SUPPLEMENTARY MATERIAL 1

1.1 Participant Information Sheet Used in the Main ATLANTIS Trial.

Amitriptyline at Low-dose and Titrated for Irritable Bowel Syndrome as Second-line Treatment: The ATLANTIS study

PARTICIPANT INFORMATION SHEET AND INFORMED CONSENT FORM

You have been invited to take part in a research study called “ATLANTIS”. Before you decide if you want to take part, we would like to give you some more information about the study.

Please read this information carefully, and feel free to discuss it with others if you like. Please ask us if anything is unclear, or if you would like more information.

If you are interested in taking part, please return the reply slip in the prepaid envelope enclosed with this letter. Alternatively, you can email the research team using the contact details provided in this document. A researcher will then contact you to talk about the study and answer any questions you may have.

This leaflet is split into 2 parts:

- **Part 1** tells you why we are doing the study and what will happen to you if you decide to take part.
- **Part 2** gives you more detailed information about how the study will be run.

How to contact us

If you have any questions about this study, please talk to the researcher at

<<Enter recruitment hub researcher name >>

<< Contact details for recruitment hub>>

Thank you for reading this information sheet.

Part 1

Why are we doing this study?

Irritable bowel syndrome (IBS) is usually a long- term problem and can have a significant impact on people's lives. Unfortunately, we know that current IBS medications do not help everyone. Amitriptyline is a drug that can be used to treat IBS. It is recommended in UK guidelines for people who continue to have troublesome symptoms, because small studies of amitriptyline have shown promising results. This study aims to see whether the drug helps patients with IBS who are looked after by their GP. Nobody has done a large study to explore this before, and we hope the results will lead to more effective treatment for IBS. The results from this study are important, as they will help doctors decide whether they should be using amitriptyline routinely as a treatment for IBS.

What is amitriptyline?

Amitriptyline is a frequently used drug, which has been in use for more than 50 years. We believe it helps with IBS at a low dose because it relieves pain and changes bowel activity. Amitriptyline is sometimes used to treat depression. However, when being used for depression, it is given in much higher doses. This study will only be using small doses of amitriptyline, and is being used because of its impact on pain, rather than mood. As with any medication, there are some potential side effects. These are listed in the second part of this leaflet.

What is a placebo?

Half the people who take part in the study will be asked to take amitriptyline. The other half will be asked to take a dummy tablet known as "placebo." A computer will randomly decide which you are given. There is more information about this process in Part 2 of this leaflet.

Why are we using a placebo?

We are using a placebo in this study because we need to find out if amitriptyline works for people with IBS. IBS symptoms vary over time and it is possible that improvements may be due to factors other

than the treatment. Comparing those on amitriptyline with those on placebo allows us to work out how much of the improvement seen is because of amitriptyline.

Will I be told if I am having amitriptyline or placebo?

Yes, you will be able to find out after 6 months if you have been taking amitriptyline or placebo. We are not able to tell you before 6 months as this may affect the results of the study (an important part of this study is how you feel and this may be affected by knowing which treatment you have received). However, if there is an urgent reason your GP needs to know what treatment you have received, they will be told.

Why have I been invited to take part in this study?

You are being invited to take part because your GP records show that you have IBS. Your GP practice has agreed to take part in this study. We are hoping to recruit more than 500 people with IBS from approximately 75 GP practices across West Yorkshire, Southampton, and the West of England.

Do I have to take part?

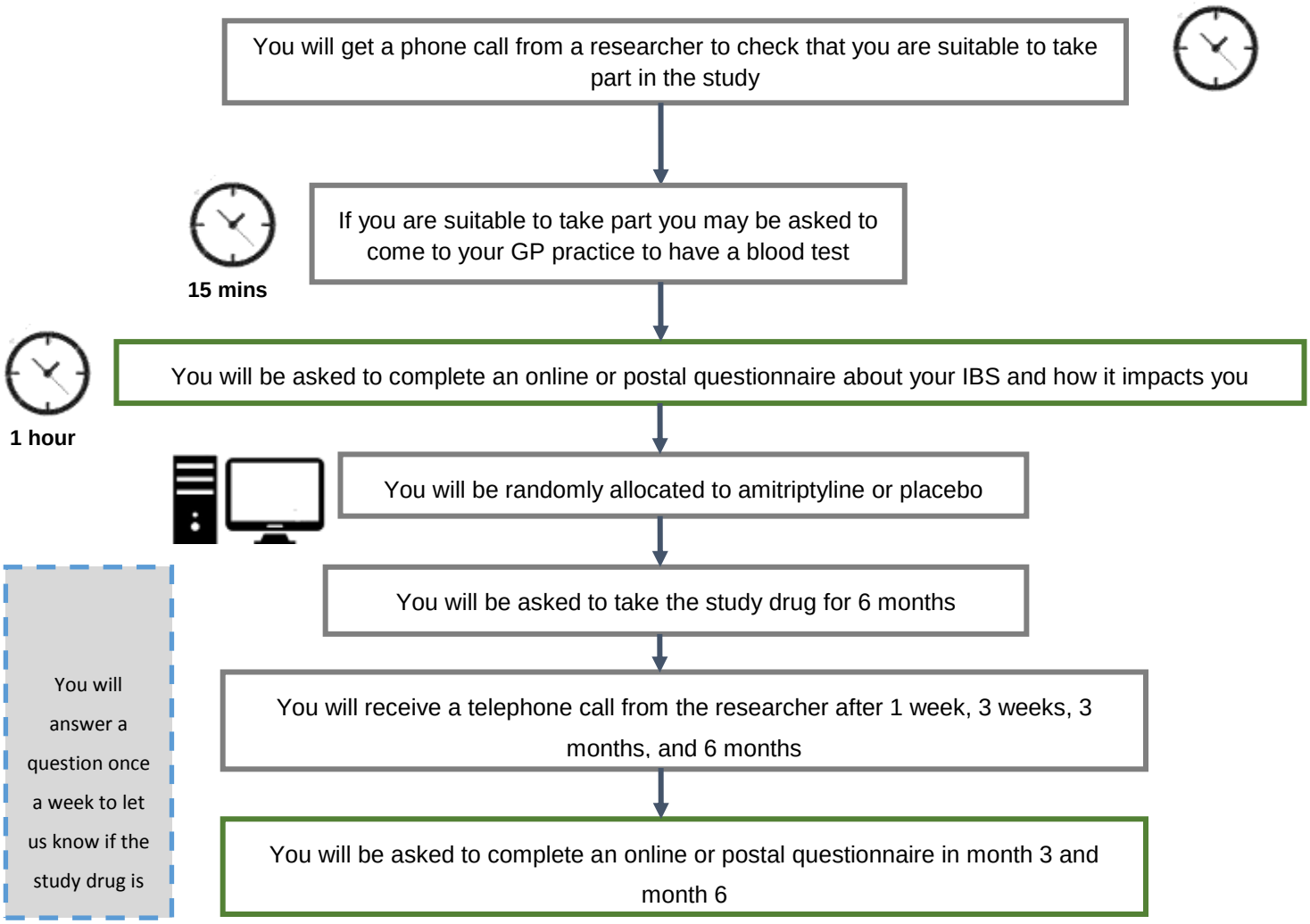
No, your participation is entirely voluntary and it is up to you to decide whether or not to take part.

If you decide to take part you will be given this information document to keep. You will be asked to sign a consent form, but you are still free to withdraw at any time and without giving a reason. If you decide not to take part, your GP will be happy to talk through alternative treatment options for your IBS. Your treatment and care will not be affected in any way.

If I want to, will I definitely be able to take part?

Unfortunately, no. Although your GP thinks you might be suitable to take part, we may still need to carry out a blood test and ask you some questions to make sure you are suitable. These are known as “eligibility screening tests” and are described below. If the eligibility screening tests show that it is not appropriate for you to take part in the study your GP will discuss alternative treatment options with you.

What will happen to me if I take part?



This completes Part 1 of the Information Sheet. If you are considering taking part, please read the extra information in Part 2 before making your decision.

Part 2

What do I have to do?

The diagram in Part 1 gives an overview of what you will be asked to do if you take part in the study. This section gives you a detailed breakdown of each part of the study.

Eligibility tests

- If you decide you would like to take part we would ask you to return the reply slip at the bottom of the invitation letter to the research team. Alternatively you can email the research team using the contact details provided.
- You will then have an initial telephone call with a researcher to find out more about you and your IBS to see if it is appropriate for you to take part in the study. The researcher may then need to check specific information about your medical history with your GP to make sure you are suitable to take part You may not be suitable to take part, for instance, if you have coeliac disease or inflammatory bowel disease, or if you have another condition which means you should not take amitriptyline (see page 8 of this information sheet for more detail)
- If you are eligible to take part you may be asked to come in to your GP practice and have some blood samples taken, to make sure you are not anaemic and that there are no signs that your bowel symptoms are due to other illnesses. The blood test is a straightforward, safe procedure but may cause some minor discomfort and you may notice some slight bruising which should go away in a couple of days. The blood samples will not be retained after testing is complete - they will be destroyed by the NHS laboratory conducting the testing according to their standard procedures.
- If you are a woman, able to have children, and are unable to confirm you are not pregnant, you will be provided with a pregnancy test to use at home before going into the study. This is to ensure it is safe for you to receive amitriptyline in the study.

Questionnaire

- You will then be asked to complete an online questionnaire or a paper questionnaire, which will ask you information about yourself, any past and current medications, how you are feeling, details about your IBS symptoms and how much of an impact it has on your daily life. The Clinical Trials Research Unit [CTRU] at the University of Leeds will email you a link to the online questionnaire or send the link to your mobile phone. Alternatively, a paper questionnaire can be posted to you.

Randomisation

- If you are eligible, you will be randomly chosen to receive either amitriptyline or placebo. Your supply of amitriptyline or placebo will be delivered to your home address by Royal Mail First Class recorded delivery. This will always be in

plain packaging. You will initially receive a supply for 1 month, then a supply for 2 months and a final supply for 3 months.

Drug treatment

- You will start by taking 10 mg (1 tablet once a day at night) for 1 week. After the first week you will have the opportunity to discuss a dose change with the researcher and then you can decide whether you would like to stay on the 10 mg dose or increase your dose to 20 mg (2 tablets once a day at night). A final increase to 30 mg (3 tablets once a day at night) can be made during the third week.
- You will also be given a dietary advice sheet, which will advise of any foods you should avoid and how to manage your IBS symptoms.

Phone calls

- You will have a telephone call with a researcher in week 1, week 3, month 3 and month 6 (of taking the study drug) to give you advice about your study medication, and check if there are any problems, as well as to answer any questions you may have.

Questionnaires

- You will complete an online or postal questionnaire three times (before entering the study, then at 3 months, and 6 months after starting the study drug). To help you remember to complete the questionnaires, the research team at CTRU will send you reminders by email and text messages to your mobile phone. The research team in your local area may also attempt to contact you. If you do not have an email or mobile phone, the researcher may phone you.
- You will answer a question once a week to let us know if the study drug is helping relieve your IBS symptoms. This can be answered online or can be recorded in a paper diary, which will be collected at the end of the study. To help you remember to answer the question CTRU will send you text reminders to your mobile phone.

