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ATLANTIS
Investigating amitriptyline as second-line treatment for IBS

CLINICAL TRIAL PROTOCOL

Study Title:	**A**mi**t**riptyline at **L**ow-dose **and** **T**itrated for **I**rritable Bowel Syndrome as **S**econd-line Treatment (The **ATLANTIS** study): A Double-blind Placebo-controlled Trial
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CONTACT LIST
UNIVERSITY OF LEEDS

UNIVERSITY OF Southampton

University of BRISTOL

Study enquiries	**Email: Atlantis@leeds.ac.uk**	**Tel: 0113 343 3914**
Randomisation/Registration:	**https://lictr.leeds.ac.uk/webrand/**	
In hours emergency unblinding:	**Tel: 0113 343 4930**	
Out of hours emergency unblinding:	0113 3922459	
SAEs/SUSARs/protocol violations:	**Fax: 0113 343 0686**	

Chief Investigator – with responsibility for regulatory compliance and medical oversight

Professor Alexander Ford - *Professor and Honorary Consultant of Gastroenterology*	
St. James's University Hospital, Room 125, 4th Floor, Bexley Wing, Beckett Street, Leeds, West Yorkshire, LS9 7TF	**Email:** A.C.Ford@leeds.ac.uk **Tel:** 01132068536

Co-Chief Investigator – with responsibility for trial delivery and oversight in primary care Southampton Hub Lead Clinician:

Professor Hazel Everitt - *Professor in General Practice*	
Primary Care and Population Sciences, University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton, SO16 5ST	**Email:** H.A.Everitt@soton.ac.uk **Tel:** 02380 591788

Sponsor:

University of Leeds	
Research & Innovation Centre, Faculty of Medicine and Health, Leeds Teaching Hospitals NHS Trust, University of Leeds, St James's University Hospital, Leeds, LS9 7TF	**Tel**: 0113 20 60454

Funder:

NIHR Health Technology Assessment (HTA) Programme	
Evaluation, Trials and Studies Coordinating Centre University of Southampton, Alpha House, Enterprise Road, Southampton, SO16 7NS	**Email:** netscomms@nihr.ac.uk **Tel:** 023 8059 5586

Lead Methodologist:

Professor Amanda Farrin – *Professor of Clinical Trials & Evaluation of Complex Interventions*	
Clinical Trials Research Unit (CTRU) University of Leeds, Leeds, LS2 9JT	**Email:** A.J.Farrin@leeds.ac.uk **Tel:** 0113 343 8017

Supervising Statistician:

Dr Tom Morris – *Senior Medical Statistician*	
Clinical Trials Research Unit (CTRU) University of Leeds, Leeds, LS2 9JT	**Email:** T.Morris@leeds.ac.uk **Tel:** 0113 343 6049

Trial Statistician:

Mr Richard Brindle – *Medical Statistician*	
Clinical Trials Research Unit (CTRU) University of Leeds, Leeds, LS2 9JT	**Email:** R.M.Brindle@leeds.ac.uk **Tel:** 0113 3438016

Supervising Safety Statistician:

Ms Sarah Brown – *Principle Statistician*	
Clinical Trials Research Unit (CTRU) University of Leeds, Leeds, LS2 9JT	**Email:** medsbro@leeds.ac.uk **Tel:** 0113 343 1475

Safety Statistician:

Mr Alasdair Fellows – ***Medical Statistician***	
Clinical Trials Research Unit (CTRU) University of Leeds, Leeds, LS2 9JT	Email: A.M.Fellows@leeds.ac.uk Tel: 0113 3436881

Project Delivery Lead:

Ms Suzanne Hartley – *Head of Trial Management*	
Clinical Trials Research Unit (CTRU) University of Leeds, Leeds, LS2 9JT	**Email** S.Hartley@leeds.ac.uk **Tel:** 0113 34 38041

Trial Manager / Data Manager

Dr Heather Cook – *Senior Trial Manager*	
Clinical Trials Research Unit (CTRU) University of Leeds, Leeds, LS2 9JT	**Email:** atlantis@leeds.ac.uk **Tel:** 0113 343 3914
Ms Taposhi Nath - *Trial Coordinator*	
Clinical Trials Research Unit (CTRU) University of Leeds, Leeds, LS2 9JT	**Email:** atlantis@leeds.ac.uk **Tel:** 0113 343 3402
Mr Christopher Taylor - *Data Manager*	
Clinical Trials Research Unit (CTRU) University of Leeds, Leeds, LS2 9JT	**Email:** atlantis@leeds.ac.uk **Tel:** 0113 343 7987

Patient and Public Involvement (PPI)

Ms Delia Muir- *Wellcome Trust Engagement Fellow – PPI Lead*	
Clinical Trials Research Unit (CTRU) University of Leeds, Leeds, LS2 9JT	**Email:** D.P.Muir@leeds.ac.uk **Tel:** 0113 343 8609
Mr Matthew Chaddock – *Co-Applicant and PPI representative*	

COLLABORATORS:

West of England Hub Lead Clinician:

Dr Matthew Ridd - *Reader in Primary Health Care and NIHR Post-Doctoral Fellow*	
Population Health Sciences, University of Bristol Bristol Medical School, Whatley Road, Bristol, BS8 2PS	**Email:** M.Ridd@bristol.ac.uk **Tel:** 0117 331 4557

West Yorkshire Hub Co-Lead Clinician:

Dr Sarah Alderson - *NIHR Clinical Lecturer in General Practice*	
Leeds Institute of Health Sciences (LIHS) University of Leeds, Leeds, LS2 9JT	**Email:** S.L.Alderson@leeds.ac.uk **Tel:** 0113 343 0867

West Yorkshire Hub Co-Lead Clinician:

Professor Robbie Foy - *Professor of General Practice and General Practitioner*

Leeds Institute of Health Sciences, University of Leeds, LS2 9JT	**Email:** R.Foy@leeds.ac.uk **Tel:** 0113 343 4879

Research Nurses/Clinical Study Officers

Each hub will have research nurses/clinical study officers (CSO) to support delivery of the trial. A CSO may or may not have a nursing qualification, but will be deemed (by the Hub Lead Clinician) to have the necessary training and expertise to undertake the tasks required of the. Contact details will be provided in the Investigator site file.

Professor of Psychological Medicine: Mental health safety and monitoring

Professor Else Guthrie - *Professor of Psychological Medicine*	
Leeds Institute of Health Sciences, University of Leeds, LS2 9JT	**Email:** e.a.guthrie@leeds.ac.uk **Tel:** 0113 343 2442

Nested Qualitative Study Lead:

Dr Felicity Bishop - *Associate Professor in Health Psychology*	
Building 44 Highfield Campus, University of Southampton SO17 1BJ	**Email:** f.l.bishop@soton.ac.uk **Tel:** 023 8059 9020

Health Economics:

Dr Roberta Longo	
Leeds Institute of Health Sciences, University of Leeds, LS2 9JT	**Email:** R.Longo@leeds.ac.uk **Tel:** 0113 3430324
Dr Daniel Howdon	
Leeds Institute of Health Sciences, University of Leeds, LS2 9JT	**Email:** D.Howdon@leeds.ac.uk

Central Pharmacy

In-Patient Pharmacy, Gledhow Wing, St James's Hospital, Leeds Teaching Hospitals NHS Trust, Leeds LS9 7TF

GPhC Registration number: 1092402

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ABBREVIATIONS

Abbreviation	Explanation
AE	adverse event
AR	adverse reaction
ASEC	Antidepressant Side-Effect Checklist
BSFS	Bristol stool form scale
CI	chief investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRP	C-reactive protein
CTIMP	clinical trial of an investigational medicinal product
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
FBC	full blood count
GCP	Good Clinical Practice
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HTA	Health Technology Assessment
IBS	irritable bowel syndrome
IBS-SSS	IBS Severity Scoring System
IMEs	important medical events
IMP	investigational medicinal product
LTHT	Leeds Teaching Hospitals NHS Trust
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMDA	N-methyl-D-aspartate
OD	once-daily
PHQ-12	Patient Health Questionnaire-12
PI	principal investigator
PPI	patient and public involvement
QALYs	quality adjusted life years
RCT	randomised controlled trial
REC	research ethics committee
SAE	serious adverse event
SAR	serious adverse reaction
SGA	Subjective Global Assessment
SPC	summary of product characteristics
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TCA	tricyclic antidepressant
ToR	terms of reference
TMG	Trial Management Group
TSC	Trial Steering Committee

tTG	tissue transglutaminase
TTO	time trade-off
WSAS	Work and Social Adjustment Scale
WCC	white cell count

1. TRIAL SUMMARY

Title:	**A**mi**t**riptyline at **L**ow-dose **an**d **T**itrated for **I**rritable Bowel Syndrome as **S**econd-line Treatment (The **ATLANTIS** study): A Double-blind Placebo-controlled Trial.		
Design:	ATLANTIS is a randomised, multi-centre, parallel-group, two-arm, double-blind, placebo-controlled trial of low-dose amitriptyline as a second-line treatment for people with irritable bowel syndrome (IBS) in primary care. It includes an internal pilot and a nested, qualitative study to explore patients' and general practitioners' (GPs) experiences of treatments and participating in the trial.		
Target Sample size:	518	**Sites:**	75 GP practices in three geographical regions
Timelines:	Planned First Patient Recruited: July 2019 Recruitment Duration: 19 months Planned Last Patient Last Visit: January 2022		
Background	IBS is a common, chronic, functional gastrointestinal disorder, and represents a significant financial burden to the health service. Current first-line treatment of IBS in primary care includes dietary and lifestyle advice, soluble fibre, and antispasmodic drugs, but if these treatments are ineffective, GPs are often left with few treatment options, meaning people are frequently referred to see a specialist in secondary care. The National Institute for Health and Care Excellence (NICE) recommends that GPs should "consider" tricyclic antidepressants (TCAs), such as amitriptyline, as second-line treatment for IBS if laxatives, loperamide, or antispasmodics have not helped. However, there is limited evidence to support this statement and, as result, there is uncertainty as to whether TCAs are effective for the treatment of IBS in primary care.		
Aim	The overall aim of this study is to determine the clinical and cost-effectiveness of low-dose amitriptyline as a second-line treatment for IBS in primary care.		
Primary Objective	What is the effect of amitriptyline, compared with placebo, on patient-reported global symptoms of IBS at 6 months?		
Secondary Objectives	For each objective, comparisons are against placebo: What is the effect of amitriptyline on: • Global symptoms of IBS at 3 and 12 months? • Relief of IBS symptoms at 3, 6, and 12 months? • Anxiety at 3, 6, and 12 months? • Depression at 3, 6, and 12 months? • Patient reported relief of IBS symptoms, measured weekly? • Self-reported health care use at 3, 6, and 12 months? • Health-related quality of life at 3, 6, and 12 months? • Ability to work and participate in other activities at 3, 6, and 12 months? • IBS-associated somatic symptoms at 6 months? What is the cost-effectiveness of amitriptyline at 6 months? What is the acceptability of amitriptyline treatment at 6 months? What is the adherence to therapy with amitriptyline at 3 weeks, 3, 6, 9, and 12 months? What is the tolerability of amitriptyline, in terms of adverse events (AEs) at 3, 6, and 12 months?		

	What are patients' and GPs' experiences of treatments and participating in the trial, and how can these inform our understanding of the quantitative results and future implementation efforts?	
Internal Pilot Objectives	To assess trial recruitment and 6-month follow-up rates, and meet clear progression criteria.	
Nested Qualitative study objectives	1. To identify factors that facilitate or impede prescribing of, acceptability of, and adherence to, low-dose amitriptyline in this patient group. 2. To identify patients' and GPs' perspectives on the broader impact of the trial, including any unanticipated effects not captured by the quantitative measures. 3. To explore psychosocial and contextual factors that might shape wider use of amitriptyline for IBS.	
Trial Population	Adults (≥18 years) with a GP diagnosis of IBS, meeting the Rome IV criteria, with ongoing troublesome symptoms (IBS severity scoring system [IBS-SSS] score ≧ 75) despite having tried dietary changes and first-line therapies, and not currently receiving secondary care management. Please refer to protocol section 6 for full inclusion and exclusion criteria.	
Trial Treatment	All participants are planned to receive 6 months of trial treatment, taking 10-30 milligrams (mg) of amitriptyline or placebo once-daily (OD). All participants will start on one tablet (placebo or 10mg amitriptyline) OD. After an initial 7 days of trial treatment, if there is inadequate improvement in symptoms and no intolerable side effects, participants may increase their dose to two tablets OD (placebo or 20mg amitriptyline). After a further 7 days of treatment, if there is inadequate improvement in symptoms and no intolerable side effects, participants may increase their dose to three tablets OD (placebo or 30mg amitriptyline). Participants may then titrate their dose (between 1 and 3 tablets) depending on symptoms and side effects. Participants have the option to continue treatment for an additional 6 months (12 months total treatment). Trial medication will be dispensed from Leeds Teaching Hospitals Trust (LTHT) Pharmacy and sent directly to the participant.	
Study Procedures	**Patient Identification**	• Potential participants identified through GP practice database search or presentation to the GP. • Contacted by letter (sent by the GP practice). • Potential participants to return reply slip to hub research team.
	Screening (following return of reply slip)	• Initial screening call by hub research team to ask questions about inclusion and exclusion criteria. • Written informed consent. • Online registration. • Blood test visit (anti-tissue transglutaminase [tTG] antibodies, full blood count [FBC] and C-reactive protein [CRP]) (if required – see section 6). • Pregnancy test (if applicable)
	Baseline measures	Participant to self-complete web or postal baseline assessment prior to randomisation.
	Randomisation	Randomisation (1:1) to the placebo or the active arm (amitriptyline) will be carried out by the Clinical Trials Research Unit (CTRU), University of Leeds.

		Randomisation will be by minimisation with a random element, on the following factors: • Presence of depression (HADS-D score ≥8) • Stool pattern (diarrhoea-predominant, constipation-predominant, mixed, or unclassified stool pattern) • Recruitment hub (West Yorkshire, Southampton, or West of England)
	Titration phase	Participants will receive an initial 1-month supply of study drug, sent to them directly from central pharmacy. Participants will be supported throughout the titration phase with telephone calls from the research nurse/CSO at approximately weeks 1 and 3; there is the option for a GP review if required at 1 month.
	Drug resupply	Further supplies of study medication will be sent to the participant following telephone assessment by the research nurses/CSOs to ensure no contraindication to further trial treatment, including assessment of suicidal ideation and participants' willingness to continue on trial medication. All participants are planned to receive resupply of study medication at month 1 and month 3. Participants who choose to continue to 12 months of trial treatment are planned to receive a further two deliveries of study medication at 6 and 9 months post-randomisation.
Evaluation of Outcome Measures	All participants will self-complete assessments online or on paper (depending on preference) at 3, 6, and 12 months following randomisation. All participants will self-complete a weekly question about relief of IBS symptoms, online or on paper. Participants will be also be assessed by telephone at 3, 6, and 12 months following randomisation. A sub-sample of participants will take part in two semi-structured telephone interviews. A sample of GPs from participating practices will take part in a semi-structured telephone interview.	

2. BACKGROUND

2.1. Irritable Bowel Syndrome

Irritable bowel syndrome is a common, chronic, functional gastrointestinal disorder, and represents a significant financial burden to the health service. Prevalence is around 10% in the community (1), and IBS accounts for >3% of all consultations in primary care (2). The total cost to the health service in the UK is >£200 million/year (3). Quality of life of people with IBS is impaired substantially, to a level comparable with that seen in some organic bowel disorders, such as Crohn's disease (4). Current first-line treatment of IBS in primary care includes dietary and lifestyle advice, soluble fibre, and

antispasmodic drugs, but if these treatments are ineffective, GPs are often left with few treatment options, meaning people are frequently referred to see a specialist in secondary care.

2.2. Role of Tricyclic Antidepressants

Medical management of IBS is unsatisfactory, with no therapy proven to alter the long-term natural history and, at best, modest symptom reduction. Previous systematic reviews and meta-analyses have identified 11 trials that suggest TCAs may be effective (5, 6), however these included a total of only 744 patients. Any beneficial effects on IBS symptoms probably stem from their well-known pain-modifying properties (7-10), as well as their influence on gut motility (11), rather than any anti-depressive effects, as the doses used in randomised controlled trials (RCTs) in IBS are considerably less than the dose required to have any effect on mood. However, most trials were conducted in secondary or tertiary care, where patients have more severe symptoms. One of these meta-analyses highlighted the need for a large, rigorously conducted trial of TCAs in patients with IBS in primary care (6), because most studies were small, few were at low risk of bias, duration of follow-up was limited to 12 weeks, and none were conducted in primary care. These limitations are important. The clinical relevance of demonstrating the effectiveness of a drug over a 12-week RCT in a condition that is chronic, and often lifelong, is debatable. In addition, although there is evidence from pooling data from secondary and tertiary care-based trials in a meta-analysis, it is not clear whether this effect would translate into a benefit in primary care, and whether this will reduce resource use and referrals to secondary care, or improve quality of life and social functioning.

