Protocol

PILOT STUDY TO ASSESS THE EFFECT OF ENZYME RICH MALT EXTRACT (ERME/JUVIA) IN TREATMENT OF IRRITABLE BOWEL SYNDROME (IBS)

Sponsored by Ateria Health Ltd

Short Title: JUVIA

PROTOCOL Version 1 (IRAS 325736)

2nd May 2023

The clinical study as detailed within this research protocol (Version 1.0 dated 2nd May 2023), or any subsequent amendments will be conducted in accordance with Research Governance Framework for Health and Social care (2005), THE World Medical Association Declaration of Helsinki (1966) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

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Appendices

Glossary of Terms and Abbreviations

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
ERME	Enzyme Rich Malt Extract
GP	General Practitioner
ICF	Informed Consent Form
JCRF	Joint Clinical Research Facility
NHS R&D	Nation Health Service Research & Development
PI	Principal Investigator
Participant	An individual who takes part in a clinical trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
IBS	Irritable Bowel Syndrome
IBS-QOL	Irritable Bowel Syndrome Quality of Life (Questionnaire)

1 **Introduction**

Irritable Bowel Syndrome (IBS) is a very common gastrointestinal complaint causing abdominal pain associated with an abnormal bowel habit – either diarrhoea or constipation. Other symptoms may include flatulence, bloating and fatigue[1].

Many sufferers have food intolerances so that IBS frequently responds to restrictive diets[2,3]. Similarly, enteral feeds lacking complex carbohydrate and long-chain triglycerides have been shown to be effective[4]. Such diets however, are not particularly appealing and can be socially disruptive. A treatment allowing patients to eat with minimal restriction would be widely welcomed.

It has become clear that the colonic microbiome in IBS is associated with abnormal overgrowth of facultative anaerobes, particularly members of the Enterobacteriaceae[5]. These organisms cause abnormal fermentation of food residues, leading to wind and discomfort[6]. Antibiotics are therefore sometimes useful[5] but unfortunately, their effects are not long lasting. Reduction in the amount of food residue available for colonic microbial fermentation offers a novel and potentially exciting way of treatment. The expression of the major carbohydrate catalysing enzyme, amylase, has been shown to vary widely in otherwise healthy subjects[7].

Enzyme-rich malt extract (ERME) is a by-product of the malting process. Customarily the enzymes generated by sprouting barley are destroyed by heat in the production of malt suitable for brewing. ERME is an extract taken before the enzymes are destroyed and it is rich in amylase, fructanases and glucanases. It is sweet, palatable and easily available at relatively low cost. ERME has been used as a foodstuff in baking and cookery for many years, and we have shown the enzymes of ERME still to be active in the equine gut[8], where intrinsic levels of amylase are low

This product has now been launched as a food supplement (JUVIA) with the aim to improve symptoms of IBS by reducing food residues passing into the large intestine for fermentation.

In a preliminary study of patients with IBS, symptoms were reduced by ERME in 4 out of 5 patients with partial benefit in the fifth. This was associated with a dramatic reduction in hydrogen excretion on the breath, strong evidence of modified colonic fermentation.

IBS, however, is not a single condition[1]. Several mechanisms produce the symptom complex apart from malfermentation. These include anxiety, constipation, (sometimes complicated by overflow diarrhoea) menstrual disturbances and musculo-skeletal problems. These can be separated by validated symptom analyses. We wish to know whether ERME is of any benefit in other IBS sub-groups[8] and to seek biomarkers in urine and stool samples, which may allow objective identification of these groups, currently separable only by symptoms[9]. This study is designed to concentrate on the malfermentation form of IBS.

2 Patient Identification and Recruitment

This will be a single site study, conducted at the Joint Clinical Research Unit (JCRF),

Institute of Life Science 2, Swansea University, Swansea.

The research team will work with local Gastroenterologists and General Practitioners to identify potential subjects: Patients with a confirmed diagnosis of IBS made by a clinician and be aged between 18 – 65 years. They will also discuss with the IBS dietician group in respect of patients who may be considered for this study.

