Pilot study to assess the effect of enzyme rich malt extract (ERME/JUVIA) in the treatment of irritable bowel syndrome (IBS)

Short title: JUVIA

Ethics Approval	23/WA01/0120 Wales REC 6	11/05/23
IRAS	325736	
ISRCTN	14003582	

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with the international council for harmonisation Guidelines on Good Clinical Practice (ICH E6 GCP) and regulatory requirements as applicable.

Summary Report Authorised

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1.Introduction

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 boring and socially disruptive. A treatment allowing patients to eat normally would be widely welcomed.

It has become clear that the colonic microbiome in IBS is abnormal with 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.

We have shown the enzymes of ERME still to be active in the equine gut[8], where intrinsic levels of amylase are low, and in a preliminary study of patients with IBS discovered that symptoms were much 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[9] and to seek biomarkers in urine samples, which may allow objective identification of these groups, currently separable only by symptoms[10].

2. Study design

This was a single site open study, conducted by the Joint Clinical Research Facilities (JCRF), with all subjects receiving JUVIA (marketed form of ERME). The study followed on from a previous study which failed to complete due to the impact of the COVID-19 pandemic which halted recruitment.

2.1 Patient population

Inclusion criteria

Patients with a confirmed diagnosis of IBS

Aged 18 – 65 years
Current symptoms of IBS (abdominal pain, and altered bowel habit) ROME IV criteria
Prepared to take JUVIA for 4 weeks
Normal blood count within last 12 months (from medical notes if available)
Previous Calprotectin level (from medical notes if available)
Previous tTG (Tissue Transglutaminase) (from medical notes if available)
Positive malfermentation as decided by IBS Questionnaire Score
Registered with GP and consent to GP being informed of study participation

Exclusion criteria

Pregnant of planning to become pregnant or lactating
Diabetic (or other co-morbidity considered inappropriate by investigators'
On a restrictive diet or unable or unwilling to change diet
Current medication (e.g opiates) that may influence bowel symptoms
(at discretion of the CI)
Antibiotics in previous 8 weeks
Other Gastrointestinal disease (e.g coeliac, Crohn's disease or ulcerative colitis)
Significant gastric surgery (clinical decision assessing if the surgical procedure could change the mechanism of gut function)
Involved in other gastroenterology study or other interventional study that would affect the results.

Patients who did not meet the entry criteria were not enrolled into the study. Patients who fulfilled the entry criteria and wished to participate had their eligibility confirmed by the local investigators or one of the research nurses who had been delegated this task.

3. Study procedures

The study team worked with local Gastroenterologist and General Practitioners (GPs) to identify potential subjects who had a confirmed diagnosis of IBS made by a clinician. These subjects were sent a Patient Information Sheet (PIS) together with a consent form in the post, together with a covering letter from either their GP or hospital Consultant. The information sheet contained the contact details of the research nurses in the JCRF, and asked patients to contact them if they were interested in taking part in the study.

Following telephone screening which included ROME IV (appendix 1) and Malfermentation Questionnaires (appendix 2), consented patients were given an appointment to attend the research clinic to undergo further baseline screening which included the IBS Severity Score (IBS SS appendix 3), IBS quality of life questionnaire (IBS QoL appendix 4) and Nijmegen anxiety questionnaire (appendix 5). Demographic data was collected which included age, gender, weight and significant medical history.

Telephone screening was discussed with the local REC who gave permission as it avoided patients attending a hospital clinic if they did not meet the entry criteria.

For patients who did not have a faecal calprotectin (FC) result, a test was requested if deemed necessary by the investigator.

Urine samples were collected at baseline and week 4 (end of study) and frozen to be sent at the end of the study to Professor Claire Turner, Brunel University Uxbridge for determination of bacterial metabolites by SIFT/MS (specific ion flow tube mass spectrometry. Faecal samples were also collected at these time points and stored frozen at -80 prior to sending to Microba in Brisbane, Australia for microbial analysis.