End of treatment

- You will have a telephone call with the researcher when you finish taking the study drug to check if there are any problems and to answer any questions you may have.

How long does the treatment go on?

You will be asked to take the study drug for 6 months. If you change your GP practice during the course of the trial, your new GP may not be able to prescribe the study medication.

Additional research

We would like to invite approximately 40 people to take part in a telephone interview to talk more about their experience in this study. If you are invited, you may be asked to take part in an interview, which will last approximately 1 hour.

You will be sent more information about this if you are selected to take part.
You can choose to end the interview at any time and you do not have to answer any questions you do not want to.

If you would be happy to be approached for a telephone interview, there is an optional section on the consent form for you to complete. Even if you do not wish to be approached for these interviews, you can still take part in the ATLANTIS study.

Future research

The research data collected about you in the Atlantis study may be shared with other research teams to answer new research questions in the future. They will not be able to identify you from this data.

We would also like your permission to obtain information held within your electronic health records, including any hospital attendances and admissions and your health conditions from your GP and hospital records. We may use this for future research linked to the Atlantis study, or for other research projects. We would only do this once any future projects had received ethical approval subject to ethical approval. To obtain your health record data, we would need to send a limited amount of your identifiable data (for example, initials, data of birth, and NHS number) to the relevant data provider to obtain the correct information from these records. Other research teams may be involved in this future research but they will not be able to identify you from the information provided to them.

What are the possible side effects of the study medication?

Amitriptyline has been used widely for over 50 years and we are using it in a low dose in this study. However all medicines may have side effects. Common side effects include:

- constipation
- dizziness
- dry mouth
- feeling sleepy, tired or weak. This is the reason we ask you to take the study drug at night.
- difficulty peeing
- headache

If you are a woman who may become pregnant, you will be asked to confirm that you are not pregnant before taking part in the study, and may be asked to take a pregnancy test. You must also agree to use a reliable form of effective contraception during this time. If you do become pregnant during the study, or you find out that you are pregnant within three months of finishing treatment, then you must tell the study research team at once. Your GP will advise you on the potential risks to your unborn child and the options available to you.

What are other possible disadvantages of taking part?

Taking part in the study will involve time commitments for seeing and talking to the researcher, and completing questionnaires.

The study drug might harm an unborn baby; therefore you should not take part in this study if you are pregnant. You should not become pregnant during the study treatment period or for a safety period of at least 7 days after taking your last study treatment tablet.

What are the possible benefits of taking part?

We cannot promise the study will help you, but you may have improvements in your IBS symptoms, and the new knowledge we gain may help others with IBS. If the study shows amitriptyline to be effective it could become widely available from your GP in the near future, and help many patients like yourself. Taking part in this study will also give you the opportunity to receive extra health checks, via the blood tests, and to discuss your IBS symptoms with healthcare professionals.

Warnings and precautions to using the study medication

Amitriptyline should not be taken by patients who have:

- recently had a heart attack (myocardial infarction)
- heart problems such as arrhythmias (disturbances in heart rhythm which are seen on an electrocardiogram (ECG)), heart block, or coronary artery disease
- severe liver disease
- acute porphyria
- during the manic phase of bipolar disorder
- or if taking certain medications, including monoamine oxidase inhibitors (MAOIs).

The researcher will discuss this with you during your initial phone call about the study.

Please tell the researcher if you have, or have had in the past, any medical problems, so that they can check with your GP if you are suitable to take amitriptyline. In particular you should mention any of the conditions listed above, as well as the following below:

Cardiovascular disease; diabetes; epilepsy; history of psychosis or bipolar disorder; hyperthyroidism; increased intra-ocular pressure; phaeochromocytoma; prostatic hypertrophy (prostate gland enlargement);

susceptibility to angle-closure glaucoma; difficulty passing urine;

What if relevant new information becomes available?

Sometimes during the course of a study, new information becomes available. If this happens we will tell you about it, and you will be able to decide whether you want to continue in the study. If you decide not to continue, your GP will continue your care. If you decide to continue you may be asked to sign an updated consent form. Occasionally, on receiving new information, your GP may consider it to be in your best interest to withdraw you from further study treatment.

Who has organised, reviewed, and funded the research and who will be supervising it?

The Chief Investigator is Professor Alexander Ford, based at the University of Leeds, who is supported by the Co-Chief Investigator Associate Professor Hazel Everitt based at the University of Southampton. The study is being sponsored by the University of Leeds, and is being organised on their behalf by the University of Leeds CTRU. The University of Southampton and the University of Bristol, along with the University of Leeds, will manage and run the study in their local area (sometimes referred to as a 'hub'). The National Institute of Health Research fund the research. All research is looked at by an independent committee of people called a Research Ethics Committee to protect your interests. The study has been reviewed and approved by Yorkshire & The Humber – Sheffield Research Ethics Committee Ref: *19/YH/0150*.

What if there is a problem?

Emergencies:

In the unlikely event that you experience any problems during the study, we will have an emergency number, which would allow a doctor to find out if you were on amitriptyline or the dummy tablets, in case this might affect your treatment. You will also be given an identity card to carry with you, which details relevant information about the study, and contact numbers in case of an emergency.

Complaints:

If you have a concern about any aspect of this study, you should ask to speak with your researcher who will do their best to answer your question. If you remain unhappy and wish to complain formally, you

can do this through the NHS Complaints Procedure. Details can be obtained from your GP practice or you can contact PALS (Patient Advice and Liaison Service) telephone << LOCAL PALS CONTACT >>

Harm:

Every care will be taken in the course of this clinical study. However, in the unlikely event that you are injured as a result of the managing organisation (University of Leeds), compensation may be available and you may have to pay your related legal costs. Your GP practice where you receive your treatment has a duty of care to you, whether or not you agree to participate in the study, and the University of Leeds accepts no liability for negligence on the part of your GP's practice. If you wish to complain about any aspect of the way you have been treated please contact your GP in the first instance.

Any claims will be subject to UK law and must be brought in the UK.

If you have private medical insurance, you should tell your insurer that you are taking part in research. They will let you know if it affects your policy.

What information will you collect about me?

As part of ATLANTIS we hope to:

1. Ask you to complete some questionnaires about you
2. Collect information about you from electronic health records, for example previous blood test results.
3. If you agree to take part, we may also ask you some questions about your experience.

Will my taking part in this study be kept confidential?

Yes. Under UK Data Protection laws the University of Leeds will act as the data controller (legally responsible for the data security). This means they are responsible for looking after your information and using it properly.

The research teams at the University of Leeds, the University of Bristol, and the University of Southampton will collect information from you and handle this in accordance, with the 2018 Data Protection Act.

This information will be sent on paper forms to the CTRU at the University of Leeds (usually using standard Royal Mail but in some cases by secure email), or will be completed by you online and stored at the CTRU.

Where possible, information collected about you for the purposes of this research study (research data) will have your name and

address removed, and a unique code, along with your initials and date of birth, will be used instead.

Your rights to access, change, or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. You can find out more about how the University of Leeds uses personal data here: https://dataprotection.leeds.ac.uk/wp-content/uploads/sites/48/2019/02/Research-Privacy-Notice.pdf

Concerns and contact details

If you have any concerns about the way your personal data is being processed or have a query about the information in this leaflet, please contact the University of Leeds Data Protection Officer using any of the following details:

- Email: DPO@leeds.ac.uk;
- General postal address: University of Leeds, Leeds LS2 9JT, UK;
- Postal address for data protection issues: University of Leeds, Room 11.72 EC Stoner Building, Leeds, LS2 9JT;
- Telephone number: +44 (0)113 243 1751.

Our data controller registration number provided by the Information Commissioner's Office is Z553814X.

If you are not satisfied with our response, or believe we are processing your personal data in a way that is not lawful, you can complain to the Information Commissioner's Office (https://ico.org.uk/).

If you withdraw from the study, we will keep the information about you that we have already obtained, and this will still be used in analysing the results of the study. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Your personal data (your name, NHS number, address, telephone number(s) and email address (if you have one) will be provided to the hub research team and CTRU. They will use this information to contact you about the research study (for example, to remind you to complete questionnaires), make sure relevant information about the study is recorded for your care, and to oversee the quality of the study

Your data will be entered onto secure databases held at the CTRU. Only data collected to answer the research question, to ensure the study is being run correctly or for safety reasons will be entered.

At the start of the study, a prescription will be posted from your GP to Leeds Teaching Hospitals Trust (LTHT) pharmacy to allow them to dispense and post the study

medication to you. This prescription will include your name, date of birth, NHS number, home address, and study number. A copy may also be sent by fax or email. During the study, if your address changes this information will be collected by the researcher and sent to LTHT pharmacy to ensure study medication is sent to the correct address.

At the end of the study, your personal data and research data will be securely stored at the University of Leeds. Data pertinent to your medical care will also be stored in your medical records at your GP practice, even if you stop taking part in the study. Only those who need to will have access to the data.

After the end of the study your data will be stored securely for a minimum of 25 years. After this time your data will be disposed of securely.

Data access

The data collected for the study will be looked at and stored by authorised persons from the research teams at the University of Leeds, the University of Bristol, and the University of Southampton. They may also be looked at by authorised people from regulatory organisations to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant, and we will do our best to meet this duty.

Your data may be passed to other organisations (possibly in other countries where the data protection standards and laws are different to the UK) to monitor the safety of the treatment that you are receiving, or to review results of analysis as part of the study. This data will have your name and other identifiable data removed.

What will happen if I don't want to carry on with the study?

If you withdraw consent from further study treatment, information will still be collected about you, unless you request otherwise. If you withdraw consent for further data collection your data will remain on file, and will be included in the final study analysis

The ATLANTIS Study Team may be required to collect some limited information about you regarding side effects you may have experienced as a result of taking part in the study. This will only be collected if required by the Regulatory Authorities.

Involvement of the general practitioner/family doctor:

Your GP will be kept informed of your participation in this study and we will share information you give us with your GP, if it is important to your care

What will happen to the results of the research study?

When the study is complete the results will be published in a medical journal and presented at a scientific conference. The data will be anonymous and none of the participants involved in the study will be identified in any report or publication. The results of the study will be available to you.

Contact for further information

You are encouraged to ask any questions you wish, before, during, or after your treatment. If you have any questions about the study, please speak to your researcher or your GP, who will be able to provide you with up to date information about the drug involved.

If you are interested in taking part, please return the reply slip provided with the invitation letter or contact the research team using the details provided. If, after talking to the researcher, you decide you would like to take part, you will be asked to read and sign the consent form. You will be given a copy of this information sheet and the consent form to keep. A copy of the consent form will be included in your patient notes, one will be filed with the study records, and one will be sent to the CTRU.

