

A RANDOMIZED CONTROLLED TRIAL TO EVALUATE THE SHORT-TERM EFFICACY AND LONG-TERM HEALTH ECONOMIC IMPACT OF A DIETARY INTERVENTION COMPARED TO PHARMACOTHERAPY WITH A MUSCULOTROPIC SPASMOLYTIC AGENT FOR NEWLY DIAGNOSED OR NEWLY TREATED IRRITABLE BOWEL SYNDROME IN PRIMARY CARE.

(The DOMINO trial: Diet Or Medication in Irritable bowel syNdrOme).

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■ GENERAL INFORMATION

A randomized controlled trial to evaluate the short-term efficacy and long-term health economic impact of a dietary intervention compared to pharmacotherapy with a musculotropic spasmolytic agent for newly diagnosed or newly treated irritable bowel syndrome in primary care.

SHORT STUDY TITLE / ACRONYM

Diet Or Medication in Irritable bowel syNdrOme (DOMINO) trial

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ROLE OF STUDY SPONSOR AND FUNDER

UZ Leuven as mentioned in KEY TRIAL CONTACT shall act as sponsor of the Study, as defined in the Law of 2004, and shall assume all responsibilities and liabilities in connection therewith and procure the mandatory liability insurance coverage in accordance with the Law of 2004. UZ Leuven shall ensure that it shall be mentioned in the Protocol, the Informed Consent Forms and in other relevant communication with the Study Subjects or the Regulatory Authorities as sponsor of the Study. UZ Leuven acknowledges and agrees for the avoidance of doubt that KCE shall under no circumstances be considered as sponsor of the Study or assume any responsibilities or liabilities in connection therewith, and UZ Leuven shall make no representations whatsoever in this respect.

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FODMAP	Fructose, Oligo-, Di and Mono-saccharides, And Polyols
GCP	Good Clinical Practice
GP	General Practitioner
HRU	Health Resource Utilization
IB	Investigator Brochure
IBS	Irritable Bowel Syndrome
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMP	Investigational Medicinal Product
IMPd	Investigational Medicinal Product Dossier

ISF	Investigator Site File
ISRCTN	International Standard Randomized Controlled Trials
KCE	Belgian Healthcare Knowledge Centre
MA	Marketing Authorization
FAMHP	Federal Agency for Medicines and Healthcare Products
MS	Member State
NICE	National Institute of Health and Care Excellence
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIS	Participant Information Sheet
RCT	Randomized Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
TMF	Trial Master File

■ STUDY PROTOCOL

A randomized controlled trial to evaluate the short-term efficacy and long-term health economic impact of a dietary intervention compared to pharmacotherapy with a musculotropic spasmolytic agent for newly diagnosed or newly treated irritable bowel syndrome in primary care (The DOMINO trial: Diet Or Medication in Irritable bowel syNdrOme).

1 BACKGROUND

The Irritable Bowel Syndrome (IBS), characterized by abdominal pain related to the stool pattern in the absence of underlying organic disease (1), is one of the most common conditions in clinical practice. Epidemiological studies in Belgium have shown a prevalence of 8 to 15% in the adult general population (2,3). Guidelines indicate that IBS can be diagnosed based on a typical symptom presentation, lack of alarm or risk symptoms, and a limited number of selected tests in specific cases (1). After a diagnosis of IBS is made, treatment is started, in Belgium most often using musculotropic spasmolytic agents as the initial pharmacotherapeutic approach (3,4). While these drugs have a very attractive safety profile, their efficacy is limited, and they are often used long-term (4,5).

Although IBS has a favorable outcome in terms of morbidity and mortality, it is a condition with major health economic and quality of life impact. This is attributable to its high prevalence, to diagnostic uncertainty in the absence of biochemical or structural markers, the chronic nature of symptoms, fear of underlying serious disease, and the limited efficacy of available therapies. This context leads to repetitive medical consultations, additional technical examinations which are often not very useful, and chronic use of sometimes multiple drug therapies, with limited therapeutic gain and often also use of alternative or complimentary medicine (1,2). For general practitioners (GPs), who treat the majority of patients, IBS is a condition that generates high diagnostic and therapeutic uncertainty (6).

Based on these considerations, there is a clear need for improving the management approach to IBS in GP practice. Recent studies from tertiary care centers have documented substantial symptom improvement in IBS using dietary interventions (low Fructose, Oligo-, Di and Mono-saccharides, And Polyols (FODMAPs), gluten-free and NICE diets), and in tertiary as well as secondary care, diet is increasingly implemented as a valid and effective treatment option. At the GP level, the potential to use dietary treatment is equally appealing, but this remains to be explored.

2 RATIONALE

The study proposal and rationale is based on a number of facts: 1) the high population prevalence of IBS in Belgium, 2) the large number of patients that are undergoing examinations and taking drugs for this condition 3) the limited efficacy of first line treatments, usually musculotropic spasmolytics, and 4) recent evidence of efficacy of dietary interventions.

2.1 POPULATION PREVALENCE

The Rome Foundation is an independent organization that provides support to create scientific data and educational information to assist in the diagnosis and treatment of functional gastrointestinal disorders (FGIDs) such as IBS. The Rome criteria form the basis for diagnosing IBS and have seen updates in 1998 (Rome II), 2006 (Rome III) and 2016 (Rome IV), although the changes in definition and hence the population that fulfils the updated criteria are limited. An international study using Rome II diagnostic criteria for IBS found a population prevalence of 6.7% in Belgium (2). A national study in 1012 adults, representative of the entire Belgian population, found a 14% prevalence according to Rome III criteria, and a 19% prevalence when using a more descriptive definition (3). Diagnostic criteria for IBS have recently been slightly adapted in the Rome IV consensus, published in May 2016 (1). However, the strict time elements (onset more than 6 months ago, symptoms on a weekly basis in the last 3 months) of these criteria are mainly rigorously applied for selecting patients in drug trials by the pharmaceutical industry. Clinicians use a less rigorous approach which identifies a larger number of patients and which is hardly influenced by changes in international consensus criteria (7), and this is the population of interest for the study.

2.2 HEALTH CARE IMPACT

International surveys have well established the high health economic and societal cost associated with IBS (8-10). The most detailed data on the health care impact in Belgium are available from a population-based survey that was conducted in 2010 and supervised by Profs. Tack and Piessevaux (3). Of those respondents in the Belgian general population study fulfilling IBS criteria, 41% had consulted a physician during the last year, and 20% stayed home from work or school for these symptoms (3). Over the preceding year, 44% underwent a radiological examination and 28% a colonoscopy. They used on average 1.6 different medications (the majority spasmolytic agents, which were used by 36% of IBS patients identified in the general population) (3). Although some general dietary recommendations are often given (regular meals, sufficient fiber, low fat, avoiding caffeine, carbonated beverages and spicy foods), there is a lack of evidence that these are efficacious and a Belgian population-based survey failed to find consistent dietary modifications in IBS sufferers (3). In detail, 54% reported drinking more water, 37% increased fiber intake, 36% avoided fatty meals and 15% reported taking smaller size meals (3).

