# UNDERSTANDING THE PATIENT PERSPECTIVE FOR TREATMENT OUTCOMES AND PREFERENCES IN FUNCTIONAL BOWEL DISORDERS

ROSEL STURKENBOOM

# UNDERSTANDING THE PATIENT PERSPECTIVE FOR TREATMENT OUTCOMES AND PREFERENCES IN FUNCTIONAL BOWEL DISORDERS

**ROSEL STURKENBOOM**

Understanding the patient perspective for treatment outcomes and preferences in functional bowel disorders



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# UNDERSTANDING THE PATIENT PERSPECTIVE FOR TREATMENT OUTCOMES AND PREFERENCES IN FUNCTIONAL BOWEL DISORDERS

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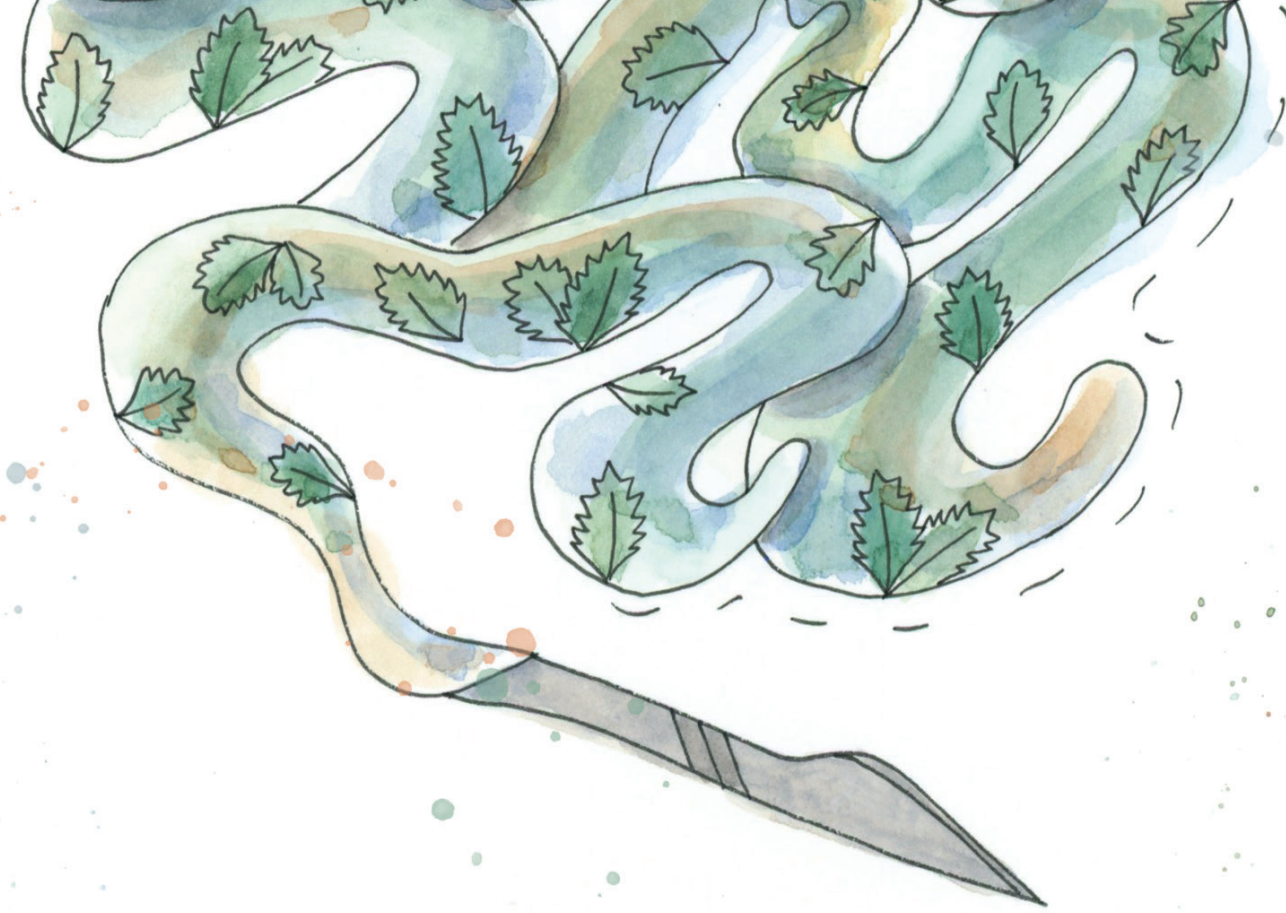

