP (2 to 5% prevalence and 1600 registered patients per GP) and 5 to 10% of those would fulfil the inclusion criteria and be willing to participate in the trial = 3 to 8 per GP. Thus 31 to 83 GPs will need to be recruited to achieve the target of 248 patients from primary care. Based on experience from the MIBS study (12), where we recruited on time to target 135 patients from primary care, we anticipate this being approximately 30 GP practices (15 in London and 15 in the Southampton Area). Invite letters will be sent out from the identified GP practices in a stepwise manner over time and response rates monitored to ensure adequate recruitment levels and a steady workload for the therapists.

Secondary Care patients will be identified from Gastroenterology clinics in Southampton and London (Kings, Guys and Thomas'). Clinic lists will be searched for patients with a diagnosis of IBS. Potential participants will be contacted by letter (sent from the clinic) informing them about the trial and inviting them to take part. The Consultants will check the lists of patients to be contacted prior to the invite letters being sent out to ensure that it is appropriate to contact them. The mailing will be as for the primary care patients. The consultants will also be able to opportunistically provide information about the trial to potential recruits during their clinics. It is estimated that over 500 patients with IBS attend Southampton hospital GI clinics each year and over 1000 attending the London GI clinics. Invite letters will be sent out in batches to achieve the required 248 sample size. Assuming a 30 to 40% response rate 620 to 827 letters will need to be sent to achieve the required sample size. Adverts will also be placed in relevant GP and gastroenterology clinics and on NHS websites. Clinics and GP practices will have information packs to hand out to potential participants. Where clinics would like more support with regards to recruitment, researchers will be available in clinics to answer questions about the study. The nurse, consultant or administrator will hand out information packs to relevant patients and ask them if they would like to hear more about the study from the researcher in the clinic. Only if the patient agrees, will the researcher tell them more about the study and answer any questions they may have. If the researcher cannot be present in the clinic – patients can either take away information packs and contact the research team if they have questions, or if they agree, the clinician can take their name and contact details and research team can contact them about study.

Study Procedures

Measures will be collected at the following timepoints:

CRF	Completed by*	Database**	Pre Consent	Baseline	3m	6m	12m	Ongoing or during treatment	Ref
Invite Reply	P	RT	X						na
Screening Questionnaire	P/TT	M	X						na
Consent	P	R		X					na

Sample Requisition Form	RN	RT		X					na
Adverse Events Form	TT	M						X	na
Drop-out Event Form	TT	M						X	na
Note Review Form	TT	M					X		na
IBS Symptom Severity Score (IBS-SSS)	P	R		X	X	X	X		(19)
Work & Social Adjustment Scale (WASAS)	P	R		X	X	X	X		(20)
Subjects Global Assessment of Relief (SGA)	P	R			X	X	X		(21)
EQ5D	P	R		X	X	X	X		(22)
Patient Enablement	P	R			X	X	X		(16)
Hospital Anxiety & Depression Scale	P	R		X	X	X	X		(23)
Client Service Receipt Inventory	P	R		X	X	X	X		(24)
Cognitive Scale CG-FBD	P	R		X	X	X	X		(25)
B-IPQ for IBS	P	R		X	X	X	X		(26)
IBS Behavioural Responses Questionnaire	P	R		X	X	X	X		(27)
Beliefs about Emotions Scale (BES)	P	R		X	X	X	X		(28)
"Impoverished Emotional Experience (IEE)" factor of the Emotional Processing Scale-25	P	R		X	X	X	X		(29)

Positive and Negative Affect Schedule (PANAS)	P	R		X	X	X	X		(30)
Demographics	P	R		X					na
About your IBS	P	R		X					na
Safety Questions	P	R			X	X	X		na
Rating of Satisfaction	P	R			X	X	X		(18)
Thoughts on my treatment	P	R			X	X	X		(31)
Therapist Database	T	MT						X	na

*Completed by
TT – Trial Team
T – Therapist
P – Patient
RN – Research Nurse/Phlebotomist
**Database
RT – Research Team database
M – MACRO CTU database
R – LifeGuide Regul8
MT – MACRO Therapist database

Those responding to the recruitment letter from their GP will be contacted by the study team to complete a screening process consisting of the Rome III criteria and questions about exclusion and inclusion criteria to check if they fulfil the eligibility criteria for the study. They will be identified with an unique ID number. Any patient indicating they may have a 'red flag' symptom that would indicate the need for further investigations (ie unexplained weight loss or rectal bleeding) will be referred back to their GP for further assessment and would not enter the study unless the GP felt the symptoms had been fully asssessed and that he or she was suitable for study entry.