The NICE guideline for the management of IBS in primary care states only that GPs should “consider” TCAs for their analgesic effect (e.g. “amitriptyline at a dose of 10mg to 30mg”) (12), as second-line treatment for IBS if laxatives, loperamide, or antispasmodics have not helped. However, these guidelines also acknowledge that there is limited evidence to support this statement. The guidelines propose that a large RCT be conducted comparing a TCA with placebo as a therapy in adults with IBS in primary care, with outcomes assessed at 3, 6, and 12 months, and including global improvement in IBS symptoms, effect on health-related quality of life, and adverse effects.

At present, therefore, there is uncertainty as to whether TCAs are effective for the treatment of IBS in primary care, and this may mean GPs are reluctant to consider using them. In a recent survey <10% of GPs used them often, and only 50% believed they were effective (13). Given that 95% of GPs use these drugs for the treatment of insomnia in primary care (14), it is presumably uncertainty over their efficacy in IBS, rather than concerns about side effects, which explains this reluctance.

If a drug that is potentially effective for treating IBS is being under-utilised, this will have a negative effect on both the health service and society, in terms of worse control of IBS symptoms, which will lead to lower quality of life for people with IBS, increased sickness absences from work, and higher costs of managing IBS in secondary care, due to greater numbers of referrals and increased rates of investigation.

2.3. Amitriptyline

Amitriptyline is a TCA and an analgesic, with marked anticholinergic and sedative properties. It prevents the re-uptake, and hence the inactivation, of noradrenaline and serotonin at nerve terminals. Preventing reuptake of these monoamine neurotransmitters potentiates their actions in the brain. This appears to be associated with the antidepressant activity.

The mechanism of action also includes ion-channel blocking effects on sodium, potassium, and N-methyl-D-aspartate (NMDA) channels at both central and spinal cord level. The noradrenaline, sodium, and NMDA effects are mechanisms known to be involved in the treatment of neuropathic

pain, chronic tension type headache prophylaxis, and migraine prophylaxis. The pain-reducing effect of amitriptyline is therefore not linked to its anti-depressive properties.

TCAs also possess affinity for muscarinic and histamine-1 receptors to varying degrees, which are associated with their side effect profile.

Amitriptyline is a recognised treatment for major depressive disorder. The dosages used for the treatment of depression (≥150mg per day) are much higher than those used for the management of pain (10-30mg). Newer antidepressants such as SSRIs and SNRIs have replaced TCAs as first line treatments for depression, although TCAs are still used cautiously as second- or third-line agents for the treatment of resistant depression, either alone or in combination with other mood -altering drugs.

Although amitriptyline is licensed to treat depression, at a lower dose of 10mg to 30mg it is commonly used "off-license" to treat migraines, insomnia, and certain types of neuropathic and chronic pain.

2.4. Amitriptyline in the ATLANTIS Study

Given the recommendations of the NICE guideline (12), together with the fact that two of the trials in the meta-analyses used low-dose amitriptyline (15, 16), both of which were small, but positive, and the proven pain-modifying properties of amitriptyline (8, 9), as well as its effects on gut motility (11), and visceral hypersensitivity (17), low-dose amitriptyline has been selected as the TCA to assess in the ATLANTIS study.

This study was successfully funded as part of a commissioned call by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (HTA no 16/162), which identified the need to address the relative short- and long-term benefits of low-dose antidepressants for IBS in primary care, to help guide treatment decisions.

3. RATIONALE

3.1. Study Aims

The overall aim of this study is to determine the clinical and cost-effectiveness of low-dose amitriptyline as a second-line treatment for IBS in primary care.

3.2. Potential Benefits

Although there is some support for the use of low-dose TCAs in IBS, including recommendations in the NICE guideline, the evidence base is not strong. As most patients with IBS are managed in a primary care setting, there is a clear need for a definitive RCT of antidepressants in primary care to assess whether the beneficial effect seen in previous meta-analyses translates into this setting. Additionally, NICE recommends such a trial be conducted (12).

ATLANTIS will assess the clinical and cost-effectiveness of low-dose amitriptyline for IBS in a well-designed, rigorous study in primary care, with long-term outcomes. As there is no gold-standard therapy for IBS in primary care, particularly after failure of first-line therapies, the comparator will be an identical-appearing placebo, titrated similarly.

If a comparable effect size to that seen in the meta-analysis of TCAs, in which most of the trials were conducted in secondary or tertiary care, were observed in a trial conducted in patients with IBS based in primary care, this would have the potential to produce a substantial impact on patient's symptoms and clinical practice. It is likely that the national guideline for the management of IBS from NICE would change, to more strongly encourage the use of amitriptyline for ongoing IBS symptoms. This could

lead to a real change in the way that IBS is managed in primary care, because use of the drug in this setting would be more strongly advocated by guidance, and hence GPs would be more likely to offer it to patients with ongoing IBS symptoms. This may lead to better control of IBS symptoms, improved quality of life for people with IBS, and reduced costs of managing IBS in primary and secondary care. Although new therapies for IBS continue to be developed, these are usually modest in terms of their efficacy, are expensive and, in recent years, several have been withdrawn due to serious concerns about side effects, whereas amitriptyline is an established, safe, and cheap drug (18). Confirmation that a drug that is widely available, safe, and of low cost to the health service is effective in IBS could reduce National Health Service (NHS) management costs for the condition substantially.

3.3. Assessment and Management of Risk

Amitriptyline has been widely used for the treatment of depression since the 1960s. Common side effects include dizziness, dry mouth, constipation, and weight gain. Side effects are more common with higher dosages. Amitriptyline is potentially lethal if taken as an overdose. It is now used as a second-line treatment for major depressive disorder, with dosages commonly prescribed between the ranges of 150mg to 200mg. Careful monitoring of suicidal ideation is usually carried out before starting the drug, and during its administration, because of the risk of suicide in patients with severe, treatment resistant depression. Although amitriptyline is only licensed for the treatment of depression, it is commonly prescribed 'off-license' at a lower dose to treat pain. It is also used off-license at a dose of 10mg to 30mg as second-line treatment for IBS. The NICE guideline for the management of IBS in adults states that TCAs should be considered as second-line treatment for people with IBS if laxatives, loperamide, or antispasmodics have not helped. The guideline advises starting on a low dose of amitriptyline and increasing if needed, but not usually beyond 30mg OD, which is the maximum used in this study. It is standard practice for patients to self-titrate amitriptyline in response to their symptoms and side effects. Because of this, the trial has been categorised as **Type A: no higher than the risk of standard medical care,** according to the Medical Research Council/Department of Health/ Medicines and Healthcare products Regulatory Agency (MHRA) risk adaptive approaches to the management of a clinical trial of an investigational medicinal product (CTIMP).

Patients with contraindications to amitriptyline will be declined entry into the trial, as detailed in the exclusion criteria. A small proportion of patients with IBS in primary care may also have mild to moderate co-morbid symptoms of depression, for which they may or may not be receiving treatment. As this is a pragmatic study, patients with depression will be not be excluded. Low-dose TCAs are commonly prescribed for a wide variety of pain-related conditions and insomnia in patients, who may or may not be depressed in the primary care setting. The dosages used for IBS, nerve pain relief, or insomnia are sub-therapeutic for the treatment of depression. The intention is therefore not to exclude patients with depressive symptoms, as these patients may benefit in terms of their IBS pain and bowel symptoms from low-dose TCAs.

A key concern, however, is patient safety, and the unlikely but possible risk of an amitriptyline overdose. Therefore we will screen for suicidal ideation at baseline, and people with active suicidal ideas or intent will be excluded. We anticipate that this will be a very small number of potential participants. Amitriptyline is potentially toxic in overdose, but the very low daily dose proposed in this trial, and the sequential dispensing, means that participants will only have a very limited total amount of drug that they can access. We will also have a protocol in place to guide research nurses/CSOs to notify the patient's GP in order to request urgent review (or other appropriate steps), in the event that someone with active suicidal ideation is identified, either at initial screening, or later interim screening checks, and prior to dispensing any drug prescriptions.

4. OBJECTIVES AND ENDPOINTS

4.1. Primary Objective and Endpoint

Objective	Endpoint	Method of data collection
What is the effect of amitriptyline, compared with placebo, on global symptoms of IBS at 6 months, measured via a widely used, validated, patient-reported, outcome measure?	IBS-SSS score at 6 months.	Questionnaire.

4.2. Secondary Objectives and Endpoints

	Objective	Endpoint	Method of data collection
1.	What is the effect of amitriptyline, compared with placebo, on global symptoms of IBS at 3 and 12 months?	IBS-SSS score at 3 and 12 months.	Questionnaire.
2.	What is the effect of amitriptyline, compared with placebo, on relief of IBS symptoms at 3, 6 and 12 months?	Subjective Global Assessment (SGA) of relief of IBS symptoms as a dichotomous measure at 3, 6 and 12 months.	Questionnaire.
3.	What is the effect of amitriptyline, compared with placebo, on anxiety at 3, 6 and 12 months?	Hospital Anxiety and Depression Scale (HADS – anxiety score) at 3, 6 and 12 months.	Questionnaire.
4.	What is the effect of amitriptyline, compared with placebo, on depression at 3, 6 and 12 months?	Hospital Anxiety and Depression Scale (HADS – depression score) at 3, 6 and 12 months.	Questionnaire.
5.	What is the effect of amitriptyline, compared with placebo, on patient reported relief of IBS symptoms, measured weekly?	Binary response to “Have you had adequate relief of your IBS symptoms?” asked electronically, or via a paper based diary. Participants will be sent a weekly text reminder from CTRU to complete the assessment.	Weekly question/ patient diary.
6.	What is the effect of amitriptyline, compared with placebo, on self-reported health care use at 3, 6 and 12 months?	Cost of health care resource use including primary, community, and social care, admitted patient care, outpatient care (specialist visits and diagnostic investigations), cost of prescribed medications for IBS, and referral to secondary care at 3, 6 and 12 months.	Questionnaire.
7.	What is the effect of amitriptyline, compared with placebo, on health-related quality of life at 3, 6 and 12	EQ-5D-3L time trade-off (TTO) summary score, EQ-5D-3L Visual Analogue Scale at 3, 6 and 12 months.	Questionnaire.

months measured via the EQ-5D-3L (5)?		
8. What is the effect of amitriptyline, compared with placebo, on ability to work and participate in other activities at 3, 6 and 12 months?	Work and Social Adjustment Scale (WSAS) total score at 3, 6 and 12 months.	Questionnaire.
9. What is the effect of amitriptyline, compared with placebo, on IBS-associated somatic symptoms at 6 months?	Patient Health Questionnaire 12 (PHQ-12) score at 6 months.	Questionnaire.
10. What is the cost-effectiveness of amitriptyline, compared with placebo, at 6 months and 12 months?	Incremental cost-effectiveness ratio expressed in terms of incremental cost per quality adjusted life year (QALY) at 6 and 12 months.	Questionnaire.
11. What is the acceptability of treatment with amitriptyline at 6 months, compared with placebo?	Patient-reported choice to continue active trial medication post-6 months.	Nurse/CSO-completed questionnaire.
12. What is the adherence to therapy with amitriptyline at 3 weeks, 3, 6, 9 and 12 months compared with placebo?	Question asked by research nurse/CSO "Since you were last asked, which of the options best describes how often you have taken at least one tablet of the trial medication daily?" A. Every day or nearly every day B. Half of the days or more than half the days C. Less than half of the days D. None or nearly none of the days At 3 weeks, 3, 6, 9 and 12 months.	Nurse/CSO-completed questionnaire.
13. What is the tolerability of amitriptyline, compared with placebo, in terms of adverse events (AEs) at 3, 6 and 12 months?	Validated Antidepressant Side- Effect Checklist (ASEC) at 3, 6 and 12 months.	Questionnaire.
14. What are patients' and GPs' experiences of treatments and participating in the trial, and how can these inform our understanding of the quantitative results and future implementation efforts?	Themes from analysis of qualitative interviews with patients and GPs.	Qualitative interviews with patients and GPs.

4.3. Internal Pilot Objective

Objective	Endpoint	Data required & how is it being collected?
To assess trial recruitment and 6-month follow-up rates, and meet clear progression criteria.	Recruitment and follow-up rates.	Recruitment and follow-up rates, collected via randomisation and questionnaire data.

4.4. Nested Qualitative Study

Objective	Endpoint	Data required & how is it being collected?
1. To identify factors that facilitate or impede prescribing of, acceptability of, and adherence to, low-dose amitriptyline in this patient group.	Thematic analysis.	Qualitative interviews with GPs and patients.
2. To identify patients' and GPs' perspectives on the broader impact of the trial, including any unanticipated effects not captured by the quantitative measures.	Thematic analysis.	Qualitative interviews with GPs and patients.
3. To explore psychosocial and contextual factors that might shape wider use of amitriptyline for IBS.	Thematic analysis.	Qualitative interviews with GPs and patients.

5. STUDY DESIGN

ATLANTIS is a randomised, multi-centre, parallel-group, two-arm, double-blind, placebo-controlled trial of low-dose amitriptyline as a second-line treatment for people with IBS in primary care. This will include an internal pilot with clear progression criteria for recruitment and follow-up rates. A nested, qualitative study will explore patients' and GPs' experiences of treatments and participating in the trial, including acceptability, adherence, unanticipated effects, and implications for the wider use of amitriptyline for IBS.

5.1. Treatment Regimens

518 adult patients with IBS in primary care, who are still symptomatic despite first-line therapies, will be randomised 1:1 to receive amitriptyline, or identical-appearing placebo. Amitriptyline and placebo will be commenced at a dose of 10mg OD (one tablet) at night, and dose titration will occur, to a maximum of 30mg OD at night (three tablets), depending on side effects and response to treatment. Participants will be followed up for 12 months. They will be randomised to 6 months of medication initially and then be able to stop or continue medication for a further 6 months. Our patient and public involvement (PPI) input revealed that 6 months of treatment was felt to be the maximum reasonable initial commitment.

Treatment Arm	Number of Patients	Period of Treatment
Amitriptyline 10mg OD for 1 week. Depending on response, increasing by 10mg OD per week to a maximum of 30mg OD (three tablets). Further titration up to, or down from, 30mg OD on an ongoing basis is allowed.	259	Minimum of 6 months. Maximum of 12 months.
Placebo One tablet OD for 1 week. Depending on response, increasing by one tablet OD per week to a maximum of three tablets OD. Further titration up to, or down from, three tablets OD on an ongoing basis is allowed.	259	Minimum of 6 months. Maximum of 12 months.
Total number of patients	**518**	

Table 1 Summary of treatment arms

5.2. Internal Pilot

An internal pilot, commencing in the first month of trial recruitment, across all three hubs, will assess recruitment after 6 months, and follow-up rates after a further 6 months. Rates will be monitored monthly by the Trial Management Group (TMG), to proactively identify areas below target requiring additional support to improve progress. To allow rates to stabilise, the recruitment progression and follow-up criterion will be assessed at separate time points. The recruitment progression criterion will be assessed after 6 months of recruitment, reviewing rates over the previous 3 months. The follow-up progression criterion will be assessed 6 months later, reviewing the 6-month follow-up rate for all patients in the internal pilot.

Green/Continue:

≥80% of target monthly recruitment rate: 80% of 32pts/month = 26 (i.e. averaged over months 4-6 of internal pilot);

≥80% follow-up for 6-month primary outcome;

Amber/Review:

50%–80% of target monthly recruitment rate: 16-26 patients/month

60-80% follow-up for 6-month primary outcome;

Red/Stop:

<50% of target monthly recruitment rate: <16 patients/month

<60% follow-up for 6-month primary outcome

If any criteria are graded as amber, a rescue plan will be developed outlining steps to be taken to improve, recruitment and/or follow-up, and will be approved by the TSC before submission to the funder (HTA). If the progression criteria are failed (red), the TSC will consider not progressing the internal pilot to the definitive study. If the progression criteria are met (green) by the end of the internal pilot, then the study will continue and outcome data from participants in the internal pilot will be included in the main study analysis.

5.3. STUDY SETTING

5.3.1. Participating Sites and Research Hubs

Participants will be recruited from approximately 75 GP practices. Each GP practice is classed as a research site with a GP who is the principal investigator (PI). Practices within urban and rural settings, and with a range of socio-demographic characteristics, will be included. Practices will be required to have obtained management approval and undertake a site initiation meeting prior to the start of recruitment into the trial.

The GP practices will be located in three geographical regions, West Yorkshire (Leeds), Wessex (Southampton), and the West of England (Bristol). These three geographical regions are referred to as

'recruitment hubs' or 'hubs'. Each hub research team will include a 'hub lead clinician' and research nurses/CSOs, and will be responsible for coordinating the majority of patient activity.