# Chapter 1

## GENERAL INTRODUCTION

# GENERAL INTRODUCTION

Definition

The majority of patients presenting for medical consultation with a gastroenterologist suffer from functional gastrointestinal disorders (FGIDs). FIGDs are now considered as disorders of the gut-brain interaction (DGBIs) and are characterized by persistent and recurring gastrointestinal symptoms. These symptoms occur due to abnormal functioning of the gut, where no structural or organic pathology is identified. The etiology consists of (a combination of) motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing.[1]

DGBIs are very common worldwide.[2] A recent global survey, performed by the Rome Foundation in 26 countries, showed that 43% of the people met the criteria for at least one DGBI. These disorders are significantly associated with lower quality of life and more frequent healthcare usage.[3]

All disorders of the Gut-Brain Interaction are divided by several subdomains: esophageal disorders, gastroduodenal disorders, bowel disorders, centrally mediated disorders of gastrointestinal pain, gallbladder and sphincter of Oddi disorders, anorectal disorders and childhood functional GI (gastrointestinal) disorders (Neonate/Toddler and Child/Adolescent). The subdomain bowel disorders consist of the irritable bowel syndrome (IBS), functional constipation, functional diarrhea, functional abdominal bloating/distention, unspecified functional bowel disorder and opioid-induced constipation.[4] Anorectal disorders include fecal incontinence, functional anorectal pain and functional defecation disorders.[5] This dissertation will focus on IBS, functional constipation and fecal incontinence.

Diagnostic criteria

For diagnosis of DGBIs the Rome Foundation has created diagnostic criteria. In 2016 the Rome IV were established, the replacement of the previous version as from 2006. Since there is more known about the effect of psychological factors, like stress, that are linked to gut function and dysfunction, illness; the term 'gut-brain interaction disorders' is therefore more appropriate.[1] A functional GI disorder relates to the patients' interpretation and the description of the experienced symptoms. These symptoms are clustered together and noticed as a syndrome which are diagnosed by Rome criteria.

Functional bowel disorders are characterized by predominant symptoms of abdominal pain, bloating, distension, and/or bowel habit abnormalities (e.g., diarrhea, constipation or mixed). These symptoms have to last for 6 months or more, is currently active (symptoms presents in the last 3 months) and symptoms are at least 1 day per week present. Besides these criteria, no organic bowel disorders can be present identified by routine diagnostic examinations. The diagnostic criteria for irritable bowel syndrome (IBS), functional constipation, functional diarrhea and fecal incontinence are present in table 1.[4,5] The Bristol stool chart is helpful in evaluating the bowel habit of the patient. It facilitates monitoring of the intestinal transit time.[6] The Bristol stool chart is illustrated in figure 1.