Those fulfilling the screening entry requirements will be contacted by one of the research team to make sure they are fully informed of trial procedures and they will be sent the login and access details for the website in order for them to complete an on-line consent form. They will then be sent arrangement details to have a blood test for full blood count (FBC), transglutaminase antibodies (TTG) and C Reactive Protein (CRP) to exclude alternative diagnoses, ie anaemia that requires further investigation and Coeliacs disease (as recommended for IBS diagnosis in the NICE guidelines (8)). These blood tests will be undertaken by practice nurses/GPs within the GP surgeries or by Phlebotomists/research nurses at the secondary care sites (Southampton University Hospitals NHS Trust; Guy's and St Thomas' NHS Foundation Trust; Kings College Hospital NHS Foundation Trust). Samples will

be sent to University Southampton Hospital pathology laboratory for testing and will then be destroyed. The blood sample will not be stored for future use. The results will be made available to the participants GP. If the Blood tests are within normal limits the participant can complete the baseline measures and the participant will be then be randomised. If patient's have had all the required blood tests in the last three months, and request that these are used instead of taking a further sample, the research team will endeavor to find the results and check these are within normal limits.If the blood tests show an abnormal result i.e. a CRP over the normal laboratory range, anaemia or a positive test for Coeliacs disease, the patient will not be randomised to the trial but will be referred back to his or her GP for further assessment.

Randomisation

Randomisation will be co-ordinated by an independent randomisation service at the UKCRC registered King's Clinical trials Unit (CTU) and accessed by study sites via a web-based system. Randomisation will be at the level of the individual, using block randomisation with randomly varying block sizes, stratified by centre (Southampton GP practices, Southampton secondary care, London GP practices, London secondary care). Confirmation emails will be generated automatically in an unblinded or blinded manner to relevant study site and co-ordination staff, to maintain blinding where needed.

Unblinding

All research and therapy staff and participants are unblinded to treatment allocation of individual participants. All outcomes are patient reported and collected via the web which will avoid bias. Therefore there will be no need for unblinding during the trial. The exception is that the trial statisticians are blind to treatment allocation, as will be the DMEC, in order to take actions on the basis of the unblinded data alone. Also the trial team member who will contact participants to capture primary outcome data by telephone on the short questionnaire for those who have not completed follow-up questionnaires after email reminders, will be blinded to the participants treatment group to avoid bias.

Safety

Adverse events (AEs)

Adverse events (AE) are any clinical change, disease or disorder experienced by the participant during their participation in the trial, whether or not considered related to the use of treatments being studied in the trial.

Serious Adverse Events (SAEs)

An adverse event (AE) is defined as serious (an SAE) if it results in one of the following outcomes:

- A life-threatening adverse event
- In-patient hospitalisation
- A disability/incapacity
- A congenital anomaly/birth defect in the offspring of a subject
- Other medical events requiring intervention to prevent one of the above outcomes

Serious Adverse Reactions (SARs)
A Serious Adverse Reaction can be defined as: A SAE considered to be a reaction to one of the supplementary therapies

Reporting serious adverse events and reactions (SAEs and SARs)
On completion of an SAE, the chief investigator, on behalf of the sponsor, will assess whether the SAE is a Serious Adverse Reaction (SAR) or a (SUSAR). A SUSAR is any adverse reaction that is classed as serious and is suspected to be caused by the intervention and is not expected. If the SAE is classified as a SUSAR, the trial team will report the SUSAR to their Ethics Committee (EC). For a SUSAR which is fatal or life threatening, the team, on behalf of the sponsor, has 7 days to report the SUSAR to the EC. For a SUSAR which is not fatal or life threatening, the team has 15 days. The SUSAR is recorded in the participants' medical notes and the participant will be followed up.