1.2 Participant Consent Form Used in the Main ATLANTIS Trial.

Participant ID:	Initials:
Date of Birth:	NHS number:
EudraCT Number: 2019-000324-17 ISRCTN: [48075063]	Principal Investigator:

ATLANTIS
Investigating amitriptyline as second-line treatment for IBS

PARTICIPANT CONSENT FORM

Please initial each box

1. I confirm that I have read and understand the information sheet dated 30 June 2021 (version 6.0) for the above study. I have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily. ☐

2. I understand that my participation in this study is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. I understand that even if I withdraw from the above study, the data and samples collected from me will be used in analysing the results of the study and, in some cases, further information about any unwanted effects of my treatment may need to be collected by the study team. ☐

3. I agree to my data (including identifiable data and contact details) being collected and used by the Clinical Trial Research Unit (CTRU) and [INSERT RECRUITMENT HUB]. I understand they will hold this data confidentially and securely ☐

4. I give permission to allow the researcher from [INSERT RECRUITMENT HUB] and CTRU to contact me at various time points throughout the study via telephone, text message, email, or post. ☐

5. I give permission to allow the CTRU to contact me with information about what treatment (amitriptyline or placebo) I have received and also the trial results at the end of the study. ☐

6. I understand that relevant sections of my medical records and data collected in the study, may be looked at by authorised individuals from the research study team, from regulatory authorities, and from the study Sponsor, where it is relevant to my taking part in the study. I give permission for these individuals to have access to my records. This may also include anonymised data being sent outside of the EU. ☐

Participant ID:	Initials:
Date of Birth:	NHS number:
EudraCT Number: 2019-000324-17 ISRCTN: [48075063]	Principal Investigator:

7. I agree to my identifiable data being collected and used by Leeds Teaching Hospitals Trust (LTHT) pharmacy for the delivery of study drug. ☐

N/A

8. **To be completed only if you are a woman who is able to have children** *(if you are a woman unable to have children, please initial the N/A box)***:** ☐
I agree for the CTRU to collect information on the outcome of any pregnancy that is recorded whilst I am in the study.

9. I agree for the CTRU to check my address with my GP. ☐

10. I agree for my personal details (which will include my initials, date of birth, and NHS number) to be shared with providers of Electronic Health Records so that information about my healthcare use can be obtained, for future research linked to the Atlantis study, or for other research projects, subject to ethical approval ☐

11. I agree to a copy of this Consent Form being sent to the CTRU. ☐

12. I agree to my GP being informed of my participation in this study and being provided with a copy of this consent form. ☐

13. I agree to take part in the study. ☐

Optional:

Even if you agree to take part in this study, you do not have to agree to this section

Please initial

I agree, if selected, to be approached for an interview to talk about my experience in this study. ☐

My preferred questionnaires (please circle one option):

Online **Paper**

Participant ID:	Initials:
Date of Birth:	NHS number:
EudraCT Number: 2019-000324-17 ISRCTN: [48075063]	Principal Investigator:

Patient:

Signature……

Name (block capitals)……

Date……

Investigator:

I have explained the study to the above named patient and I have given the patient the opportunity to discuss with a GP if they wish. The patient has indicated his/her willingness to participate.

Signature……..……

Name (block capitals)……..……

Date……..……

(If used)Translator:

Signature……..……

Name (block capitals)……..……

Date……..……

(1 copy for patient; 1 for the CTRU; 1 held in patient notes, original stored in Investigator Site File)

1.3 Participant Unblinding Leaflet Used in the ATLANTIS Trial for Those Receiving Amitriptyline.

Amitriptyline at Low-dose and Titrated for Irritable Bowel Syndrome as Second-line Treatment: The ATLANTIS study

THANK YOU

Thank you for taking part in the ATLANTIS study. This research would not be possible without people like you generously giving their time. Research is an important part of improving NHS treatments. By taking part you have helped us to test whether a tablet called amitriptyline, prescribed at a low dose, helps people with irritable bowel syndrome (IBS). We were interested in finding out its effect on both the symptoms of IBS and costs of managing it.

Your study treatment

Everyone who took part in the study was given either amitriptyline or dummy (placebo) tablets. This was randomly decided by a computer.

You were in the **active** treatment arm. This means that you have been taking **amitriptyline tablets** during the study.

What does this mean for me?

You may have some questions about the study tablets and what to do next. Below you will find some frequently asked questions about amitriptyline tablets that you may find helpful.

Frequently asked questions

Q	**My IBS symptoms improved during the study. Can I continue taking amitriptyline?**
A	If you wish to carry on taking amitriptyline for your IBS, **you can now speak to your GP to discuss the option for you to continue taking amitriptyline tablets**. Amitriptyline is a frequently used drug, which has been in use for more than 50 years. Amitriptyline can already be used to treat IBS at a low dose and guidelines suggest using it when people with IBS have ongoing symptoms. We believe it helps with IBS because it relieves pain and changes bowel activity. This has been shown in some small studies that have looked at people with IBS seeing specialist doctors in hospital clinics.

Q	**What are the results of the study?**
A	The ATLANTIS study data have yet to be analysed so we do not know the results yet. We have recruited 463 people with IBS. You will receive a summary of the results when the study ends, and all the data have been analysed. Please let the study team know if you change your email address. The study results will also be made available on the study website: https://ctru.leeds.ac.uk/atlantis/ Before the ATLANTIS study, nobody had done a large study to explore whether amitriptyline benefits people with IBS who are looked after by their GP. We hope the

	results will lead to more effective treatment for IBS. The results from this study are important, as they will help doctors decide whether they should be using amitriptyline routinely as a treatment for IBS.

Q	**My IBS symptoms improved during the study, but I experienced side effects. Can I take amitriptyline?**
A	It may be helpful to discuss this with your GP. As with any medication, amitriptyline has some potential side effects. You can discuss with your GP whether the benefits you experienced in terms of your IBS outweigh the negative impact of any side effects. It is possible that these side effects may not happen when taking amitriptyline again. You could also speak to your GP about trying other tablets that are like amitriptyline but may have fewer side effects (e.g. nortriptyline).

Q	**My IBS symptoms did not improve or got worse during the study. What does this mean and what can I do next?**
A	This may mean that amitriptyline has not worked for you. Unfortunately, some participants in the active arm of a study like ATLANTIS will see little or no improvements in their symptoms. This does not mean that other treatment options will not work for you. **If your IBS symptoms have not improved or got**

	worse, you can speak to your GP to discuss alternative treatment options such as other medicines, dietary advice, or referral for psychological therapies, such as a type of cognitive behavioural therapy (CBT) for IBS. **You must seek urgent advice from your GP if you have:** • lost a lot of weight for no reason • bleeding from your bottom or bloody diarrhoea

Q	**I still have questions: who can I talk to about this?**
A	It will not be possible to speak to your research nurse about your study tablets. Research nurses are not allowed to know which tablets people in the study are taking, as this may affect the results of the study. Instead, you can contact one of the Chief Investigators, at atlantis@leeds.ac.uk who will be able to answer any questions or discuss any concerns you may have.

Q	**Where can I find further information and support?**
A	Please find some sources of information and support for people with IBS below: **NHS website** https://www.nhs.uk/conditions/irritable-bowel-syndrome-ibs/ *Advice on IBS symptoms and treatment options.* **Guts UK** https://gutscharity.org.uk/

		UK-based charity for the digestive system.
	IBS and Diet: Food Fact Sheet	https://www.bda.uk.com/resource/irritable-bowel-syndrome-diet.html *Dietary advice for IBS produced by the British Dietetic Association and recommended by the National Institute for Health ad Care Excellence (NICE).*
	IAPT	https://www.england.nhs.uk/mental-health/adults/iapt/ *Improving Access to Psychological Therapies (IAPT) services provide evidence-based psychological therapies to people with long term physical health problem.*
	IBS Network	https://www.theibsnetwork.org/ *UK-based charity for people living with IBS (membership required to access full content).*
	IBS Network support groups	https://www.theibsnetwork.org/self-help-groups/ *Information on local support groups.*
	Contact me IBS	https://www.contactme-ibs.co.uk/ *A research register of adults interested **in hearing about and taking part in IBS** research.*

Thank you again for supporting this research!

1.4 Participant Unblinding Leaflet Used in the ATLANTIS Trial for Those Receiving Placebo.

Amitriptyline at Low-dose and Titrated for Irritable Bowel Syndrome as Second-line Treatment: The ATLANTIS study

THANK YOU

Thank you for taking part in the ATLANTIS study. This research would not be possible without people like you generously giving their time. Research is an important part of improving NHS treatments. By taking part you have helped us to test whether a tablet called amitriptyline, prescribed at a low dose, helps people with irritable bowel syndrome (IBS). We were interested in finding out its effect on both the symptoms of IBS and costs of managing it.

Your study treatment

Everyone who took part in the study was given either amitriptyline or dummy (placebo). This was randomly decided by a computer.

You were in the **control** treatment arm. This means that you have been taking **placebo tablets** during the study.

What does this mean for me?

You may have some questions about placebo tablets and what to do next. It is not uncommon to feel disappointed or to experience some concerns when finding out you have been taking placebo tablets. Below you will find some frequently asked questions about placebo tablets that you may find helpful.

Frequently asked questions

Q	**Why did we use a placebo in the ATLANTIS study?**
A	The ATLANTIS study is a placebo-controlled clinical trial. A placebo contains no medication (no active ingredients) but looks, tastes, and feels like the medicine in the trial. Placebo-controlled clinical trials aim to find out if a medicine works better than a placebo. We have used a placebo in this study because we needed to find out if amitriptyline works for people with IBS and using a placebo tablet is a good way to test if a medicine works. We use a placebo because IBS symptoms vary over time and so improvements in patients' symptoms during a trial may be due to these natural variations, rather than the medicine. Comparing participants on amitriptyline with those on placebo allows us to work out how much of the improvement seen is because of amitriptyline.

Q	**What are the results of the study?**
A	The ATLANTIS study data have yet to be analysed so we do not know the results yet. We have recruited 463 people with IBS. You will receive a summary of the results when the study ends, and all the data have been analysed. Please let the study team know if you change your email address. The study results will also be made available on the study website: https://ctru.leeds.ac.uk/atlantis/ Before the ATLANTIS study nobody had done a large study to explore whether amitriptyline benefits people

	with IBS who are looked after by their GP. We hope the results will lead to more effective treatment for IBS. The results from this study are important, as they will help doctors decide whether they should be using amitriptyline routinely as a treatment for IBS.

Q	**Is amitriptyline effective in treating IBS symptoms? Can I start taking amitriptyline for my IBS?**
A	The ATLANTIS study data have yet to be analysed so we do not know the results of the study yet. If you wish to try taking amitriptyline for your IBS, **you can now speak to your GP to discuss the option for you to start taking amitriptyline tablets.** Amitriptyline is a frequently used drug, which has been in use for more than 50 years. Amitriptyline can already be used to treat IBS at a low dose and guidelines suggest trying it when people with IBS have ongoing symptoms. We believe it helps with IBS because it relieves pain and changes bowel activity. This has been shown in some small studies that have looked at people with IBS seeing specialist doctors in hospital clinics.