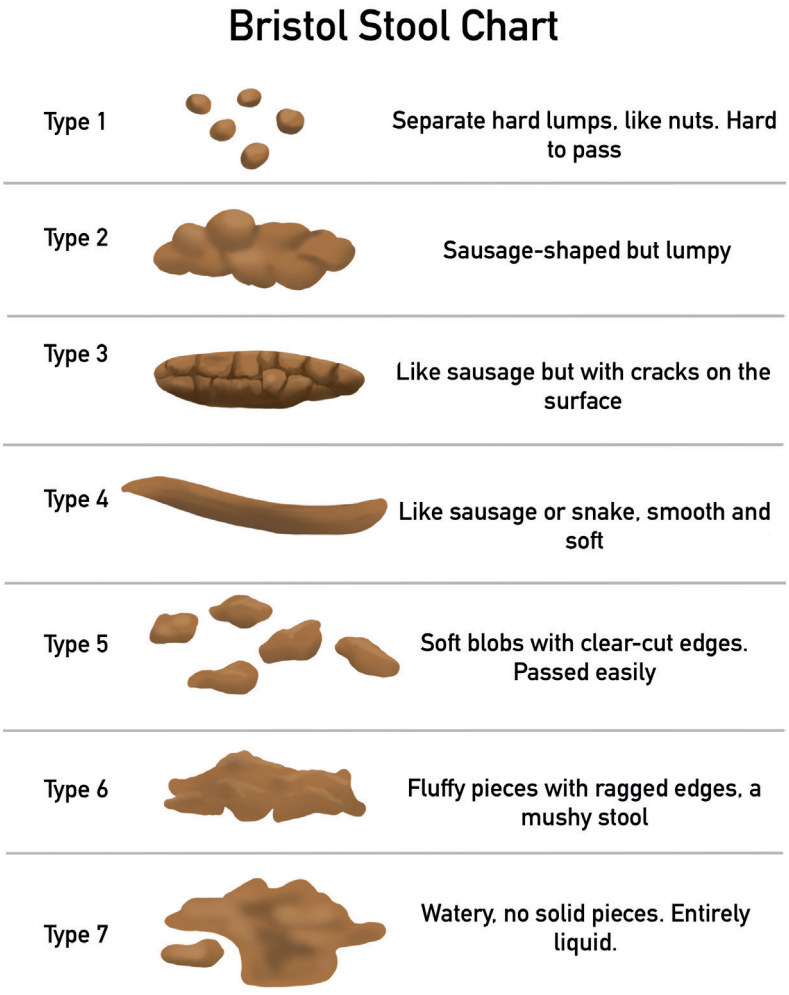


*Figure 1: Bristol Stool Chart*

*Table 1: Diagnostic criteria for the most common functional bowel disorders and anorectal disorders, according to the Rome IV criteria*[7]

| Bowel disorders – Division | Diagnostic Criteria |
|---|---|
| Irritable Bowel Syndrome<br>- IBS-C: IBS with predominant constipation (>25% of bowel movements with Bristol stool form types 1 and 2)<br>- IBS-D: IBS with predominant diarrhea (>25% of bowel movements with Bristol stool form types 6 or 7)<br>- IBS-M: IBS with mixed bowel habits (>25% of bowel movements with Bristol stool form type 1 or 2 and >25% with Bristol stool form type 6 or 7)<br>- IBS-U: IBS unclassified (patients whose bowel habits cannot be accurately categorized into 1 of the 3 groups above) | C1[a]. Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:<br>1. Related to defecation<br>2. Associated with a change in frequency of stool<br>3. Associated with a change in form (appearance) of stool<br><br>[a] Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis. |
| Functional Constipation<br>A functional bowel disorder in which symptoms of difficult, infrequent, or incomplete defecation predominate. Patients do not meet IBS criteria, although abdominal pain and/or bloating may be present but are not predominant symptoms. | 1[a]. Must include 2 or more of the following:<br>a) Straining during more than one-fourth (25%) of defecations<br>b) Lumpy or hard stools (BSFS 1-2) more than one-fourth (25%) of defecations<br>c) Sensation of incomplete evacuation more than one-fourth (25%) of defecations<br>d) Sensation of anorectal obstruction/ blockage more than one-fourth (25%) of defecations<br>e) Manual maneuvers to facilitate more than one fourth (25%) of defecations (e.g., digital evacuation, support of the pelvic floor)<br>f) Fewer than 3 spontaneous bowel movements per week<br>2. Loose stools are rarely present without the use of laxatives<br>3. Insufficient criteria for irritable bowel syndrome<br><br>[a] Criteria fulfilled for the last 3 months with symptom<br>onset at least 6 months prior to diagnosis. |