5.4. Study flow chart

Figure 1 Study flow chart: participant identification and screening

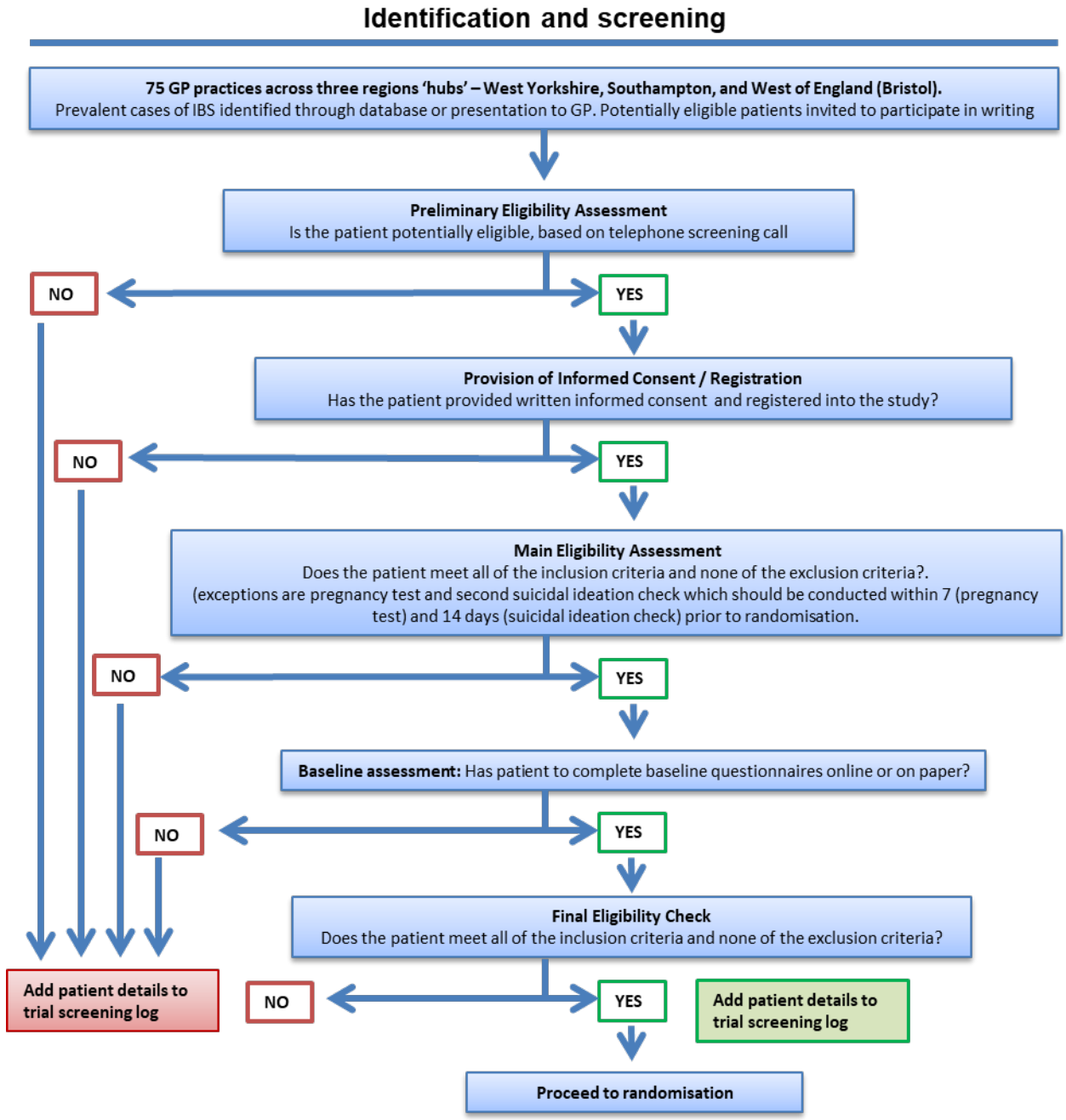
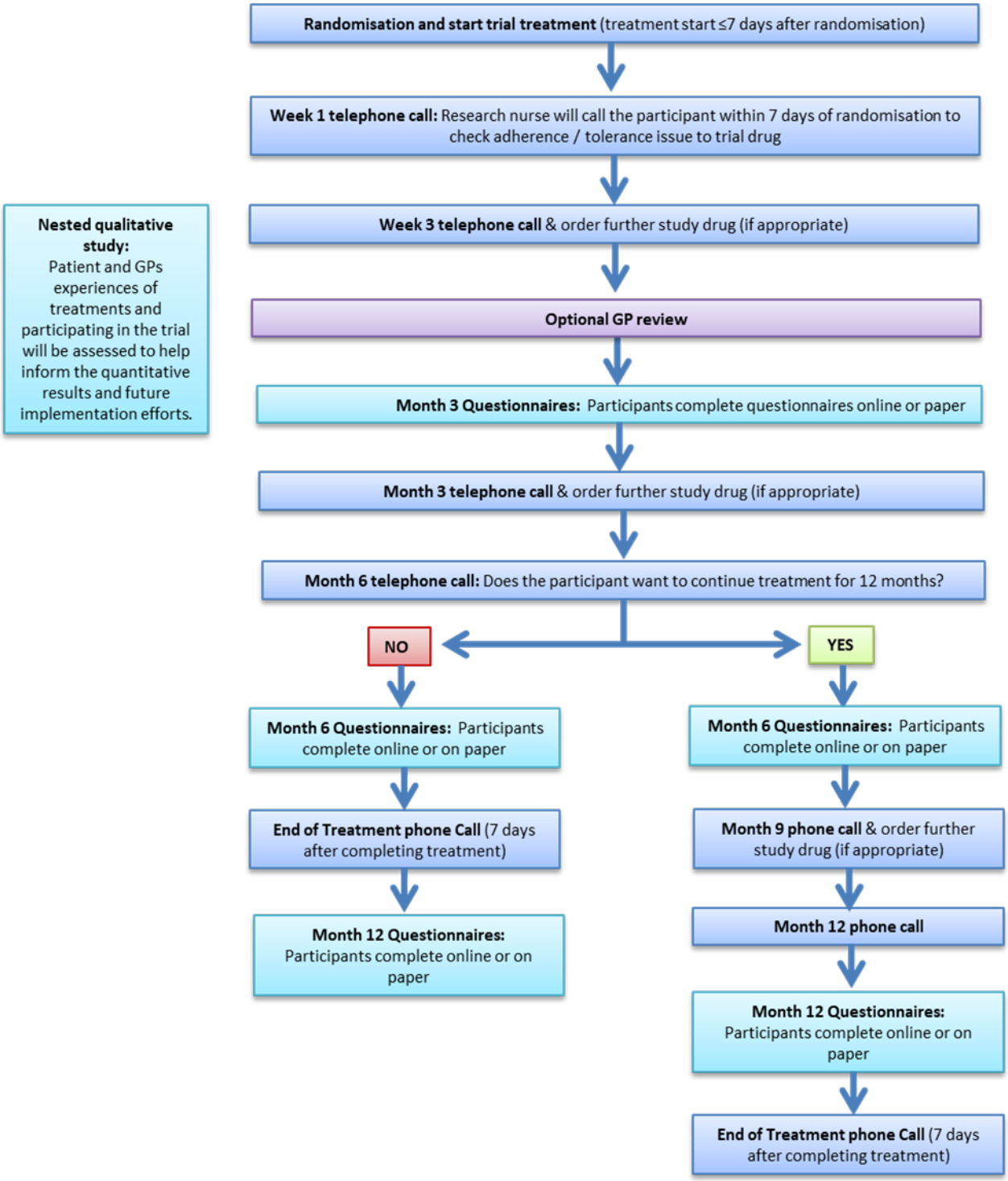


Figure 2 Study flow chart: randomisation, treatment and follow up



6. ELIGIBILITY CRITERIA

Eligible patients who take part in the study must meet all of the listed inclusion criteria, and none of the exclusion criteria. Eligibility waivers to inclusion/exclusion criteria are not permitted. Please refer to section 7.5 for further information on eligibility assessments.

6.1. Inclusion Criteria

Eligible patients will fulfil all of the following:

1. A diagnosis of IBS (of any subtype of stool pattern [diarrhoea, constipation, mixed, unclassified]) in primary care record, and fulfilling the Rome IV criteria;

2. Age ≥18 years;

3. Ongoing symptoms, defined as an IBS-SSS score of ≥75 at screening, despite having tried dietary changes and first-line therapies as defined by NICE (antispasmodics [e.g. mebeverine], fibre supplements [e.g. fybogel], or anti-diarrhoeals [e.g. loperamide]), which are also assessed at screening via patient self-report;

4. A normal haemoglobin, total white cell count (WCC), and platelets within the last 6 months prior to screening[1];

5. A normal CRP within the last 6 months prior to screening;

6. Exclusion of coeliac disease, via anti-tTG antibodies, as per NICE guidance (7);

7. No evidence of active suicidal ideation, as determined by three clinical screening questions below, and no recent history of self-harm (an episode of self-harm within the last 12 months prior to screening). These clinical questions are used in preference to a formal suicidal risk rating scale, as such scales perform poorly in clinical practice (any positive response on any of the three questions will trigger urgent review by the patient's GP)[2]:

    (i) Whether the patient has experienced any thoughts of harming themselves, or ending their life in the last 7-10 days?

    (ii) Whether the patient currently has any thoughts of harming themselves or ending their life?

    (iii) Whether the patient has any active plans or ideas about harming themselves, or taking their life, in the near future?

8. If female, must be:
    a. post-menopausal (no menses for 12 months without an alternative medical cause), or;

b. surgically sterile (hysterectomy, bilateral salpingectomy or bilateral oophorectomy), or;
c. using highly effective contraception[3] (and must agree to continue for 7 days after the last dose of the investigational medicinal product [IMP]).

9. Able to complete questionnaires and trial assessments;

10. Able to provide written informed consent.

6.2. Exclusion Criteria

Ineligible patients will be any of the following:

1. Aged >60 years with no GP review in the 12 months prior to screening[4] (7);

2. Meeting locally adapted NICE 2-week referral criteria for suspected lower gastrointestinal cancer[5] (19);

3. A known documented diagnosis of inflammatory bowel disease or coeliac disease;

4. A previous diagnosis of colorectal cancer;

5. Patients currently participating in, or who have within the 3 months prior to screening been involved in, another CTIMP;

6. Pregnancy[6] or breastfeeding;

7. Planning to become pregnant within the next 18 months;

8. Current use of a TCA, or use of a TCA within the last two weeks prior to randomisation, for another indication;

9. Allergy to TCAs;

10. Other known contraindications to the use of TCAs, including patients with any of the following:
    - taking monoamine oxidase inhibitors (MAOIs), or receiving them within the last 2 weeks;
    - already prescribed a TCA for the treatment of depression
    - previous myocardial infarction;
    - recorded arrhythmias, particularly heart block of any degree, prolonged Q-T interval on ECG;
    - mania;
    - severe liver disease;
    - porphyria;
    - congestive heart failure;

- coronary artery insufficiency;
- receiving concomitant drugs that prolong the QT interval (e.g. amiodarone, terfenadine, or sotalol)[7].

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1. Any other minor abnormalities on FBC will not be an exclusion to participation, but the patient's GP will be informed and provided with standard advice.
2. Suicidal ideation should be assessed on the screening telephone call, prior to registration, and again within 14 days prior to randomisation.
3. Highly effective contraception is defined as one of the following: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomised partner; practising true abstinence (when this is in line with the preferred and usual lifestyle of the subject).
4. Potential participants aged >60 years will only be included if they have had a GP review within the 12 months prior to study entry, in order to confirm that their symptoms are related to IBS, and that other serious bowel conditions have been excluded.
5. Any potential participant meeting NICE 2-week referral criteria for suspected lower gastrointestinal cancer, which would indicate the need for further investigations (e.g. recent unexplained weight loss, rectal bleeding, abdominal pain, a recent change in bowel habit, or anaemia), 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 assessed, and that he or she was suitable for study entry.
6. For women of childbearing potential (those not post-menopausal or surgically sterile), who cannot definitely confirm they are not pregnant, this must be confirmed by a pregnancy test within 7 days prior to randomisation. Post-menopausal is defined as no menses for 12 months without an alternative medical cause.
7. Other cautions to the use of TCAs will not be an exclusion, but these will be recorded at screening and clarified with the patient's GP and the lead GP in each hub prior to study entry.

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7. TRIAL PROCEDURES

7.1. Patient Identification and Screening process

7.1.1. Patient Identification

518 patients will be recruited from approximately 75 GP practices (approximately 25 per recruitment hub). The Clinical Research Network will support GP practice identification, recruitment, and trial implementation. GP practices willing to participate in the study will search their list for potentially eligible adult patients aged ≥18 years with a diagnosis of IBS, using a Read code list. These individuals will be contacted by letter (sent by the GP practice) informing them about the trial, and inviting them to take part. A GP will check the list of patients to be contacted prior to the invite letters being sent out, to ensure that it is appropriate to contact them. The postal invitation will include the patient information sheet and informed consent form. Potential participants interested in taking part in the study will return a reply slip in a pre-paid envelope or contact the study team via email. The reply slip includes a section for the potiential participant to agree to be contacted about the study, and following this, for information to be requested from their GP to confirm their suitability to take part in the trial. For patients who express interest in the trial by email, this agreementshould be obtained by email.

The reply slip will also include a 'reason to decline' section so that we can gather information on reasons people chose not to participate in the trial. We will ask the recruiting GP centres to provide an anonymised list of the gender,age, and invite number (this number will also be printed on the invite letter and reply slip) so that we can compare the characteristics of those declining to participate with those entering the trial.

GPs will also be able to opportunistically provide information about the trial to potential recruits during their GP surgeries. Posters and leaflets will be displayed in waiting rooms and the trial will be advertised on GP practice websites, if possible. Thus, if a patient with IBS attends a GP consultation, they will be able to ask the GP about the study and be given contact details for the study team if appropriate.

7.1.2. Trial Advertising

The ATLANTIS study will also be adverstised by sign-posting by GP practice staff, posters in GP waiting rooms, and information on practice websites. These will direct the patient to their local recruitment hub and the ATLANTIS website. Promotional material may also be sent to specialist IBS organisations to send out via their mailing list or advertise on their website, Facebook and Twitter pages. This will direct patients to the ATLANTIS website.

The ATLANTIS website will contain the patient information documentation for the study and contact details for the local recruitment hubs.

The ATLANTIS Twitter account will be raise awareness of the study and will be for information purposes only.

7.1.3. Initial Eligibility Assessment

The hub research nurses/CSOs will contact potential participants who reply to the study invitation in order to arrange a screening call. On this call they will provide further information about the trial and obtain verbal consent to telephone-screen the potential participants, using a questionnaire consisting of the Rome IV criteria (20), IBS-SSS (34) and questions about the inclusion and exclusion criteria. All potential participants will be assigned a unique screening identification number.

Following this telephone call, the study team may need to request information from the GP practice (eg. FBC), to support the screening process. The need for this will be made transparent to the patient through the patient information materials (including the postal invitation, patient information sheet, and website) and through communications from the hub research team.

To allow generalisation of the trial results, and in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines, each recruitment hub, on behalf of each GP practice, will maintain and provide to the CTRU an anonymised screening log of all patients who are screened for entry into the study, including all those who confirm interest. Furthermore, each recruitment hub will be required to complete a screening form for all patients who undergo screening. Documented reasons for ineligibility or declining participation should be recorded and will be closely monitored by the CTRU as part of a regular review of recruitment progress. Screening logs and forms should be returned to the CTRU on a monthly basis.

Anonymised information will be collected including:

- Age;
- Gender;
- Method of identification;
- Whether written informed consent was provided;

- Whether the potential participant was registered into the trial or not;
- Whether the potential participant was randomised into the trial or not.

Screened patients who are not registered, or randomised, either because they are ineligible or because they decline participation, will also have the following information recorded:

- The reason they are not eligible for study participation;
- The reason that they declined if they were eligible.

7.2. Informed Consent

The PI at each site retains overall responsibility for the informed consent of patients at their site and must ensure that any person who is delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate, according to the ethically approved protocol, principles of Good Clinical Practice (GCP), and Declaration of Helsinki 1996.

Where a test has been performed as part of local care, and is within the required time-frame, it does not have to be repeated but cannot be used for trial purposes until the patient has given verbal consent.

Patients who are potentially eligible, after telephone screening, will be asked to provide written informed consent. Patients will have as long as they need (at least 24 hours, unless the participant wishes to participate sooner) to consider participation, and will be given the opportunity to discuss the study with their family and healthcare professionals before they are asked whether they would be willing to take part. The research nurse/CSO (or investigator or designee), in each recruitment hub will be suitably trained in the informed consent process and the study. Informed consent will always be obtained from the patient during a face-to-face visit with the research nurse/CSO. They will provide the patient with full and adequate oral and written information about the study, including the background, purpose, and risks/benefits of participation, and ensure that each patient is given the opportunity to ask questions they have concerning study participation. Consent will take place at the GP practice, and a GP will be available to answer any questions or concerns as required. The research nurse/CSO will also confirm that the patient is free to withdraw from the study at any time without it affecting their future care. The consent discussion will be recorded within the patients' medical record.

Informed consent from participants will also include a request to take part in qualitative interviews at 6 and 12 months, with information concerning the likely duration of these interviews provided. Finally, permission will also be sought to collect longer term routine GP data on amitriptyline and other IBS medication prescriptions, GP consultations for IBS, and secondary care referrals, outside the timeframe of the trial itself, should further funding become available.