2.3 EFFICACY OF FIRST-LINE THERAPY

While muscolotropic spasmolytic agents are the most frequently used IBS therapy in Belgium (3), their efficacy is limited. A recent meta-analysis found a response to spasmolytics in 61% of IBS patients compared to 44% with placebo, but there was considerable heterogeneity amongst studies and a possibility of publication bias (4). A more recent large placebo-controlled study of 15 weeks with otilonium bromide showed only a modest margin over placebo, with uncertain clinical relevance over the first 10 weeks (5). An extensive analysis of an earlier similarly designed study with otilonium bromide demonstrated that symptomatic benefit over placebo could already be observed during weeks 5-8 of treatment (11).

2.4 DIETARY INTERVENTION

Many IBS patients experience worsening of symptoms in relation to meals (12), and in a Belgian survey 40% of IBS sufferers in the general population identified food as a main trigger for symptom exacerbations (3). In spite of these findings, medical management of IBS made little use of well-structured dietary adjustments, and there was a general belief that the efficacy of diet in IBS was low (13). The view on dietary approaches to IBS management changed dramatically with the development and controlled trials of the low FODMAP diet. The low FODMAP diet was developed in Monash University, Melbourne, Australia and validated based on a rigorous scientific approach. Dr. Jessica Biesiekierski, who is a member of the trial Steering Committee, was actively involved in the Australian FODMAP studies. The diet aims at eliminating foods with “Fructose, Oligosaccharides, Disaccharides, Monosaccharides And Polyols” (14). Controlled studies, in which patients were given a low FODMAP diet or a normal diet, showed a significant favorable effect of the low FODMAP diet on IBS symptoms (15). Symptom benefit was significant for overall symptom evaluation and for individual symptoms of abdominal pain, bloating and flatulence. Nevertheless, the evidence of efficacy of low FODMAP dietary intervention in IBS is still considered insufficient by some, using rigorous standards (16).

In secondary and tertiary care, diet is usually implemented through referral to a dietician. Indeed, the low FODMAP diet is complex, and requires individualized explanation, follow-up and reintroduction by a skilled and trained dietician. These limitations make it less suitable for first-line therapy, as it cannot be the intent to have every IBS patient presenting to medical care to be sent to a specialized dietician for dietary intervention and follow-up (17). An electronic app was developed to assist (Australian) patients in adhering to the low FODMAP diet and has received widespread usage and adherences since 2012 (18). Furthermore, the low FODMAP diet is associated with reduced calorie intake and changes in fecal microbiota that are potentially unfavorable, which also argues against broad implementation as first-line therapy in primary care (19,20). Most recently, a randomized study from Sweden, conducted in a tertiary care center, demonstrated that a mixed approach composing of a simpler diet and altering eating patterns, based on guidelines from the United Kingdom’s National Institute of Health and Care Excellence (NICE) and the British Dietetic Association, yielded similar symptom benefit as the low FODMAP diet (20,21). Additionally, this was largely confirmed in a preliminary report from a similar randomized study in a tertiary care setting in the U.S. (21). In secondary and tertiary care, diet is usually implemented through referral to a dietician. This approach is not attractive for the primary care level, and GPs lack time and expertise to explain dietary interventions. Hence, dietary instructions should be provided in a format that allows the patient to understand and implement it independently. The Monash low FODMAP diet smartphone app, launched in 2012, is a downloadable electronic application that instructs and guides patients on the diet (http://med.monash.edu.au/news/2012/fodmap-app.html?_ga=2.233580380.374340172.1494521256-1858659098.1494521256). It has been extensively used in Australia and abroad, is created by the center from which our Dietician expert originated and will provide the conceptual basis for a Belgian app, based mainly on the simpler NICE-diet, which will be developed and made available for the trial.

The NICE-based diet is more suitable for primary care through its less complex design, and can be easily implemented using written instructions or an app, without active face-to-face intervention of a dietician. It should be noted that the NICE guidelines also result in a reduction in FODMAP

intake; for example, there is a dietary instruction to reduce intake of onions and beans, foods high in fermentable oligosaccharides (21).

2.5 STUDY RATIONALE

While Belgian GPs readily use musculotropic spasmolytic agents (3), the systematic use of dietary interventions seems to be under-developed or even absent. The national survey mentioned above already identified the heterogeneous nature of dietary adjustments that IBS sufferers in the Belgian general population apply (3). A recent small-scale survey in 8 Belgian GPs revealed that 88% provide dietary advice to most of their IBS patients. However, this advice consists mainly of general lifestyle recommendations (regular meals, restricting alcohol and caffeine, ...), with only 12% using a lactose elimination trial, 25% adding fibers and none of them using low FODMAP or NICE-based diets. In a feasibility assessment in 10 GP practices, 50% mentioned using high fiber diet, one GP used lactose elimination occasionally and only 1 GP used the low FODMAP diet or related diets (low gluten, NICE) regularly. Hence it seems that systematic dietary interventions for IBS are not really being applied in Belgian general practice, and there is an unmet need for a valid and effective dietary intervention for IBS patients that is easily administrable by GPs, who generally lack dietary expertise.

There are obvious advantages to an easily applicable and successful dietary intervention in IBS, including the low cost, the benefit of the patient having control over the symptoms, the reassuring confirmation of symptom response to diet, and the long-term efficacy potential. Based on these possible benefits, a comparison of an easily applicable diet with first-line pharmacotherapy in a broad IBS population is needed. Indeed, the availability of an easy-to-use dietary intervention (custom made app or booklet), with established efficacy in primary care could majorly facilitate the care of IBS patients by general practitioners and would probably make the disease management process more rewarding for both patient and physician. It seems logical that this should also lead to cost savings: good response to a diet is expected to significantly decrease the drive towards additional examinations for both patients and physicians, and the national survey mentioned above exposed the high cost associated with IBS in Belgium (3).

A search of ongoing trials through trial registration websites (clinicaltrials.gov; Nederlands trial register, EU clinical trial register, UK clinical trials gateway, ISRCTN registry, ...) in April 2017 (and repeated in September 2017) identified less than 20 unpublished, ongoing or planned dietary intervention trials in adult IBS patients. Most of them address low FODMAP diet, or gluten-free diet. None of them are set in primary care and none of them compares to standard medical therapy. Hence, there is an unfulfilled need to study whether diet and first-line medications have similar efficacy in first-line IBS patients, and whether the dietary approach decreases the health economic impact of IBS.

2.6 RELEVANCE TO PARTIES INVOLVED (PATIENTS, GPs)

The feasibility and relevance to both patients and GPs was assessed in feasibility/relevance assessments starting in May 2017. Face-to-face brief evaluations of this protocol with IBS patients seen in Leuven confirmed the patient interest in the trial, the protocol and its interventions. Blood sample and stool sample analysis were also favourably received, but these are of course tertiary care and thus perhaps more highly motivated patients.