*Table 1: Continued*

| Bowel disorders – Division | Diagnostic Criteria |
|---|---|
| Functional Diarrhea<br>A functional bowel disorder characterized by recurrent passage of loose or watery stools. Patients do not meet criteria for IBS although abdominal pain and/or bloating may be present, but are not predominant symptoms. | Loose or watery stools, without predominant abdominal pain or bothersome bloating, occurring in >25% of stools.[a,b]<br><br>[a] Criterion fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis<br>[b] Patients meeting criteria for diarrhea-predominant IBS should be excluded |
| **Anorectal disorder** | **Diagnostic criteria** |
| Fecal Incontinence<br>Fecal incontinence is defined as the recurrent uncontrolled passage of fecal material for at least 3 months. Clear mucus secretion must be excluded by careful questioning. FI is often multifactorial and occurs in conditions that cause diarrhea, impair colorectal storage capacity, and/or weaken the pelvic floor. | Recurrent uncontrolled passage of fecal material in an individual with a developmental age of at least 4 years.[a]<br><br>[a] Criteria fulfilled for the last 3 months. For research studies, consider onset of symptoms for at least 6 months previously with 2-4 episodes of FI over 4 weeks. |

As the vast majority of diagnostic criteria for DGBIs are based on symptoms, there is considerable overlap within these diagnostic categories which potentially represents difficulties for symptom management as the same symptom can have a different pathophysiological background. There is, however, one aspect that all DGBIs have in common, i.e., they may lead to reduced quality of life and increased health care demands. The disorders are often associated with patients' psychological status and lifestyle. However, an important difference is the fact that abdominal pain is predominant in IBS patients, whereas bowel movements are predominant in patients suffering from functional constipation and fecal incontinence. Nevertheless, some patients are suffering from multiple syndromes at the same time. The simultaneous presence of common symptoms results in the overlap of different DGBIs. A recent study of patients with DBGIs showed that 81% of the patients (total n = 3555) had overlap disorders.[8] IBS was never found isolated, but were always associated with other upper or lower GI disorders. Also, fecal incontinence was rarely found isolated in patients with DGBIs. Fecal incontinence was reported up to 43.4% in IBS patients[9], whereas 40% of patients who were referred for anorectal investigation met criteria for both fecal incontinence and constipation.[10] Of patients with functional constipation, 11% met criteria for IBS-C according to the Rome definition.[11] The comparison between these three disorders, is further illustrated in figure 2.

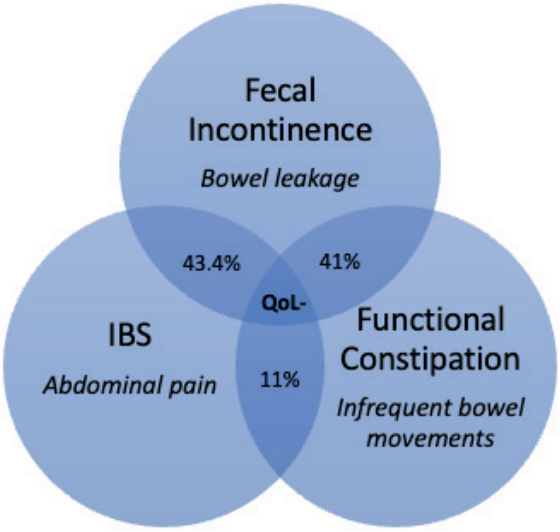


*Figure 2: Similarities and differences between IBS, fecal incontinence and functional constipation, summarized in a Venn Diagram. The percentages show the number of patients who experience overlap symptoms with another DBGI.*

Clinical evaluation

The evaluation of bowel disorders consists of several steps: careful clinical history; physical examination (including rectal examination: dyssynergy? Sphincter defects/ weakness?), minimal laboratory tests; and, when clinically indicated, in case of alarm features, a colonoscopy or other appropriate tests.[4] Because some diseases have similar symptoms, limited testing may be required to rule out colorectal cancer, inflammatory bowel disease (IBD), celiac disease and microscopic colitis. However, diagnostic tests should be used minimally, because the majority of the patients fulfills the diagnostic Rome IV criteria for bowel disorders and alarm features are often absent.[12] A screening colonoscopy is only indicated in patients 50 years and older, or in the presence of alarm symptoms, a family history of colorectal cancer, persistent diarrhea that has failed empiric therapy (to rule out microscopic colitis) or recent change in bowel habit.[13] To evaluate colonic transit time, radiopaque markers could help in diagnosing slow-transit constipation.[14] Anorectal manometry and balloon expulsion testing may also help in diagnosing dyssynergic defecation and in fecal incontinence. For diagnosing a rectocele and intussusception a defecography or similar radiographic diagnostic modality is essential.[15]