Written informed consent for the study will be collected from each patient before they undergo any blood tests and/or pregnancy test that are required specifically for the purposes of the study. The right of a patient to refuse participation without giving reasons will be respected. The patient will remain free to withdraw at any time from the study without giving reasons, and without prejudicing his/her further treatment. All patients will be provided with a contact point where he/she may obtain further information about the trial. Where a patient is required to re-consent, or new information is required

to be provided to a patient, it will be the responsibility of the hub research team to ensure this is done in a timely manner, and according to any timelines requested by the CTRU.

Where the patient is able to provide fully informed consent, but is unable to sign or otherwise mark the consent form, provision for completion of the consent form by a witness will be made. This should be a carer, friend/family member, or a local member of the clinical team who is independent of the research team.

A record of the consent process, detailing the date of consent and those involved in the consent process, will be added to the patient's notes. The original copy of the signed, dated, informed consent form will be stored in the investigator site file. A copy is also filed in the medical records (as per local practice), one given to the patient, and one returned to the CTRU.

7.2.1. Loss of Capacity Following Informed Consent

Where valid informed consent is obtained from the patient, and the patient subsequently becomes unable to provide ongoing informed consent by virtue of physical or mental incapacity, the consent previously given, when capable, remains legally valid.

Patients who lose capacity after informed consent has been obtained will continue with protocol treatment and assessments in consultation with the PI and patient's carer/family with the patient's best interests foremost in the decision making process. Ongoing collection of safety and follow-up data (where possible) will continue via the clinical care team for inclusion in the trial analysis, in order to preserve the integrity of the trial's analysis, and fulfil regulatory requirements specifically for pharmacovigilance purposes.

7.3. Participant Payments

All participants randomised into the study will receive a £20 gift voucher. This will be sent to the participant within the first 3 months of the trial.

7.4. Registration

Following confirmation of written informed consent, patients will be registered into the trial as soon as possible by an authorised member of the hub research staff. Informed consent for entry into the trial must be obtained prior to registration. Registration will be performed centrally using the CTRU automated web-based registration and randomisation system. Authorisation codes and PINs will be provided by the CTRU, and will be required to access the registration and randomisation system.

The following information will be required at registration:

- Personal authorisation codes and PIN;
- Name of person making the registration;
- Name of study research site and site code;
- Confirmation of eligibility;
- Patient details, including initials, gender, date of birth, email address, mobile telephone number and home address
- Confirmation of written informed consent, and date.

All patients will be allocated a unique trial identification number after they have been registered.

ONLINE ACCESS FOR 24-HOUR REGISTRATION

Online Access: https://lictr.leeds.ac.uk/webrand/

As trial-specific data collection is carried out post-registration, recruitment into the study is classed as a two-step process involving an initial registration of all potential participants, followed by randomisation for eligible patients. Randomisation of eligible patients will not take place until all inclusion and exclusion criteria have been confirmed.

Following registration, an automated email will be send to the hub research team to confirm that a participant has been registered.

7.5. Confirmation of Eligibility

The following assessments must be carried out **prior to randomisation** in order to establish eligibility (see section 6 above for full eligibility criteria):

- Rome IV criteria;
- Suicidal ideation assessment;
- IBS-SSS;
- Blood tests to check FBC, CRP, and anti-tTG antibodies;
- Pregnancy test for women of childbearing potential (those not post-menopausal or surgically sterile), who cannot definitely confirm verbally to the research nurse/CSO that they are not pregnant.

Rome IV criteria, suicidal ideation assessment, and IBS-SSS for eligibility should be assessed on the screening telephone call prior to registration. A second suicidal ideation assessment should be performed by phone within 2 weeks of randomisation.

Some patients will have already undergone screening for coeliac disease with anti-tTG antibodies, and this will not need to be repeated in these individuals. Likewise, a normal FBC and CRP within the 6 months prior to screening will not need to be repeated.

Blood test results will be made available to the hub lead clinician (or delegate), to the research nurse/CSO, and to the patient's GP. In accordance with the trial inclusion criteria, if the blood tests show an abnormal result (i.e. a CRP over the normal laboratory range, anaemia, raised or lowered total WCC, raised or lowered platelet count, or positive anti-tTG antibodies), the individual will not be randomised into the trial, but will be referred back to their GP for further assessment. In the case of an abnormal blood result for CRP, WCC or platelets that the hub lead clinician assesses, which may be a temporary abnormality (e.g. secondary to a recent infection), the blood test may be repeated 2-4 weeks later if the participant wishes to undertake further screening for the study. If on repeat testing total WCC, platelet count and CRP are normal, the patient may then continue with screening if they wish. Any other abnormal results will need to be flagged to the patient's GP by the recruitment hub.

If blood results are within acceptable limits, the investigator (GP) from the research site will be asked to confirm eligibility and sign the study-specific prescription form. A copy of the prescription will be faxed, emailed or sent via secure encrypted electronic transfer to central pharmacy (LTHT pharmacy) and the wet ink prescription will be posted to central pharmacy prior to randomisation, to enable study medication to be dispensed swiftly when the patient is randomised. Patients will be provided with questionnaires (web-based or postal questionnaires, depending on preference) to complete baseline measures. Patients will not be randomised until the baseline questionnaires are complete. Baseline questionnaires should be completed within 7 days prior to randomisation for the online questionnaire and 14 days for the paper questionnaire.

Prior to randomisation, women of child bearing potential will be asked to confirm verbally that they are not pregnant. If they are unable to do so, they will be asked to perform a urine pregnancy test within 7 days of randomisation. They will be provided with a pregnancy test to use at home, to facilitate a result as close as possible to randomisation, and hence treatment commencing. Please see appendix 18.3 for pregnancy testing risk assessment. Because this forms part of the eligibility criteria, the lead clinician (their delegate or site PI) at each hub will review and sign the final eligibility for these patients. If the test is positive or unclear the individual will not be randomised into the trial, but will be referred back to their GP.

If the patient is ineligible, or no longer wishes to take part in the trial, the local research team will withdraw the participant. They will not undergo any other study assessments and they will be referred back to their GP. Reasons for non-randomisation will be documented where available.

All participants will continue their GP's usual treatment for IBS during the trial, and will be provided with the NICE IBS and dietary advice sheet (22). All GP recruiting centres will also be provided with NICE guidelines on managing IBS.

7.6. Randomisation

Registered patients who have been confirmed eligible and have completed baseline assessments, will be randomised into the trial by an authorised member of the hub research team using a web randomisation service based at the CTRU. Authorisation codes and PINs will be provided by the CTRU and will be required to access the randomisation system.

The following information will be required at randomisation:

- Personal authorisation codes and PIN;
- Name of person making the randomisation;
- Name of trial research site and site code;
- Patient details, including trial number and date of birth;
- Confirmation of eligibility;
- Confirmation of completion of baseline assessments;
- Stratification factors (see list below)

ONLINE ACCESS FOR 24-HOUR RANDOMISATION

https://lictr.leeds.ac.uk/webrand/

Patients will be randomised 1:1 to receive amitriptyline or placebo. Randomisation will be by minimisation with a random element, on the following factors:

- Presence of depression (HADS-D score ≥8)
- Stool pattern (diarrhoea-predominant, constipation-predominant, mixed, or unclassified stool pattern)
- Recruitment hub (West Yorkshire, Southampton, or West of England)

Confirmation emails will be generated automatically and sent to the research nurse/CSO at the appropriate hub and the site PI. These will not reveal treatment allocation, in order to maintain the blinding of the trial.

Participants will be sent a text confirming their entry into the study. This will not reveal treatment allocation.

Central pharmacy at LTHT will also be sent a confirmation, which will contain two unique kit codes that identify the containers that need to be dispensed. The confirmation to pharmacy will also include a unique code break envelope ID. The selected code break envelopes will be updated with participant details.

7.6.1. Initial Recruitment Hub Post-randomisation Activities

Once the patient has been randomised, the following activities should also be completed by the recruitment hub.

- **Telephone the participant -** participants will be telephoned by the research nurse/CSO within 1 week of the initial dispatch of trial medication, in order to deal with any queries, and to provide standardised advice about dose titration (see section 7.11.4).

7.6.2. Central Pharmacy Post-randomisation Activities:

Following randomisation, the central (LTHT) pharmacy will be notified of the kit numbers assigned to the participant. They will send out an initial 1-month supply of trial medication (plus excess to ensure there is no gap between deliveries) to the participants' home address. Clear instructions regarding dose titration and ongoing management of dose will be included. There will be a request for the participant to confirm medication receipt with the study team. Each participant will also be provided with a trial identification card, they should carry this with them and present it to medical staff should they be admitted to hospital during their time on the trial, or should they visit their GP.

7.7. Blinding

As the trial is double-blind, neither the participant nor those responsible for their care and evaluation (treating team and research team) will know which treatment they have been allocated. This will be achieved by identical packaging and labelling of both the amitriptyline and placebo. The process for

dose titration will be the same for amitriptyline and placebo. Each bottle of amitriptyline/placebo will be identified by a unique randomly generated kit code. Lists of the kit codes and their corresponding treatments will be generated by the CTRU and sent to MODEPHARMA who will supply the kits.

Management of kit codes on the kit logistics application, which is linked to the 24-hour randomisation system, will be conducted by the CTRU safety statistician in addition to maintaining the back-up kit code list.

Access to the code break envelopes at CTRU will be restricted to the safety statistician and designated safety team. Code breaks will be permitted in emergency situations, where treatment allocation knowledge is needed to optimise treatment of the patient.

Central pharmacy will also be blind to treatment allocation.

Any unblinded interim reports provided to the Data Monitoring and Ethics Committee (DMEC) will be provided by the CTRU safety statistician and the reports will be securely password-protected.

At study entry, all patients will be asked to provide their consent to be contacted by the CTRU in order to send them the results of the study and their treatment allocation. Participants will be able to find out their treatment allocation after they have reached the 12 month assessment point in the trial.

7.8. Unblinding

Although the safety of patients in the trial must always take priority, maintenance of blinding is crucial to the integrity of the trial. Unblinding is strongly discouraged and investigators should only break the blind when information about the patient's trial treatment is clearly necessary, and will alter the appropriate medical management of the patient.

Unblinding may be requested on the grounds of safety by the chief investigator (CI), local PI, or authorised delegate, or treating physician. It is anticipated that requests for unblinding will most likely originate from a patient, carer (or friend/family member), or personal physician (e.g. GP) at the time of an AE or planned change in non-trial related drug therapy. In the event of a serious adverse event (SAE), all patients should be treated as though they are receiving the active medication (i.e. amitriptyline).

Should an alternative to unblinding not be identified, and if unblinding is required to optimise medical management of the participant, investigators should follow the emergency unblinding process.

7.9. Emergency Unblinding

Should the imminent safety of a patient be either in question or under threat, the responsibility to break the allocation code resides solely with the treating physician/investigator responsible for the patients' medical care. In this situation they would be allowed to perform an emergency unblinding if no other alternative can be identified.

Emergency unblinding is provided by the CTRU during office hours and by LTHT Pharmacy at all other times, thereby covering each 24-hour period.

The following information will be needed to perform an emergency unblinding:

- Trial name;
- Participant details, including trial identification number, initials and date of birth;
- Name of person making the request for a code-break;
- Reason for requesting a code-break.

7.9.1. Emergency Unblinding During Office Hours

The emergency unblinding process will be undertaken by telephoning the CTRU during office hours, 9.00 to 17.00 Monday to Friday. Exceptions: public/bank holidays, the period between Christmas Eve and New Year, Thursday afternoon before Good Friday and all Tuesdays following a bank holiday except for Mayday and New Year's Day.

DIRECT LINE FOR CTRU EMERGENCY UNBLINDING: 0113 343 4930

This number is located within the central pharmacovigilance team and is manned during CTRU office hours. Following the emergency unblinding of a participant, the CTRU will send a notification to the caller, requester (if this is different person), the site PI, the hub lead clinician, the hub research nurse/CSO and central pharmacy. The details of the emergency unblinding should be recorded on the ATLANTIS unblinding log provided by CTRU.

Further information on emergency unblinding can be found in the emergency unblinding study site operating procedure. The reason for emergency unblinding will be collected on the emergency unblinding case report form (CRF).

7.9.2. Emergency Unblinding Out of Hours

Outside of office hours, or where the investigator or treating physician is unable to contact CTRU, emergency unblinding will be performed by LTHT out of hours pharmacy service, using the telephone number below.

The responsible pharmacist will complete the unblind request CRF, retrieve the code-break information, and reveal the treatment allocation to the person requesting the unblind. Following the emergency unblind of the participant, the out of hours pharmacy team will notify the caller and requester (if this is a different person) and the Pharmacy Clinical Trials Team at Leeds General Infirmary, who will notify the CTRU on the next working day.

All code-break envelopes will be returned to CTRU by LTHT pharmacy department at the end of trial. Code-break envelopes must not be opened for participants when they have completed trial therapy.

OUT OF HOURS LTHT EMERGENCY UNBLINDING: 0113 3922459

7.9.3. Treatment of Participants Following Emergency Unblinding

Following an emergency unblinding the participant should be treated according to the treating clinician's assessment.

7.10. Discontinuation of Study Treatment and Withdrawal Criteria

In line with usual clinical care, cessation or alteration of regimens at any time will be at the discretion of the attending clinicians, or the patients themselves.

The PI, or delegate (including research nurse/CSO) should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented using the Withdrawal CRF in order that the correct processes are followed by the CTRU and site, following the withdrawal of consent.

It should be made clear to any participant specifically withdrawing consent for further data collection that data pertaining to safety will continue to be collected for regulatory reporting purposes and will be included in any safety analysis. Furthermore, if any significant new information becomes available in regard to the treatment they have received in the trial it may be necessary to contact them in the future about this.

7.10.1. Discontinuation of Study Treatment

Patients who discontinue the study treatment would still be expected to complete the participant questionnaires at 3, 6, and 12 months, unless they withdraw from the trial (see section 7.10.2). They may also be invited to participate in telephone interviews as part of the qualitative sub study, unless they withdraw consent for this. Reasons for study treatment discontinuation would include:

- Patient decision;
- SAEs;
- Severe non-compliance to this protocol as judged by the investigator;
- Safety, including allergic reaction to IMP;
- If the investigator considers that a patient's health will be compromised due to AEs or concomitant illnesses that develop after entering the study;
- Receipt of a restricted concomitant medication after entering the study;
- Pregnancy;
- Overdose;
- Suicidal ideation.

The reason for discontinuing study medication will be recorded. Once study medication is permanently discontinued it cannot be restarted as part of the study. Patients should return all unused IMP and packaging on cessation of trial treatment.

7.10.2. Withdrawal from trial

Patients who withdraw from the trial would not need to complete further participant questionnaires. Reasons for withdrawal from the follow-up assessments would include:

- Patient decision;
- Lost to follow-up;
- Death.

7.10.3. Procedures for Withdrawal from Study

The PI or delegate (including hub research nurse/CSO) should ensure that the specific wishes of any patient who wishes to withdraw consent for further involvement in the trial, be that from further treatment and/or follow-up data collection, are defined and documented using the withdrawal CRF within 24 hours of the research team becoming aware, in order that the correct processes are followed by the CTRU and site, following the withdrawal of consent.

Where the patient has withdrawn due to an AE, the investigator or delegate should follow the procedures documented in section 7 in order to assess the safety of the IMP.

It will be made clear to any patient specifically withdrawing consent for further data collection in a CTIMP that data pertaining to safety will continue to be collected for regulatory reporting purposes, and will be included in any safety analysis and the final analysis. Data already collected will be retained.

In addition, it is suggested that the patient is made aware of the fact that if any significant new information becomes available in regard to the treatment they have received in the trial, it may be necessary to contact them in the future.

If it is the decision of the GP to withdraw the patient from further involvement in the trial then this should be documented on the relevant CRF.

7.10.4. Treatment After Study

Following participation in the study, subsequent patient care will be decided by their GP according to usual practice.

7.11. Participant Assessments

Data will be collected via paper CRFs and questionnaires, or electronically via the CTRU registration/randomisation system and the electronic patient reported outcome software “REDCap”.

Participants will self-complete assessments directly into REDCap or by returning paper postal questionnaires to the CTRU. They will be sent SMS and email reminders to prompt completion. If questionnaires are not been completed, the hub study team will attempt to contact the participant to collect the data over the telephone.

Staff will complete paper CRFs and return these directly to CTRU. Please refer to section 11 and 14 for more information on data handling and data protection.

Prior to study medication replenishment, the research nurses/CSOs will contact the participant by telephone for safety reasons, and other data items will also be collected during this call (please refer to sections 7.11.1 – 7.11.12 below for details of data to be collected).

Participating GP practices will be expected to maintain a file of essential trial documentation (investigator site file), which will be provided by the CTRU. Further essential documentation will be held by each of the three hubs, who will also keep copies of all completed CRFs for the trial.