Follow-up after adverse events
After an SAE or SAR, a decision will be made by trial team, after advice from the relevant authorities and the participant's GP, as to whether the participant should be withdrawn from either their randomised treatment or from the trial. Arrangements will be made by the trial team for further assessment and management as agreed with the relevant authorities, GP and participant. The investigator will provide the trial team with a one month follow-up report on all SAEs and SARs. Further monthly reports should be provided in the absence of resolution. These reports will be communicated to the TSC, DMEC and MREC, and to the local R&D office. Blank Adverse Event Forms will be distributed to sites that are recruiting and therapists, and patients will be prompted to self-report SAEs in the follow up questionnaires.

Adverse events that do not require reporting
Expected adverse events include planned/elective hospitalisations, and these will not be collected as SAEs.

Stopping Rules

The trial may be prematurely discontinued by the Sponsor or Chief Investigator on the basis of new safety information or for other reasons given by the Data Monitoring & Ethics Committee, Trial Steering Committee, Regulatory Authority or Ethics Committee concerned.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from a Trial Steering Committee (if applicable), who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

Proposed Sample size

A 35 point difference between therapy groups and TAU on IBS SSS at 12 months is regarded as clinically significant (assuming a 15 point placebo response in the TAU arm in the trial – see primary outcome measure section for justification (12, 19). Assuming a within-group IBS SSS standard deviation of 76 points (taken from MIBS pilot study (12)) this equates to an effect

size of 0.46. To achieve 90% power to detect such an effect or larger using a two-sided independent samples t-test at the 2.5% significance level (adjusting for 2 primary outcomes) would require 119 subjects per group. Based on each of 10 therapists delivering therapy to 17 patients within LIBT and TCBT groups and an intraclass correlation of 0.02, taken from Baldwin (32), this sample size needs to be increased by an inflation factor of 1.32 to take account of therapist effects. We will measure IBS SSS at baseline and assume that baseline values are predictive of post treatment values (correlation 0.4). Accounting for this in our statistical analysis model allows us to decrease the sample size by a deflation factor of 0.84. Finally, assuming that attrition will be less than 20% we apply a further inflation factor (factor 1.25) to allow for this. The final sample size requirement is 165 patients per group or 495 patients in total.

In terms of our second primary outcome (WASAS) this sample size would be sufficient to detect a clinically important difference between the LIBT (or TCBT) and TAU groups in the WASAS. Specifically, we can assume inflation factors of 1.32 for correlation of outcomes within therapists and of 1.25 for attrition and a deflation factor of 0.84 for correlation between baseline and follow-up measures. Therefore, a moderate effect size of 0.46 could be found with 90% power at the 2.5% significance level, given 119 participants per group. Assuming a standard deviation of 8.0 (as estimated in a study of CBT for IBS (6)) this would equate to a clinically meaningful treatment difference of 3.7 points on this scale. This is less than the difference of 5.4 points in change of means was found in a trial of a CBT-based self-management intervention for IBS (17).

Statistical Analysis

Statistical analyses aim to evaluate effectiveness and will follow the intention-to-treat principle. Group differences on the primary IBS-SSS outcome will be assessed using a mixed linear regression model for repeated measurements. In this model IBS-SSS at post treatment time points (3, 6 and 12 months) will feature as the dependent variable. Explanatory variables will be baseline IBS-SSS, treatment group, IBS symptoms type, stratifier (centre), time and a time by treatment interaction term to allow for different group differences at the various assessment time points. (The assessment time point of primary interest is 12 months. The modelling provides the treatment effect estimates at the 12 month time point as well as for further post treatment secondary time points). Correlation between repeated measures and due to sharing the same therapist will be allowed for by including subject-varying random intercepts as well as therapist-varying random intercepts for TCBT and LIBT groups in the mixed models. Mixed models account for missing outcome data under the missing at random assumption (MAR). The effect of departures from this assumption will be checked using sensitivity analyses (33). WASAS scores will be analysed using mixed models in a manner similar to the analysis of IBS-SSS. Secondary outcomes and mediators (Subjects Global assessment of relief (SGA), EQ-5D, Enablement, Hospital Anxiety and Depression Scale, Brief Illness perception Questionnaire (IPQ), Cognitive Scale for Functional Bowel disorders, The Belief about Emotions Scale (BES), The “Impoverished Emotional Experience (IEE)” factor of the Emotional Processing Scale, The Positive and Negative Affect Schedule (PANAS), adverse events and health care utilisation are important to measure the wider IBS effects and will be analysed similarly (as appropriate for continuous or dicotomous outcomes). Treatment effect moderation by important baseline variables (treatment by variable interactions) will be

explored. A complier average causal treatment effect (CACE) will be estimated using instrumental variable methods to assess efficacy if there is appreciable lack of compliance (34).