No Belgian IBS patient organization exists. The Dutch IBS patient group has a vivid interest in the dietary approach to IBS and published extensively on this therapeutic modality in their magazine “Prikkel”. Otilonium bromide is not available in the Netherlands and hence the interest in this medication is high as it is perceived as “novel”, which differs from the Belgian situation. The IBS dietary app developed in Australia (see above) is extremely popular amongst patients in Australia and other English-speaking countries. The book on “The Complete Low-FODMAP Diet: A Revolutionary Plan for Managing IBS and Other Digestive Disorders” by Sue Shepherd, also in Australia, is the Amazon.com #1 Best Seller book on IBS. Hence, it seems appropriate to conclude that interest among patients is high.

2.7 STUDY AIM

The primary aim of the study is to assess the difference in IBS symptom control benefit between newly managed IBS patients in primary care treated with a musculotropic spasmolytic agent or a patient-administered dietary intervention. Both groups will receive the standard lifestyle recommendations (exercise, sleep sufficient number of hours, eat regular meals, avoid fatty meals, avoid caffeine, spicy foods and carbonated beverages) that are currently already applied by the majority of Belgian GPs. The most frequently used options for spasmolytic therapy in Belgium are peppermint oil or otilonium bromide (3,4). The latter is preferred as recent large and high-quality data with this agent are available (5,11). The dietary intervention will be based mostly on the NICE dietary guidelines, with a focus on reducing large serving sizes of the fermentable oligosaccharides, which has shown symptom benefit in recent trials (20,22). The dietary guideline, with illustrative meal plans, will be made available on paper (small booklet) and as a smartphone app, which will be developed for this trial, and made publicly available after the trial if efficacy is confirmed.

Except for the health economic aspect, all evaluations will be filled out by the patient through the eCRF. The questionnaires used are all self-administered and this will minimize impact on GP time. Symptom evaluation will primarily be done using the IBS Symptom Severity Scale (IBS-SSS) (20,23,24) (see appendix **Error! Reference source not found.**). The IBS-SSS is a well-validated questionnaire which is available in many languages and easy to use (19,22,23). In keeping with previous studies using the IBS-SSS, response is defined as a decrease in score of more than 50 points (20,23,24). In addition, quality of life impact will also be assessed using a validated questionnaire, the IBS-QoL (see appendix **Error! Reference source not found.**) (24-26).

The secondary aim is to evaluate whether symptom control gain with the dietary approach leads to health economic benefits, in terms of less doctor visits, investigations, use of medication or complementary and alternative medicine, absence from work, etc. Here, we will use the IBS Work Productivity and Activity Impact questionnaire, and a simplified version of a health economic impact questionnaire that has been applied in a recent multinational health economics survey of IBS in specialist care, spearheaded by Prof. Tack (published as abstracts 27-29; full manuscript on 525 patients from 6 European countries is submitted with JT as first and corresponding author).

Some exploratory outcomes will also be assessed. We will explore patient satisfaction during and after the different treatment modalities. We will also evaluate whether IBS subtypes, determined from retrospective analysis using the Bristol Stool Scale scores (appendix **Error! Reference source not found.**), predict response to dietary or musculotropic spasmolytic therapy. We will also explore

whether microbiota composition and diversity, assessed from stool samples predicts response to either therapies, whether changes in these microbiota parameters associate with symptom benefit, and whether serotonin synthesis-related genetic polymorphisms predict response to therapies.

2.8 ADDITIONAL PATIENT PHENOTYPING

IBS is highly prevalent in the general population, but probably represents a heterogeneous group of patients, which can be subdivided according to symptom characteristics, co-morbidities or biomarkers. Several treatment options display different levels of efficacy in IBS patient subgroups and, based on the heterogeneity of the condition, it is highly unlikely that any single treatment modality would benefit all (types of) IBS patients. In the current study, we will analyse whether any of the parameters collected in the trial determine differential treatment response. If this is the case, it may help to choose individualized treatment approaches with increased success rate in clinical practice.

Per international consensus, IBS is subdivided into stool pattern-dependent subtypes of IBS-D (IBS with diarrhoea), IBS-C (with constipation), IBS-M (mixed stool pattern) and IBS-U (unclassified) (1). The first three groups are the largest ones, comprising close to 30% of the patient population (1). The subdivision is relevant as it determines the choice of and response to specific therapies in current treatment algorithms (1,23). While otilonium bromide may improve pain in IBS regardless of the subtype, some data suggest that diet may be most effective in IBS-D, although literature is not consistent on this aspect (5,11,15,19-22). The Rome IV consensus states that “for clinical trials, the IBS subtype should be based on 14 days of daily diary reports” (1). This requirement cannot be reconciled with a pragmatic trial and, hence, stool pattern will be determined by retrospective questions as used in recent health economic studies (27-29).

IBS is also characterized by numerically major psychosocial co-morbidity, with elevated levels of anxiety, depression and somatization compared to the general population, but with large variability at the individual patient level (30). Psychological distress is an important determinant of IBS symptom severity, but its impact on treatment outcomes is less clear (1,24,30,31). These characteristics will be collected at baseline through patient-administered questions in the eCRF.

In addition, very recent observations reported that faecal microbiota profile (dysbiosis index) and genetic polymorphisms altering serotonin synthesis may predict response to dietary interventions in IBS (32,33).

Although not yet part of clinical routine, such genetic or stool microbiota analyses are increasingly easy to implement in clinical practice, both in terms of sample collection and because relevant analyses are already being offered commercially by several companies (34,35). In addition, it is clinically relevant to know whether basal microbiota composition predicts response to the NICE-based diet, and whether the NICE-based diet is associated with less marked effects on gut microbiota composition than reported in previous studies using a strict low FODMAP diet (19).

Nevertheless, as these sample collections are not part of the usual care of IBS, these will be covered by a separate scientific research budget, and participation in this aspect of the study will be optional for all parties involved (patient and GP).

3 OBJECTIVES AND OUTCOME MEASURES/ ENDPOINTS

3.1 PRIMARY OBJECTIVE

The primary outcome is the improvement in IBS-Symptom Severity Score after 8 weeks of otilonium bromide compared to dietary intervention. The proportion of responders with the two treatment arms will be compared. A responder is defined as a patient with an improvement of 50 points or more on the IBS-SSS being the established cut-off used in clinical trials. Based on our clinical experience and the available clinical data, we hypothesize that the dietary intervention will be superior to treatment with otilonium bromide 40 mg t.i.d. in improving IBS-SSS.

3.2 SECONDARY OBJECTIVES

As a secondary hypothesis, we hypothesize that initial treatment with diet, compared to medication, generates less health economic costs 6 months before and, over a 6-months follow-up period.