Participants were asked to complete the IBS SS questionnaire and IBS QoL at 2 and 4 weeks post dosing with JUVIA. A member of the research team telephoned subjects to remind them to complete the questionnaires at 2 weeks and to discuss any problems with the food supplement. Subjects attending the research clinic at week 4 (end of study) completed relevant questionnaires.

4. Study Intervention

Subjects were supplied with 3 X 450mL bottles of JUVIA (marketed form of ERME), and instructed to take 40mLs daily with meals. The participants were given sufficient product to last for 4 weeks. They were instructed to take the product with food (20mLs at breakfast and 20mLs with the last meal of the day). They were provided with a measuring spoon and instructions regarding storage of JUVIA at home.

Note: T*he research team offered patients an opportunity to taste the product before enrolling so that they could assess if they could take the product daily for the 4-week study period.*

JUVIA was supplied by Muntons Maltsters of Stowmarket Suffolk who shipped the product to Ateria's packaging distributor, Chrysalis Creation House 50-72 Gauntley Street, Nottingham NG7 5HF.

On receipt of the product details were entered onto an accountability log at JCRF, and stored appropriately (cool<25 degrees C, dry and in a secure environment).

Patients were 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.

5. Study recruitment

This study aimed to recruit up to 30 subjects with at least 20 completing.

Due to the long-term effects caused by COVID patient recruitment was slower than expected. Although Gastrointestinal Clinics had re-opened, they prioritised more urgent cases i.e., patients who symptoms were suggestive of cancer rather than IBS, patients were also still reluctant to be exposed to any risks associated with COVID

and tended to want to avoid hospital settings, GP involvement was limited due to priorities associated with COVID. A number of other recruitment strategies were instigated which included working with local dieticians who had a programme for IBS patients and they shared the invite to participate with them.

The study was planned to complete within 12 months following regulatory approvals but due to slow recruitment and funding constraints the sponsor company decided to terminate the study.

6. Results

The study commenced following receipt of regulatory approvals. Nine patients were recruited and attended the baseline visit 1 having completed the relevant questionnaires and given formal written consent. At screening all patients were given a unique research number to ensure their confidentiality. The patients comprised of 6 females and 3 males with the first patient recruited in September 2023 with a further 8 recruited over a 6-month period with the final patient recruited in February 2024. Despite numerous efforts the study failed to recruit further subjects in a timely period and in line with the sponsors deadline.

The study flow is shown in appendix 6.

The following table depicts baseline demographic data. All patients met ROME IV criteria.

Table 1. Subject demography and Malfermentation score

Research number	Gender	Age	Weight	Malfermentation Score
01	F	63	72.8	14
02	M	60	79.2	16
03	M	46	79	14
04	M	35	73.6	15
05	F	61	54.4	11
06	F	51	56.6	15
07	F	48	89.8	18
08	F	42	120.9	11
09	F	27	105.8	11

- Subjects needed to score 11 or more on the Malfermentation Questionnaire to meet the entry criteria

The results from all questionnaires undertaken at Baseline, week 2 and week 4 are shown in the following tables

Table 2. IBS Severity Score at baseline, 2 and 4 weeks

Research no	Baseline	2 weeks	4 weeks
01	410	365	388
02	167	115	118
03	152	126	117
04	311	256	231
05	414	332	277
06	259	333	301
07	386	ND	ND
08	285	ND	ND
09	273	155	76

Table 3. IBS Quality of Life at baseline, 2 and 4 weeks

Research no	Baseline	2 weeks	4 weeks
01	39.7	13.2	12.5
02	16.9	11.7	6.6
03	20.6	13.9	16.9
04	51.4	44.9	36.2
05	69.8	69.1	69.1
06	19.8	24.3	22.8
07	45	ND	ND
08	55	ND	ND
09	55.4	22.5	12.5

Table 4. Nijmegen at baseline and 4 weeks

Research no	Baseline	4 weeks
01	18	10
02	4	4
03	12	6
04	12	9
05	41	44
06	21	15
07	34	ND
08	33	ND
09	17	7

6.1 Adverse events

Three subjects reported adverse events during the course of the study these are shown in the following table 5.