Data collection

Research data will be entered onto a GCP compliant online data entry system at CTU (InferMed MACRO). Participant data will be collected and entered by the study site staff and the database will be maintained by the CTU. Baseline data will be collected prior to randomisation and will be co-ordinated by the trial management team. Baseline and outcome data will be patient self-completed on a separate data collection section of the Regul8 website (as was done sucessfully for the MIBS study), away from the study team, thus avoiding any influence of the study team on the responses and reducing bias. This website will be maintained by the computer support team at Southampton who are hosting the website. Participants will be given a unique password to log on to the website. Their data will be identified by a unique identification number and will be kept separate from any personal identifying data to maintain confidentiality.

Baseline Measures

The screening questionnaire will capture baseline data including Rome III questionnaire, duraction of IBS, type, previous CBT, medications previously taken for IBS and inclusion and exclusion criteria. The participant will complete an online baseline assessment questionnaire which includes:

- socio-demographic details
- current medication
- past medical history and medications
- duration of IBS symptoms
- previous or current psychiatric diagnoses
- IBS symptom severity score (IBS SSS)
- Work and Social adjustment Scale (WASAS)
- Quality of life (EQ-5D)
- Client Service receipt Inventory (CSRI)
- HADs (hospital anxiety and depression scale)
- Cognitive scale for Functional Bowel Disorders (CG-FBD)
- Brief Illness Perception Questionnaire for IBS (IPQ)
- The Irritable Bowel Syndrome-Behavioural Responses Questionnaire
- Beliefs about Emotions Scale (BES)
- “Impoverished Emotional Experience (IEE)” factor of the Emotional Processing Scale-25
- Positive and Negative Affect Schedule (PANAS)

Those randomised to the self management programme will also complete on-line symptom severity questions, symptom, food and exercise diaries, questions about stress and triggers and their symptoms and their coping strategies. These data will be collected and stored and may be used to provide information to assess the self management programme but will mostly be used by the participants themselves to monitor their progress and inform

themselves about their own symptoms, triggers and coping strategies as part of the cognitive behavioural therapy based self-management programme.

Outcome Measures

Outcome data and questionnaires will be completed at 3, 6 and 12 months after randomisation by all participants. Participants will be sent a reminder email at 3, 6 and 12 months to prompt them to complete to data one week prior to the questionnaire due date. If it has not been completed within one week of the reminder, a further 2 reminders will be sent. One week after that, if no data have been entered, the research team will ring the participant to ask if they can collect the data by hard copy or over the telephone. 90% follow up was achieved (at 12 weeks) in the MIBS trial which collected very similar baseline and outcome measures to those proposed for this study.

Additional 24 Month Outcome

The HTA offered expressions of interest to extend the original trial. We proposed an additional follow up at 24 months (funding permitting). New patient's entering the trial will be told at screening that the trial is in transit and that there will be an additional consent to collect 24m FU data. Patients already in the trial and new patients would receive an email from the research team asking them to complete a new consent form on the data collection section of the Regul8 website (currently used for consent, baseline and outcome data). Non responders would be chased up with a further two reminders. Patients would then receive an automated email at the relevant time point to complete the 24 month questionnaire. New patients would have an amended PIl which includes details of the 24 month follow up.**Primary outcomes**: **IBS-SSS and WASAS.**

IBS Symptom Severity Score (IBS SSS) (19) is widely used in IBS studies (and a 50 point change from baseline is regarded as clinically significant (19)). In the resistant symptom group to be studied in this trial we have powered to detect a 35 point difference between groups at 12 months for the sample size calculations. This is to account for a 15 point placebo response in the TAU arm (the placebo response is known to be important in IBS and the MIBS trial (35) showed a 24 point difference in the no website group from baseline to 12 week follow up thus allowing for 15 point placebo response at 12 months would be prudent).