Healthcare resource utilization (HRU) related to IBS (medical consultations, diagnostic tests, therapies, hospitalizations, management of adverse reactions) will be collected using an ad-hoc questionnaire, as recently used in international studies on IBS health impact, conducted by Prof. Tack (refs. 27-29 are abstracts of the studies; full manuscript on 525 patients in 6 European countries submitted).

We will also assess the impact of IBS on work productivity using the Work Productivity and Activity Impairment (WPAI) questionnaire-irritable bowel syndrome version (36,37).

We will also evaluate quality of life using a syndrome-specific instrument (IBS-QoL) as well as the generic EuroQol instrument (25,26).

In addition, we will quantify changes in levels of psychosocial co-morbidity through the validated PHQ questionnaire, as it has been suggested that psychosocial co-morbidity may respond to (dietary) therapeutic intervention (39-41).

3.3 EXPLORATORY OBJECTIVES

We will explore the improvement in treatment satisfaction question after 8 weeks of otilonium bromide compared to dietary intervention. The proportion of responders with the two treatment arms will be compared. A responder is defined as a patient that scores “quite satisfied” and “very satisfied” to the satisfaction question.

Finally, we incorporate the option to collect blood samples and a stool sample before and after the initial 8 weeks of therapy from all participants, to assess genetic polymorphisms and microbiota composition markers of response (32,33). A separate informed consent for this part will be provided; GPs and patients will be compensated from a separate budget for this additional effort. In an exploratory analysis, we will evaluate whether genetic polymorphisms and gut microbiota diversity and composition (at baseline or changes during treatment) predict/correlate with symptom improvement (32,33).

These analyses may identify methods to select the best personalized treatment approach in future clinical management, which is likely to have access to genetic profiles and diversity quantifications of dysbiosis (34,35).

In addition, it is important to know whether the NICE-based diet would be associated with similar (potentially unfavourable) changes in gut microbiota as the low FODMAP diet (19). A budget for sample collection and transport is included. This will be done in collaboration with the laboratory of Jeroen Raes who have extensive experience with the logistic and analysis aspects of large scale microbiota studies in the general population (42). The actual analyses will be done on separate research budgets.

3.4 OUTCOME MEASURES/ENDPOINTS

The primary outcome variable of the trial will be the response rate to treatment at 8 weeks, based on the IBS Symptom Severity Score (IBS-SSS), with a 50-point drop being the established cut-off used in clinical trials. Hence, the primary endpoint of the present study is the proportion of responders who improved with 50 points or more on the IBS-SSS after 8 weeks of each of the two treatments, compared to baseline.

IBS-specific quality of life will be assessed using IBS Quality of Life Questionnaire (IBS-QoL) and the EuroQoL questionnaire (25,26).

Psychosocial co-morbidity status (and changes herein) will be measured through validated modules of the Patient Health Questionnaire (PHQ) (38).

The health economic impact will be assessed retrospectively at inclusion and will be prospectively followed during the randomized treatment and follow-up, using an internationally applied questionnaire. Health utilities will be evaluated using the European quality of life (EuroQoL) questionnaire 5D (EQ-5D). Loss of work time lost and activity impairment secondary to IBS will be measured using the WPAI-IBS.

3.4.1 Primary endpoint/outcome

The primary endpoint is based on the improvement of the **IBS-SSS score** from baseline after 8 weeks of treatment. A responder is defined as a patient who has an improvement with 50 points or more on this validated scale after 8 weeks of treatment compared to baseline.

The IBS-SSS is a validated and easy-to-use score for IBS symptom severity, and has been used in multiple international studies (20,23,24). The severity score is calculated as the sum of five IBS-SSS questions that are scored from 0 to 100. The baseline score serves as a severity grading, with moderate severity in case of a score between 175 and 300 and severe symptoms in case of a score above 300. Response is defined as a drop of more than 50 points compared to baseline (20,23,24).

3.4.2 Secondary endpoints/outcomes

Secondary endpoints are the improvement of the IBS-SSS score from baseline after 8 weeks of treatment (short term treatment response after 8 weeks is relevant for clinical practice), and at the follow-up visits of 4 and 6 months (long-term treatment outcome in terms of symptom control).

Furthermore, the continuous outcome of the mean IBS-SSS scores will be analysed as a secondary outcome variable, to indicate magnitude of symptom improvement, taking into account that treatment modalities (diet vs. medication) after 8 weeks may vary as this is then left to the discretion of the patient and the GP. We will also sample the same symptom severity scales at the very early time point of 4 weeks to detect rapid onset of therapeutic effects.

Quality of life will be assessed using the syndrome-specific IBS Quality of Life Questionnaire (IBS-QoL) and the generic EuroQol questionnaire. The changes over time in IBS-QoL and EuroQOL will be evaluated. Psychosocial status (anxiety, depression and somatization, and changes herein) will be measured through validated modules of the Patient Health Questionnaire (PHQ).

Both direct and indirect health costs, including self-costs to patients, will be compared at the different time points. They will also be compared to the (retrospective) cost assessment at baseline.

Productivity losses will be described in the week prior to baseline and at the different visits using the WPAI-IBS.

3.4.3 Exploratory endpoints/outcomes

We will explore patient satisfaction during and after the different treatment modalities. We will also evaluate whether IBS subtypes, determined from retrospective analysis using the Bristol Stool Scale scores, predict response to dietary or muscolotropic spasmolytic therapy.

Considering the psychosocial co-morbidities in IBS, and the uncertainty regarding their impact on treatment outcome, we will explore whether baseline psychosocial co-morbidities predict therapeutic outcome of either treatment arms. We will also evaluate whether the severity of these psychological disturbances changes in relation to IBS symptom benefit in both treatment arms.

In those who gave separate informed consent for blood and stool samples, we will also explore whether microbiota composition and diversity, assessed from stool samples predicts response to either therapies, whether changes in these microbiota parameters associate with symptom benefit, and, whether serotonin synthesis-related genetic polymorphisms predict response to therapies. These additional analyses may generate important information on predictors of treatment response, which may be an important first step towards personalized treatment approaches which are currently lacking in IBS. While GPs are unlikely to use an instrument like the PHQ to quantify anxiety, depression or somatization, they may readily identify or know from the patient's personal history the presence of anxiety, depression or multiple somatic symptoms. If these are predictors of response to either treatment, they can be applied in treatment selection for future clinical management.