Q	**What is a placebo and how can taking placebo tablets affect IBS?**
A	A placebo (often called a dummy medicine) contains no medication but looks, tastes, and feels like the medicine in the study. The placebo tablets for the ATLANTIS study

	are made of sugar. Many people believe that taking a placebo will have no effect on IBS symptoms. However, rigorous clinical tests have shown placebos can still have real effects on people despite having no medication in them. Some people find their symptoms get better when they are given a placebo. Some people also report side effects after taking placebos. **There is more information about why this happens below.**

Q	**I feel disappointed that I have taken placebo tablets and seen no improvement in my IBS? What can I do next?**
A	Not everyone who takes a placebo will notice an effect on their symptoms. This doesn't mean that other IBS treatments won't work for you. It is not possible to predict who will respond to a placebo. You have played a very important role in the study. Although you have not had the potential benefit of taking amitriptyline in the study, **you can now speak to your GP to discuss the option for you to start taking amitriptyline tablets for your IBS, if you wish.**

Q	**My IBS symptoms have got worse. What can I do?**
A	**If your IBS symptoms have got worse, please speak to your GP to discuss treatment options** such as

	medicines, dietary advice, or referral for psychological therapies, such as a type of cognitive behavioural therapy (CBT) for IBS. **You must seek urgent advice from your GP if you have:** • lost a lot of weight for no reason • bleeding from your bottom or bloody diarrhoea

Q	**I have taken placebo tablets but seen an improvement in my IBS. Why is that?**
A	Sometimes we can feel better when we have taken a placebo. This is called the **placebo effect.** You are not alone. Lots of people with IBS (and other conditions) experience the placebo effect. Research evidence suggests that a high proportion of people with IBS respond to placebo in clinical trials (estimated at about 40%). Placebo effects are produced through a number of different mind-body self-healing processes. Scientists have found that placebo effects work in these ways: • Placebos can work by making our brains release natural chemicals that **relieve pain**. In IBS, this may lead to relief of abdominal pain. • Placebos can also **work because we expect them to and because of what a medicine means to us.** For example, if we expect symptom relief from a medicine, it tends to work better. • Placebos can work **because of the way the doctor or nurse talks to us.** For example, feeling supported and understood by a medical professional can help us feel better without taking any medication. • Placebos can work **because of a process called**

	‘conditioning’. Conditioning is when cues we associate with a medicine can help us feel better without taking any medicine. For example, after years of seeing doctors and nurses and taking medicines, people are ‘conditioned’ to feel better automatically after taking something that looks like medicine. And placebos are tablets that are designed to look just like medicine. Conditioning can seem similar to ‘expecting’ medicines to work as described above. However, having expectations is a conscious process (in the mind) but ‘conditioning’ is a subconscious process (the body automatically responds to a placebo).

Q	**Why did I experience side effects on placebo tablets?**
A	The placebo tablets you have taken in the study are safe, as they do not have real medicine in them (they are made of sugar). Placebos are often safer than active treatments. Some people do still experience side effects when taking placebo tables. These side effects are due to what is called **a nocebo effect.** This is when a placebo makes us feel worse rather than better. Nocebo effects are the worsening of symptoms due to our expectations and the meaning we give to a particular medicine, rather than because the medicine itself is dangerous. **Any nocebo effects should stop when you stop taking the tablets. If you continue to feel unwell, please speak to your GP.**

Q	**I still have questions: who can I talk to about this?**
A	It will not be possible to speak your research nurse about your study tablets. Research nurses are not allowed to know which tablets people in the study are taking, as this may affect the results of the study. Instead, you can contact one of the Chief Investigators, at atlantis@leeds.ac.uk who will be able to answer any questions or discuss any concerns you may have.

Q	**Where can I find further information and support?**
A	Please find some recommended sources of information and support for people with IBS below: **NHS website** https://www.nhs.uk/conditions/irritable-bowel-syndrome-ibs/ *Advice on IBS symptoms and treatment options.* **Guts UK** https://gutscharity.org.uk/ *UK-based charity for the digestive system.* **IBS and Diet: Food Fact Sheet** https://www.bda.uk.com/resource/irritable-bowel-syndrome-diet.html *Dietary advice for IBS produced by the British Dietetic Association and recommended by the National Institute for Health ad Care Excellence (NICE).* **IAPT** https://www.england.nhs.uk/mental-health/adults/iapt/ *Improving Access to Psychological Therapies (IAPT) services provide evidence-based psychological therapies*

		to people with long term physical health problem.
	IBS Network	https://www.theibsnetwork.org/ *UK-based charity for people living with IBS (membership required to access full content).*
	IBS Network support groups	https://www.theibsnetwork.org/self-help-groups/ *Information on local support groups.*
	Contact me IBS	https://www.contactme-ibs.co.uk/ *A research register of adults interested **in hearing about and taking part in IBS** research.*

Thank you again for supporting this research!

1.5 Standardised Written Guidance Concerning Dose Titration of Trial Medication Used in the ATLANTIS Trial.

ATLANTIS

Participant Dose Adjustment Information

During the first month of your treatment, you will need to work out the daily dose of the ATLANTIS trial medication that suits you best. This process is called 'dose titration.'

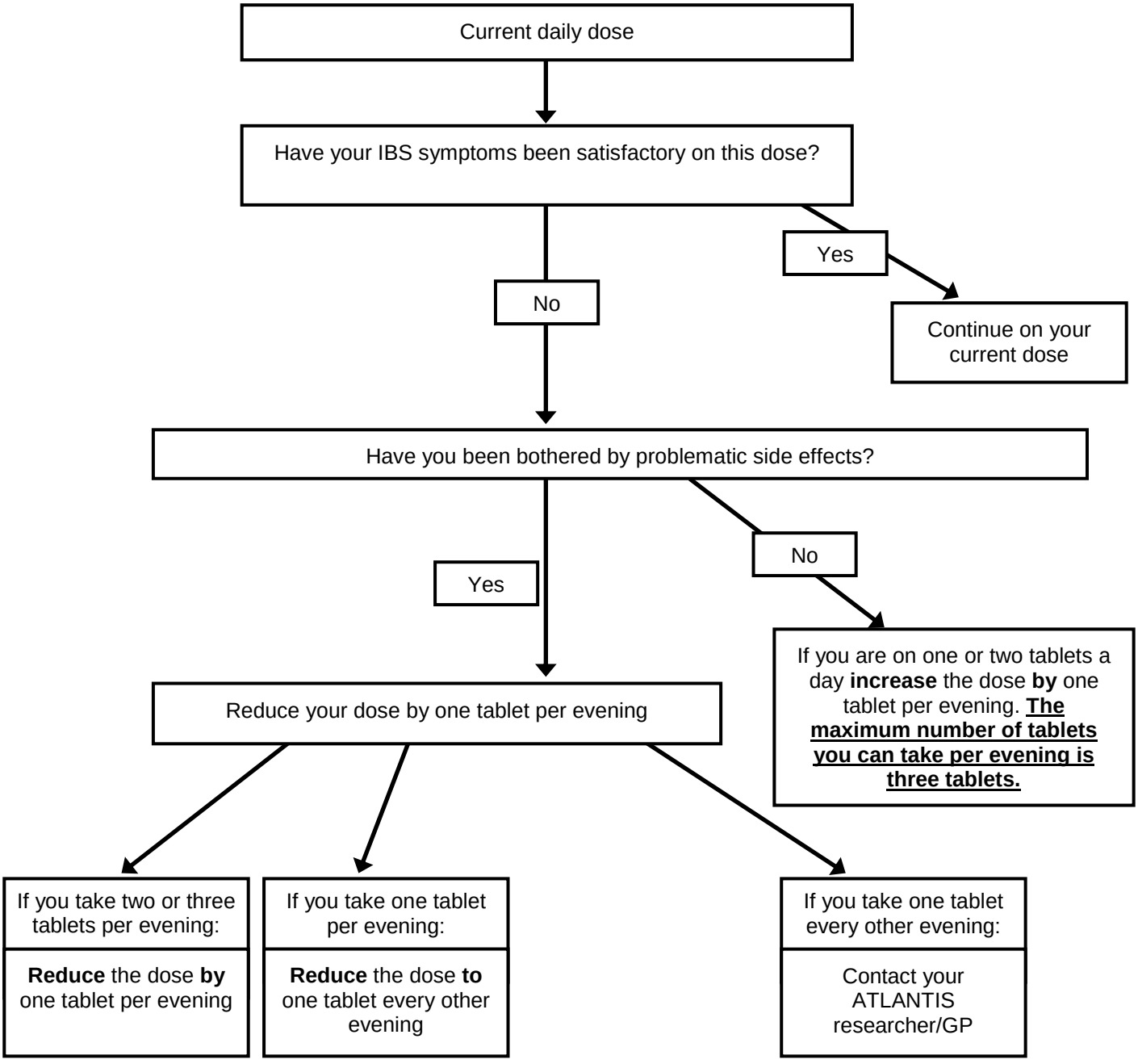
Initially, you will start on one tablet each day in the evening for the first week of the ATLANTIS trial. After this you will decide whether to stay on one tablet or increase to two tablets at night for the second week of the study. You will do this by considering whether your IBS symptoms have stayed the same, improved, or worsened on the trial medication and whether you are experiencing any side effects.

The medication can be further increased to three tablets at night in the third week of the study. This will again depend on your response to the tablets.

If you forget to take a dose at any point during the study, you should miss this dose and continue as normal the next day.

This booklet should be used for guidance during the dose titration period. You can contact the ATLANTIS researcher or your GP if you have any questions or concerns about taking your ATLANTIS trial medication.

Guidance Flowchart.



Treatment Guidance.

Please remember to complete your ATLANTIS Participant Symptom question each week. You will receive an email or text to remind you to log on to our ATLANTIS website to do this.

Please contact your ATLANTIS researcher or your GP at any point if you experience any problems.

This medicine can be taken with or without food.

Swallow the tablets with a drink of water. Do not chew them.

This medicine may increase the sedative effect of alcohol – so avoiding alcohol is recommended.

This medicine may cause drowsiness and dizziness, especially at the beginning of the treatment. Do not drive or work with tools or machinery if you are affected.

You will initially receive enough tablets for just over 1-month of treatment (including enough to titrate your dose up if needed).

- **Day 1:**
  - You should begin taking treatment the day you receive your trial medication through the post. Take **one** tablet in the evening. Most people find that taking the tablet mid-evening suits them best (e.g., 7-8pm) as this can reduce any side effects the next morning, but you can take the tablet any time before bedtime.
  - We advise to take the medication at night as drowsiness may be a side effect. If you are a night shift worker, then it is best to take your amitriptyline prior to sleep – if you are unsure regarding timings, please discuss with the ATLANTIS researcher or your GP.

- **Days 2-7:**
  - As you did on day 1, take **one** tablet in the evening.
  - All medications potentially have side effects. These tend to occur when you first start a new medication and often settle after the first week or two if you persist with taking your medication. The most common side effect for amitriptyline is a dry mouth in the morning. This can be helped by taking the tablets mid evening rather than just before bedtime, and by taking sips of water as needed. If you are worried or concerned about any possible side effects and would like to discuss them, you can contact the ATLANTIS researcher or your GP for advice. Please refer to your medication card for contact information for your ATLANTIS researcher.

- You will receive a routine follow-up telephone call between day 6 and day 8 from the ATLANTIS researcher to ask you some questions about taking the trial medication and to answer any queries that you have.