Conservative management

The general principles of IBS treatment are related to the dysregulation of the gut-brain axis. The type of predominant symptom, the severity of the symptoms and the psychological determinants will influence the choice of treatment.[4] The clinician needs to identify which treatments are most likely to lead to improvement. A possible management strategy for IBS is represented in figure 3. Mild severity of IBS symptoms and more transit related problems will benefit more from peripheral approaches, like laxatives, fiber, diet restrictions (see figure 3).[16]

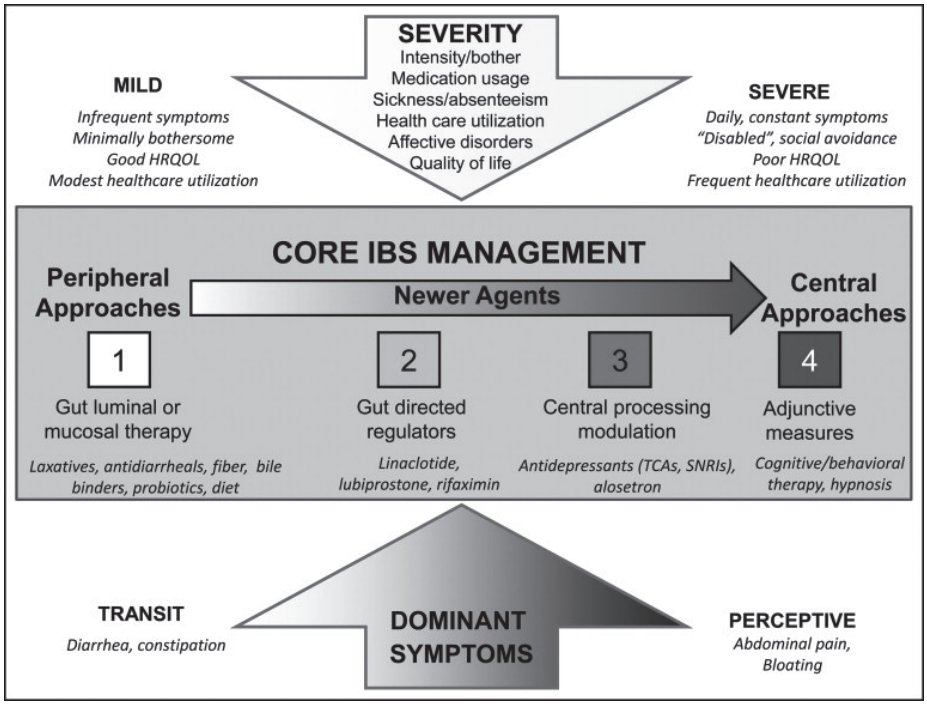


*Figure 3: Management strategy*[16]

Gut directed regulators could be a helpful strategy in IBS-C (linaclotide, lubiprostone) and IBS-D (antidiarrheals such as loperamide) with mild symptoms. Complex presentations (severe symptoms, dominant symptom of abdominal pain) could achieve improvement with treatments that address central nervous system influences on symptom presentation (antidepressants, hypnosis).

Many different therapies for IBS are nowadays available. Treating IBS patients remains challenging, because of the presence of a clinical heterogenous population and the fact that no single treatment will suit all patients. The efficacy of all pharmacological agents, dietary therapies and psychological interventions could be described by the Number needed to treat (NNT), which are displayed in table 2.[13,17–19]

The treatment of functional constipation starts with appropriate education about constipation, fiber intake, exercise, scheduling routine bathroom time after the morning or evening meal and elevating the feet with a foot stool or using a toilet that is lower to the ground to help straighten out the rectum.[4] If this regimen is not efficient, fiber supplement (e.g., psyllium) is the way further. Osmotic laxatives, PEG, saline laxatives (magnesium citrate), stimulant laxatives (e.g., bisacodyl) are also possible effective pharmacological options.[20] Newer agents, such as linaclotide (discussed also above in 'IBS management'), or prucalopride, may provide improvement in overall constipation symptoms.[21]

The conservative treatment of fecal incontinence consists of: psyllium and loperamide (given at an adequate dose (i.e., 2-4mg, 30 minutes before meals). Pelvic floor therapy could be effective in patients suffering from pelvic floor dysfunction.