Table 5. Summary of adverse events

Research no	Description	Severity	JUVIA related	Comment
1	Bloating	Mild	Yes	
1	Worsening indigestion	Moderate	Yes	Omeprazole commenced
1	Increased wind	Mild	Yes	
1	Noisy bowel	Mild	Yes	
1	Acid reflux	Moderate	Yes	Omeprazole commenced
6	Worsening IBS symptoms	Moderate	Yes	
9	Chest infection	Mild	No	Antibiotics *

*Patient stopped JUVIA during course of antibiotics and recommenced following a 6-week period.

8. Subjects lost to follow up

Two subjects (7 and 8) failed to complete questionnaires at visit 2 and did not respond to telephone requests from the study team.

Subject 6 stopped taking JUVIA at 2 weeks due to increased IBS symptoms.

9. Urine and faecal samples

Due to the small sample size, it was decided that results from these assays would not contribute to the outcome. In accordance with direction from the Sponsor and in line with regulatory procedures these samples were destroyed with a full chain of custody documented.

10. Conclusion

The cause of IBS is unknown, and currently no cure, but it has been suggested that many symptoms result from undigested carbohydrates reaching the large bowel (colon). When this happens the gut bacteria living in the large bowel can ferment undigested food producing chemicals that cause symptoms. These chemicals can be detected in both blood and urine. Reducing the number of carbohydrates within the diet can improve the symptoms of IBS in some patients.

The study planned to explore whether giving the food supplement JUVIA, an enzyme rich malt extract would improve the symptoms of IBS in this group of subjects.

The study sample size was too small to make any meaningful conclusions and insufficient for statistical analysis to be valid. As to the benefits of JUVIA anecdotally some of the subjects noted an improvement which is reflected in some of the questionnaires. Two subjects continued taking JUVIA after the study ended as it was available commercially.

Appendix 1 (completed at Telephone Screening) Rome IV questionnaire

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

Appendix 2 **(completed at baseline)**

IBS subtype “malfermentation” symptom Questionnaire

IBS SUBTYPE ‘MALFERMENTATION’

SYMPTOM QUESTIONNAIRE

1. Are your stools loose and runny?

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

2. Are your stools hard and pellet like?

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

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

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

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

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

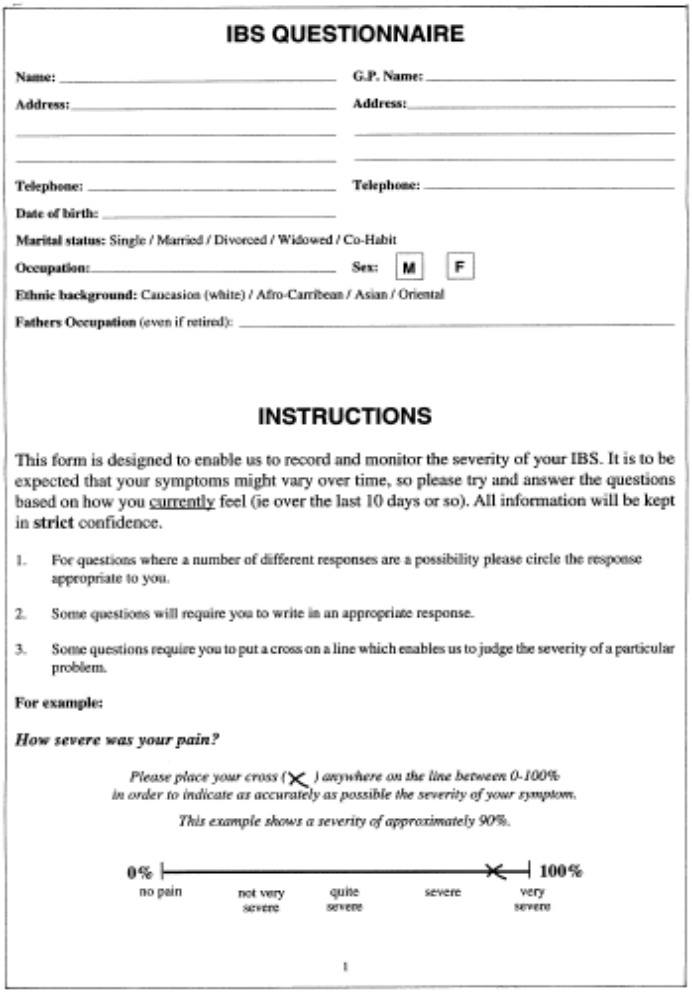
5. Do you ever feel that you have you have not emptied your bowels completely?