- **Days 8-14:**
  - You will decide, based on your response to the trial medication so far, whether you would like to increase your dose to take two tablets each evening, or stay on one tablet.
    - If you feel that you have had a good response to the trial medication and that your IBS symptoms are well-controlled, you can opt to stay on one tablet.
    - If you feel that you have had a little or no improvement in your IBS symptoms, then you can opt to increase to two tablets each evening.
    - If you are unsure, or if you have some side effects from the tablets and want to see if these will settle, you have the choice to stay on one or increase to two tablets.
  - If you chose to increase your tablets to two each evening but then feel that this increased dose doesn't suit you – you can choose to reduce back to one tablet each evening.
  - We know that IBS symptoms can vary from day to day – so it might take a week or longer to know if increasing the dose has had an effect on your IBS symptoms.
  - If you have mild side effects from the trial tablets (e.g., a dry mouth), but these are not troublesome, then it is fine to continue with the trial medication.

- **Day 15 onwards:**
  - On day 15, you have the option to increase your trial medication to three tablets in the evening if you would like to.
  - You will decide based on your response to the trial medication so far whether you would like to increase your dose to take three tablets each evening or stay on one or two tablets.
    - If you feel that you have had a good response to the trial medication and that your IBS symptoms are well-controlled, you can opt to stay on your current dose of tablets.
    - If you feel that you have had a little or no improvement in your IBS symptoms, then you can opt to increase your dose to three tablets each evening.
    - If you are unsure, or if you have some side effects from the tablets and want to see if these will settle, you have the choice to stay on one or two tablets or increase to three tablets.
  - If you chose to increase your tablets to three each evening but then feel that this increased dose doesn't suit you – you can choose to reduce back to two tablets each evening.
  - We know that IBS symptoms can vary from day to day – so it might take a week or longer to know if increasing the dose has had an effect on your IBS symptoms.
  - If you are unsure what to do, use the flowchart on page 2 of this booklet to guide you as to what dose you should take.
  - Hopefully, you will find the most suitable number of tablets (one, two, or three) to help your IBS symptoms, which you will continue to take for the rest of the study. However, if your IBS symptoms fluctuate, you can increase or decrease your dose to reflect this at any time during the study, but you must **not** take **more than three tablets** per evening. The flowchart on page 2 is there to help you with this. We do not recommend very frequent changes in medication dose; try at least 1 week on a new dose before changing again.

- You must **not** take **more than three tablets** of the trial medication per evening – if you accidentally do this please contact your GP or the ATLANTIS researcher to inform them.
- You will receive a routine follow-up telephone call at around 3 weeks from the ATLANTIS researcher to ask you some questions about taking the trial medication, to answer any queries that you have, and to order a further 2 months supply of medication to be delivered to you.
- You will receive another routine follow-up telephone call at around 3 months from the ATLANTIS researcher to ask you some questions about taking the trial medication, to answer any queries that you have, and to order a further 3 months supply of medication to be delivered to you.
- Please continue taking your ATLANTIS trial medication for a total of 6 months during the ATLANTIS trial.

Please refer to Page 2 of this booklet for guidance on how to adjust your dose.

If at any point you have questions about what dose you should take, or any concerns surrounding side effects of the treatment, please contact your ATLANTIS researcher or GP using the details provided on your patient card.

1.6 Participant Invitation Letter Used in the Nested Qualitative Study.

1.6.1 Participant Cover Letter/Email.

Dear << Add Name>>

We are writing to you as part of the ATLANTIS study. You may recall at the start of the study we asked if we could contact you about taking part in an interview. We are now talking to some participants about their experiences in the ATLANTIS study, and you have been selected to take part. This part of the study is being led by researchers at Southampton University.

What does the interview involve?

We would like to invite you to take part in a telephone interview to talk more about your experience in this study. You will be asked to take part in two interviews, which will last approximately 1 hour each. You can choose to end the interview at any time and you do not have to answer any questions you do not want to.

Your participation is completely voluntary. Please find enclosed the participant information sheet, which tells you all about why we are doing these interviews and what it involves. The information sheet also includes the researcher's details to contact if you have any questions.

If you decide you would like to talk to a researcher about your experiences in the ATLANTIS study, then please email me or complete the consent form attached and email it to me at e.j.teasdale@soton.ac.uk

If you decide you would not like to take part, you are welcome to email me on e.j.teasdale@soton.ac.uk to let me know.

Thank you very much for taking the time to read the information sheet and consider this part of the study.

Yours sincerely,

E J Teasdale

Dr Emma Teasdale (Qualitative Research Fellow, on behalf of the Atlantis study team)

1.6.2 Qualitative Email Invitation from RNs to Participants Who Have Consented to be Approached for the Qualitative Interviews.

Dear <<Insert name of participant>>

You may recall at the start of the study we asked if we could contact you about taking part in an interview. We would now like to invite you to take part in a telephone interview to talk more about your experience in this study. The interview will last about 1 hour.

I've attached a copy of the study invite letter, information sheet and consent form for your information. If you are interested in chatting to one of our researchers about your experience of the ATLANTIS study, please contact Emma Teasdale at e.j.teasdale@soton.ac.uk

Please do not hesitate to contact us or Emma if you have any questions about the interview study.

Many thanks

PS You may have already received a paper invite to undertake a telephone interview and returned a reply slip. Unfortunately because of Covid19 we are struggling to receive post (although your post will be stored securely) and thus have also contacted everyone electronically in case we have missed a reply slip. Please email if you would like to take part.

1.7 Participant Information Sheet Used in the Nested Qualitative Study.

We would like to talk to you about your experiences in the ATLANTIS study.

We want to find out about patients' experiences by asking some questions in an interview. This leaflet tells you why these interviews are being done and what they involve. You can choose whether or not you want to take part. Feel free to discuss it with others if you wish. Please contact us using the contact details on page 7 if you have any questions or comments, we would be happy to hear from you.

What's This About? A Quick Summary

- We would like to hear about your experiences in the ATLANTIS study.
- We would like to talk to you over the phone on up to two occasions, for up to an hour each time. This will take place 6 months after you start the study, and potentially then again after another 6 months (if you have consented to 12 month follow up).
- What you say in these phone calls will help us to understand patients' experiences of using amitriptyline or taking placebo for irritable bowel syndrome (IBS).
- It will also help us to understand what it is like to take part in a research study and might help us to improve future studies.
- This work is being run by the ATLANTIS study team and funded by the National Institute of Health Research.

The rest of this leaflet contains more detailed information. Please read on if you think you may be interested in taking part.

Why are we interviewing patients?

We want to find out about people's experiences of taking amitriptyline and placebo for IBS, within the ATLANTIS study. We want to find out what it is like to take amitriptyline and explore the benefits and drawbacks from patients' perspectives. We also want to find out what it was like for patients to take the placebo drug. Lastly, we would like to hear about what it was like to take part in the study. This information will help us:

- To understand the results of the ATLANTIS study;
- To understand how amitriptyline could be used more widely depending on the results of the main ATLANTIS study; and
- To improve how we do future studies with placebos.

Why have I been asked to take part?

You have been invited because you are taking part in the main ATLANTIS study. We are hoping to speak with approximately 40 patients in total, and are asking a range of patients to take part. This is because we want to speak with patients of different ages and genders, and some patients who received placebos and some who received amitriptyline.

Do I have to take part?

No, your participation is entirely voluntary and it is up to you to decide whether or not to take part.

If you decide to take part you will be given this information document to keep. You will be asked to sign a consent form, but you are still free to withdraw at any time and without giving a reason.

Your treatment and care will not be affected in any way.

What will happen to me if I do take part?

If you are interested in taking part:

- Please complete the consent form and email it to the researcher at University of Southampton at e.j.teasdale@soton.ac.uk
- The researcher will then contact you (by email or telephone) to arrange a mutually convenient time to telephone you to talk about your experiences in ATLANTIS.
- The researcher will ask you about your experiences of IBS and your health in general, your experiences of taking the study medication, and your experiences of the ATLANTIS study in general.
- We anticipate that this call will last around one hour, but this depends on how much information you would like to share with us.
- After 6 months, the researcher will contact you again, if you have consented to 12 months follow up, to ask if you would be willing to be interviewed again, this time about your experiences since your first interview. We anticipate this will also take approximately one hour.

What are the possible pros and cons of taking part?

Some patients find it helpful or even enjoyable to talk about their experiences of being in a study. There are no expected risks or disadvantages associated with taking part in this study.

What happens to the information I share with you?

- The interview will be audio-recorded.
- The recording will be typed up by a professional transcriber or a member of the research team. They will keep everything they hear private and will type code names instead of your name and any other names or places, so no-one can find out who you are. We will delete all audio recordings on completion of the study.
- We will review what you have told us and put that together with what other patients tell us about their experiences.
- This will help us understand patients' experiences of taking amitriptyline and placebo for IBS and taking part in research.
- Your personal details and code name will be stored separately from the typed up interviews and audio-recordings; all of this information will be stored securely on computers at the University of Southampton.
- We will delete the personal details that match your code name after this interview study. This will not affect your personal details held by the main ATLANTIS study.

Will information about me be kept confidential?

Your participation and the information we collect about you will be kept strictly confidential. We will not share your interview with your doctor or anyone else who is not a member of the ATLANTIS team.

We follow strict regulations about how health research is carried out. At times, people may need to access the information we collect about you to check that we are carrying out the research correctly. Only individuals from regulatory authorities will be able to see your information. These people have a duty to keep your information strictly confidential.

What happens if I change my mind?

If you decide you do not want us to use the information from your interview you must notify us within 2 weeks after being interviewed. To do this, please contact the researcher, using the contact information provided below. You do not have to give a reason, your routine care will not be affected, and your participation in the main ATLANTIS study will not be affected.

What will happen to the results of the research?

Your personal details will remain strictly confidential. The results of the study will be published in scientific journals and presented at research conferences. We may use quotes from the

interview but none of your personal details that could identify you will be used (like your name).

Who is conducting this study?

This interview study is part of the ATLANTIS study, which is sponsored by the University of Leeds and is being organised on their behalf by the University of Leeds Clinical Trials Research Unit. The ATLANTIS study is funded by the National Institute of Health Research. Our interview study team includes GPs, doctors, academic researchers and patient representatives from Southampton, Leeds and Bristol. This interview study has been approved by the Health Research Authority and the Yorkshire & The Humber – Sheffield Research Ethics Committee Ref number: 19/YH/0150.

What happens if there is a problem?

If you have a concern about any aspect of this study, you may wish to speak to the researcher (contact details below) who will do their best to answer your questions. Alternatively you could to speak to your local ATLANTIS research team.

If you remain unhappy or have a complaint about any aspect of this study, please contact the University of Southampton Research Integrity and Governance Manager (023 8059 5058, rgoinfo@soton.ac.uk).

Where can I get more information?

If you would like to know more or have any questions about this interview study, then please contact the researcher, [INSERT NAME and contact details]

What should I do if I want to take part?

Thank you for taking the time to read this information sheet. If you would like to take part, then please complete the enclosed consent form and return it to the researcher using the freepost envelope provided.