If all above treatment fails, patients could try to use retrograde washouts by using an enema continence catheter.[22] Because the distal colon and rectum can be emptied, the patients suffer from fewer complaints of constipation/fecal incontinence and quality of life can be improved.[23] Moreover, anal plugs or inserts may be considered.[24]

Surgical management

If all conservative treatments are ineffective for patients suffering from functional constipation and/or fecal incontinence, several surgical options are available. In case of limited sphincter injury, sacral neuromodulation (SNM) could be considered by operating as electrical stimulation of the sacral nerve root by placement of a permanent electrode connected to an embedded stimulator.[25,26] The overall results for both constipation and fecal incontinence are promising so far.[26–29] Larger trials are necessary to explore the efficacy, mainly for long-term outcomes in constipation.

*Table 2: Summary of evidence from randomized controlled trials of pharmacological, dietary and psychological therapies for management of IBS.*

| Pharmacological agents | | Dietary therapies |
|---|---|---|
| *Type of treatment* | *NNT** | *Type of treatment* |
| Antidepressants (overall)<br>- SSRI**<br>- Tricyclic antidepressants (TCA) | 4 (3.5-6)<br>5 (3-16.5)<br>4 (3.5-7) | Low FODMAP diet |
| Antispasmodics | 5 (4-8) | Soluble fiber (e.g., psyllium) |
| Peppermint oil | 4 (3-6) | Elimination diet |
| Antibiotics (rifaximin)*** | 10.5 (8-16) | |
| Probiotics | 7 (5 – 12) | |
| Linaclotide | 6 (5-8) | |
| Lubiprostone**** | 12.5 (8-25) | |
| Eluxadoline**** | 12.5 (8-33) | |
| Alosetron**** | 7.5 (5-16) | |

* NNT = Number needed to treat (95% CI)
** SSRI = Selective serotonin reuptake inhibitors

If sacral neuromodulation fails and/or the patient does not prefer a more invasive solution for therapy resistant constipation, a Malone antegrade continence enema (MACE) could be an option where antegrade washouts could be administered to accomplish production of stool (see figure 4).[30] This method was first introduced in patients with fecal incontinence to become pseudo continent.[31–33] Later studies have shown that it could also be effective in patients who suffer from constipation.[34–36] The long-term results of the MACE are still not clear and more studies about these effects are necessary.

The percutaneous endoscopic colostomy (PEC) is a less invasive option compared to the MACE for treatment of chronic constipation, because this technique is administered endoscopically by the gastroenterologist by performing the pull technique. Long-term efficacy is around 50%.[38]

In case of greater sphincter defects, an artificial bowel sphincter (ABS) could be considered. This device consists of synthetic material and operates to stimulate adequate closure of the anal canal.[39,40] The long-term use opposes a major risk of infection due to usage of synthetic material. More information about the complications that arise with this procedure are needed. Also, a sphincteroplasty could result in reduction of fecal incontinence complaints.

| | Psychological interventions | |
|---|---|---|
| *NNT** | *Type of treatment* | *NNT** |
| 5 (3-11) | Psychological therapies (overall) | 4 (3.5-5.5) |
| 7 (4-25) | Hypnotherapy | 5 (2-10) |
| 9 | Cognitive behavioral therapy | 2-4 |
| | | |
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*** No reimbursement possible in the Netherlands for this indication
**** Not available in the Netherlands