These potential subjects will be sent a Patient Information Sheet (PIS) and consent form in the post, together with a covering letter from either their local GP or the Consultant Gastroenterologist (whoever is the most appropriate i.e. who has provisionally identified them as suitable for the study). The Information Sheet will contain the contact details of the research team at JCRF and ask patients to get in touch if they would like to know more about the study.

With permission from the Research Ethics Committee to do so, the research team may telephone recipients of the patient information sheet to see whether they have any questions about the study and whether they might be interested in taking part.

Initial Screening by telephone

For any patient who may be interested in taking part, the research team will undertake initial 'screening' over the telephone if this is acceptable to the patient. The purpose of this would be to avoid patients traveling to the hospital unnecessarily (if they do not meet the inclusion criteria).

A Case Record File will document the research team's telephone 'screening' conversation with the patient. This will commence with a check that the patient has received the PIS and is happy to answer some initial screening questions over the telephone.

Patients will be asked to complete two questionnaires over the telephone, appendix 1 (Rome IV) to assess current symptoms of IBS (Both abdominal pain and altered bowel habit), and Questionnaire (Appendix 2) to confirm malfermentation. If the responses deem them suitable for inclusion and they have none of the exclusion criteria they will be invited to attend a research appointment at the JCRF. Where there is doubt as to a patient's potential eligibility the CI/PI will be asked for a view before the patient is invited for an appointment.

Patients will be asked to bring a urine and stool sample to the screening visit. The research team will post collection kits to the patient in advance with information on collection of the sample. The stool sample will be processed by Microba Laboratory in Brisbane, Australia and the urine sample will be analysed by Professor Claire Turner at Brunel University, Uxbridge. Chain of custody and storage will be maintained as required for the samples. Stool sample collection is easy, just requires a smear of stool sample from toilet paper onto a swab, and then placed in a pouch sealed and bought into the clinic. The sample does not go in the fridge but stays at room temperature until they attend clinic and it will be frozen at -20 for subsequent batch dispatch to the laboratory.

Research Clinic Visit

On arrival at clinic, the research nurse will confirm that the patient has received the PIS and discuss the study with the patient. The research nurse will answer any initial questions that the patient may have and confirm eligibility criteria.

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At this clinical appointment and the eligibility, criteria discussed previously by telephone will be confirmed during this appointment.

We plan to recruit at least 20 subjects who complete the study. In case of dropouts, we would plan to recruit up to 30 subjects to accommodate subjects that withdraw or are lost to follow up.

Inclusion Criteria:

1. Aged 18-65
2. Current symptoms of IBS (abdominal pain and altered bowel habit) ROME IV criteria
3. Prepared to take ERME (JUVIA) for duration (taste test available for patient)
4. Normal full blood count within last 12 months (from medical notes if available)
5. Previous Calprotectin (from medical notes if available) <80.ug/g
6. Previous tTG (Tissue Transglutaminase) (from medical notes if available)
7. Positive for malfermentation as decided by IBS Questionnaire Score
8. Registered with a GP and consent to GP being informed

Exclusion Criteria:

1. Pregnant, planning to become pregnant or lactating
2. Diabetic (or other co-morbidity which the CI considers inappropriate)
3. On a restrictive diet or unwilling or unable to change diet
4. Current medication (e.g. opiates) that may influence bowel symptoms (at discretion of the CI)
5. Antibiotics in the previous 6 weeks
6. Other gastrointestinal disease (e.g. coeliac, Crohn's disease or Ulcerative colitis)

7. Significant gastrointestinal surgery (this will be a clinical decision and any patient who has had a surgical procedure that would change the mechanics of gut function would be excluded)

8. Involved in other gastroenterology research project or other interventional study that would affect results

Patients who do not meet the entry criteria will not be enrolled into the study, but will attend their routine clinic appointments and or general practitioner care. Patients who meet the inclusion criteria and would like to take part will have eligibility confirmed by the local investigator who will also take informed consent or delegate to the research nurse **Note**: The research team will offer the patient an opportunity to taste the product before enrolling so that they can assess whether they will be able to take the product daily for the 4-week period required.