Data Protection Privacy Notice

The University of Southampton conducts research to the highest standards of research integrity. As a publicly-funded organisation, the University has to ensure that it is in the public interest when we use personally-identifiable information about people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use information about you in the ways needed, and for the purposes specified, to conduct and

complete the research project. Under data protection law, 'Personal data' means any information that relates to and is capable of identifying a living individual. The University's data protection policy governing the use of personal data by the University can be found on its website (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page).

This Participant Information Sheet tells you what data will be collected for this project and whether this includes any personal data. Please ask the research team if you have any questions or are unclear what data is being collected about you.

Our privacy notice for research participants provides more information on how the University of Southampton collects and uses your personal data when you take part in one of our research projects and can be found at http://www.southampton.ac.uk/assets/sharepoint/intranet/ls/Public/Research%20and%20Integrity%20Privacy%20Notice/Privacy%20Notice%20for%20Research%20Participants.pdf

The University of Leeds is the 'Data Controller' for this study, which means that they are overall responsible for looking after your information and using it properly. The University of Southampton are "Data Processors" for this study and we will collect and store your data securely. The University of Leeds will ensure that any personal data we collect in this study will be used only for the purposes of carrying out our research and will be handled according to the consent you have given, and with the 2018 Data Protection Act. If any personal data is used from which you can be identified directly, it will not be disclosed to anyone else without your consent unless the University of Southampton is required by law to disclose it. Data protection law requires us to have a valid legal reason ('lawful basis') to process and use your Personal data. The lawful basis for processing personal information in this research study is for the performance of a task carried out in the public interest. Personal data collected for research will not be used for any other purpose. The University of Southampton will keep identifiable information about you for 1 year after the study has finished after which time any link between you and your information will be removed. To safeguard your rights, we will use the minimum personal data necessary to achieve our research study objectives. Your data protection rights – such as to access, change, or transfer such information - may be limited, however, in order for the research output to be reliable and accurate. The University of Southampton will not do anything with your personal data that you would not reasonably expect. If you have any questions about how your personal data is used, or wish to exercise any of your rights, please consult the University's data protection webpage (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page) where you can make a request using our online form.

If you have any concerns about the way your personal data is being processed or have a query about the information in this leaflet, please contact the University of Leeds Data Protection Officer using any of the following details:

- Email: DPO@leeds.ac.uk;
- General postal address: University of Leeds, Leeds LS2 9JT, UK;
- Postal address for data protection issues: University of Leeds, Room 11.72 EC Stoner Building, Leeds, LS2 9JT;
- Telephone number: +44 (0)113 243 1751.

Our data controller registration number provided by the Information Commissioner's Office is Z553814X.

1.8 Participant Consent Form Used in the Nested Qualitative Study.

I have read and understood the patient interview information sheet (V3.0 FINAL 30 June 2021)
I confirm that I have had the opportunity to ask questions about the study and if I asked, my questions were answered fully.
I agree to allow any information or results arising from this study to be used for healthcare and/or further medical research upon the understanding that my identity will remain anonymous.
I understand my participation is voluntary and I may withdraw at any time for any reason without my medical care or participation in the main ATLANTIS study being affected.
I agree to take part in the interview for the purposes set out in the participation information sheet, and understand that these will be audio-recorded and transcribed.
I understand that I may be quoted directly in reports of the research but that I will not be directly identified (i.e., that my name will not be used).
I understand that personal details I provide for this interview study will be held securely at The University of Southampton in line with General Data Protection Regulation and Data Protection Act 2018.

Please type your initials in each of the boxes if you agree with the statements and type your name below:

Your name (type):……

Date……

Please supply a phone number and/or email address that we can use to contact you about the interview:

……

Please now email this form to the researcher at e.j.teasdale@soton.ac.uk

1.9 GP Information Sheet Used in the Nested Qualitative Study.

We would like to talk to you about your experiences in the ATLANTIS study.

We want to find out about GPs' experiences by asking some questions in an interview. This leaflet tells you why these interviews are being done and what they involve. You can choose whether or not you want to take part. Feel free to discuss it with others if you wish. Please contact us if you have any questions or comments, we would be happy to hear from you.

What's This About? A Quick Summary

 We would like to hear about your experiences in the ATLANTIS study.

 We would like to interview you over the phone once.

 What you say in this phone call will help us to understand GPs' thoughts on amitriptyline for irritable bowel syndrome (IBS) and GPs' experiences in this trial.

 This information might help us to improve our understanding of how amitriptyline might be used in practice for IBS and could improve the way we do things in future studies.

 This interview study is being run by the ATLANTIS study team and funded by the National Institute of Health Research.

The rest of this leaflet contains more detailed information. Please read on if you think you may be interested in taking part.

Why are we interviewing GPs?

We want to find out about GPs' thoughts about amitriptyline for IBS and their experiences within the ATLANTIS study. We want to find out how amitriptyline relates to current primary care practice for IBS and explore the benefits and drawbacks from GPs' perspectives. We also want to find out what it was like for GPs to take part in the study. This information will help us:

 To understand the results of the ATLANTIS study;

 To understand how amitriptyline could be used more widely depending on the results of the main ATLANTIS study; and

 To improve how we do future studies.

Why have I been asked to take part?

You have been invited because your practice is taking part in the main ATLANTIS study. We are inviting all of the GPs from the main study to take part in an interview.

Do I have to take part?

No, it is entirely up to you to decide whether or not to take part. If you decide you want to take part, you will need to sign a consent form to show you have agreed to take part.

What will happen to me if I do take part?

If you are interested in taking part:

 Please complete and sign the consent form and return it to the researcher at University of Southampton.

 The researcher will contact you (by email or telephone) to arrange a mutually convenient time to telephone you to talk about your experiences in ATLANTIS.

 In the interview, the researcher will ask you some questions about your experiences in the main ATLANTIS study.

 Topics that the researcher may ask you about include your approach to IBS, your thoughts about amitriptyline for IBS, and your experiences of the ATLANTIS study in general.

 We anticipate that this call will last around 30 minutes, but this depends on how much information you would like to share with us.

What are the possible pros and cons of taking part?

Some people find it helpful to talk about their practice and their experiences of being in a study. There are no expected risks or disadvantages associated with taking part in this interview study.

What happens to the data being collected?

 The interview will be audio-recorded.

 After the interview, the recording will be put on the university password-protected computer and deleted from the device.

 The recording will be typed up by a professional transcriber or a member of the research team. They will keep everything they hear private and will type code names instead of your

name and any other names or places, so no-one can find out who you are. We will delete all audio recordings on completion of the study.

 We will review what you have told us and put that together with what other GPs tell us.

 This will help us understand GPs' views on amitriptyline for IBS and GPs' experiences of being part of a placebo-controlled trial.

 Your personal details and code name will be stored separately from the typed up interviews and audio-recordings; all of this information will be stored securely on computers at the University of Southampton.

 We will delete the personal details that match your code name after this interview study. This will not affect your personal details held by the main ATLANTIS study.

Will my participation be confidential?

Your participation and the information we collect about you will be kept strictly confidential. We will not share your interview with anyone who is not a member of the ATLANTIS team.

We follow strict regulations about how health research is carried out. At times, people may need to access the information we collect about you to check that we are carrying out the research correctly. Only individuals from regulatory authorities will be able to see your information. These people have a duty to keep your information strictly confidential.

What happens if I change my mind?

If you decide you do not want us to use the information from your interview you must notify us within 2 weeks after being interviewed. To do this, please contact the researcher, using the contact information provided below. You do not have to give a reason.

What will happened to the results of the research?

Your personal details will remain strictly confidential. The results of the study will be published in scientific journals and presented at research conferences. We may use quotes from the interview but none of your personal details that could identify you will be used (like your name).

Who is conducting this study?

This interview study is part of the ATLANTIS study, which is sponsored by the University of Leeds and is being organised on their behalf by the University of Leeds Clinical Trials Research Unit. The study is funded by the National Institute of Health Research. Our interview

study team includes GPs, doctors, academic researchers and patient representatives from Southampton, Leeds and Bristol. This interview study has been approved by the Health Research Authority and the Yorkshire & The Humber – Sheffield Research Ethics Committee Ref number: 19/YH/0150.

What happens if there is a problem?

If you have a concern about any aspect of this study, you may wish to speak to the researcher (contact details below) who will do their best to answer your questions. Alternatively you could to speak to your local ATLANTIS research team.

If you remain unhappy or have a complaint about any aspect of this study, please contact the University of Southampton Research Integrity and Governance Manager (023 8059 5058, rgoinfo@soton.ac.uk).

Where can I get more information?

If you would like to know more or have any questions about this interview study, then please contact the researcher, [INSERT NAME and contact details].

What should I do if I want to take part?

Thank you for taking the time to read this information sheet.

If you would like to take part, then please complete the consent form sent as an email attachment and return it to the researcher by email.

Data Protection Privacy Notice

The University of Southampton conducts research to the highest standards of research integrity. As a publicly-funded organisation, the University has to ensure that it is in the public interest when we use personally-identifiable information about people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use information about you in the ways needed, and for the purposes specified, to conduct and complete the research project. Under data protection law, 'Personal data' means any information that relates to and is capable of identifying a living individual. The University's data protection policy governing the use of personal data by the University can be found on its website (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page).

This Participant Information Sheet tells you what data will be collected for this project and whether this includes any personal data. Please ask the research team if you have any questions or are unclear what data is being collected about you.

Our privacy notice for research participants provides more information on how the University of Southampton collects and uses your personal data when you take part in one of our research projects and can be found at http://www.southampton.ac.uk/assets/sharepoint/intranet/ls/Public/Research%20and%20Integrity%20Privacy%20Notice/Privacy%20Notice%20for%20Research%20Participants.pdf

The University of Leeds is the 'Data Controller' for this study, which means that they are overall responsible for looking after your information and using it properly. The University of Southampton are "Data Processors" for this study and we will collect and store your data securely. The University of Leeds will ensure that any personal data we collect in this study will be used only for the purposes of carrying out our research and will be handled according to the consent you have given, and with the 2018 Data Protection Act. If any personal data is used from which you can be identified directly, it will not be disclosed to anyone else without your consent unless the University of Southampton is required by law to disclose it. Data protection law requires us to have a valid legal reason ('lawful basis') to process and use your Personal data. The lawful basis for processing personal information in this research study is for the performance of a task carried out in the public interest. Personal data collected for research will not be used for any other purpose. The University of Southampton will keep identifiable information about you for 1 year after the study has finished after which time any link between you and your information will be removed. To safeguard your rights, we will use the minimum personal data necessary to achieve our research study objectives. Your data protection rights – such as to access, change, or transfer such information - may be limited, however, in order for the research output to be reliable and accurate. The University of Southampton will not do anything with your personal data that you would not reasonably expect. If you have any questions about how your personal data is used, or wish to exercise any of your rights, please consult the University's data protection webpage (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page) where you can make a request using our online form.

If you have any concerns about the way your personal data is being processed or have a query about the information in this leaflet, please contact the University of Leeds Data Protection Officer using any of the following details:

- Email: DPO@leeds.ac.uk;
- General postal address: University of Leeds, Leeds LS2 9JT, UK;

 Postal address for data protection issues: University of Leeds, Room 11.72 EC Stoner Building, Leeds, LS2 9JT;

 Telephone number: +44 (0)113 243 1751.