The IBS SSS (19) is a 5 item self-administered questionnaire measuring: severity of abdominal pain, duration of abdominal pain, abdominal distension/tightness, bowel habit, quality of life. Maximum score 500: <75 normal bowel function, 75-174 mild IBS, 175-299 moderate IBS, 300-500 severe IBS).

The Work and Social Adjustment Scale (WASAS) measures the effect of the IBS on people's ability to work and manage at home, participate in social and private leisure activities and relationships (20). WASAS has been shown to be sensitive to change in IBS trials (6, 17). It has 5 aspects scored 0 (not affected) to 8 (severely affected), total possible score 40.

Secondary outcome measures:

The Subjects Global Assessment of Relief (SGA of Relief) (21) is frequently used in treatment trials to identify IBS responders to therapy (21). Participants rate their relief from IBS symptoms on a scale of 1 to 5 ranging from "completely relieved" to "worse". Scores are

dichotomized so that patients scoring from 1-3 are considered responders and those 4-5 non-responders. The Hospital Anxiety and Depression Scale (HADS) (23) is a well validated, commonly used, self-report instrument for detecting depression and anxiety in patients with medical illnesses.

Patient Enablement Questionnaire (16) assesses participants' ability to cope with their illness and life.

The acceptability of the self-management treatment will be assessed using questions where patients rate the overall effectiveness of the programme, the efficacy of programme compared to other treatments they have tried, and whether they enjoyed the programme.

The Client Receipt Inventory (CSRI) (24) and EQ5D (22) will be used to gather information on use of health services and quality of life.

Patients GP notes will be reviewed at 12 months to assess GP and other consultations in the year prior to entering the study and in the 12 months since entry into the study. Other studies have shown an impact on GP contacts from patient self management programmes (17, 36).

Process/mediator Variables

Cognitive Scale for Functional Bowel Disoders (CG-FBD) (25) is a 31 item scale assessing unhelpful cognitions related to IBS.

Brief Illness Perception Questionnaire for IBS (IPQ) (26) consists of an 8 point scale to assess participants perception of their illness.

The Irritable Bowel Syndrome-Behavioural Responses Questionnaire (27) is a 26 item scale which measures changes in behaviour specific to managing IBS symptoms .

The Belief about Emotions Scale (BES) (28) is a 12-item questionnaire that measures beliefs about the unacceptability of experiencing and expressing negative emotions. These beliefs are likely to have implications for emotion regulation and processing. Principal components analysis identified one factor and the scale had high internal consistency (0.91) (28)

The "Impoverished Emotional Experience (IEE)" factor of the Emotional Processing Scale (29) is composed of 5 items and relates to the labelling and awareness of emotional events, which influence the way people process their emotions. The sub-scale has high internal consistency (0.82) (29)

The Positive and Negative Affect Schedule (PANAS) (30) measures both positive and negative affect. The reliabilities of the PANAS, as measured by Cronbach's a, were 0.89 for positive affect and 0.85 for negative affect (37). The current results indicate that positive and negative affect are relatively independent dimensions. Participants will complete only the positive affect sub-scale because the HADS scale will already measure Negative affect.

Patients' adherence to the treatments will be measured through recording the number of phone sessions and an automated count of web sessions accessed. Completing 4 or more sessions of the website and one or more of the telephone support calls will be deemed as compliant with the website. In the TCBT arm, completing 4 or more of the initial telephone

CBT sessions will be deemed as compliant. Patients will also keep a simple log of homework tasks to complete.