3 Study Procedures

1. Following telephone screening, informed consent and enrolment, patients will be asked to complete the IBS Severity Score (appendix 3) and IBS Quality of Life Questionnaire (appendix 4). Additionally they will be asked to complete the Nijmegen anxiety questionnaire (appendix 5) & the Cambridge IBS type questionnaire. Demographic data will be collected as per the clinical record form as described in the patient information sheet.
2. Where a patient does not have a faecal calprotectin (FC) result, a test may be requested if the investigator feels it is necessary.
3. A urine sample will be collected at baseline and frozen to be sent to Prof Claire Turner, Brunel University Uxbridge for determination of bacterial metabolites by SIFT/MS (specific ion flow tube mass spectrometry). A faecal sample will also be collected and stored prior to sending to Microba in Brisbane, Australia and again at week 4 for microbial analysis.
4. ERME (labelled as JUVIA) a total of 40mls daily (to be taken with meals) Subjects will be supplied with 3 x 450ml containers of JUVIA. Muntons Maltsters of Stowmarket Suffolk will supply the product to our current packers Chysalis Creation house 50-72 Gauntley Street Nottingham NG7 5HF. On receipt of the product from the supplier details will be entered onto an accountability log at JCRF, and stored appropriately. The product will be stored by the research team in a cool (<25 degrees C), dry and secure environment.
5. The participants will be given enough product (JUVIA) to last for 4 weeks and instructed how to take the product with food daily (20mls at breakfast and 20mls with last meal of the day).
6. Patients will be provided with information as to how to store the product at home and asked to contact the team if they have any concerns.
7. Participants will be asked to complete the IBS severity score questionnaire and IBS Quality of Life Questionnaire at 2 weeks and 4 weeks post their first research hospital appointment. A member of the research team will telephone the patient to remind them to do this and, if preferred, can complete the 2-week questionnaires with the patient over the telephone. Week 4 will be undertaken when they attend the final clinic visit.
8. Patients will be made aware that due to the effects of JUVIA, they may

experience bacterial 'die-offs' when essential nutrients for these bacteria are no longer available in the gut, where symptoms are exacerbated during the first few days and encouraged to continue as symptoms will settle.

9. At 4 weeks post Visit 1, a final hospital (Visit 2) will take place and the same procedures undertaken at Visit 1 will be repeated. A further faecal and urine sample will be collected and urine again frozen prior to transporting to the laboratory for analysis.
10. IBS severity score, IBS QoL questionnaires, Nijmegen and will again be completed at week 4 and the patient will be weighed.

4 Adverse Events and Patient withdrawal

1. It is unlikely that malt extract, which is already widely used in the food industry, will cause any major difficulties or unwanted effects. In the unlikely event that the patient becomes ill while participating in the study they must report this to the Research team at JCRF, Swansea Bay University Health Board who will discuss with the Chief Investigator/Principal investigator whether or not the participant should be withdrawn from the study.

Adverse events will be collected by asking patients about their symptoms during enrolment in the study. The adverse event will be recorded and reported following the Sponsor's normal procedures.

In the event of a Serious Adverse Event in a patient taking part in the study, the Sponsor's normal reporting procedures apply.

Should the participant find the product unpalatable or unacceptable, they will be asked to remain in study follow-up if they are prepared to do so. If a patient stops taking the product then this must be recorded, along with the reason why. Where patients are agreeable the research team will follow up with them 2 weeks after stopping the product and patients will be asked for permission to use the data and samples already collected to that point, together with any subsequent follow-up data.

If the participants wish to withdraw at any point during the study for whatever reason, they will be asked to remain in follow-up and to allow any data and/or samples collected to that point to be included in the analysis. Participants are free to withdraw without prejudicing their future care and details of withdrawal will document in the Case Record Form.

5 Treatment preparations

<u>ERME (Enzyme rich malt extract) – JUVIA – marketed food supplement. 450mls per bottle</u>
40 mls daily JUVIA provided by Muntons, maltsters of Stowmarket and repacked by Chrysalis. Each subject will be given 2 bottles of JUVIA.