Objectives	Outcome Measures	Time point(s) of evaluation of this outcome measure (if applicable)
Primary Objective To assess the difference in IBS	Improvement in IBS symptom severity scale (IBS-SSS). The	8 weeks after the start of the randomized treatment.

symptom control benefit between newly managed IBS patients in primary care treated for 8 weeks with a musculotropic spasmolytic agent or a dietary intervention.	proportion of responders with the two treatment arms will be compared. A responder is defined as a patient with an improvement of 50 points or more on the IBS-SSS.	
Secondary Objectives To evaluate whether different symptom control gain with both treatments during the first 8 weeks leads to different health economic benefits.	A. Quality of life will be assessed using IBS-QoL and EuroQol questionnaire. Anxiety, depression and somatization, and changes herein will be measured through the PHQ questionnaire. B. Health resource utilisation (HRU), such as doctor visits, investigations, use of medication or complementary and alternative medicine, absence from work, etc. C. Work activity impairment as quantified by the Work Productivity Activity Impairment-IBS (WPAI-IBS) questionnaire.	The 6-month treatment period after the start of the randomized treatment.
Tertiary Objectives Exploratory analysis of predictors of response to either treatment modality.	IBS-SSS responder rate, patient satisfaction during and after the different treatment modalities, HRU and WPAI-IBS score in subgroups according to IBS stool pattern subtype, psychosocial co-morbidity, faecal microbiota and serotonin synthesis genetic polymorphisms.	Same as above: 8 weeks for symptom control, 6 months for health economic outcomes.

4 TRIAL DESIGN

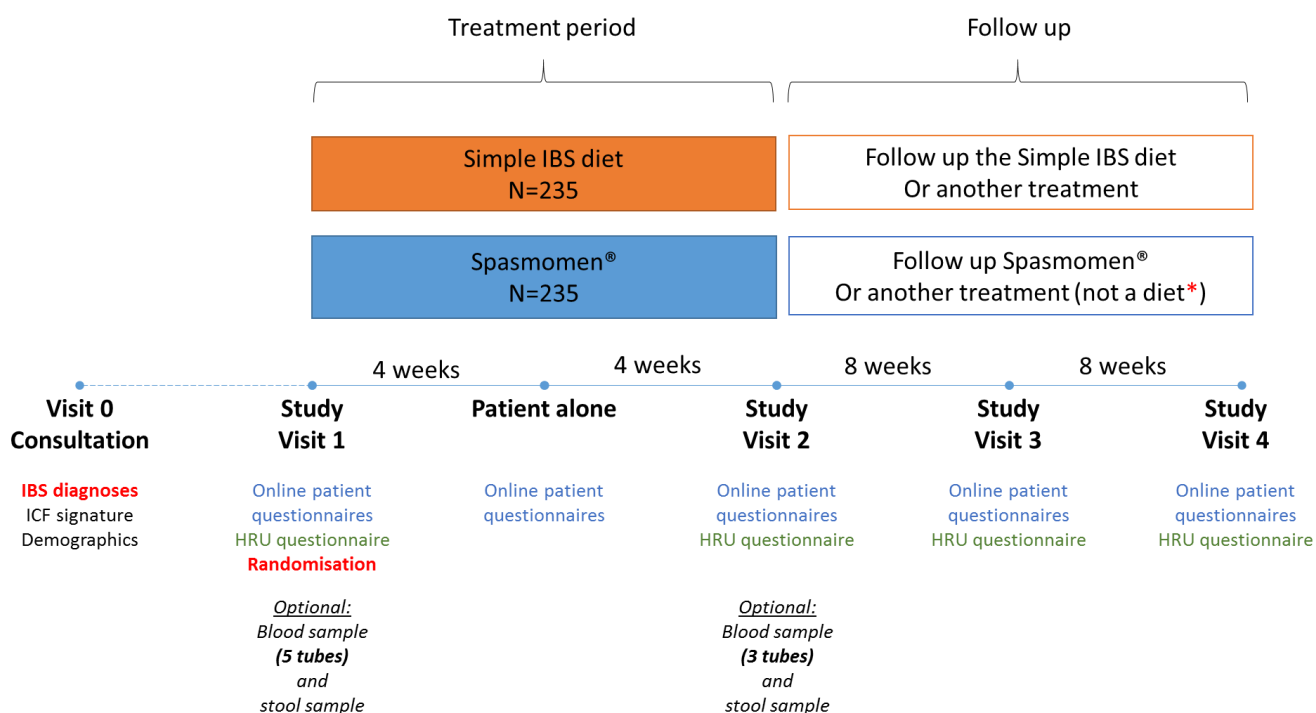
This is an open, randomized, parallel-group design study, in which patients with newly diagnosed or newly treated IBS are randomized to traditional first-line medical therapy (spasmolytic agent) or a relatively simple diet which has been shown to improve IBS symptoms.

This study will only be conducted in Belgium. The target patient population is to be recruited from primary care practices, and thus the trial will only involve general practitioners. The study will be conducted both in Dutch- and French-speaking sites and patients and intends to recruit from GP practices in all Belgian provinces.

All recruitment and study visits are carried out in the general practice setting. Eligible patients are those diagnosed with IBS, in whom a first treatment course is being initiated. In agreement with a pragmatic trial, the diagnosis will be based on clinical evaluation and judgement by the general practitioner (GP). However, all participating GPs will receive state-of-the-art information on the current consensus for diagnosing IBS at investigator meetings.

The sample size is 235 per arm (470 patients in total) to allow drop-outs. In the group on medication, the option for the GP, in agreement with the patient, will be to stop after 8 weeks.

Treatment can be continued if considered appropriate by the physician. Ongoing medical therapy and its compliance during follow-up will be recorded in the eCRF. In the diet group, diet can be continued as considered clinically useful by the patient. Diet adherence will be assessed by a simple question during follow-up.



Visit 0 (baseline assessment) is the visit at which the IBS diagnosis is made or confirmed by the GP. At this visit, after the IBS diagnosis is confirmed, informed consent is obtained, the patient is registered in an online eCRF application and demographics are completed. The patient receives access to her/his patient-accessible part of the eCRF, the online PRO questionnaires. This access might include the use of the patients' email address. Nevertheless, the use of the email address will be limited and in agreement with the necessary legislation to assure the privacy of the patients. The patient is instructed to use the online application to answer questions on IBS symptom severity, stool pattern (using recall questions as done in a recent international study of health economic impact of IBS), quality of life, work productivity impact and psychosocial co-morbidity status. These questions can be filled out at home before the next planned visit.

Visit 1 (study day 0) is the start of the study (start of the treatment phase). For practical reasons, it will often be scheduled over the next few days, when the general practitioner has sufficient time to perform the study-initiation procedures. During this visit, the physician completes the medical history data and health economic information (retrospective). Patients will fill out the online PRO questionnaire at home before the visit. During the visit, the GP is able to see the status of the ePRO questionnaire (completed, partially completed and incomplete). If the questionnaires are partially completed or incomplete, the GPs will give a reminder to the patient. The patient will also be reminded to fill out the questionnaires by an email.

Visit 1, treatment is started in a randomized fashion, generated through the online eCRF, either with otilonium bromide at standard doses, or with a dietary intervention (the simple IBS diet).

The diet is self-administered by the patient and is based on information and instructions provided in an electronic application (smartphone or tablet) or a paper booklet. The dietary application and booklet also contain examples of meal plans that are compliant with the diet. The app is free of charge and can be download during the visit with the help of the GP.

Patients in the medication arm will be prescribed otilonium bromide, to be obtained from the pharmacy. Hence, the time needed for the physician to start both treatment options should be comparably short. Treatment is started for 8 weeks.