Economic evaluation

We will measure costs and assess cost-effectiveness from both a health service and a societal perspective. To calculate the cost of TCBT the number of sessions with therapists will be recorded and combined with the unit cost of therapist time. The latter will be calculated using information on the salary band of therapists, with additional costs representing capital, overheads, training and qualifications (38). We will ask therapists to estimate how much time during a typical working week is spent in telephone contact with patients and combine this with the total cost and total hours worked per week, in order to produce a cost per hour of direct patient contact time. For LIBT the number of times therapist support is provided will be recorded and costed in a similar way. The LIBT development costs will be estimated and apportioned over those using the intervention. Other service use will be measured with a service receipt schedule at baseline (going back 6 months) and each follow-up (with measurement covering the whole period since the prior interview). The schedule will be based on other questionnaires used in similar research (24). Services will include primary and secondary healthcare, and medication. Service costs will be generated by combining these data with appropriate unit cost information (e.g. NHS Reference Costs (38), and the British National Formulary) and these costs added to the intervention costs in order to generate total health costs per person.

Societal costs will be calculated by including family care costs and lost production. Family care costs will be recorded by asking patients to state how much time per week family members (and friends) spent providing support in specific areas *because of the IBS*. This time will be combined with average wage rates. Lost days and hours from work will be recorded on the schedule and combined with average wage rates to generate lost production costs. Cost comparisons between the 3 groups will be made at 3, 6 and 12 months and over the entire follow-up period, in both cases controlling for baseline costs. Cost data are usually skewed and cost comparisons will use a bootstrapped regression model to generate appropriate 95% confidence intervals around the cost differences.

Cost-effectiveness will be assessed (from health and societal perspectives) by combining the cost data with the change score on the IBS-SSS, WASAS and QALYs. The latter will be generated from the EQ-5D combined with UK-specific tariffs. Area under the curve methods, controlling for baseline utility, will be used to calculate the number of QALYs accrued over the follow-up period. If outcomes are better for one group compared to another and costs lower then it will be defined as being 'dominant'. If outcomes are better and costs are higher then an incremental cost-effectiveness ratio will be generated to indicate the extra cost incurred to achieve an extra point reduction in symptoms or extra QALY. Cost-effectiveness planes will be produced, using 1000 cost and outcome differences (from bootstrapped regression models) for each 2-way comparison to explore the uncertainty around the results. Cost-effectiveness acceptability curves will also be produced using bootstrapped regression models with net benefit values as the dependent variables. The net benefit approach requires an assumption about the value placed on a unit improvement in outcome. For QALYs, a range from £0 to £60,000 will be used, thus including the threshold thought to influence NICE

decisions. For the IBS-SSS and WASAS there are no accepted threshold so a range will be chosen such that the points at which one intervention has a 60%, 70%, 80% and 90% likelihood of being the most cost-effective option can be identified.

Sensitivity analyses will be conducted by changing the intervention costs upwards and downwards by 50%, using minimum wages to value lost production, family care and travel time, and by also using the replacement cost approach to value family care with the cost of a homecare worker used a shadow price.

Modelling beyond the trial period and making comparisons with other interventions is not in the scope of this project.

Qualitative component

A nested qualitative study will explore patients' experiences of treatments. The objectives of this study will be: to identify factors that facilitate or impede adherence to web-delivered and therapist-delivered CBT in this patient group; to provide insight into the quantitative results of this complex trial; to identify social and psychological processes of change that occur during the trial. Semi-structured interviews will be conducted at 3 and 12 months with approximately 17 to 20 participants per arm (i.e. 10% to 12%, sampled purposively to encompass a mix of gender and ages and a range of baseline symptom severity scores). Interviewing participants from each active arm will enable us to identify factors related to adherence and change processes; including participants from the TAU arm will provide insight into the quantitative results. Interviewing the same participants at 3 and 12 months will allow us greater depth to explore change processes over time and the potential to understand better any differences in the quantitative results between 3 and 12 months. Interviews will be transcribed verbatim and analysed using constant comparison and other rigorous qualitative techniques as appropriate to address each objective. The qualitative results can thus provide scientific value concerning understanding of change processes and practical value concerning the relative merits of each type of CBT and delivery issues to attend to in any future widespread implementation.

Research Governance

This study will be conducted in accordance with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines; and the Research Governance Framework for Health and Social Care. The University of Southampton has agreed to be the Sponsor for this study.

A Trial Steering Committee (TSC) will oversee the trial procedures and ensure good conduct of the study, they will meet at least annually. The TSC will have an independent chair and at least two independent members and a Patient and Public Involvement Representative along with the lead investigator (HE). Observers from the HTA will be invited to all TSC meetings.