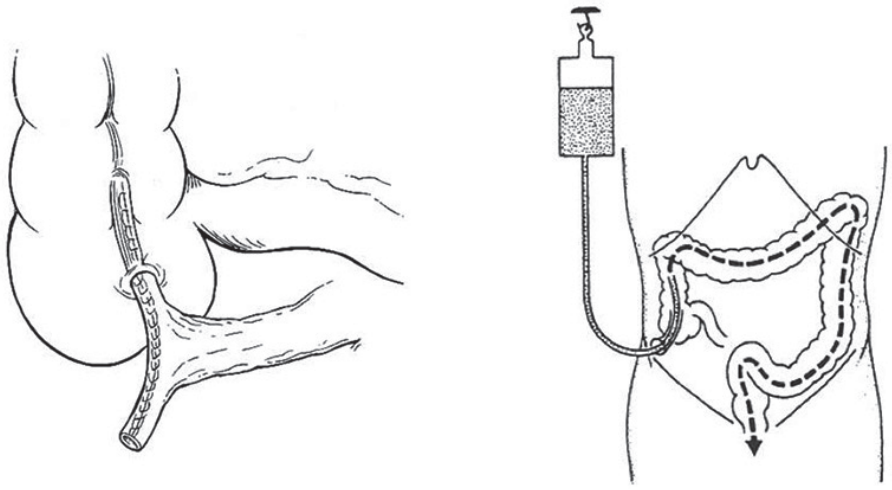

*Figure 4: The Malone Antegrade Continence Enema (MACE)*[37]

A subtotal colectomy with ileorectal anastomosis could be a treatment of last resort for refractory constipation. A final option to treat fecal incontinence, is to receive a colostomy.[24]

Patient reported outcomes

The cornerstone of evaluating therapeutic effects in DGBIs (which are characterized by the lack of biomarkers), is the appropriate assessment of subjective symptoms. The outcomes of all above mentioned treatments should be evaluated to determine if the therapy is effective from a patient perspective. Possible treatment outcomes could be: relieving symptoms and/or improving functional health status and health-related quality of life (HRQOL), improve ability to cope with symptoms and decrease use of health care resources.[41] Since there are no appropriate biomarkers available to measure the effect of a therapy in clinical trials involving functional bowel disorders, guidelines were developed by the US Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) which has led to the definition of PROs, patient reported outcomes, and PROMs, patient reported outcome measures.[42–44] PROMs are tools and/or instruments used to report PROs. Using these measures, patients' perceptions of their illness experience are captured in a structured format. The PRO measure should capture all of the clinically important signs and symptoms of the target population. To measure the overall patient illness severity in IBS clinical trials, the IBS Severity Scoring System instrument is a widely used PROM.[45] This is a condition-specific questionnaire, because it is focused on the specific symptoms and complaints of IBS patients. Another example is the Irritable Bowel Syndrome Quality of Life questionnaire (IBS-QoL).[46] This instrument is often used in clinical trials and captures specific domains relevant for IBS patients, such as 'dysphoria', 'body image', 'food avoidance', 'social reaction'. In general, condition-specific HRQOL instruments appear to be more responsive than generic HRQOL instruments for specific symptoms and complaints of a disease. However, when assessing the cost-effectiveness of treatment, the use of a generic health related quality of life questionnaire, the EQ-5D-5L is required in most countries. Patients are asked to fill in the EQ-5D-5L at different measurement moments after which utility scores are calculated based on a combination of their responses and a social tariff.[47] These utility scores are subsequently used to calculate a quality adjusted life year (QALY) which in turn enables comparison of cost-effectiveness between new and established treatments.[48] Hence, although, it may be more meaningful to use a condition-specific questionnaire in clinical studies, because they capture more disease-specific or relevant aspects of the disease. This questionnaire does not allow calculation of QALYs for use in economic evaluations. The question is whether empirical mapping to predict EQ-5D-5L utility values from the scores of the non-preference-based IBS-QoL instrument could be a solution.

Practical implications for health care

To determine which treatment is a good fit for the individual patient in clinical practice, the treatment benefit derived from clinical trials needs to be reviewed. One efficacy endpoint that could be evaluated is the NNT (Number Needed to Treat). This is an index which shows the probable clinical efficacy of a therapy where the higher the NNT, the less effective the treatment is in terms of trial outcome and timescale. The NNT shows if the tested therapy gives benefit compared to a control group (placebo) in a clinical trial.