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

A score of 11 or more confirmed malfermentation

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

IBS 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?

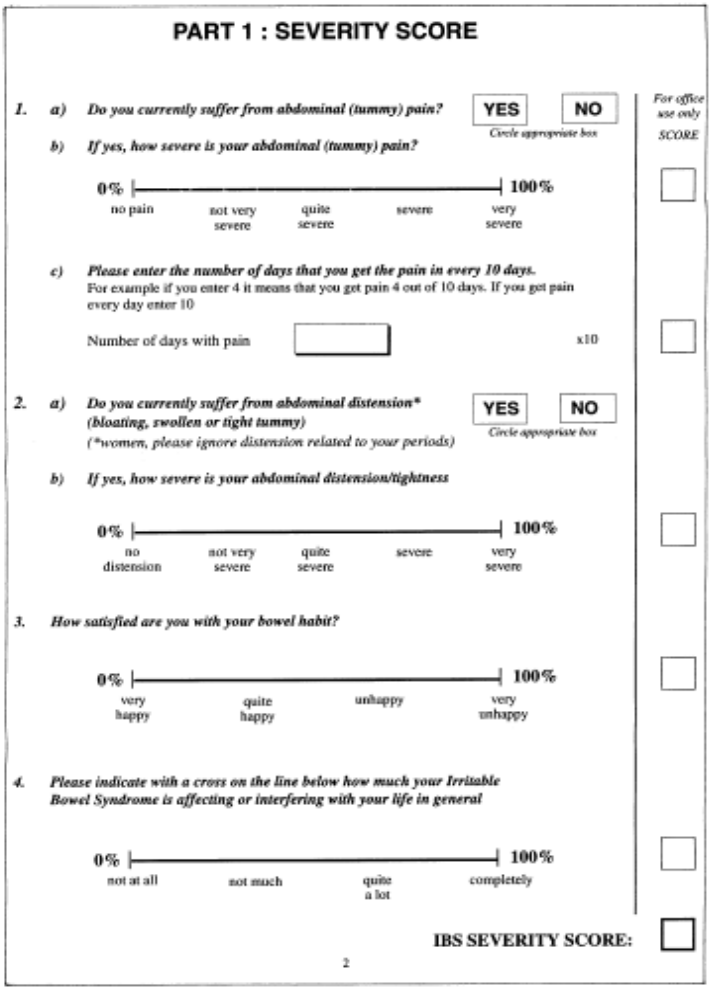
Please place your cross (✕) anywhere on the line between 0-100% in order to indicate as accurately as possible the severity of your symptom.

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* — *For office use only* *SCORE*

   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

IBS SEVERITY SCORE: _____

2

Appendix 3 continued

IBS 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:

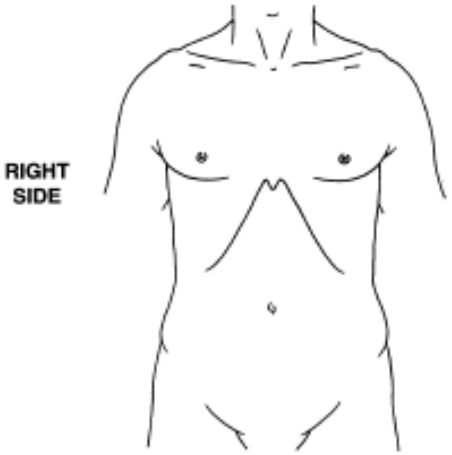
Do you ever: *Circle appropriate box*

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:***

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

Circle appropriate box

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-Quality of Life 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 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.