7.11.1. Baseline Assessments

Prior to randomisation the following baseline information will be collected by a member of the research team:

- ;
- Past medical history and medications;
- Duration of IBS symptoms (via participant self-report);

In addition, the participant will self-complete the following baseline assessments (online or on paper) prior to randomisation. Ideally, these will be completed within 7 days prior to randomisation for the online questionnaire and 14 days for the paper questionnaire. If randomisation has not taken place within 4 weeks of the baseline assessments being completed, the baseline assessments should be repeated.:

- Socio-demographic details
- History of previous depression or anxiety;
- HADS questionnaire;
- IBS-SSS;
- EQ-5D-3L;
- WSAS;
- Patient Health Questionnaire-12 (PHQ-12);
- Health resource use.
- Bristol stool form scale (BSFS)

The HADS-D score from the HADS baseline questionnaire will be used at randomisation to stratify the participant. Stool pattern from the BSFS will be used to stratify the participant.

7.11.2. Weekly Participant Reported Assessment of Irritable Bowel Syndrome Symptom Relief

Once participants have commenced treatment with the study medication, they will be asked to answer a weekly question “Have you had adequate relief of your IBS symptoms?” electronically, or via a paper based diary. Participants will be sent a weekly text and email reminder from CTRU to complete the assessment. We will stop collecting this information for all participants at 6 months.

7.11.3. Week 1 Telephone Call

The hub research nurse/CSO will call the participant **within** 1 week of randomisation, in order to deal with any queries, provide standardised advice about dose titration, and to ensure there are no contraindications to continuing medication.

- Information to be collected:
  - Dose of study medication;
  - Toxicity assessment: collection of AEs or reactions using the ASEC, which have occurred since randomisation, including SAEs/serious adverse reactions (SARs)/suspected unexpected serious adverse reactions (SUSARs);
  - Prohibited medications check.

7.11.4. Week 3 Telephone Call (+/- 3 working days)

The hub research nurse/CSO will call the participant at the end of 3 weeks post-randomisation, to confirm the dose reached during titration, and to ensure there are no contraindications to further medication being issued.

- Information to be collected:
    - Dose of study medication;
    - Toxicity assessment: collection of AEs or reactions using the ASEC, which have occurred since week 1 telephone call, including SAEs/SARs/SUSARs;
    - Prohibited medications check;
    - Acceptability of treatment via participant self-report;
    - Adherence to therapy;
    - Completion of CRF to ensure no suicidal ideation. If there is any evidence of suicidal ideation, the participant will not be issued with further trial medication, and their GP must be informed of the need for urgent review;
    - Confirm participant contact details.
- Complete study medication replenishment CRF prior to order study medication through the CTRU web-based system. A further 2 months' supply (plus excess) of medication will be supplied, if appropriate.
- Optional GP review to be arranged (either via telephone or face-to-face) at approximately 1 month, for safety purposes, if the research nurse/CSO or participant have any queries or concerns.

7.11.5. Month 3 Telephone Call (+/- 3 working days)

The hub research nurse/CSO will call the participant 1 week before month 3, to ensure there are no contraindications to further medication being issued.

- Information to be collected:
    - Dose of study medication;
    - Collection of SAEs/SARs/SUSARs since week 3 telephone call (note: AEs and adverse reactions (ARs) will be collected by participant self-report on the ASEC at 3 months – see section 7.11.6 below);
    - Prohibited medications check;
    - Acceptability of treatment via participant self-report;
    - Adherence to therapy;
    - Completion of CRF to ensure no suicidal ideation. If there is any evidence of suicidal ideation, the participant will not be issued with further trial medication, and their GP must be informed of the need for urgent review;
    - Confirm participant contact details.

- Complete Study Medication Replenishment CRF prior to ordering study medication through the CTRU web-based system. A further 3 months' supply of medication (plus excess) will be supplied, if appropriate.
- Remind participant to complete month 3 assessments.

7.11.6. Month 3 Participant-reported Assessments (+/- 7 days)

At month 3 the participant should complete the following assessments via web-based or postal questionnaires, depending on preference:

- HADS;
- IBS-SSS;
- EQ-5D-3L;
- WSAS;
- SGA;
- ASEC;
- Health resource use.

Participants will be sent a text and email reminder by CTRU to prompt completion. If the questionnaires have not been completed within 1 week of the reminder, further reminders will be sent, and the hub research team will attempt to contact the participant to collect the data over the telephone.

7.11.7. Month 6 Telephone (+/- 3 working days)

1 week before the end of month 6, the research nurse/CSO will call the participant to determine whether the participant wishes to continue taking the trial treatment for a further 6 months, and ensure there are no contraindications to further trial treatment.

- Information to be collected:
  - Dose of study medication;
  - Collection of SAEs/SARs/SUSARs since month 3 telephone call (note: AEs and ARs will be collected by participant self-report on the ASEC at 6 months – see section 7.11.8 below);
  - Prohibited medications check;
  - Completion of CRF to ensure no suicidal ideation. If there is any evidence of suicidal ideation, the participant will not be issued with further trial medication, and their GP must be informed of the need for urgent review;
  - Acceptability of treatment via participant self-report;
  - Adherence to therapy;
  - Confirm participant contact details.
- Confirm if the participant wishes to continue on study medication.
  - *If yes:*

- Request wet-ink prescription from GP and send to central pharmacy at LTHT (fax / email to central pharmacy to facilitate timely replenishment of drug).
- Complete study medication replenishment CRF prior to ordering study medication through the CTRU web-based system. A further 3 months' supply of medication (plus excess) will be supplied, if appropriate.

▪ *If no*

- No further medication to be sent to the participant.
- See section 7.11.12 for further end of treatment assessments required.

- Remind the participant to complete month 6 assessments *(for participants NOT continuing study medication, remind them that they will need to complete assessments at both 6 AND 12 months).*
- Complete exit poll with the participant (including changes to diet, exercise, IBS treatment, participant experience of ATLANTIS medication and a question asking which treatment they think they were allocated to and why).

7.11.8. Month 6 Participant-reported Assessments (+/- 7 days)

At month 6 the participant should complete the following assessments via web-based or postal questionnaires, depending on preference:

- HADS;
- IBS-SSS;
- EQ-5D-3L;
- WSAS;
- SGA;
- ASEC;
- Health resource use;
- PHQ-12.

Participants will be sent a text and an email by the CTRU to prompt completion. If the questionnaires have not been completed within 1 week of the reminder, further reminders will be sent, and the hub study team will attempt to contact the participant to collect the data over the telephone.

7.11.9. Month 9 Telephone Call (+/- 3 working days) *(Participants who continued treatment beyond 6 months only)*

1 week before the end of month 9, the research nurse/CSO will call the participant for safety reasons and to ensure there are no contraindications to further medication being issued.

- Information to be collected:
  - Dose of study medication;

- Toxicity assessment: collection of AEs or reactions using the ASEC, which have occurred since month 6, including SAEs/SARs/SUSARs. Completion of CRF to ensure no suicidal ideation. If there is any evidence of suicidal ideation, the participant will not be issued with further trial medication, and their GP must be informed of the need for urgent review;
- Prohibited medications check;
- Acceptability of treatment via participant self-report;
- Adherence to therapy;
- Confirm participant contact details.

- Complete Study Medication Replenishment CRF, prior to ordering study medication through the CTRU web-based system. A final 3 months' supply of medication (plus excess) will be supplied, if appropriate.

7.11.10. Month 12 Telephone Call (+7 working days) *(Participants who continued treatment beyond 6 months only)*

At the end of 12 months, the research nurse/CSO will call the participant for safety reasons. This call may be combined with the end of treatment telephone call (7.11.12).

- Information to be collected:
  - Dose of study medication (if applicable);
  - Collection of SAEs/SARs/SUSARs since month 9 telephone call (note: AEs and ARs will be collected by participant self-report on the ASEC at 12 months – see section 7.11.11 below);
  - Prohibited medications check;
  - Adherence to therapy;
  - Confirm participant contact details.
- Remind participant to complete month 12 assessments.
- Refer to section 7.11.12 for end of treatment assessments.

7.11.11. Month 12 Participant-reported Assessments (+/- 7 days) (All participants)

At month 12, the participant should complete the following assessments via web-based or postal questionnaires, depending on preference:

- HADS;
- IBS-SSS;
- EQ-5D-3L;
- WSAS;
- SGA;
- ASEC.
- Health resource use

Participants will be sent a text and email by the CTRU to prompt completion. If the questionnaires have not been completed within 1 week of the reminder, further reminders will be sent, and the hub study team will attempt to contact the participant to collect the data over the telephone.

7.11.12. End of Treatment (at least 7 days post-treatment)

- Collection of SAEs/SARs/SUSARs
- Unused study medication to be returned to central pharmacy by the participant, using pre-paid envelopes provided by CTRU.

7.12. Study Schedule

The schedule of study assessments in Table 2 below summarises the trial procedures to be performed at each time point. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the research team.

Table 2 Study Schedule

TIMEPOINT	Screening		REGISTRTION	Baseline[5]		Pre-randomisation[6]	RANDOMISATION	Week1[7]	Week 3	Week 4	Month 3		Month 6		Participants will have 6 months of initial treatment. They have the option to continue for a further 6 months[8]	Month 9	Month 12		Post treatment
ASSESSMENTS	Screening Call	Consent/ Blood Test Visit		Nurse collect	Patient complete[5]	Phone Call		Phone Call	Phone Call	GP Appt	Phone call	Patient complete	Phone call	Patient complete		Phone call	Phone call	Patient complete	
Verbal consent and preliminary evaluation of inclusion/exclusion criteria	X																		
Rome IV criteria	X																		
Suicidal ideation	X					X			X		X		X			X			
Written informed consent[1]		X																	
tTG[2] & FBC[3] & CRP		X																	
Pregnancy Test[4]						X													
duration of IBS symptoms; previous depression or anxiety				X															
Confirm eligibility. Obtain study prescription.						X													
HADS questionnaire					X							X		X				X	
Bristol Stool Form Scale					X														
IBS-SSS	X				X							X		X				X	
EQ-5D-3L					X							X		X				X	
WSAS					X							X		X				X	
PHQ-12					X									X					
Dose								X	X		X		X			X	X		
Nurse toxicity assessment via ASEC								X	X							X			
SAE/SAR/SUSAR check by nurse								X	X		X		X			X	X		X
Prohibited medication check								X	X		X		X			X	X		
Study medication replenishment									X		X		X			X			
Optional GP review										X									
SGA of relief of IBS symptoms												X		X				X	
ASEC (participant completed)												X		X				X	
Acceptability									X		X		X			X			
Adherence									X		X		X			X	X		
Confirm participant contact details									X		X		X			X	X		
Health resource use questionnaire					X							X		X				X	
Exit Poll													X						
Unused medication return																			X
Adequate relief of IBS symptoms?								*Weekly yes/no question completed by participant* [9]											

[1] Written Informed Consent must be obtained before blood test is carried out. [2]Coeliac serology (tTG) only to be carried if not performed previously. [3] FBC and CRP to be carried out if not performed in the last 6 months. [4] For women of child bearing potential. [5] Participant completed online questionnaires should be completed ≤ 7 calendar days prior to randomisation or ≤ 14 calendar days for paper questionnaires [6] Pregnancy test should be performed within 7 days prior to randomisation for women of child bearing potential who are unable to confirm they are not pregnant. Suicidal ideation assessment should be performed within 14 days prior to randomisation. [7] Week 1 phone call should be within 1 week of randomisation. [8] Only those continuing for a further 6 months should be issued with a new supply of study medication. For those finishing treatment at 6 months, refer to post treatment assessments. [9] Up to 6 months.

7.13. Nested Qualitative Study

A nested qualitative study will explore participants' and GPs' experiences of treatments and participating in the ATLANTIS trial.

7.13.1. General Practitioner Interviews

Objectives

1. To identify factors that facilitate or impede prescribing of, acceptability of, and adherence to, low-dose amitriptyline in this patient group

2. To identify GPs' perspectives on the broader impact of the trial

3. To explore psychosocial and contextual factors that might shape wider use of amitriptyline for IBS

Design and Procedure

GPs from participating practices will be invited by email by the qualitative researcher to take part in a one-off brief semi-structured telephone interview. We will aim to interview approximately 30 GPs and will use maximum variation sampling, where possible, to achieve a diverse range of GP characteristics (full and part-time, gender, rural/urban practice, practice deprivation index, and years as a GP). GP interviews will take place after the participant recruitment period. Interviews will be audio-recorded with consent and field notes made to capture the interviewer's impressions and reflections, and any aspects not captured by the audio-recorder. At the end of the interview GPs will be thanked and debriefed.

Topic Guide

The interview topic guide will primarily comprise open-ended questions designed to explore GPs' experiences of use of amitriptyline within the trial (and within the broader contexts of primary care and IBS management), and potential barriers and facilitators to widespread post-trial implementation in primary care. The topic guide will be informed by relevant literature, key domains from normalisation process theory (23), and discussions with the PPI group. However, we will be mindful to remain open to exploring GPs' individual experiences and perspectives in-depth, to allow novel and unanticipated insights to emerge. Normalisation process theory provides a framework that specifies the factors and processes likely to hinder or enable widespread implementation of new practices. By drawing on this theory here we will be able to explicate the factors and processes relevant to the specific context of amitriptyline for IBS in primary care.

7.13.2. Participant Interviews

Objectives

1. To identify factors that facilitate or impede acceptability of, and adherence to, low-dose amitriptyline in this patient group

2. To identify patients' perspectives on the broader impact of the trial, including any unanticipated effects not captured by the quantitative measures

3. To explore psychosocial and contextual factors that might shape wider use of amitriptyline for IBS

Design and Procedure

Through the main study informed consent procedures, all participants will be asked for consent to be invited to take part in interviews. A sub-sample of participants will subsequently be invited to take part in two semi-structured 1-hour telephone interviews. CTRU will send the invitations to patients who will be asked to reply to the qualitative researcher. The qualitative researcher will be responsible for obtaining informed consent before conducting the interviews. Each participant in this qualitative

study will be interviewed twice. Interviews will be audio-recorded with consent and field notes made to capture the interviewer's impressions and reflections, and any aspects not captured by the audio-recorder. At the end of the interview, participants will be thanked and debriefed.

Approximately 20 participants will be interviewed from each arm of the trial (i.e. 10%), with the final sample size dependent on saturation and when we achieve a rigorous, credible analysis in relation to our aims. The majority of the interviews will be conducted at approximately 6 and 12 months post-randomisation. Approximately five participants per arm will be interviewed during the internal pilot phase of the trial (between 2 and 6 months) to explore recruitment and inform the main trial.

Participants will be sampled for variation to encompass a mix of gender and ages, a range of baseline symptom severity scores (IBS-SSS), and to include those who have decided to continue or stop treatment at 6 months. We will also endeavour to interview participants from each recruitment hub. This sampling should help us to explore a range of experiences, and thus increase confidence in achieving a comprehensive account of participants' perspectives. The interviewer will remain blinded to treatment allocation, with sampling done by the CTRU safety statistician. Interviewing participants from the amitriptyline arm will enable us to identify factors related to acceptability, adherence, and psychosocial context; including participants from the placebo arm will enable between-group qualitative comparisons to provide insight into the quantitative results. Interviewing the same participants at 6 and 12 months will allow us greater depth to explore changes over time, as well as the potential to better understand any differences in the quantitative results between 6 and 12 months.

Researchers will be trained, with input from our PPI group, and supervised, to ensure they have the necessary skills to effectively engage with this population.

Topic Guide

The interviews will explore participants' experiences of recruitment, randomisation, and the trial in general, and experiences of initiating and (dis)continuing amitriptyline/placebo and its perceived impacts. The topic guide will be informed by relevant literature, the common-sense model of illness perception (24), and discussions with our PPI group. However, we will be mindful to remain open to exploring participants' individual experiences and perspectives in-depth, to allow novel and unanticipated insights to emerge. The common sense model provides a framework for understanding how participants experience treatments and make treatment decisions within the context of chronic illness; this has proved relevant in previous qualitative work on IBS (25).

8. STUDY MEDICATION

8.1. Investigational Medicinal Product

Within the trial, the following are classed are as IMPs:

Amitriptyline

- Composition: one film-coated tablet contains 10mg of amitriptyline
- Manufactured by: Teva, Netherlands

Placebo

- Composition: The placebo tablets will be formulated and manufactured according to a standard placebo composition to match the appearance (shape, dimension, and colour) of the active Teva amitriptyline 10mg film-coated tablets. Manufactured by: Piramal Healthcare UK Limited (hereafter referred to as 'Piramal')

For handling of both amitriptyline and placebo, please refer to the latest summary of product characteristics (SPC) for amitriptyline (as supplied by Teva; Netherlands RVG 110148) and the investigational medicinal product dossier (IMPD).

8.2. Supply, Storage, and Dispensing.

8.2.1. Investigational Medicinal Product and Placebo Supply

A blinded, trial-specific supply of amitriptyline and placebo will be held in the central LTHT pharmacy and sent directly to participants free of charge. Amitriptyline 10mg tablets will be purchased by MODEPHARMA, a MHRA-licensed wholesale distributer of human medicinal products. MODEPHARMA's subcontractor, Piramal will undertake all GMP activities including QP release. Piramal Healthcare Morpeth is licensed by the MHRA for the manufacture and release of IMPs. Piramal will deblister and repackage the amitriptyline 10mg tablets. They will also develop and manufacture a matching pressed tablet placebo, whose composition will be approved by the MHRA. This will be formulated and manufactured according to standard placebo composition to match the appearance of the active amitriptyline tablets, in order to maintain the blind of the trial. It will be manufactured in accordance with good manufacturing practice.