Our data controller registration number provided by the Information Commissioner's Office is Z553814X.

1.10 GP Consent Form Used in the Nested Qualitative Study.

Please initial the boxes if you agree with the statements and sign below:

I have read and understood the GP interview information sheet (Version 2.0 / 14 June 2019)

I confirm that I have had the opportunity to ask questions about the study and if I asked, my questions were answered fully.

I agree to allow any information or results arising from this study to be used for healthcare and/or further medical research upon the understanding that my identity will remain anonymous.

I understand my participation is voluntary and I may withdraw at any time for any reason.

I agree to take part in the interview for the purposes set out in the participation information sheet and understand that these will be audio-recorded and transcribed.

I understand that I may be quoted directly in reports of the research but that I will not be directly identified (i.e., that my name will not be used).

I understand that personal details I provide for this interview study will be held securely at The University of Southampton in line with General Data Protection Regulation and Data Protection Act 2018.

Your signature:……

Your name (print):……

Date……

Please supply a phone number and/or email address that we can use to contact you about the interview:

……

Please now return this form to the researcher by email.

1.11 Interview Topic Guides for the Nested Qualitative Study: 6-month Participant Interview Topic Guide.

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 study, 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

Iteration and Flexibility

The topic guide will evolve as the interviews progress in response to researchers' reflections, initial analysis, and feedback from participants. The scope of the interviews will always remain consistent with the objectives specified above. Within this scope, the topic guide will be used flexible in that the researcher may adjust the questions asked and the order in which they are asked as appropriate for the individual participant. It may not always be necessary to ask all of the questions in order to elicit the relevant information.

Introduction

Thank you for agreeing to take part in a research interview today. I am (*researcher name*), a researcher at University of Southampton. Just so you know, I am not a medical doctor so I'm afraid I can't offer any advice about your IBS today. [short hello]

I'm currently contacting a number of people who are taking part in the Atlantis study to find out about their experiences of the study, the study treatments, and their IBS.

How long this will take depends a bit on how much you want to tell us, but we anticipate it will take approximately one hour. Just let me know if you need to finish sooner and we can do that.

I would like to record the conversation we have today so that I can refer back to it at a later date. It enables me to listen to you better. We will store the recordings securely on a university password-protected computer. What we talk about will be used as part of the study, but what you say will remain anonymous. We're going to ensure this by not using your real name, or any other names that you mention, when we type up the interview. The typed up interviews will then be stored securely too. Is that ok?

Before we start there are a few things I'd just like to mention.

If I ask a question that you don't want to answer that is absolutely fine, just say so and I'll ask you a different question. If at any point you would like to take a break or stop altogether just tell me and we can do that.

Anything you can tell me about your experiences including good and bad points would be useful. What you say to me today will not impact your care in any way at all.

Do you have any questions before we start? Are you happy to continue?

TURN ON THE RECORDING DEVICE

Topic Guide

Opening (6m only)

I'm really interested in finding out about how you came to take part in the study and what it was like for you. Please could you tell me all about it?

Initiating Atlantis (6m only)

Thinking back to when you first heard about the Atlantis study, can you tell me what your IBS was like then?

Can you tell me about the first time you became aware of IBS in your life? (Prompts: What symptoms did you have? Have symptoms changed over time?)

Do you have a sense about what causes your IBS?

Can you tell me about what, treatments you have tried prior to taking part in this study?

Have you noticed anything that helps symptoms? Or makes it worse?)

How does having IBS make you feel? (Prompts: your work life? your social life? What about physical activity?)

Can you describe how IBS affects your relationships to others?

Has having IBS introduced any positive/negative consequences to your life?

Still thinking back to when you first heard about the Atlantis study, can you tell me anything about why you agreed to take part in it? Anything that made you want to be in it? Anything that concerned you about it? Had you ever been involved in medical research before?

What did you expect/how did you feel about taking part?

What did other people think about you taking part in the study?

As you know, being in this study involved you taking some tablets. At the start of the study the researchers explained that some people would get amitriptyline and some people would get placebo pills. Can you tell me how you felt about this at the start of the study?

Did you have any thoughts or feelings about how taking amitriptyline might affect your IBS? [probe expectations of effect and concerns]

Did you have any thoughts or feelings about how taking a placebo might affect your IBS? [probe expectations of effect and concerns]

Experiences during Atlantis (6m)

How has your IBS been since you've been in the study? And your health/quality of life in general? [probe for anything getting better or worse] [probe for impacts of COVID-19 pandemic if mentioned]

Could you tell me all about your experience of taking part in the study so far? [probe for impacts of COVID-19 pandemic if mentioned]

Could you tell me about any consultations that you've had with your GP about your IBS since starting the study?

Could you tell me how you felt about the optional GP consultation offered at month 1?

Could you tell me all about taking the tablets as part of the study? How was the process of dose adjustment? And talking to the research nurse on the phone?

There are lots of things that can mean we don't always take our medicines as prescribed. Was there anything that made it easier for you to take your tablets as prescribed? Was there anything that made it harder for you to take your tablets as prescribed? Have you had any concerns about the tablets? [prompt re side effects and probe re impact of these]

What did other people think about you taking the ATLANTIS tablets? [e.g. family, friends]

When you were taking the pills: Did you have any thoughts about whether they were amitriptyline or placebo? Did you think you received real pills or placebo pills? Why did you think so? What were the clues?

If you felt that you had placebo tablets, could you tell me what made you want to continue with the trial?

Is there anything else you would like to tell me about the pills that you were taking in the study?

Did you decide to continue or stop taking the tablets at 6 months? Can I ask how you came to that decision?

Have you started or stopped any other treatments for your IBS during the ATLANTIS study so far? [what and why] (prompt re prescribed and OTC meds and other treatments e.g. CBT/diet/complementary medicines)

Experiences of Study Procedures (6m+12m)

How have you found being in the study, for example filling in the consent forms and the questionnaires (prompt about using online/telephone questionnaires), getting the medicines through the post, talking to the research nurse about the tablets? (prompt on each element of this question)

What did you think/how did you feel about the information you received about the study or information you had explained to you by the research nurses?

Have you looked at the study website and twitter account? Can you tell me about your experiences of this?

How did you feel about using text message correspondence?

Could you tell me how you felt about having more frequent follow up calls at the start of the study? eg week 1, week 3 compared with lengthier periods such as month3, month 6, month 9, month 12?What, if anything, do you suggest researchers should do differently during the study process or to make it easier to take part?

Is there anything else you would like to say about taking part in the study? Do you think you would consider taking part in a study like this again in the future?

Thoughts about the Future (6m+12m)

Looking back on the treatment you've had in the study, what do you think about this treatment for IBS? Do you have any particular feelings about the use of amitriptyline for IBS?

Now that you've been in the study for (6/12m), what do you think will happen next with your IBS?

Is there anything that doctors could do differently to improve things for people with IBS?

And finally, is there anything else you would like to tell me about your experiences in the Atlantis study?

Thoughts about COVID-19 pandemic

Could you tell me how you have found being in the study during the COVID-19 pandemic?

Could you tell me how your IBS has been affected by the COVID-19 pandemic?

Could you tell me how you have found managing your IBS during the COVID-19 pandemic and lockdown?

General prompts to be used flexibly include: What was that like? Can you give me an example of that? How did you feel about that?

Debrief

Ask if the participant has any questions about the study.

Revisit consent – still happy for their interview to be used (anonymously)?

TURN OFF THE RECORDER

Thank participant for taking part in the interview

If this has raised any clinical issues please consult your GP in the first instance.

Offer copy of transcript when available – note that this might be a couple of weeks.

Offer copy of study findings when available – note that this might be a year or so.

1.12 Interview Topic Guides for the Nested Qualitative Study: 12-month Participant Interview Topic Guide

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 study, 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

Iteration and Flexibility

The topic guide will evolve as the interviews progress in response to researchers' reflections, initial analysis, and feedback from participants. The scope of the interviews will always remain consistent with the objectives specified above. Within this scope, the topic guide will be used flexible in that the researcher may adjust the questions asked and the order in which they are asked as appropriate for the individual participant. It may not always be necessary to ask all of the questions in order to elicit the relevant information.

Introduction

Thank you for agreeing to take part in a follow up research interview today. I am (*researcher name*), a researcher at University of Southampton. Just so you know, I am not a medical doctor so I'm afraid I can't offer any advice about your IBS today. [short hello]

I'm currently contacting a number of people who are taking part in the Atlantis study to find out about their experiences of the study, the study treatments, and their IBS.

How long this will take depends a bit on how much you want to tell us, but we anticipate it will take approximately one hour. Just let me know if you need to finish sooner and we can do that.

I would like to record the conversation we have today so that I can refer back to it at a later date. It enables me to listen to you better. We will store the recordings securely on a university password-protected computer. What we talk about will be used as part of the study, but what you say will remain anonymous. We're going to ensure this by not using your real name, or any other names that you mention, when we type up the interview. The typed up interviews will then be stored securely too. Is that ok?

Before we start there are a few things I'd just like to mention.

If I ask a question that you don't want to answer that is absolutely fine, just say so and I'll ask you a different question. If at any point you would like to take a break or stop altogether just tell me and we can do that.

Anything you can tell me about your experiences including good and bad points would be useful. What you say to me today will not impact your care in any way at all.

Do you have any questions before we start? Are you happy to continue?

TURN ON THE RECORDING DEVICE

Topic Guide – Follow up interview (post unblinding if applicable)

Experiences during Atlantis (12m)

How has your IBS been since we last spoke? And your health/quality of life in general? [probe for anything getting better or worse]

Have you started or stopped any other treatments for your IBS since we last spoke? [what and why] (prompt re prescribed and OTC meds and other treatments eg CBT/diet/complementary medicines))

Did you take the study tablets for the whole trial (12 months)?

[For non-continuers]:

Can you tell me what made you decide to stop taking the study tablets?

What do you think was good about taking the study tablets? [perceived benefits]

What was not good about taking the study tablets? [perceived disadvantages]

Can you tell me what made you decide to continue in the trial?

[For continuers only]:

Can you tell me what made you decide to continue taking the study tablets?

There are lots of things that can mean we don't always take our medicines as prescribed. Since we last spoke, was there anything that made it easier for you to take your tablets as prescribed? Was there anything that made it harder for you to take your tablets as prescribed? What you concerns did you have about the tablets?

Is there anything else you would like to tell me about the pills that you were taking in the study?

Thoughts about debrief and unblinding process [For all]

Now you have completed trial, how have you found no longer having contact/support with research nurse?

How did you feel about finding out which study tablets you have been taking?

What are you expecting to happen at the 12-month timepoint? How was the process of finding out?

When did you find out? [duration of unblinding process]

Now you have found out, how do you feel about the study tablets you were taking?

[For participants in placebo treatment arm]

How do you feel about the placebo tablets? [Prompt for any concerns]

What do you think is good about taking a placebo tablet?

What do you think is not good about taking a placebo tablet?

Why do you think a placebo tablet might have an effect/not have an effect on the body?