Online Questionnaires moment (patient alone) is an online-only follow-up visit after 4 weeks. Patients will fill out the online PRO questionnaire at home to assess treatment adherence and short-term changes in symptom severity. For practical reasons, there will be a window of time of a 7 extra days to fill out the questionnaires. The patient also be reminded to fill out the questionnaire by email.

Visit 2 is the efficacy endpoint visit, where improvement of IBS symptoms will be measured after 8 weeks of therapy. For practical reasons, there will be a window of time of +/- 7 days before V2 planned date. The timing is a compromise between IBS medication trials, where the endpoint is usually evaluated after 12 weeks; IBS diet trials, where the endpoint is usually evaluated after 3 to 4 weeks, and, clinical practice by dedicated dieticians, where IBS dietary interventions are usually followed up after 6 weeks. Health economic data will be prospectively collected during the randomized treatment period.

Patients will fill out the online PRO questionnaire at home before the visit. During the visit, the GP is able to see the status of the ePRO questionnaire (completed, partially completed and

incomplete). If the questionnaires are partially completed or incomplete, the GPs will give a reminder to the patient. The patient will receive reminders to complete the questionnaires up to 3 days ahead of the planned visit and 2 days after date of visit if not completed (or if partially completed).

The patient had the option to provide blood samples and stool samples (before start treatment and after 8 weeks, at visit 1 and 2) for scientific purpose. The blood samples include 2 EDTA tubes for genetic analysis (at visit 1) and routine blood samples (3 tubes: 1x SST, 1x EDTA and 1x Fluoride, at visit 1 and 2) needed to help interpreting the microbiota analysis.

* From this point on, the patients are allowed to change their treatment guided by the expert opinion of their GP. The GPs are instructed not to propose the simple IBS diet, nor the NICE or FODMAP diet or variations of these diets to the patients recruited in the medication arm. The aim of the trial is to assess the effect of the simple IBS diet, which is not yet available for use in primary care clinical practice, on symptoms and economic impact of the patients (see below). Introduction of this diet or the closely related NICE and low FODMAP diets at this point of the trial will impact on the data. Nevertheless, it is still allowed to introduce other diets normally used in clinical practice, such as a lactose free diet, a diet rich in fibre, or possibly gluten free diet (this is not scientifically recommended) or others. At the end of the follow up period, in accordance with the guidance of their GP patients are allowed to follow the simple IBS diet and the use of the app and the diet booklet will be provided free of charge.

Between week 8 and week 24, a further health economic **follow-up** is planned, thereby generating a total prospective health economic data collection time of 6 months (follow up phase). In keeping with a pragmatic trial, it is up to the patient and physician to decide whether treatment is continued or interrupted or switched after the first 8 weeks, or at any time point during the follow-up until the final visit. Visits are planned at 16 (**Visit 3**) and 24 (**Visit 4**) weeks, mainly to collect health economic impact data, but the IBS symptom severity score, independently entered by the patient in the eCRF, will also be followed up at these visits. For practical reasons, there will be a window of time of +/- 7 days before V2 planned date. During the visit, the GP is able to see the status of the ePRO questionnaire (completed, partially completed and incomplete). If the questionnaires are partially completed or incomplete, the GPs will give a reminder to the patient. The patient will receive reminders to complete the questionnaires up to 3 days ahead of the planned visit and 2 days after date of visit if not completed (or if partially completed).

Compensation: In the “Belgisch Centrum voor Farmacotherapeutische Informatie” or BCFI vzw website, it is indicated that the price of a box of Spasmomen® (40 mg, 60 tablets) is 16.01 euros. Therefore, for this trial, it is expected that patients will have to expend 48.03 euros for three boxes of Spasmomen® (40 mg) needed during the treatment period (8 weeks). The participating patients will receive a compensation to reimburse these expenses. Patients in the diet arm will receive a smartphone diet app or booklet with instructions and recipes ideas to ensure the compliance to the treatment. Hence, it is possible that patients will have additional expenses to buy the required nutritional products. It is difficult to make an estimation of these additional costs for reimbursement; therefore, patients will receive the same compensation as the patients in the medication arm. Furthermore, both treatment arms will be compensated for their time and

additional travel expenses. As a result, in total, all patients participating in this trial will receive a compensation of 100 euros.

Storage and analysis of samples: For this section of the trial we will use the similar procedures previously successfully used for the “Flemish Gut Microbiota Project” (49).

End of trial: The KCE, Ethics committee and regulatory authorities will be notified by the sponsor of the end of the trial within 90 days of its completion. Trial completion is defined as the moment of data base lock, which is estimated to occur on February 2020.

5 ELIGIBILITY CRITERIA

5.1 INCLUSION CRITERIA

- Eligible patients are those of either gender, above the age of 18, eligible to give informed consent.
- Newly diagnosed with or newly to be treated for IBS in primary care, as this is the setting where the majority of these patients is managed. The diagnostic gold standard, in line with clinical practice, will be clinician’s diagnostic judgment.
 - Supportive information for the diagnosis of IBS will be provided to the GPs at the initial investigators meeting. This includes: a guidance for diagnosis and potentially useful additional tests based on the Rome IV management algorithm, a Rome IV-based diagnostic questionnaire with pictograms and a list of alarm symptoms (1).

Patients who did not receive treatment over the preceding 3 months, and who did not receive long-term treatment (>3 consecutive weeks) with otilonium bromide in the past are eligible for the trial.

5.2 EXCLUSION CRITERIA

Exclusion criteria applies to the following points:

- Patients not capable to understand or be compliant with the study.
- Patients with concurrent organic gastrointestinal disease (inflammatory bowel disease), a history of major bowel surgery (not including minimal invasive surgery such as appendectomy or cholecystectomy, but including sigmoidectomy, hemicolectomy and small bowel resections)
- Patients who received treatment with otilonium bromide in the past for more than 3 weeks consecutively or who received otilonium bromide recently for any duration in the last 3 months.
- Patients who have used FODMAP or NICE diet before.
- Patients who recently (last 3 weeks) used other medication for IBS, or who changed their diet for IBS or for any other reason over the last 3 months. To be included in the trial patients should stop these treatments following the advice of their GP (see paragraph 8.9).
- Patients with diabetes, uncontrolled thyroid disease, active malignant disease (not including patients with cancer free diagnosis for more than 5 years), symptomatic uncontrolled endometriosis.

- Patients with a major psychiatric disease. The use of a single antidepressant on a stable dose for at least 3 months is allowed (see paragraph 8.9).
- Patients with drug abuse and/or alcohol abuse.
- Patients on pharmacologically prepared probiotic formulations (i.e. bought in the pharmacy) will be excluded. The use of probiotic drinks or yoghurts available from food stores, such as Activia®, Yakult®, Actimel®, is allowed but should be registered as “complementary treatment”(see paragraph **Error! Reference source not found.**).
- Women with active pregnancy plans in the coming 6 months are not eligible and women of childbearing potential are only eligible if they use effective contraception throughout the study. Also excluded are women of childbearing potential not using effective contraception or women planning to become pregnant the next 6 months (see paragraph **Error! Reference source not found.**). Methods of contraception considered highly effective are: combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, a vasectomized partner or sexual abstinence (http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf).