A Data Monitoring and Ethics Committee (DMEC) will be set up once suitable members have been identified with the support of the TSC.

Regular updates and meetings will ensure good communication. The collaborators will hold meetings at least 4 times a year. The research assistant will circulate a monthly update to review progress relative to the project plan, highlighting any issues that need to be addressed.

Each team member will consult the other team members immediately by email and/or phone on any issues that arise.

Monitoring and Audit:

The study will be monitored and audited in accordance with Southampton University procedures. All trial related documents will be made available on request for monitoring and audit by the University of Southampton, the relevant REC and other licencing bodies.

Data protection and anonymity: Data will be collected and retained in accordance with the Data Protection Act 1998.

The Data Protection policy of the School of Medicine, Southampton University, will be complied with.

GP participants will be identified from Health Authority lists – these are available in the public domain.

The responses to questionnaires will be stored in an anonymised form on a password protected university or CTU computer. Any anonymised paper questionnaires will be stored in a locked filing cabinet at Primary Medical Care – University of Southampton or at King's College London.

Storage of Records: Study documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All source documents will be retained for a period of 10 years following the end of the study.

4) Project timetable

Pre-Study start	April 2013 – Aug 2013	Gain NRES approval, prepare job adverts
1-8 months	Sept 2013 – April 2014	Recruit research staff, Complete R&D, register trial, publish protocol, prepare recruitment & assessment materials, update & test website, recruit & train therapists, design data collection forms and study database, set up randomisation service, contact GP surgeries and Hospital clinics to make recruitment arrangements.
9-30 months	May 2014 – March 2016	Recruitment (23 patients/month over 22 months), screening, intervention delivery, assessments, qualitative interviews.
31-42 months	Mar 2016 – Feb 2017	Therapy booster sessions, 12mth follow-up assessments, qualitative interviews.
43-46 months	Mar 2017 – Jun 2017	Data preparation, cleaning and analysis
47-48 months	July 2017 – Aug 2017	Writing final reports, dissemination

49-55 months	Sep 2017 – March 2018	Continuing 24 month follow-up collection pending funding decision