6 Samples

Stool Analysis plan
Faecal samples will be stored before being sent as a batch to Microba Brisbane,

Australia for genomic assay using the Shotgun technique for analysis of the microbiome and comparison with their extensive data collection. Microba have developed and validated a method of faecal sampling which involves taking a smear from lavatory paper and storing it in a specially developed container. Full chain of custody will be maintained.

Urine sample
These will be frozen and stored and sent as a batch to Prof C Turner at Brunel University, London for subsequent Flow tube/Mass spectrometry (SIFT/MS) analysis.

Sample identification, Storage and destruction
All samples will have a unique research number ensuring the laboratory analysing samples have no information about participants or can identify them in any way. Samples once analysed will be destroyed in accordance with regulatory practice.

7 Safety Reporting

There not expected to be any safety issues however all Adverse Events (AE) will be documented in line with details in Appendix 6 “Safety Reporting in Non-CTIMP Research.

7.1 Annual Safety Reporting

The CI/PI will send the Annual Progress Report to the REC using the NRES template (the anniversary date is the date of the REC “favorable opinion letter” and to the Sponsor.

8 Ethical and Regulatory Issues

8.1 Ethics Committee (EC)

The protocol and Patient Information Sheet, informed consent forms will be reviewed and approved by the EC prior to commencing the study.
The Ethics Committee written, signed approval letter must contain approval of the designated investigator, the protocol (identifying protocol title and version number) and the patient information and consent.

By signing the protocol, the investigators agree to conduct the study in accordance with the Declaration of Helsinki, Good Clinical Practice and ISO 14155:20011 (1).

8.2 Informed Consent

This will be obtained for each participant prior to initiating any trial procedures (however, interested subjects will be asked if willing to undertake the short questionnaire on initial telephone screening). A copy of the informed consent will be given to the patient and the master copy signed by the subject will be retained in the Investigator File.

8.3 Quality Assurance

Responsibility for accuracy and completeness of the study records and for the data management will lie with the JCRF

8.4 Record Retention

The investigator will maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The documents will be retained in accordance with regulatory guidelines and those of its institution. Records will be stored in the JCRF, prior to off-site storage at a long-term storage facility.

The Investigator will notify the Sponsor prior to destroying any study essential documents following the Clinical Trial completion or discontinuation.

9 General statistical considerations

All baseline, disposition, protocol compliance, exposure and outcome variables (efficacy, safety and exploratory) will be listed and summarized.

The standard summary statistics for continuous baseline and outcome variable are N.mean, standard deviation, median, quartiles, minimum and maximum. The standard summary statistics for categorical baseline and outcome variable are: count and proportion (expressed as percentage).

Sample size calculation

No formal sample size has been calculated for this pilot study.

Endpoints

Primary Efficacy Endpoints

The primary endpoint is the change in IBS severity score from baseline (visit 1) to four weeks (visit 2).

Secondary Efficacy Endpoints

The secondary efficacy endpoints comprise the change in IBS severity score from baseline at two and four weeks will include:

1 Severity of abdominal pain
2 Frequency of abdominal pain
3 Change in abdominal bloating
4 Change in bowel habit “satisfaction”
5 Change in impact of IBS upon lifestyle
6 Change in bowel frequency
7 Change in stool consistency
8 Change in absence from work days related to IBS (as defined by IBS severity score scales)
9 Change in IBS Qol Questionnaire Scores.

Safety Endpoints

The safety endpoints are the incidence, nature, severity, relatedness, duration,

outcome, seriousness and expectedness of treatment emergent adverse events.

Missing Data

Subjects with missing efficacy data will be analysed on a last-observation-carried-forward basis.

8 Study conduct

Any protocol deviations will be categorized as 'major' or 'minor', listed, and summarized. All subjects will be given a unique patient identifier number at time on consent which will be used to record all data on the CRF and study database. This ensures patient confidentiality and only staff involved in the study will have access to this database. The database will be shared with the study statistician, who will not have any linked patient identifiers.

The sponsor company representative will be given access to relevant patient information for the purpose of study monitoring to ensure the study and subjects have been recruited and managed in accordance with the protocol and REC approval.

9 Efficacy analysis

Summary statistics will be presented for each efficacy endpoint at baseline, two and four and for the change from baseline at two and four weeks.