6 TRIAL MEDICATION

The medication arm in the study will use a well-established and well-tolerated treatment modality: otilonium bromide 40 mg t.i.d. In agreement with standard clinical practice, treatment for 8 weeks will be prescribed by the treating physician and obtained by the patient from the pharmacy. The drug information leaflet for physicians is added to this protocol (Appendix **Error! Reference source not found.**).

The dietary arm will be the so-called traditional IBS diet based on the dietary recommendations from the National Institute for Health and Care Excellence (NICE) and the British Dietetic Association. Specifically, the participants will be instructed to regularly eat 3 meals and 3 snacks a day, never too much or too little each time, never to be hungry or too full; to eat in peace and quiet and to chew thoroughly.

Furthermore, they will be instructed to reduce intake of fatty or spicy foods, coffee, alcohol, onions, cabbage, and beans; avoid soft drinks and carbonated beverages, chewing gums, and sweeteners that end with -ol, and to eat fibres but distribute the intake evenly during the day. Participants will also be given simplified instruction to avoid frequently eating large servings of other high FODMAP containing foods: wheat, rye, garlic, artichokes, apples, pears, stone fruits, and watermelon. The dietary instructions will include suggestions of suitable alternatives to ensure diets remain balanced, including meal and recipe ideas, and tips for when eating outside of the home. An example of a one-week meal plan is shown in appendix **Error! Reference source not found.**

As the aim of this trial is a “real-life” pragmatic study, it is our opinion that we should omit any interventions that would not occur in clinical practice, where physicians are limited in contact time for explaining IBS treatment. For the treatment arm, the intervention is a standard prescription and explanation of dosage modalities by the GP, for a drug which is devoid of adverse events. Our aim is to minimize the physician intervention to handing out a link to a downloadable app which will explain the diet and will include draft menus. A paper version (small booklet) will be available to hand out for patients who prefer a non-digital explanation. The physician does not need to be skilled in explaining the diet or assessing adherence to it. The intention-to-treat is providing diet information with simple explanations and a set of sample menus. The outcome is symptom control with this simplified approach.

In the drug treatment arm, there will be no reminders or specific compliance follow-up. Hence, we will apply the same low-key intervention for the diet arm: no reminders or monitoring. At follow-up visits compliance to diet and drug will be assessed by a simple question estimating non-adherence incidence. This will allow to explore response in well versus poorly adhering patients for each treatment. If this is better with high adherence, it may implicate that a diet app with reminders is required, but this is a different, potentially future and refined approach.

7 REFERENCES

- 1) Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R. Bowel Disorders. *Gastroenterology*. 2016 Feb 18. pii: S0016-5085(16)00222-5.
- 2) Hungin AP, Whorwell PJ, Tack J and Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40000 subjects. *Aliment Pharmacol Ther*. 2003 March; 17: 643-50.
- 3) Piessevaux H, Fischler B and Tack J. Prevalence and impact of irritable bowel syndrome in the Belgian general population. *Gastroenterology* 2008; 134, M1801 (abstract).
- 4) Ford AC, Talley AC, Spiegel BMR, Foxx-Orenstein AE, Schiller L, Quigley EMM and Moayyedi P. Systematic review and meta-analysis of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome. *BMJ* 2008;337;a2313.
- 5) Clavé P, Acalovschi M, Triantafyllidis JK, Uspensky YP, Kalayci C, Shee V, Tack J; OBIS Study Investigators. Randomised clinical trial: otilonium bromide improves frequency of abdominal pain, severity of distention and time to relapse in patients with irritable bowel syndrome. *Aliment Pharmacol Ther*. 2011 Aug;34(4):432-42.
- 6) Seifert B, Rubin G, de Wit N, Lionis C, Hall N, Hungin P, Jones R, Palka M, Mendive J. The management of common gastrointestinal disorders in general practice A survey by the European Society for Primary Care Gastroenterology (ESPCG) in six European countries. *Dig Liver Dis*. 2008 Aug;40(8):659-66.
- 7) Corsetti M, Tack J. Are symptom-based diagnostic criteria for irritable bowel syndrome useful in clinical practice? *Digestion*. 2004;70(4):207-9.
- 8) Masion-Bergemann S, Thielecke F, Abel F, Bergemann R. Costs of irritable bowel syndrome in the UK and US. *Pharmacoeconomics*. 2006;24(1):21-37.
- 9) Nellesen D, Yee K, Chawla A, Lewis BE, Carson RT. A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. *J Manag Care Pharm*. 2013 Nov-Dec;19(9):755-64
- 10) Canavan C, West J, Card T. Review article: the economic impact of the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2014 Nov;40(9):1023-34.
- 11) Glende M, Morselli-Labate AM, Battaglia G, Evangelista S. Extended analysis of a double-blind, placebo-controlled, 15-week study with otilonium bromide in irritable bowel syndrome. *Eur J Gastroenterol Hepatol*. 2002 Dec;14(12):1331-8.
- 12) Posserud I, Strid H, Störsrud S, Törnblom H, Svensson U, Tack J, Van Oudenhove L, Simrén M. Symptom pattern following a meal challenge test in patients with irritable bowel syndrome and healthy controls. *United European Gastroenterol J*. 2013 Oct;1(5):358-67.
- 13) Rees GA, Davies GJ, Parker M, Trevan M. Gastrointestinal symptoms and diet of members of an irritable bowel self-help group. *J R Soc Health*. 1994 Aug;114(4):182-7.
- 14) Ong DK, Mitchell SB, Barrett JS, Shepherd SJ, Irving PM, Biesiekierski JR, Smith S, Gibson PR, Muir JG. Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. *J Gastroenterol Hepatol*. 2010 Aug;25(8):1366-73.
- 15) Halmos EP, Power VA, Shepherd SJ, Gibson PR and Muir J. A Diet Low in FODMAPs Reduces Symptoms of Irritable Bowel Syndrome. *Gastroenterology* 2014; 146: 67-75.