5) Dissemination

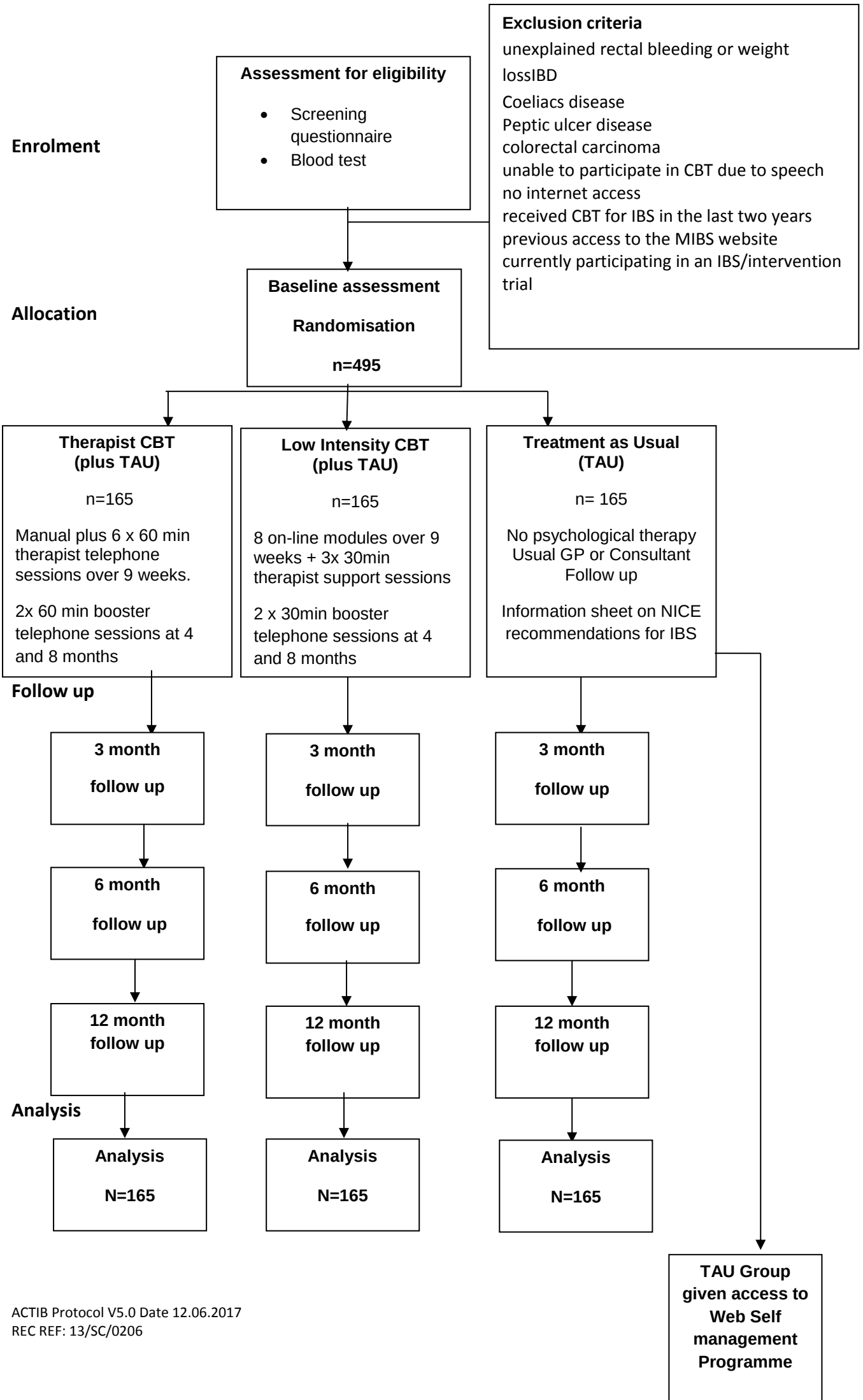
Publication of the trial protocol in an open access journal, presentation of the findings of this research at local and national and international meetings by the research team and publication in high profile journals will disseminate the results widely and ensure that the findings contribute to the body of high quality research available. The results of a trial such as this are likely to be incorporated into systematic reviews of the evidence such as the Cochrane review which will help disseminate its findings to the research and clinical communities.

6) Service Users

IBS patients and the IBS network, a patient self-help group, have been involved in the providing feedback for the design of the MIBS (12) trial (in which the Regul8 website to be used in this study was developed and piloted). Patients were substantially involved in the website design with service users working through each on-line module during development and providing 'Think Aloud' feedback to inform the design. Participants from the MIBS trial have also provided input and feedback on the proposals for this research proposal. Two of them have also agreed to be the PPI representatives for the study providing ongoing input (both informal feedback and participating in TSC and research meetings) for this study to ensure it addresses issues relevant to users.

Indemnity

Each centre taking part in the trial will seek local approval and indemnity through their NHS R&D department. As an automatic consequence of this, local NHS indemnity will apply to the ACTIB trial. Details of local indemnity arrangements can be obtained through each centre's NHS R&D department.


Enrolment
Assessment for eligibility
Screening questionnaire
Blood test
Exclusion criteria
unexplained rectal bleeding or weight lossIBD
Coeliacs disease
Peptic ulcer disease
colorectal carcinoma
unable to participate in CBT due to speech
no internet access
received CBT for IBS in the last two years
previous access to the MIBS website
currently participating in an IBS/intervention trial
Allocation
Baseline assessment
Randomisation
n=495
Therapist CBT (plus TAU)
n=165
Manual plus 6 x 60 min therapist telephone sessions over 9 weeks.
2x 60 min booster telephone sessions at 4 and 8 months
Low Intensity CBT (plus TAU)
n=165
8 on-line modules over 9 weeks + 3x 30min therapist support sessions
2 x 30min booster telephone sessions at 4 and 8 months
Treatment as Usual (TAU)
n= 165
No psychological therapy
Usual GP or Consultant Follow up
Information sheet on NICE recommendations for IBS
Follow up
3 month follow up
6 month follow up
12 month follow up
Analysis
Analysis
N=165
TAU Group given access to Web Self management Programme

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