What have you done since completing the trial? Have you been to GP for more tablets and or further info? How has that been?

[If chosen to take amitriptyline outside of trial] how are you choosing to use amitriptyline? Prompt: Daily? As and when required?

Who will you go to now for advice/support for you IBS? Prompt: GP? Forum?

[For participants in amitriptyline treatment arm]

How do you feel about the amitriptyline tablets now? [Prompt for any concerns]

What do you think is good about taking amitriptyline?

What do you think is not good about taking amitriptyline?

Why do you think amitriptyline might have an effect/not have an effect on the body?

What have you done since completing the trial? Have you been to GP for more tablets and or further info? How has that been?

Are you still taking amitriptyline? Can you explain what you are currently doing? [just amitriptyline or amitriptyline plus other things]

[If chosen to take amitriptyline outside of trial] how are you choosing to use amitriptyline? Prompt: Daily? As and when required?

If still taking amitriptyline, how do you feel about adjusting your dose? Prompt: are they referring to dose titration information or do they feel confident in what they are doing?

If stopped amitriptyline, would you consider trying it again? Can you explain that to me?

Who will you go to now for advice/support for you IBS? Prompt: GP? Forum?

Experiences of Study Procedures (6m+12m)

Since we last spoke, how have you found being in the study, for example filling in and the questionnaires (prompt about using online/telephone questionnaires), getting the medicines through the post, talking to the research nurse about the tablets and receiving a new prescription from GP? (prompt on each element of this question)

Since we last spoke have you looked at the study website and twitter account? Can you tell me about your experiences of this?

How did you feel about using text message correspondence?

Could you tell me how you felt about having more frequent follow up calls at the start of the study? eg week 1, week 3 compared with lengthier periods such as month3, month 6, month 9, month 12? What, if anything, do you suggest researchers should do differently during the study process or to make it easier to take part?

Is there anything else you would like to say about taking part in the study?

Thoughts about the Future (6m+12m)

Looking back on the treatment you've had in the study, what do you think about this treatment for IBS? Do you have any particular feelings about the use of amitriptyline for IBS?

Now that you've been in the study for (6/12m), what do you think will happen next with your IBS?

And finally, is there anything else you would like to tell me about your experiences in the Atlantis study?

Would you like to take part in a study again in the future?

Thoughts about COVID-19 pandemic

Last time we spoke you said the COVID-19 pandemic had [no impact/some impact] on your IBS and involvement in the trial. Can you tell me what you think now about the impact of the COVID-19 pandemic?

On being in the trial?

On your IBS?

General prompts to be used flexibly include: What was that like? Can you give me an example of that? How did you feel about that?

Debrief

Ask if the participant has any questions about the study.

Revisit consent – still happy for their interview to be used (anonymously)?

TURN OFF THE RECORDER

Thank participant for taking part in the interview

If this has raised any clinical issues please consult your GP in the first instance.

Offer copy of transcript when available – note that this might be a couple of weeks.

Offer copy of study findings when available – note that this might be a year or so.

1.13 Interview Topic Guides for the Nested Qualitative Study: GP Interview Topic Guide.

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

Iteration and Flexibility

The topic guide will evolve as the interviews progress in response to researchers' reflections, initial analysis, and feedback from participants. The scope of the interviews will always remain consistent with the objectives specified above. Within this scope, the topic guide will be used flexible in that the researcher may adjust the questions asked and the order in which they are asked as appropriate for the individual participant. It may not always be necessary to ask all of the questions in order to elicit the relevant information.

Introduction

Thank you for agreeing to take part in a research interview today. I am (*researcher name*), a researcher at University of Southampton.

The aim of this interview today is to explore your experiences and views of amitriptyline for IBS and the Atlantis study.

With your agreement I will audio-record our conversation. The recording will be transcribed but everything you say will be anonymous. Your name along with any names you mention, any places you mention and all other identifiable information will be taken out, so that if someone read the transcript of your interview they would not know who you are or where you work. We will store the recordings and transcripts securely on a university password-protected computer.

Your interview will remain confidential.

If at any time you do not wish to answer a question that's okay, and if at any stage you wish me to stop the recorder, please let me know.

We can take a break at any time – let me know and I will stop the recording. We can either continue after the break, arrange another time to talk or stop there.

I would like to encourage you to be as honest as you can. There are no right or wrong answers. We are very interested in your views and experiences.

Do you want to ask me anything before we start? Are you happy to continue?

TURN ON THE RECORDING DEVICE

Topic Guide

[Informed by Normalization Process Theory, NPT: http://www.normalizationprocess.org/what-is-npt/npt-core-constructs/]

Starting the Atlantis Trial [NPT: Coherence]

When you first heard of the Atlantis study, what did you think about low-dose amitriptyline for IBS?

How does offering amitriptyline for IBS differ from your usual practice for managing IBS? (prompt to get them to explain in detail their usual practice and any previous experiences of prescribing amitriptyline for IBS)

If you have previously prescribed amitriptyline for IBS – How did patients respond to a suggestion of trying amitriptyline for IBS? Prompt - did you encounter any resistance among patients to taking amitriptyline for IBS? What were patient's main concerns? How did you respond to that?

What is your sense of how the rest of your practice viewed amitriptyline for IBS prior to the ATLANTIS trial starting?

Interactions with Patients

Did you talk to any participants about amitriptyline or placebo for IBS during the ATLANTIS trial, e.g. at an optional GP review at 1 month, or at a routine appointment? [if no, do not continue this section] If yes how many?

How did patients invited to take part in ATLANTIS respond to a suggestion of trying amitriptyline or placebo for IBS? Prompt - Did you encounter any resistance among patients to taking amitriptyline or placebo for IBS? How did you response to that?

Did ATLANTIS participants report any difficulties taking the trial medication for IBS? How did you respond to that? Prompt – How did participants find the dose titration?

Can you tell me what you thought about the dose titration information provided to participants? [prompt what was helpful/unhelpful about the information]

[If they have not seen this information prompt whether they would like to see it and why]

Impact of COVID-19 pandemic

How have you found being involved in the trial during the COVID-19 pandemic?

How do you think the trial has been affected by the COVID-19 pandemic? [prompt around how they found the process of pausing and restarting?]

Reflections on Amitriptyline for IBS [NPT: Reflexive monitoring]

Now that you've completed work on the Atlantis study, what do you think about amitriptyline for IBS?

Did your thoughts change at all over the course of the trial, if so how?

What do you see as the benefits and drawbacks of amitriptyline for IBS? [For patients, for you, for your practice – probe on each element]

What is your sense of how the rest of your practice now view amitriptyline for IBS?

What changes did you have to make to your routine practice in order to offer amitriptyline for IBS in the Atlantis trial?

Are there any implications for your workload? Resource utilisation?

Amitriptyline for IBS in the Future [NPT: Reflexive monitoring]

Would you like to offer patients amitriptyline for IBS? Can you explain why?

What, if anything, would have to change for you to offer amitriptyline for IBS in routine practice? What could make this harder, what could make this easier?

Within the consultation, can you think of anything that might make it easier to prescribe amitriptyline for IBS? Anything that might make it more difficult? [Could be anything about you, the interaction, the patient, the setting, etc. etc.]

And what, if anything, would be the consequences of you offering amitriptyline for IBS in routine practice?

Debrief

Ask if the participant has any questions about the study.

Revisit consent – still happy for their interview to be used (anonymously)?

TURN OFF THE RECORDER

Thank participant for taking part in the interview

Offer copy of transcript when available – usually within -1-2 weeks

Offer copy of study findings when available – may be approximately 1 year before dissemination

Supplementary Table 1. The Rome IV Criteria for IBS.

<table>
<tr><th colspan="4">Rome IV IBS Diagnostic Criteria</th></tr>
<tr><td colspan="4">1. Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months and associated with two or more or the following:
a. Related to defaecation;
b. Associated with a change in frequency of stool;
c. Associated with a change in stool form.
AND
2. Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis</td></tr>
<tr><th>IBS-C</th><th>IBS-D</th><th>IBS-M</th><th>IBS-U</th></tr>
<tr><td>≥25% of bowel movements of Bristol stool form types 1 or 2, and <25% of Bristol stool form types 6 or 7.</td><td>≥25% of bowel movements of Bristol stool form types 6 or 7, and <25% of Bristol stool form types 1 or 2.</td><td>≥25% of bowel movements of Bristol stool form types 1 or 2, and ≥25% of bowel movements of Bristol stool form types 6 or 7.</td><td>Individuals who meet criteria for IBS, but who do not fall into one of the other three subgroups according to Bristol stool form type.</td></tr>
</table>

Supplementary Table 2. Summary of All Protocol Changes Made in the ATLANTIS Trial.*

Protocol v2.0	Addition of clinical study officer to undertake the role of a research nurse. Clarification that patients who express interest in the trial will provide agreement for the screening telephone call and for the hub research team to contact their GP practice to clarify details from their health records as part of screening. This will be provided either on the postal paper reply slip or via email from the patient. Clarification that the End of Treatment Visit clarified that it should be done at least 7 days post-treatment, to ensure sufficient time has elapsed for SAE reporting.
Protocol v3.0	The use of GP practice patient identification centres (PICs). Wording to the inclusion/exclusion criteria have been added for clarification. Addition of trial posters to be displayed in community pharmacies Addition of the use of the ATLANTIS Twitter account as a tool for recruitment. Addition of video to the ATLANTIS website to explain and promote the trial to potential participants Clarification that for patients who change their GP whilst on the trial, their new GP can provide a new prescription (and therefore allow the patient to continue on the trial), providing the new GP practice is participating in the trial. Clarification that in the instance that randomisation has not taken place within 4 weeks of the baseline questionnaire being completed, the baseline questionnaire should be repeated. Additional wording relating to repeat blood tests has been added for consistency with the inclusion/exclusion criteria.
Protocol v4.0	Included the option for participants and their GP to be unblinded to the participant's treatment allocation following the completion of 12-month

	questionnaires, to allow continuation of treatment by GP prescription once the participant had completed trial procedures The End of Treatment (at least 7 days post-treatment) phone call was removed as researchers found it to be time-consuming, without providing additional relevant information; instead participants were asked to self-report any safety events to their research nurse in the 7 days following completion of their 12 month questionnaires. Text in the Secondary Outcome Measures section has been updated to clarify that if participants opt to continue up to 12-month follow-up, the recall period of health care use, use of other medications for IBS and need for referral to secondary care will be 6-months.
Protocol v5.0	Reduction in the trial duration for newly randomised participants, where participants, recruited in the later stage of the trial, will be randomised to receive 6 months of study medication only, unlike participants recruited in the early stage of the trial who had the option to continue study medication for a further 6 months (total study duration 12 months). Qualitative interview will only be conducted at 6 months in participants who have consented to a total study duration of 6 months follow-up and have consented to take part in a qualitative interview (unlike participants consenting to 12 months follow-up, who will be invited to take part in qualitative interviews at 6 months and 12 months, with their consent) Participants who consent to 6 months duration will be able to find out their treatment allocation after 6 months Health economic analysis will be conducted subject to successful application for further funding. However, all health economic data will continue to be collected during the delivery of the trial.

***Minor changes have not been included**