10 Safety analysis

The incidence, nature, severity, relatedness, duration, outcome, seriousness and expectedness of treatment emergent adverse events will be listed and tabulated. Reporting of events will be as outlined in Appendix 6.

11 Exploratory analysis

This may include but not limited to:

- Analyzing completing subjects only, repeating parametric analyses using non-parametric analyses, analyzing using a longitudinal model, and investigating different methodologies for adjusting for missing values.

12 Funding

The study will be funded by Ateria Health Ltd. As the sponsor, they have confirmed patient indemnity with CAN Insurance Co. Ltd. For £5,000,000.

13 Reporting and Publication

A final report will be completed and either a full report or summary will be submitted to the REC and R&D after perusal and consent from the Sponsor.

It is intended to publish the results whether positive or negative, in both abstracts and major gastroenterological journals.

14 References

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Appendix 1 (completed at Telephone Screening)
Rome IV

Rome IV Criteria for Diagnosing IBS:

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

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool.

Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Source: Lacy BE, et al. Bowel Disorders. Gastroenterology. 2016;150:1393-1407; Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders. Accessed 8/10/16 at: http://www.romecriteria.org/assets/pdf/19_RomeIII_apA_885-898.pdf

Questionnaire 2 **(completed at Telephone Screening and 4 weeks)**
IBS subtype "malfermentation" symptom Questionnaire

IBS SUBTYPE 'MALFERMENTATION' SYMPTOM QUESTIONNAIRE

1. Are your stools loose and runny?

Never Score 0	**Rarely Score 0**	**Sometimes Score 1**	**Often Score 1**	**Very often Score 2**

2. Are your stools hard and pellet like?

Never Score 4	**Rarely Score 3**	**Sometimes Score 2**	**Often Score 1**	**Very often Score 0**

3. Do you have to rush to the lavatory to open your bowels with great urgency?

Never Score 0	**Rarely Score 1**	**Sometimes Score 2**	**Often Score 3**	**Very often Score 4**

4. Do you ever have to strain or push to pass a motion?

Never Score 4	**Rarely Score 3**	**Sometimes Score 2**	**Often Score 1**	**Very often Score 0**

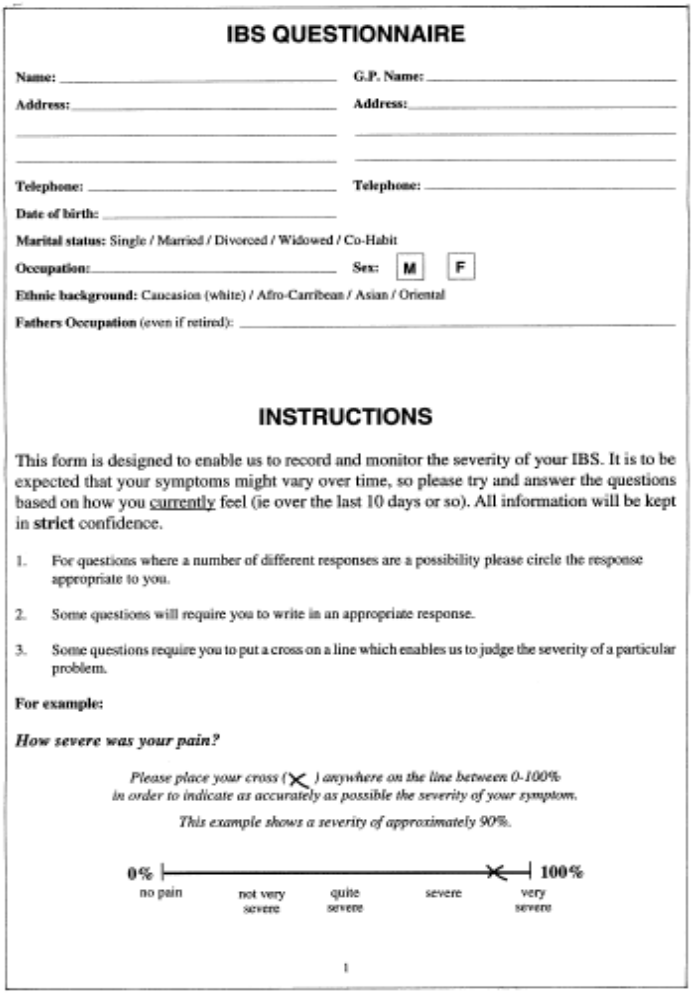
5. Do you ever feel that you have you have not emptied your bowels completely?