Piramal will package, label and QP release (carried out by the designated person) the trial IMPs to provide identical treatment bottles for amitriptyline and placebo, each containing 65 identical tablets for oral administration. In order to maintain the blinding of the trial, the tablets and bottles will be identical and labelled with the same study-specific label in accordance with Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended). Containers will be identified only by a unique kit code (see section 8.2.2).

Piramal will store the blinded IMP treatment packs and these will be shipped at regular intervals to LTHT pharmacy, who will be responsible for storing and dispensing the study medication in accordance with the ATLANTIS Pharmacy and IMP study site operating procedure. Shipments will be under temperature-controlled conditions. The trial IMPs will be stored in a temperature-controlled, ring-fenced location. LTHT pharmacy will be responsible for completing individual participant details on each label as part of the dispensing process. In addition to the trial IMP containers, central pharmacy will receive code break envelopes to allow out of hours, emergency unblinding where necessary.

8.2.2. Kit Allocation

The kit allocation application operates as follows. Each bottle will be allocated a unique kit code. Management of kit codes on the kit allocation application and maintenance of the backup randomisation list will be conducted by the CTRU safety statistician or delegate. Any information that could unblind members of the trial team will be stored electronically in folders accessible only to the safety statistician and authorised unblinded individuals, or physically in a locked cupboard. At the time of randomisation participants will be allocated two bottles, and

subsequent bottles will be replenished at appropriate trial times. The number of bottles sent will depend on the dose the participant has titrated up to during the initial titration phase.

8.2.3. Dispensing

The investigational product should only be dispensed and administered as directed in the protocol, and only by staff authorised to do so. Dispensing of trial medication must be recorded by an authorised person at the central pharmacy. Only participants randomised in the trial may receive trial IMP.

For new participants, central pharmacy will be sent a wet ink prescription from the participant's GP following confirmation of eligibility. This will authorise the dispensing of study medication for the entire initial 6 months, following the randomisation of the participant into the study. Following randomisation, LTHT pharmacy will be notified of the participant's trial identification number, and allocated kit numbers by CTRU. It is the pharmacist's responsibility to ensure the correct trial identification number is added to the correct IMP bottles. An initial 1-month supply (two bottles) will then be sent to the participant. This will include a small excess to ensure the participant does not run out before the next delivery.

Central pharmacy will be notified to send the participant a further 2 months, and then 3 months, supply of study medication by CTRU, when the hub research nurse/CSO orders this through the CTRU web-based kit allocation system. In each instance the amount sent to the participant will take into account their current dose and include a small excess to this, to ensure they do not run out between shipments, and also to allow the participant to make short term increases to their dose in response to their IBS symptoms (see section 8.4 for more information).

For participants who opt to continue study medication for a further 6 months (i.e. 12 months in total), a new 6-month prescription, signed by the participant's GP, will be sent to central pharmacy prior to dispensing further medication. This will authorise the dispensing of study medication for the entire 6 months, and an initial 3 month supply will be sent to the participant. Central pharmacy will be notified to send the participant a further 3 months' supply by CTRU, when the hub research nurse/CSO orders this through the CTRU kit allocation system.

Trial IMP packs will be sent directly to the participant by first class Royal Mail Signed For® delivery to their home address (see 18.4 for risk assessment). They will be shipped at ambient temperature without temperature monitoring. Alternatively, trial IMP packs will be sent to the patient's GP practice when preferred by the patient, and if acceptable to the GP practice. The participants will be asked to confirm receipt either to the hub research team or by returning a 'Confirmation of Receipt Form' to central pharmacy.

8.2.4. Replacing Dispensed Study Medication/Ordering Additional Study Medication

If the study medication bottle is lost or damaged between randomisation and the end of the participant's treatment period, the study medication should be replaced by using the CTRU kit allocation system, which will allocate new bottle(s) with new kit codes.

Additional bottles may also be allocated by the CTRU kit allocation system, if a participant consistently increases their dose in response to their IBS symptoms (see section 8.4).

Hub staff should complete the kit replacement CRF prior to using the CTRU kit allocation system, a copy of which is available in the investigator site file. Further details are given in the procedures for randomisation/kit replacement study site operating procedure.

8.3. Dosage and Duration

On randomisation, participants will be allocated two bottles of 65 tablets of either 10mg amitriptyline or placebo of identical appearance, for their first 1-month treatment period.

Participants will be instructed to start their treatment at 10mg (one tablet) OD at night. Participants will be asked to increase their dose by 10mg OD per week up to a maximum dose of 30mg (three tablets) OD, if there is inadequate improvement in symptoms and no intolerable side effects. Therefore, participants will take 10mg OD for the first week. They may then increase to 20mg OD for the second week. A final increase to 30mg OD could be made during the third week. After the first 3 weeks it is expected that most participants will continue the study on a steady dose of drug. However, participants will be able to modify their dose in response to their IBS symptoms and AEs - see section 8.4 for more information. This reflects how amitriptyline is used in standard practice. To facilitate the titration, participants will be telephoned by a research nurse/CSO within 1 week of the initial dispatch of trial medication, in order to deal with any queries, and to provide standardised advice about dose titration.

There will be a further telephone call from the research nurse/CSO at the end of week 3 in order to confirm the dose reached during titration, and to check that there is no contraindication to further medication being issued. The research nurse/CSO will check AEs and ensure there is no evidence of suicidal ideation. A study site operating procedure will be provided to the hubs to guide research nurses/CSOs through the dose titration period. Participants will be offered a GP review (either via telephone or face-to-face) at approximately 1 month, for safety purposes, if the research nurse/CSO or participant have any queries or concerns.

A further 2 months of trial medication will then be supplied, if appropriate. See section 8.2.3. A further telephone call from the research nurse/CSO will take place just before 3 months, again for safety purposes, before a further 3 months of trial medication can be dispensed.

All participants will have 6 months of initial treatment, and will then be offered the option of continuing with their allocated treatment for a further 6 months. If the participant chooses to continue trial medication after 6 months, this will be via two 3-month supplies. The participant will undergo telephone screening by the research nurse/CSO 1 week prior to each individual 3-month supply of trial medication, to ensure there has been no development of suicidal ideation and to check AEs. If there is any evidence of suicidal ideation, the participant will not be issued with further trial medication, and their GP will be informed of the need for urgent review.

8.4. Dosage Modification

After the initial three week titration, although it is expected that the majority of participants will then remain on a steady dose of study medication, participants will be able to modify their dose throughout the study in response to their IBS symptoms and AEs. We expect most participants to find a dose that it suitable for them between 10mg OD and 30mg OD, but participants will be allowed to reduce their dose further, to 10mg every other day if they continue to experience troublesome side effects at 10mg OD. The maximum dose that patients will be allowed to take is 30mg OD. This reflects how amitriptyline is used in standard practice. Participants will be provided with guidance on modifying their dose, and study teams and GPs will be available to provide support to the participant if they have any queries or concerns. Participants will be issued with some excess of study medication to facilitate a temporary increase in dose. However, if the participant needs to make a consistent increase to their dosage, they will be instructed to contact the hub research team to ensure they do not run out of study medication; the hub research team will then be able to order additional bottles of medication (see section 8.2.4). Participants will be asked about their dosage on the week 3, and months 3, 6, 9, and 12 telephone calls by a research nurse/CSO.

8.5. Assessment of Adherence

In order to assess participant adherence with the trial treatment, at the assessment telephone calls (week 3, and months 3, 6, 9, and 12) the research nurse/CSO will ask the participant the following question about adherence:

"Since you were last asked, which of the options best describes how often you have taken at least one tablet of the trial medication daily?"

A. *Every day or nearly every day*
B. *Half of the days or more than half of the days*
C. *Less than half of the days*
D. *None or nearly none of the days*

This information will be recorded on the appropriate assessment CRF.

8.6. Concomitant Treatments

The use of restricted concomitant medications will be reviewed from the medical notes by the GP at the time of confirming eligibility. The research nurse/CSO will also ask the participant about concomitant medications prior to confirmation of eligibility. Participants that are unable to stop taking restricted medication will be unable to enter the study. Participant-reported concomitant medication reviews will also take place on the week 3, and months 3, 6, and 9 telephone calls, prior to issuing new study medication. **Use of MAOIs and drugs that prolong the QT interval (e.g. amiodarone, terfenadine, or sotalol) are prohibited for the participant for the duration of the trial.** Confirmation that the participant is not taking any prohibited medication will be recorded on the CRF. Treatment with MAOIs may be introduced 14 days after discontinuation of amitriptyline. For management of concomitant therapies, including the full list of combinations that are not recommended, please refer to the latest SPC for amitriptyline.

8.7. Most Frequently Anticipated Toxicities

The most frequent anticipated toxicities of amitriptyline are as follows:

Aggression
Somnolence

Dizziness	Dry mouth
Headache	Constipation
Drowsiness	Nausea

For a full list of toxicities please refer to the latest SPC for amitriptyline.

8.8. Accountability

Product accountability records will be maintained throughout the course of the study by central pharmacy. In accordance with local regulatory requirements, the designated pharmacy staff will document the amount of study drug received (from Piramal) and the amount dispensed to study participants. Participants will return all unused study drug and empty packaging to central pharmacy, via pre-paid envelopes at the end of their treatment.

8.8.1. Investigational Medicinal Product Destruction

Processes will be put in place to allow for unused study medication to be returned to central pharmacy in pre-paid envelopes for destruction. This is to ensure any unused medication is removed from the community and safely disposed of. Central pharmacy will keep a log of returned kit numbers and return to the CTRU. A full reconciliation (tablet count) will not be performed, since this is a pragmatic trial and the self-titration of dose by participants in response to their IBS symptoms and side effects, and the dependency on participants to post back unused medication, would render the information difficult to interpret. The key concern is to safely remove the medication from the community. Trial IMP stock (dispensed and returned, or un-dispensed) will be destroyed by central pharmacy after approval for destruction is issued by CTRU. Unused IMP must not be discarded or used for any other purpose than the present study. IMP that has been dispensed to a participant must not be re-dispensed to a different participant.

9. PHARMACOVIGILANCE

9.1. General Definitions

Adverse event - any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

Adverse reaction - all untoward and unintended responses to an IMP related to any dose administered, or to trial treatment. This definition covers also ARs resulting from medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. This definition implies a reasonable possibility of a causal relationship between the event and IMP. This means there are facts (evidence) or arguments to suggest a causal relationship.

Serious adverse event - any untoward medical occurrence or effect that at any dose*:*

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

- Any other important medical event (IME)***.

** "Life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

*** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).*

**** **IMEs** are events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the participant, or may require intervention to prevent one of the other outcomes listed in the definitions above. In this study **any reported form of self-harm, overdose or suicide** are classed as IMEs and should be considered serious.*

Medical and scientific judgement must be exercised in deciding whether an event is 'serious' in accordance with these criteria.

Where an SAE is deemed to have been related to an IMP used within the trial, the event is termed as a SAR. Any suspected transmission via a medicinal product of an infectious agent is also considered a SAR.

Serious adverse reaction – reference is made to the criterion of 'seriousness' above in relation to SAE and definition of AR.

Suspected unexpected serious adverse reactions - a SAR, the nature and severity of which is not consistent with the reference safety information. The term 'severity' is used here to describe the intensity of a specific event. This has to be distinguished from the term 'serious'. Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious AR constitute unexpected events.

Reference Safety Information - section 4.8 of the supplied pharmacovigilance reference copy of the amitriptyline SPC (as supplied by Teva; Netherlands RVG 110148)

9.2. Operational Definitions for (Serious) Adverse Events

For general definitions of AEs, ARs, SAEs, SARs, and SUSARs please see section 9.1 above.

9.2.1. Causality and Expectedness

As this is a blinded trial, all AEs and SAEs should be assessed for causal relationship, assuming that the participant has been receiving amitriptyline. Routinely breaking the blind could compromise the integrity of the trial. For this reason unbinding will only take place where information about the participant's trial treatment is clearly necessary for the appropriate medical management of the participant. In all cases the causality of AEs or SAEs should be evaluated as though the participant was receiving the active medication.

When determining whether an SAE or SAR is expected or not, please refer to the reference safety information (section 4.8 of the pharmacovigilance reference copy of the amitriptyline SPC (as supplied by Teva; Netherlands RVG 110148)

9.3. Recording and Reporting of Adverse Events/Serious Adverse Events/Suspected Unexpected Serious Adverse Reactions

AEs will be collected for all participants. Participants will self-report AEs occurring in the trial via the ASEC. AEs will be evaluated for intensity and causal relationship with the trial medication or other factors, according to the ASEC.

Research nurses/CSOs will also use the ASEC to collect AEs reported to them by the participant at weeks 1, 3 and month 9 (the participant will not be self-reporting AEs at these time point). They will also use the ASEC to collect AEs reported to them by the GP.

Further toxicity assessments conducted by research nurses/CSOs at months 3, 6 and 12 during telephone calls are for safety purposes only, prior to dispensing study medication, and to ensure SAEs/SARs/SUSARs are collected and reported. AEs and ARs will not be recorded on CRFs, in order to prevent dual reporting with the patient's ASEC self-report.

All SAEs/SARs/SUSARs will be collected throughout the study, from time of randomisation until 7 days following discontinuation of the study drug. After this period, investigators are still required to report any SARs or SUSARs that they become aware of.

Serious Adverse Events/Suspected Unexpected Serious Adverse Reactions

All SAEs/SUSARs should be reported to the CTRU within 24 hours of the PI, designee or hub research team becoming aware of the event.

The following details will be collected for each SAE:

- Country SAE started in;
- Treatment details including dose;
- Full details in medical terms with a diagnosis, if possible;
- Duration (date of onset and date of resolution);
- Seriousness criteria;
- Causality, in the opinion of the PI (or designee);
- Action taken with regard to study medication;
- Outcome.

In addition to the above, the following details will be collected for each SUSAR:

- Relevant medical history;
- Concomitant medications;
- Treatment for SUSAR;
- Relevant diagnostics tests.

To report an SAE/SUSAR please complete as much detail as you can regarding the event in the SAE/SUSAR CRF and ensure that the Hub Lead Clinician or designee has reviewed the event for causality and expectedness and has signed the form.

Once completed a copy of the SAE/SUSAR CRF should be Faxed to the study team at CTRU on 0113 343 0686

All SAEs/SUSARs will be followed-up until the resolution or a final outcome has been reached. All follow-up information should be faxed/emailed to the CTRU as soon as it is available.

Please retain the original SAE/SUSAR CRF until the CTRU confirm all information is complete and any resulting queries have been resolved. At this point the original should be posted to the CTRU in real time and a copy retained in the site file.

All SAEs/SUSARs will be reviewed by the CI or designated representative to confirm causality and expectedness (appendix 18.2).

In the event of a SUSAR the CTRU will take responsibility for unblinding the participant, prior to submission of the SUSAR to the MHRA and the research ethics committee (REC). Investigators will only receive information on the results of the unblinding if it is judged necessary for the safety of the participant. SUSARS will be reported to the MHRA, REC, and Sponsor within the required expedited reporting timelines.

9.3.1. Events Not Classified as an SAE

The following events will not be recorded as SAEs within this study

Hospitalisation for:

- Routine treatment or monitoring of IBS that is not associated with any deterioration in condition;
- Treatment that was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition;
- Admission to hospital or other institution for general care, not associated with any deterioration in condition;
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions for serious as given above, and not resulting in hospital admission.

9.4. Responsibilities

9.4.1. Principal Investigator (or Delegate) at Site

1. Checking for SAEs and SARs when participants attend the GP surgery.

2. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the local Hub and CTRU within 24 hours of becoming aware of the event, and providing further follow-up information as soon as available.
3. Using medical judgement in reviewing/assigning seriousness.
4. Assisting Hub Lead Clinician in assigning causality when required.
5. Ensuring that SAEs and SARs (including SUSARs) are chased with the Hub and/or CTRU if a record of receipt is not received within 2 working days of initial reporting.

9.4.2. Research Nurse/CSO at Hubs

1. Ensuring that AEs and ARs are recorded and reported to the CTRU in line with the requirements of the protocol.
2. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the CTRU within 24 hours of becoming aware of the event, and providing further follow-up information as soon as available.
3. Ensuring research Hub Lead Clinician (or delegate) reviews all SAEs and SARs (including SUSARs) and assigns causality and expectedness.
4. Ensuring that SAEs and SARs (including SUSARs) are chased with CTRU if a record of receipt is not received within 24 hours of initial reporting.

9.4.3. Hub Lead Clinicians

1. Using medical judgement in reviewing/assigning seriousness, causality and expectedness.
2. Requesting input from PI and/or participant's GP where necessary to assign causality.