- 16) Moayyedi P, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, Soffer EE, Spiegel BM, Ford AC. The Effect of Dietary Intervention on Irritable Bowel Syndrome: A Systematic Review. *Clin Transl Gastroenterol*. 2015 Aug 20;6:e107
- 17) Thomas LV, Jenkins G, Belton J, Clements S, Jacob C, Johnson N, Joy D, Low J, Munson E, Sheppard J. Nutritional advice for community patients: insights from a panel discussion. *Br J Community Nurs*. 2016 Mar;21(3):130-7.
- 18) Chen J, Lieffers J, Bauman A, Hanning R, Allman-Farinelli M. The use of smartphone health apps and other mobile health (mHealth) technologies in dietetic practice: a three country study. *J Hum Nutr Diet* 2017, in press.
- 19) Halmos EP, Christophersen CT, Bird AR, Shepherd SJ, Gibson PR, Muir JG. Diets that differ in their FODMAP content alter the colonic luminal microenvironment. *Gut*. 2015 Jan;64(1):93-100.
- 20) Böhn L, Störsrud S, Liljebo T, Collin L, Lindfors P, Törnblom H, Simrén M. Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. *Gastroenterology* 2015; 149: 1399-1407.
- 21) Blanchard-Smith J, Bullock I, Dalrymple J, et al. NICE Guidelines: irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care. Published February 2008. Available at: <https://www.nice.org.uk/guidance/cg61>.
- 22) Eswaran SL, Chey WD, Han-Markey T, Jackson K and Ball, S. A United States, Randomized, Controlled Trial Comparing the Simple IBS diet vs. Modified NICE Guidelines in Adults With IBS-D: Primary and Key Secondary Endpoints. *Gastroenterology* 2016, Volume 150, Issue 4, Supplement 1, Page S160 (abstract).
- 23) Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther*. 1997;11:395–402.
- 24) Irvine EJ, Tack J, Crowell MD, Gwee KA, Ke M, Schmulson MJ, Whitehead WE, Spiegel B. Design of Treatment Trials for Functional Gastrointestinal Disorders. *Gastroenterology*. 2016 May;150(6):1469-1480.e1.
- 25) Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL. (1998). Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. *Digestive Diseases and Sciences*, 43(2), 400-411.
- 26) Spiegel B, Harris L, Lucak S, Mayer E, Naliboff B, Bolus R, Esrailian E, Chey WD, Lembo A, Karsan H, Tillisch K, Dulai G, Talley J, Chang L. Developing valid and reliable health utilities in irritable bowel syndrome: results from the IBS PROOF Cohort. *Am J Gastroenterol*. 2009 Aug;104(8):1984-91.
- 27) Mearin F, Cortes X, Mackinnon J, Bertsch J, Fortea J, Tack J. Economic And Quality-Of-Life Burden Of Moderate-To-Severe Irritable Bowel Syndrome With Constipation (Ibs-C) In Spain: The Ibis-C Study. *Value Health*. 2014 Nov;17(7):A365.
- 28) Layer P, Andresen V, Diemert S, Mackinnon J, Bertsch J, Fortea J, Tack J. Economic Burden and Quality of Life of Moderate-To-Severe Irritable Bowel Syndrome With Constipation (Ibs-C) In Germany: Results From The Ibis-C Study. *Value Health*. 2015 Nov;18(7):A624
- 29) Coffin B, Follet M, Mackinnon J, Bertsch J, Fortea J, Tack J. The Burden of Moderate-To-Severe Irritable Bowel Syndrome With Constipation (Ibs-C) In France: A Comparison With

- The European Results From The Ibis-C Observational Study. *Value Health*. 2015 Nov;18(7):A632.
- 30) Sibelli A, Chalder T, Everitt H, Workman P, Windgassen S, Moss-Morris R. A systematic review with meta-analysis of the role of anxiety and depression in irritable bowel syndrome onset. *Psychol Med*. 2016 Nov;46(15):3065-3080.
 - 31) Van Oudenhove L, Törnblom H, Störsrud S, Tack J, Simrén M. Depression and Somatization Are Associated With Increased Postprandial Symptoms in Patients With Irritable Bowel Syndrome. *Gastroenterology*. 2016 Apr;150(4):866-74
 - 32) Bennet SMP, Bohn L, Storsrud S, Liljebo T, Collin L, Lindfors P, Tornblom H, Ohman L and Simren M. Multivariate modelling of gut microbial profiles predicts responsiveness to a diet low in FODMAPS. *UEG Journal* 2016, 4, supplement, OP003.
 - 33) Merchant JL, Photenhauer A, Eswaran SL, Jackson K and Chey WD. A US, Randomized, Controlled Trial Comparing the Simple IBS diet vs NICE Guidelines in Adults IBS-D Adults: Predictive Value of a Tryptophan Hydroxylase 1 (TPH1) Promoter Variant. *Gastroenterology*, Vol. 150, Issue 4, S953 (abstract).
 - 34) Example: www.genetic-analysis.com accessed on 10/1/17.
 - 35) Example: www.23andme.com accessed on 10/1/17
 - 36) Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993 Nov;4(5):353–65.
 - 37) Reilly MC, Bracco A, Ricci J-F, Santoro J, Stevens T. The validity and accuracy of the Work Productivity and Activity Impairment questionnaire--irritable bowel syndrome version (WPAI:IBS). *Aliment Pharmacol Ther*. 2004 Aug 15;20(4):459–67.
 - 38) Kroenke K, Spitzer RL, Williams JB, Löwe B. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. *Gen Hosp Psychiatry*. 2010 Jul-Aug;32(4):345-59.
 - 39) Biesiekierski JR, Newnham ED, Irving PM, Barrett JS, Haines M, Doecke JD, Shepherd SJ, Muir JG, Gibson PR. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol*. 2011 Mar;106(3):508-14.
 - 40) Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. *Gastroenterology*. 2013 Aug;145(2):320-8.
 - 41) Peters SL, Biesiekierski JR, Yelland GW, Muir JG, Gibson PR. Randomised clinical trial: gluten may cause depression in subjects with non-coeliac gluten sensitivity - an exploratory clinical study. *Aliment Pharmacol Ther*. 2014 May;39(10):1104-12
 - 42) Falony, G., Joossens M, et al. Population-level analysis of gut microbiome variation. *Science* 352, 560–4 (2016).
 - 43) Van Gool S, Piessevaux H, Fischler B, and Tack J. Accuracy of a Simplified IBS Self-Report Questionnaire Compared to the ROME III Criteria in Distinguishing IBS from Organic Disease. *Gastroenterology* 2009; 136(5): A377 (abstract)
 - 44) Tack J, Broekaert D, Fischler B, Van Oudenhove L, Gevers A, Janssens J. A controlled cross-over study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. *Gut*. 2006 Aug;55(8):1095-103.

- 45) Lacy et al., Responders vs clinical response: a critical analysis of data from linaclotide phase 3 clinical trials in IBS-C. NMO 2014; 26: 326-33.
- 46) Lu et al., Optimal recall period and response task for self-reported HIV medication adherence. Aids Behav 2008; 12: 86-94.
- 47) Arts J, Tack J, Holvoet A, Decock S, Lanssens T, Van Hootegeem P. Largest reported prospective evaluation of a simple IBS diet in IBS patients in a regional hospital. UEG journal 2015; 3, A277 (abstract).
- 48) Vierron, E. and B. Giraudeau (2009). "Design effect in multicenter studies: gain or loss of power?" BMC Med Res Methodol 9(1): 39.
- 49) Raes, J et al. Population-level analysis of gut microbiome variation Science. 2016 Apr 29;352(6285):560-4.