Never Score 4	**Rarely Score 3**	**Sometimes Score 2**	**Often Score 1**	**Very often Score 0**

A score of 11 or more confirms malfermentation

Appendix 3**: completed at clinic visit 1,2 weeks, 4 weeks**

IB patient severity score completed 3 times during the course of the study



IBS QUESTIONNAIRE

Name: _____ **G.P. Name:** _____

Address: _____ **Address:** _____

_____ _____

_____ _____

Telephone: _____ **Telephone:** _____

Date of birth: _____

Marital status: Single / Married / Divorced / Widowed / Co-Habit

Occupation: _____ **Sex:** M F

Ethnic background: Caucasion (white) / Afro-Carribean / Asian / Oriental

Fathers Occupation (even if retired): _____

INSTRUCTIONS

This form is designed to enable us to record and monitor the severity of your IBS. It is to be expected that your symptoms might vary over time, so please try and answer the questions based on how you currently feel (ie over the last 10 days or so). All information will be kept in **strict** confidence.

1. For questions where a number of different responses are a possibility please circle the response appropriate to you.
2. Some questions will require you to write in an appropriate response.
3. Some questions require you to put a cross on a line which enables us to judge the severity of a particular problem.

For example:

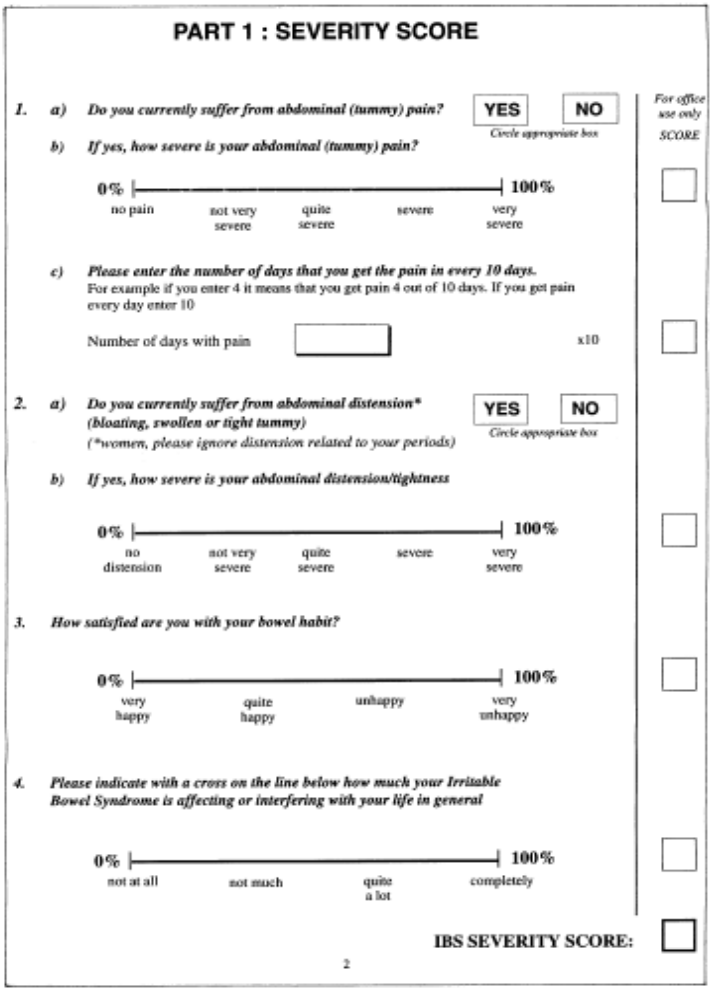
How severe was your pain?

Please place your cross (✕) anywhere on the line between 0-100% in order to indicate as accurately as possible the severity of your symptom.