9.4.4. Chief Investigator

1. Clinical oversight of the safety of participants participating in the trial, including an ongoing review of the risk/benefit.
2. Using medical judgement in reviewing/assigning causality and expectedness of SAEs.
3. Timely review of all SUSARs.
4. In the event of disagreement between local assessment and CI review with regards to SUSAR status, local assessment will not be overruled, but the CI may add comments prior to expedited reporting.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
6. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all reportable AEs and SAEs.
7. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

9.4.5. CTRU (as Delegated by the Sponsor)

- Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a trial database.
- Record all SUSARs and ensure that recording, reviewing, assessment, and notifications are completed within agreed timelines. Notification to:
    a. the competent authority (MHRA);

b. the REC;
c. and the Sponsor.

In any event not later than 7 days (fatal or life threatening) or 15 days (non-fatal or non-life threatening) after the first awareness of the reaction. A report of additional information to be sent to the MHRA, REC, and Sponsor within 8 days.

- Ensure that all other recruiting sites and research hubs involved are promptly informed of SUSARs and any changes are made to the research protocol in light of ongoing risk/benefit analyses of safety data.
- Ensure that sites (GP practices) are notified of SAEs, SARs, and SUSARs that occur in participants from their site.
- Reporting safety information to the CI, delegate, or independent clinical reviewer for the ongoing assessment of the risk/benefit according to the Trial Monitoring Plan.
- Reporting safety information to the independent oversight committees identified for the trial (DMEC and/or TSC) according to the Trial Monitoring Plan.
- Notifying investigators of SUSARs that occur within the trial.
- The unblinding of a participant for the purpose of expedited SUSAR reporting.
- Annually checking for, and notifying, PIs and Hub Lead Clinicians of updates to the reference safety information for the trial.
- Preparing standard tables and other relevant information for the DSUR, in collaboration with the CI, and ensuring timely submission to the MHRA and REC.

9.4.6. Trial Steering Committee Duties

In accordance with the Trial terms of reference (ToR) for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

9.4.7. Data Monitoring and Ethics Committee Duties

In accordance with the Trial ToR for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

9.5. Notification of Death

All deaths occurring from randomisation until the end of follow-up or withdrawal from the study, irrespective of their relationship to the IMP, should be reported to CTRU as an SAE.

In addition, if the investigator becomes aware of a patient death, outside this period, that appears to be IMP related, this should also be reported as a SUSAR.

9.6. Pregnancy Reporting

Pregnancies in female trial participants should be reported within 24 hours of the PI or designee becoming aware of the event to the CTRU, and a pregnancy CRF should be completed and returned by fax. The pregnancy should be followed for outcome and any adverse outcome of pregnancy assessed for causality to the treatment received.

9.7. Overdose Definition and Reporting

In the event of an overdose (>**200mg** [20 tablets] ingested), all study medication should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Additionally in the event of any deliberate overdose (however small) all study medication should be stopped and the participant should be reviewed for suicidal ideation. The participant should be withdrawn from trial treatment, and assessed by a study team PI for consideration if ongoing data collection (completion of participant questionnaires) is suitable.

Overdose is considered an IME and should be reported as a SAE.

9.8. Reporting Urgent Safety Measures

The Sponsor or Investigator may take appropriate urgent safety measures in order to protect the participants of a clinical trial against any immediate hazard to their health or safety. Urgent safety measures identified shall take immediate effect and the event will be notified to the REC and MHRA no later than 3 calendar days from the date the measures are taken.

9.9. Change of GP practice

If a participant changes GP practice during the course of the trial, their new GP will be notified of the patient's participation in the trial and the participant may continue treatment up until the end of their existing prescription only. The new GP will not be able to issue a new trial prescription. The participants will continue to complete trial questionnaires and assessments as per protocol.

10. Statistical Analyses

10.1. Data Analysis

10.1.1. General Considerations

Statistical analysis is the responsibility of the CTRU Statisticians. The analysis plan outlined in this section will be expanded upon in a final statistical analysis plan, which will be written before any analysis is undertaken. The analysis plan will conform to current CTRU standard operating procedures (SOPs) and will be finalised and agreed by the following people: the trial statistician, supervising statistician, safety statistician, CI, co-CI, the CTRU lead methodologist, project delivery lead, and trial manager. Any changes to the final analysis plan and reasons for change will be documented. Any deviation(s) from the final statistical plan in the final analysis will be described and justification given in the final report.

Methods to handle missing data are described for each analysis. Analysis and reporting will be in line with CONSORT. As ATLANTIS is a double-blind study, the trial statistician will be blinded to treatment group allocation throughout the trial, until the database has been locked and downloaded for final analysis. Only the safety statistician, supervising statistician, back-up safety statistician, and authorised unblinded individuals at the CTRU will have access to unblinded treatment group allocation prior to final analysis. Outside of CTRU, the DMEC and central pharmacy will also be unblinded to treatment allocation.

10.1.2. Frequency of Analyses

Outcome data will be analysed once only, at final analysis, although statistical monitoring of safety data will be conducted throughout the trial, and reported at agreed intervals to the DMEC.

The final analysis will take place after all follow-up data have been collected and entered onto the trial database, and data queries have been resolved and the database locked.

10.1.3. Analysis Populations

Analyses will be on the intention-to-treat population, which will include all randomised participants, analysed in the study arm to which they were randomised, irrespective of adherence to treatment. All analyses will be conducted at the 5% significance level and reported according to CONSORT guidance. A per protocol analysis of the primary outcome will also be conducted, based on pre-defined criteria associated with intervention adherence.

10.1.4. Internal Pilot

Data related to recruitment and follow-up rates from the internal pilot will be analysed using descriptive statistics to evaluate the progression criteria. Outcome data from participants in the internal pilot will be included in the main trial analysis.

10.1.5. Descriptive Statistics

Descriptive statistics will be presented for demographics and baseline data, endpoints, and safety data. Continuous variables will be summarised by mean, standard deviation, median, minimum, and maximum, as well as interquartile range, if appropriate. Categorical variables will be summarised by frequencies and percentages. A CONSORT diagram will display the flow of patients through the trial. Baseline characteristics of those lost to follow-up will be compared with those not lost to follow-up and the characteristics of non-responders will be compared between randomised groups, to assess for bias.

10.1.6. Primary Analysis

The primary intention-to-treat analysis will compare the IBS-SSS at 6 months between the treatment groups, using a linear regression model, adjusted for the stratification variables and the IBS-SSS at baseline. Missing data will be imputed via multiple imputation, where appropriate. Sensitivity analyses on a per-protocol population, and on participants with complete data, will test the robustness of the results. Results will be expressed as point estimates, together with 95% confidence intervals and P-values.

10.1.7. Secondary Analyses

Secondary continuous endpoints at 6 months (HADS anxiety and depression scores, the WSAS total score, the PHQ-12 score and the ASEC total score) will be analysed in the same manner as the primary endpoint, with the endpoint in question at baseline replacing the IBS-SSS at baseline in the model, with the exception of the ASEC total score, which is not collected at baseline. Secondary binary endpoints (SGA of relief of IBS symptoms, acceptability of treatment, continuation of trial medication, adherence) at 6 months will be analysed similarly in logistic regression models.

In addition, exploratory analyses of all endpoints at 3 months and 12 months will be carried out, as well as repeated measures models incorporating all time points, whilst taking into account within-participant correlation. IBS symptoms reported weekly will also be analysed using a repeated measures model. Exploratory moderator analyses will be conducted to investigate if treatment effect varies by IBS subtype or by mood.

10.1.8. Safety Analyses

All participants who receive at least one dose of study treatment will be included in the safety analysis set.

Descriptive statistics of self-reported AEs and reactions, as reported on the ASEC, will be presented by arm. These will include the total number of AEs and the number of patients reporting at least one AE. The ASEC total score will be used to assess tolerability as part of the efficacy analysis of secondary endpoints (section 10.1.7 above).

The number of participants reporting a SAE (up to 7 days after the last dose of treatment) and details of all SAEs will be reported for each treatment group.

The number of participants withdrawing from study treatment will be summarised by treatment arm, along with reasons for withdrawal.

All safety analyses performed prior to final analysis will be undertaken by the safety statistician (rather than the trial statistician), thus ensuring that the trial team remain blinded.

10.1.9. Cost-effectiveness

A within study cost-effectiveness analysis will be conducted adopting the perspective of the NHS and Personal Social Services and a societal perspective. The time horizon will be 6 months, hence costs and outcomes will not be discounted. The primary outcome will be QALYs.

Resource use associated with amitriptyline and placebo will be collected through the health resource use questionnaire administered to patients at 3, 6, and 12 months. The questionnaire includes questions on use of primary, community, and social care, IBS-related medications, hospitalisation, outpatient specialist visits, and diagnostic investigations. Because of the societal perspective, the questionnaire also includes questions on out-of-pocket expenses, employment status, and days lost due to illness. Unit costs for health service resources will be obtained from national sources (Personal Social Services Research Unit [PSSRU]; NHS Reference Costs and British National Formulary for medicines). Societal costs will be calculated by adding healthcare costs to the costs of lost production, based on self-reported days off work, combined with wage rates, and

other reported private costs related to IBS. The intervention cost will include blood tests, drug prescriptions, and GP medication reviews. We will assess uncertainty using a within trial probabilistic sensitivity analysis undertaken using Monte Carlo simulation, with results presented as incremental cost-effectiveness ratios and cost effectiveness acceptability curves, assuming willingness-to-pay (lambda) of £20,000 per QALY. Sensitivity analyses will include a 12-month horizon, as well as a scenario as close as possible to a real NHS context, where the treatment is prescribed by the GP with repeated prescriptions, tests, and required appointments.

10.2. Sample Size and Power Considerations for the Randomised Controlled Trial

We estimate that 518 participants will provide 90% power to detect the minimum clinically important difference of 35 points (26) on the IBS-SSS between amitriptyline and placebo at 6 months (a small to moderate effect size of 0.32). This assumes a maximum IBS-SSS standard deviation of 110 points (27, 28), 5% significance, and 20% loss to follow-up. The 35-point between group difference was defined as the minimum clinically important difference on the IBS-SSS in another large trial of treatment for IBS in primary care – the HTA–funded ACTIB trial (11/69/02) (26). We believe this difference is both clinically relevant to patients and clinicians, and plausible to achieve, given the variability in IBS-SSS scores in the resistant symptom group to be studied in this trial, who are still symptomatic despite first-line therapies.

In terms of our key secondary endpoint, the sample size also gives at least 85% power to detect a 15% absolute difference in the key secondary outcome (SGA of relief of IBS symptoms) (29), considered by industry and regulators as the threshold at which uptake of a drug is more likely.

10.3. Qualitative Analysis

10.3.1. Analysis of General Practitioner Interviews

Thematic analysis (30) will be augmented with coding techniques from grounded theory (e.g. open coding, line-by-line coding, constant comparison) (31). Analysis will be primarily inductive, but we will draw on normalisation process theory to assist in interpreting findings related to wider implementation of amitriptyline for IBS in primary care.

10.3.2. Analysis of Participant Interviews

As above, thematic analysis will be augmented with coding techniques from grounded theory (e.g. open coding, line-by-line coding, and constant comparison). Analysis will be primarily inductive, but we will draw on the common-sense model of illness perception, if appropriate, to assist in interpreting findings related to participants' experiences of IBS and treatments. After having identified initial themes, and after final trial unblinding, we will construct cross-tabulations ("matrices") of themes by trial arm to help us relate the qualitative findings to the quantitative results. We have used this approach to mixed methods analysis successfully in the HTA ACTIB trial, and other previous trials (32). We will also hold a data interpretation workshop with our PPI group. Members of this team have experience of involving members of the public in qualitative data interpretation in an accessible and meaningful way (33).

10.3.3. General Considerations

All interviews will be transcribed verbatim prior to analysis. Throughout the qualitative component we will use NVivo to facilitate data management and record-keeping. We will employ established techniques to enhance the quality and credibility of our work, including maintaining an audit trail to ensure transparency, involving multiple individuals in analysis to ensure diverse perspectives are brought to bear on the data and to avoid idiosyncratic interpretations, deliberately seeking out anomalous/'deviant' cases and using them to identify important, but rare, views and the limits of the analysis. Our themes will be based on importance and relevance, not prevalence, consistent with best practice in qualitative research involving in-depth analysis of small, diverse samples.

10.4. Primary Outcome Measure

The IBS-SSS is widely used in trials of medical therapies in IBS (34). It is a 5-item self-administered questionnaire measuring presence, severity, and frequency of abdominal pain, presence and severity of abdominal distension/tightness, satisfaction with bowel habit, and degree to which IBS symptoms are affecting, or interfering with, the person's life in general. The maximum score is 500 points: <75 points indicates symptoms that are felt to be in remission, with normal bowel function; 75-174 points indicates mild IBS symptoms; 175-299 points moderate IBS; and 300-500 points severe IBS. PPI input felt that 6 months of blinded treatment was probably the maximum reasonable initial commitment from a patient perspective. Hence the primary outcome measure will be collected at this time point, however all participants will be followed up for 12 months and participants will be allowed the option to continue their assigned treatment out to 12 months, if they desire, which reflects requirements of the NIHR commisioning brief.

10.5. Secondary Outcome Measures

SGA of relief of IBS symptoms is frequently used in treatment trials in IBS to identify responders to therapy (29). Participants rate their relief from IBS symptoms on a scale of 1 to 5 ranging from "completely relieved" to "worse". Scores are dichotomised so that those scoring from 1-3 are considered responders and those 4-5 non-responders.

HADS is a well-validated, commonly used, self-report instrument for detecting anxiety and depression in people with medical illnesses (21). It consists of a total of seven items measuring anxiety, and seven measuring depression, scored from 0 to 3, with a total score of 21 for each. Higher scores indicate more severe anxiety or depression.

Acceptability of treatment will be measured by participant self-report, as well as the decision to continue trial medication beyond 6 months. Participants will be asked "On balance do you find this medication acceptable to take and would you want to keep taking it".

Adherence to therapy will be measured by the research nurse/CSO during the planned phone calls at 3 weeks, 3 months, 6 months, 9 months, and 12 months. Participants will be asked "Since you were last asked, which of the options best describes how often you have taken at least one tablet of the trial medication daily?"

E. Every day or nearly every day
F. More than half of the days
G. Less than half of the days
H. None or nearly none of the days

AEs to amitriptyline or placebo will be collected via a validated self-completed questionnaire, the ASEC, which consists of 21 potential AEs rated on a scale of 0 (absent) to 3 (severe), and also asks the individual whether they deemed the AE to be treatment-related. This has been shown to demonstrate good agreeement with a psychiatrist's rating of the occurrence of treatment-related AEs with antidepressants (35). All reported AEs will be assessed with respect to seriousness, relationship to trial medication (suspected or not suspected) and expectedness (expected or unexpected, for serious AEs), as per section 9.

All reportable AEs, SAEs, and SUSARs (considered highly unlikely in this trial) will be reported to the independent DMEC within the relevant time frames, and appropriate action will be taken. Any reported form of self-harm, suicide, or overdose is considered an IME and will be treated as a SAE, whether or not related to taking the trial medication.

Health care use, use of other medications for IBS, and need for referral to secondary care will be self-reported by the participant via a resource use questionnaire, using a 3-month recall period. This will collect data concerning all resource use and medications in the community, and in primary and secondary care. Private costs and days off work related to IBS will also be collected.

EQ-5D-3L is the most frequently used measure for generating QALYs (36). It has been demonstrated to be appropriate in patients with IBS (37).

WSAS measures the effect of chronic diseases on peoples' ability to work and manage at home, and participate in social or private leisure activities and relationships (38). The WSAS has been shown to be sensitive to change in IBS trials (39, 40). It has five aspects scored from 0 (not affected) to 8 (severely affected), with a total possible score of 40.

PHQ-12 The PHQ-12 comprises 12 somatic symptoms from the PHQ, each symptom scored from 0 ("not bothered at all") to 2 ("bothered a lot") (41). Higher scores indicate the presence of somatoform-type behaviour, which is a measure of psychological health.

11. Data Handling

In compliance with GCP, the medical records/medical notes should be clearly marked and allow easy identification of a patient's participation in the clinical trial. After randomisation the research nurse/CSO will send a letter to the GP confirming participation in the trial, to be coded and scanned into the participant's electronic medical notes.

11.1. Source Data

All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial are classified as source data. Source data are contained in source documents.

11.2. Source Documents

These include original documents, data, and records e.g., GP medical records, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

It is the responsibility of staff at participating sites to obliterate all personal identifiable data on any hospital reports, letters, etc., prior to sending to the CTRU. Such records should only include trial identification number, initials, and date of birth to identify the participant. The exception to this is the patient consent form, where the patient name and signature must not be obliterated. If signed consent forms are posted to the CTRU, they must be sent in a separate envelope, and not accompanied by any CRFs or other documents containing clinical data.

Source data from all the phone calls and visits with the participant, including the initial screening call and consent visit, will be entered onto source data worksheets by the research nurses/CSOs. There will be no direct entry onto the CRF. Source data worksheets will be held at the recruitment hubs while the patient is in the participating study. Subsequently, source data pertinent to the participant's medical care will be made available to the patient's GP practice so that it can be uploaded into the patient's electronic medical notes. The remaining source data will be held at the recruitment hub prior to archiving.