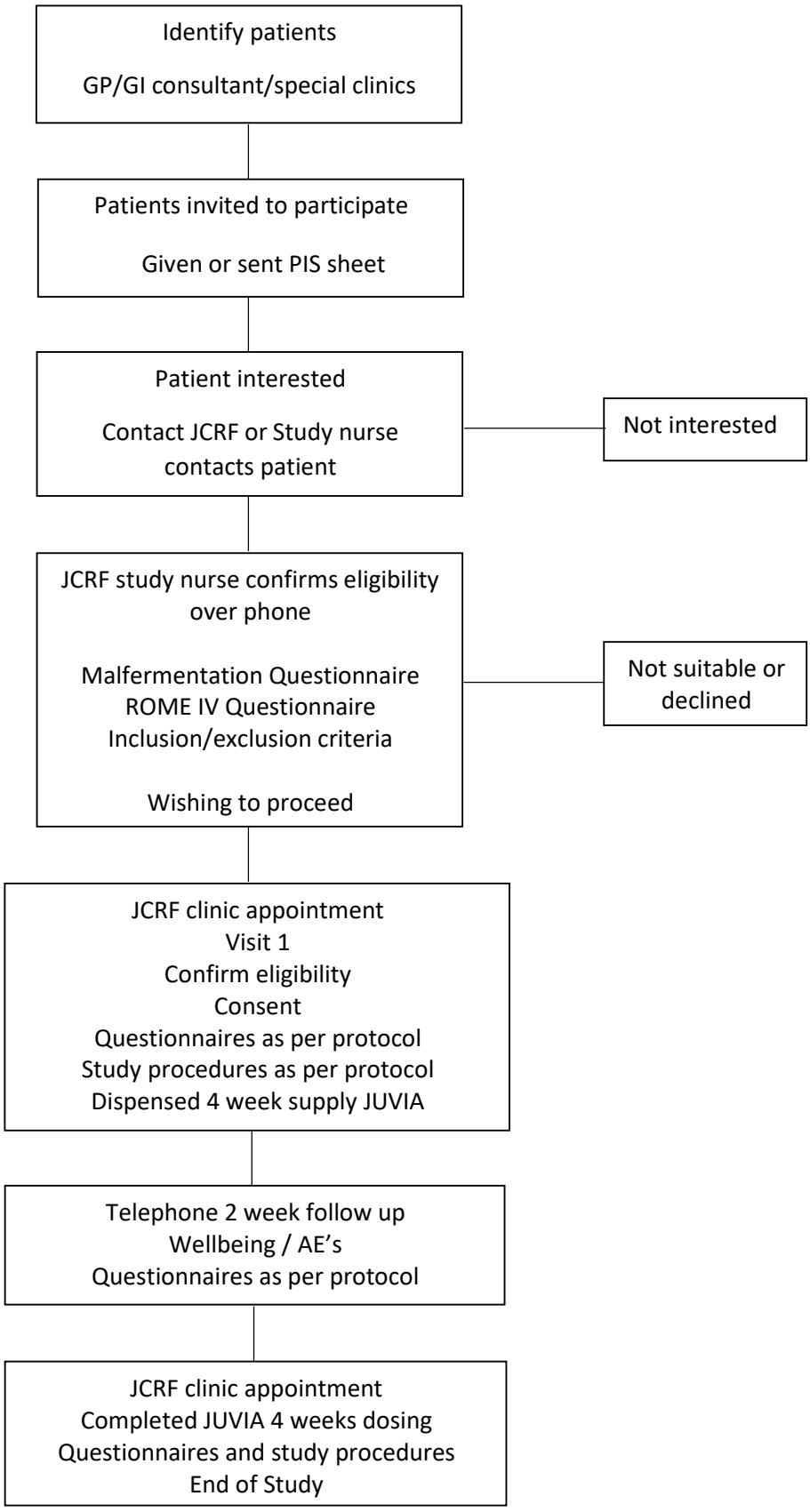
Appendix 5: Nijmegen Questionnaire: completed at screening and 4 weeks

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: Study Flow Diagram



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