This example shows a severity of approximately 90%.

0% ——————————✕—— 100%
no pain | not very severe | quite severe | severe | very severe

1



PART 1 : SEVERITY SCORE

1. a) ***Do you currently suffer from abdominal (tummy) pain?*** YES NO *Circle appropriate box*

   b) ***If yes, how severe is your abdominal (tummy) pain?***

   0% —————————— 100%
   no pain | not very severe | quite severe | severe | very severe

   c) ***Please enter the number of days that you get the pain in every 10 days.***
   For example if you enter 4 it means that you get pain 4 out of 10 days. If you get pain every day enter 10

   Number of days with pain _____ x10

2. a) ***Do you currently suffer from abdominal distension* (bloating, swollen or tight tummy)*** YES NO *Circle appropriate box*
   *(*women, please ignore distension related to your periods)*

   b) ***If yes, how severe is your abdominal distension/tightness***

   0% —————————— 100%
   no distension | not very severe | quite severe | severe | very severe

3. ***How satisfied are you with your bowel habit?***

   0% —————————— 100%
   very happy | quite happy | unhappy | very unhappy

4. ***Please indicate with a cross on the line below how much your Irritable Bowel Syndrome is affecting or interfering with your life in general***

   0% —————————— 100%
   not at all | not much | quite a lot | completely

For office use only
SCORE

IBS SEVERITY SCORE:

2

IB patient severity score completed 3 times during the course of the study

PART 2 : OTHER IBS DATA

BOWEL HABIT

5. a) ***What is the most number of times you open your bowels per day/week/month?***

Number of times [ ] per day / week / month *(Circle appropriate)*

Note: For some people the answer to part a and b could be the same

b) ***What is the least number of times you open your bowels per day/week/month?***

Number of times [ ] per day / week / month *(Circle appropriate)*

6. In the following questions you may circle more than one answer:

Are your motions ever:

a)	***normal***	often / occasionally / never	*(Circle appropriate)*
b)	***hard***	often / occasionally / never	*(Circle appropriate)*
c)	***very thin (like string)***	often / occasionally / never	*(Circle appropriate)*
d)	***in small pieces (like rabbit pellets)***	often / occasionally / never	*(Circle appropriate)*
e)	***mushy (like porridge)***	often / occasionally / never	*(Circle appropriate)*
f)	***watery***	often / occasionally / never	*(Circle appropriate)*

7. In the following questions you may circle more than one answer:

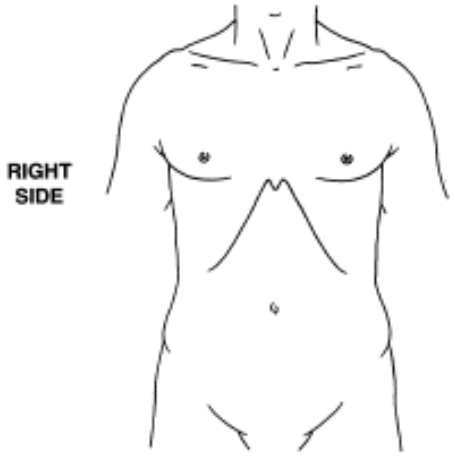
Do you ever:

		Circle appropriate box	
a)	***pass mucus (or slime or jelly) with your motions***	YES	NO
b)	***pass blood with your motions***	YES	NO
c)	***have to hurry/rush to the toilet to open your bowels***	YES	NO
d)	***strain to open your bowels***	YES	NO
e)	***feel you haven't emptied your bowel completely after you have passed a motion***	YES	NO

PART 2 : Continued

SITE OF PAIN

Please mark with a cross (x) on the diagram below where you get your pain *(use more than one x if necessary)*



8. ***Do you ever:***

				Circle appropriate box
a)	***notice your stools are more frequent or loose when you get pain***	YES	NO	
b)	***notice whether the pain is frequently eased by opening your bowels***	YES	NO	

9. ***In the last year on approximately how many weeks were you:***

i) ***absent from work due to IBS*** *(enter 52 if you have given up completely work because of IBS)* _____

ii) ***at work suffering from IBS*** _____

Appendix 4

IBS-QOL – questions (need approval to down load actual questionnaire)
Completed at screening / week 2 / week 4