Questionnaires completed directly by the participant (electronic and paper) are also considered as source documents. In the event that the participant does not complete the questionnaires after reminders have been sent, and the research nurse/CSO completes the questionnaires over the phone with the participant, the research nurse/CSO will enter the data directly into the questionnaire pack, and this will be considered source data.

11.3. Case Report Forms and REDCap

Data will be collected via paper CRFs and questionnaires, or electronically via electronic patient reported outcome software called REDCap. CRFs must only be completed by personnel authorised to do so by the PI, as recorded on the trial-specific authorised personnel log. The original 'wet ink' version of the completed CRFs should be returned to the CTRU within 2 weeks of being collected. Photocopies of the completed CRFs should be retained by the hub and stored in the investigator site file (or a statement of their location). A number of CRFs require expedited reporting to the CTRU:

- Within 24 hours of the site research team becoming aware: SAE/SAR, notification of pregnancy, protocol violations and withdrawal CRFs.

11.4. Archiving

11.4.1. Trial Data and Documents Held by CTRU

At the end of the trial, all data held by the CTRU and all trial data will then be securely archived at the University of Leeds in line with the Sponsor's procedures, for a minimum of 25 years. Site data and documents will be couriered to the CTRU for archiving. Anything pertinent to the medical care of the patient will also be made available to the patient's GP practice so that it can be uploaded into the patient's electronic medical notes. This includes, but is not limited to, the source data worksheet confirming consent and eligibility.

Identifiable data will be stored separately to other trial data. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

12. Monitoring, Audit, and Inspection

12.1. Monitoring

Trial supervision will be established according to the principles of GCP and in-line with the UK Policy Framework for Health and Social Care Research. This will include establishment of a core Project Team, TMG, an independent TSC, and an independent DMEC. A Trial Monitoring Plan will be developed and will be informed by a Trial Risk Assessment, which will consider the safety or physical or mental integrity of the trial participants, and the scientific value of the research.

This Trial Monitoring Plan will detail the timing and content of reports to monitor trial conduct, implementation, and adherence with CONSORT. Procedures will be in place to assess risk on an ongoing basis, with adjustments made accordingly.

12.2. Data Monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until they are received, confirmed as not available, or the trial is at analysis.

The CTRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access to patient notes at the participating GP practices and the ongoing central collection of copies of consent forms, and other relevant investigation reports.

12.3. Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by patients during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual GP practices.

13. Ethical and Regulatory Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland [1996]. Informed written consent will be obtained from the patients prior to registration into the study. The

right of a participant to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment.

13.1. Independent Research Ethics Committee/Health Research Authority/Regulatory Authority Approval

13.1.1. Initial Approval

The trial will be submitted to, and approved by, a REC, the MHRA, the Health Research Authority (HRA) and the appropriate local R&D department for each participating site prior to entering patients into the trial. The CTRU will provide a copy of the final protocol, patient information sheets, consent forms, and all other relevant trial documentation that will be provided to the patients, any advertisements that will be used, and details of any patient compensation.

13.1.2. Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted for ethical, HRA and, where relevant, regulatory approval by the CTRU once Sponsor and funder review has been obtained. Amendments requiring approval may be implemented only after a copy of the approval letter has been obtained.

Urgent safety measures that result in a substantial trial amendment may be implemented prior to receiving Sponsor or ethical/regulatory approval. However, in this case, approval will be obtained as soon as possible after implementation.

13.1.3. Suspected Unexpected Serious Adverse Reaction Reports, Annual Safety Reports and End of Trial Notification

The main REC/MHRA will be sent all SUSAR reports and annual safety updates in order to facilitate their continuing review of the study, and will also be informed about the end of the trial, within the required timelines.

13.2. Peer Review

This study has been peer reviewed and endorsed by the British Society of Gastroenterology (BSG) Food & Function Clinical Research Group, the IBS Network, and the Primary Care Society for Gastroenterology. It has also been reviewed by the NIHR HTA panel, in competition with other applications, as part of their commissioned call for studies of low-dose antidepressants for the treatment of IBS in primary care, and funded.

13.3. Protocol Compliance

Protocol compliance will be assessed throughout the study.

Protocol deviations, unplanned non-compliance, or breaches are considered departures from the approved protocol.

Frequently re-occurring deviations are not acceptable and could potentially be classified as a serious breach. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on clinical trials.

Protocol violations should be reported immediately to the CTRU using the protocol violations CRF. Protocol violations that need to be reported include:

- Breaches of the eligibility criteria;
- Drug administration errors related to the study drugs which lead to an SAE (note that other drug administration errors, that do not lead to an SAE, may also constitute a violation)
- Overdose.

If the protocol violation is also associated with an event which meets the criteria of an SAE or SUSAR this should also be reported in accordance with section 9 of the protocol.

14. Quality Assurance

14.1. Quality Assurance

The trial will be conducted in accordance with the principles of GCP in clinical trials, as applicable under UK regulations, the UK Policy Framework for Health and Social Care Research and through adherence to CTRU SOPs.

14.2. Serious Breaches of Good Clinical Practice or Trial Protocol

The CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol, are picked up and reported. Investigators will promptly notify the CTRU of a serious breach (as defined in Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928) that they become aware of. A "serious breach" is a breach which is likely to effect, to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.

Sites should contact the CTRU Trial Manager/Trial Co-ordinators for further information.

14.3. Data Protection and Patient Confidentiality

Precautions will be taken to ensure that patient confidentiality is preserved at all times. The University of Leeds will act as the Data Controller for this study under the General Data Protection Regulations (GDPR). The University of Southampton and University of Bristol are data processers, and the University of Leeds will ensure data processors appropriately safeguard patient information.

Where a third party is involved in the delivery of the trial the University of Leeds will ensure patient information is safeguarded, and an appropriate confidentiality and data security agreement will be put in place.

The information provided to the patient will identify those individuals who will require access to patient data and identifiable details and obtain appropriate permission from the consenting patient.

The research staff at participating sites/hubs will be responsible for ensuring that any data/documentation sent to the CTRU is appropriately anonymised, as per instructions given by CTRU in accordance with the trial procedures to conform to the 2018 Data Protection Act (and successor legislation).

The CTRU will comply with all aspects of the 2018 Data Protection Act (and successor legislation). All data collected as part of the qualitative interviews will be transferred and stored securely at the University of Southampton in accordance with the Data Protection Act 2018 (and successor legislation). Recordings of semi-structured interviews will be transcribed verbatim.

Operationally this will include (but is not limited to):

- Explicit written consent from patients to record personal details including name, date of birth, NHS number, home address, telephone number, and email address, and for this information to be used by appropriate, named individuals including the research hub, CTRU, and LTHT pharmacy to deliver the trial;
- Copies of patients consent forms, which will include patient's names and NHS numbers, will be collected when a patient is randomised into the trial by the CTRU;
- Wet ink prescriptions containing personal details and trial number will be sent to LTHT pharmacy to permit dispensing of the study medication. These will be sent by post and copies sent by fax/email;
- Appropriate storage, restricted access, and disposal arrangements for patients' personal and clinical details;
- Consent from patients for access to their medical records by responsible individuals from the research staff, or from regulatory authorities, where it is relevant to trial participation;
- Consent from patients for the data collected for the trial to be used to evaluate safety and develop new research.

If a patient withdraws consent from further trial treatment and/or further collection of data, their data will remain on file, and will be included in the final trial analysis.

14.4. Insurance and Indemnity

The University of Leeds is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent harm caused by the design of the trial.
Clinical negligence indemnification for GP practices will rest with the individual GP practices' insurance and indemnity arrangements. Clinical negligence indemnification for research nurses/CSOs performing trial associated tasks will rest with their employing organisation under their local institutional insurance arrangements.

14.5. End of Trial

The end of the trial is defined as the date of the last patient's last data item.

15. Trial Organisational Structure

15.1. Responsibilities

Chief investigator is responsibility for regulatory compliance and medical oversight of patient safety.

Co-Chief Investigator is responsible for trial delivery and oversight in primary care.

CTRU: The CTRU will have responsibility for design and conduct of the trial in accordance with relevant GCP standards and CTRU SOPs. The CTRU will also be responsible for the site payments. The CTRU are also responsible for in hours emergency unbinding.

Sponsor: The Sponsor is responsible for trial initiation, management, and financing as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU, as detailed in the trial contract.

MODEPHARMA: MODEPHARMA is responsible for the IMP supply, including the purchase of amitriptyline and project managing the manufacture of IMPs.
Piramal: MODEPHARMA's subcontractor, will undertake all GMP activities including packaging, labelling, and QP release. They will store the IMP treatment packs and ship them at regular intervals to LTHT Pharmacy.

LTHT Pharmacy: Will be responsible for storing and dispensing the study medication. They will be responsible for completing individual patient details on each label, as part of the dispensing process. LTHT pharmacy are also responsible for out of hours emergency unblinding.

The University of Leeds: Will be responsible for holding the grant.

15.2. Operational Structure

Chief investigator and co-Chief investigator: As section 15.1

Trial Sponsor (University of Leeds): As section 15.1

CTRU: The CTRU at the University of Leeds will have responsibility for the design and conduct of the trial in accordance with the UK Policy Framework for Health and Social Care Research and CTRU and Sponsor SOPs as per the Delegation of Duties. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, including randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, ongoing management (including training), monitoring reports and trial promotion, monitoring schedule, and statistical analysis for the trial. In addition, the CTRU will support ethical approval submissions, any

other site-specific approvals, and clinical set-up. The CTRU will be responsible for the overall day-to-day running of the trial, including trial administration, database administrative functions, data management, safety reporting, and all statistical analyses. At the end of the trial, CTRU will be responsible for archiving all data and trial data held by the CTRU, in line with the Sponsor's procedures, and for a minimum of 25 years.

15.3. Trial Oversight/Monitoring Groups

15.3.1. Trial Management Group

A TMG will be convened, including the CI, Co-CI, co-investigators and identified key collaborators, the trial statistician, and trial manager. PIs and key study personnel may be invited to join the TMG, as appropriate, to ensure representation from a range of sites and professional groups and, where possible, membership will also include a lay/consumer representative. Notwithstanding the legal obligations of the Sponsor and CI, the co-CI and TMG will have operational responsibility for the conduct of the trial.

The TMG ToR will define the membership, roles, and responsibilities of the TMG, each member of the committee will be required to confirm participation on the committee under the ToR. The TMG will meet quarterly as a minimum. Specifically the TMG will be responsible for:

- Protocol completion;
- CRF development;
- Obtaining approval from the HRA, UK REC, and supporting applications, and local approvals;
- Submitting a Clinical Trial Authorisation application and obtaining approval from the MHRA;
- Nominating members and facilitating the TSC and DMEC;
- Monitoring of screening, recruitment, treatment, and follow-up procedures;
- Monitoring of consent procedures, data collection, and trial end-point validation.
- Ensuring appropriate reporting of trial results at the end of the study, in accordance with the publication policy.

15.3.2. Data Monitoring and Ethics Committee

A DMEC will be convened to monitor data collected during the study, and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue. It will consist of an independent chair, an independent statistician, and an independent clinician.

The DMEC ToR will define the membership, roles, and responsibilities of the DMEC. Each member of the committee will be required to confirm participation on the committee under the ToR. The DMEC will meet annually as a minimum.

15.3.3. Trial Steering Committee

A TSC will be convened with an independent majority. It will include, as a minimum, an independent chair, an independent statistician, an independent clinician, a PPI representative, the CI, co-CI, the Sponsor's representative, and other members of the TMG as required to update on trial progress. The role of the TSC will be to provide overall supervision of the trial progress and, as necessary, advice to the TMG on operational issues. The TSC will meet annually as a minimum.

The TSC ToR will define the membership, roles, and responsibilities of the TSC. Each member of the committee will be required to confirm participation on the committee under the ToR.

15.4. Patient and Public Involvement

The study has a co-applicant who leads a local IBS support group and a PPI Officer who will lead on the development and implementation of PPI throughout this study. In addition, there is PPI representation on the TMG and TSC. The aim of PPI at this level is to ensure that the patient perspective is included in all decisions related to the trial. Patients will input into design considerations, patient leaflets, invitation letters, recruitment strategies, and the protocol.

During recruitment, PPI perspective will be sought on emerging issues. We will offer free places on the CTRU 'Introduction to Clinical Trials' training.

Financial reimbursement will be offered in line with INVOLVE guidance.

16. Funding

This project is funded by the NIHR HTA Programme (Grant Ref: 16/162/01).

17. Publication Policy and Data Disclosure

The trial will be registered with an authorised registry, according to International Committee of Medical Journal Editors guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all investigators. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contribution. Authorship decisions will be guided by standard requirements for authorship relating to submission of manuscripts to medical journals. These state that authorship credit should be based only on the following conditions being met (http://www.icmje.org):

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data;
- Substantial contribution to drafting the article or revising it critically for important intellectual content;
- Substantial contribution to final approval of the version to be published.

In light of this, the CI, other grant co-applicants, and relevant senior CTRU staff will be named as authors in any publication, subject to journal authorship restrictions. In addition, all collaborators will

be listed as contributors for the main trial publication, giving details of roles in planning, conducting, and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the TSC. In addition, individual collaborators must not publish data concerning their patients that is directly relevant to the primary endpoint, until the first publication of the analysis of the primary endpoint.

18. Appendices

18.1. Rome IV Criteria

Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with 2 or more of the following criteria:

1. Relieved or aggravated by defaecation
2. Associated with a change in the frequency of stool
3. Associated with a change in the form (appearance) of stool

These criteria should be fulfilled with symptom onset at least 6 months prior to diagnosis (20).

18.2. Expectedness and Causality of SAEs

Expectedness - The investigator or authorised medical designee will also assess the expectedness of the AE, in relation to previously known information about the IMP found in the reference safety information. As this is a double-blinded study, investigators should evaluate expectedness as though the patient is receiving amitriptyline.

Expected:	The event is known to be associated with the IMP or condition under study.
Unexpected:	The nature or severity of the event is not consistent with information about the IMP within the SPC or the condition under study.

Causality - The investigator or authorised medical designee will assess the causal relationship between the event and the IMP for each SAE. As this is a double blinded study, investigators should evaluate causality as though the patient is receiving amitriptyline.

18.3. Pregnancy testing

The SPC states that amitriptyline is not recommended in pregnancy, unless clearly necessary, and only after careful consideration of the risk/benefit, therefore pregnancy is an exclusion criteria in this study. Any woman who is pregnant, or is planning to become pregnant during the time period covered by the trial, will be refused entry into the trial. All women of childbearing potential (defined as women who have had any menstrual bleeding in the last 12 months and who are not surgically sterile) must be willing to use medically approved contraception whilst receiving treatment.

NICE guidance recommends the use of TCAs such as amitriptyline for the second-line treatment of IBS, which is used at a much lower concentration (10 – 30 mg) than it is licenced for in depression (150 mg – 200 mg). In normal practice, patients do not undertake pregnancy testing prior to commencing low dose amitriptyline for treatment of IBS. Furthermore, amitriptyline has been used for many years in low dose for other conditions, including pain relief, without the need for pregnancy testing. Because this is a real world study mimicking normal practice, pregnancy testing will not be mandated prior to study entry **unless** a woman of child bearing potential cannot definitely confirm they not pregnant prior to study entry, in which case they will be asked to undertake a home urine pregnancy test within 7 days of study entry and confirm the result to the research nurse/CSO. No further routine pregnancy

testing is planned for the study. This strategy has been informed by the Co-CI of the study, Dr Hazel Everitt, who is an Associate Professor in GP, a fellow of the RCGP and a senior GP clinician.

18.4. Shipment of study medication directly to patients via Royal Mail Signed For® 1st Class delivery

Delivery of the study medication by Royal Mail Signed For® delivery directly to participant's home address (or GP practice if requested by the participant and acceptable to the GP practice) under ambient shipping conditions, has been risk assessed and considered acceptable and appropriate based on the following:

- Amitriptyline is a not a controlled drug and is widely prescribed in primary care with over 50 years of use data.
- It is being used at a low dose (10mg rather than 75mg tablets).
- Amitriptyline is very stable with a good margin of safety and a long shelf life. Study medication will be re-packaged to ensure it is protected from light and moisture.
- The IMP will be dispensed by the pharmacy and posted to the patient under ambient shipping conditions. This is similar to clinical practice and standard care where a patient would take the medication home with them in ambient conditions once it has been dispensed.
- Recorded delivery is being used to ensure the intended recipient receives the medication and to prevent an unintended person picking up study medication that has been posted through the door. Participants will confirm receipt of the medication. In the event that they do not receive the medication, central pharmacy will keep a log of the tracking numbers so that the parcel can be traced.
- Low dose (10mg) amitriptyline is being sent, using small quantities while at the same time keeping the study logistically possible. Therefore in the unlikely event that the medication is received by an unintended recipient, the amount they have access to has been limited.
- Tamper evident/child-proof caps will be used.
- A small excess has been included to ensure that the participant does not run out of study medication in the event that delivery is delayed.
- Study medication will be sent in plain packaging so that anyone handling the package will not know a) that it contains amitriptyline b) that the participant is in a trial or has IBS.
- The delivery method has been discussed, developed and agreed acceptable by PPI groups.

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