Life Measure (IBS-QOL)

The IBS-QOL consists of 34 items, each with a five-point response scale:

Items 1, 2, 4, 8-10, 12, 13, 16, 25-29, 34
1. Not at all 2. Slightly 3. Moderately 4. Quite a bit 5. Extremely

Items 3, 5-7, 11, 14, 15, 17-24, 30-33
1. Not at all 2. Slightly 3. Moderately 4. Quite a bit 5. A great deal

1. I feel helpless because of my bowel problems.
2. I am embarrassed by the smell caused by my bowel problems
3. I am bothered by how much time I spend on the toilet.
4. I feel vulnerable to other illnesses because of my bowel problems.
5. I feel fat because of my bowel problems.
6. I feel like I'm losing control of my life because of my bowel problems.
7. I feel my life is less enjoyable because of my bowel problems.
8. I feel uncomfortable when I talk about my bowel problems.
9. I feel depressed about my bowel problems.
10. I feel isolated from others because of my bowel problems.
11. I have to watch the amount of food I eat because of my bowel problems.
12. Because of my bowel problems, sexual activity is difficult for me.
13. I feel angry that I have bowel problems.
14. I feel like I irritate others because of my bowel problems
15. I worry that my bowel problems will get worse.
16. I feel irritable because of my bowel problems
17. I worry that people think I exaggerate my bowel problems.
18. I feel I get less done because of my bowel problems.
19. I have to avoid stressful situations because of my bowel problems
20. My bowel problems reduce my sexual desire.
21. My bowel problems limit what I can wear.
22. I have to avoid strenuous activity because of my bowel problems.
23. I have to watch the kind of food I eat because of my bowel problems.
24. Because of my bowel problems, I have difficulty being around people I do not know well.
25. I feel sluggish because of my bowel problems.
26. I feel unclean because of my bowel problems.
27. Long trips are difficult for me because of my bowel problems.
28. I feel frustrated that I cannot eat when I want because of my bowel problems.
29. It is important to be near a toilet because of my bowel problems.
30. My life revolves around my bowel problems.

31. I worry about losing control of my bowels
32. I fear that I won't be able to have a bowel movement.
33. My bowel problems are affecting my closest relationships
34. I feel that no one understands my bowel problems.

How is the IBS-QOL scored?

The individual responses to the 34 items are summed and averaged for a total score and then transformed to a 0-100 scale for ease of interpretation with higher scores indicating better IBS specific quality of life. There are also eight subscale scores for the IBS-QOL (Dysphoria, Interference with Activity, Body Image, Health Worry, Food Avoidance, Social Reaction, Sexual, Relationships).

The transformation formula used for the IBS-QOL total and scale scores is:

$$\text{Score} = \frac{\text{The sum of the items - lowest possible score}}{\text{Possible raw score range}} * 100$$

How is the IBS-QOL administered?

The IBS-QOL is designed to be self-administered, and takes an average of 10 minutes to complete. The IBS-QOL can be interviewer-administered if necessary.

Appendix 5: Nijmegen Questionnaire: completed at screening visit and 4 weeks

Please just tick the box which describes best the frequency of your symptoms. At the top of each column is a figure from 0 – 4, which gives you the number of points to score for each tick in that column. Write down the total for each column beneath it (e.g. 3 ticks in column 3 will be 9 points) then add up the column totals.

	Never 0	**Rarely** 1	**Sometimes** 2	**Often** 3	**Very often** 4
Chest pain					
Feeling tense					
Blurred vision					
Dizzy spells					
Feeling confused					
Faster or deeper breathing					
Short of breath					
Tight feelings in the chest					
Bloated feelings in the stomach					
Tingling fingers					
Unable to breathe deeply					
Stiff fingers or arms					
Tight feelings around mouth					
Cold hands or feet					
Heart racing (palpitations)					
Feelings of anxiety					

A score of 24 or more is considered positive.

Appendix 6 – Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information	Main REC with a copy to be sent to the sponsor

			should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	