However, the extent of the placebo response has major implications for the success of the trial outcome. Recent meta-analysis showed a pooled placebo response rate in pharmacological trials in IBS of 27.3% for the global improvement responder endpoint.[49] Also, in other DGBIs rates up to 40% are reported.[50] Therefore, due to this high placebo rate the findings of DGBI studies and the NNT, should be interpreted with caution. In addition, many studies in DGBIs use different outcome parameters, making comparison particularly troublesome.

In the management of functional bowel disorders, multiple appropriate therapies are available to choose from. There is no single effective therapy that suits all these patients, because they all have heterogenous complaints with underlying different (psychological) comorbidities and triggers. These various aspects may challenge the management of functional bowel disorders and forces clinicians to seek different strategies during decision making. Therefore, apart from reviewing efficacy endpoints from clinical trials, other treatment aspects are important.[51]

Shared-decision making is a suitable mode to operate during clinical decision making, especially in the area of DGBIs where more than one reasonable path forward exists.[52,53] This principle consists of a process in which both patient and clinician can share equally in the decision-making process with the clinician explaining the treatment options and the patient exploring their needs, wishes and priorities in life. This patient-centered care will improve the quality of healthcare where clinicians and patients work together to produce the best outcomes possible.[54] Decision aids could be helpful in providing guidance throughout the process of decision-making to help with preference-sensitive decisions.[55,56] A preference-sensitive decision implies that there is more than one appropriate option and that patients will decide based on their wishes, depending on the balance of benefits and harms.[57] This kind of decisions are prominent in shared-decision making and are therefore extremely relevant in the management of DGBIs.

Understanding these important treatment factors, like preferences for the duration of therapy, side effects or time required to complete therapy, is fundamental in the process of shared-decision making. This information contributes to a better patient-centered care and a higher compliance to treatment.[58] Identifying patient wishes during consultation could have a major positive impact on the patient satisfaction with the current IBS health care.[59] Being acquainted which aspects of disease management could be discussed, may provide guidance throughout the consultation with the treatment-seeking patient and improve communication between clinicians and patients.

Patients' perspectives could be used as input for obtaining values or weights indicating trade-off preferences for treatment. PROMs in clinical trials quantify health outcomes, but these instruments unfortunately do not incorporate patient preferences and their trade-offs.[60] Identifying patient preferences could therefore be relevant. A technique to quantify these subjective preference weights in health care, is to perform a discrete choice experiment.[61] This methodology asks patients to make trade-offs between various attributes of health services to elicit their preferences and show the relative importance of the attributes. As patients' preferences play a key role in patient satisfaction, which in turn influences adherence and ultimately clinical outcomes, DCE-measured preference data add value to the shared decision-making process. DCE is ideally useful to perform when multiple appropriate treatments are available. However, these exact treatment preferences are not yet identified e.g., in IBS patients.

## AIM AND OUTLINE OF THE THESIS

The overall aim of this thesis is to explore different patient-centered measurement techniques that contribute in quantifying outcomes in the field of functional bowel disorders. We aim to explore different outcomes using PROs and preferences. The numerous available treatment options for DGBIs where no therapy suits all patients, drive us to search for new insights in long-term outcomes and decision-making, wherein revealing preferences of patients becomes more important. Different steps of quantifying treatment outcome will be discussed in this thesis. These steps are summarized in figure 5.

In accordance with the aim, this thesis is divided in three parts.
**Part I** focuses on the measurement of quality of life and the evaluation of treatment preferences of IBS patients. At first, we focus on the measurement of HRQOL to explore the treatment benefits. We aimed to ascertain what kind of QoL questionnaire was the most responsive in capturing HRQOL in IBS patients. Therefore, in **Chapter 2** we aimed to explore the convergent and known-group validity of both a frequently used questionnaire for health-related Quality of Life worldwide, the EQ-5D-5L, and a condition-specific questionnaire often used in clinical trials with IBS patients, the IBS-QoL. Because the IBS-QoL is not preference-based and does not allow calculation of QALYs, we aimed to develop a novel mapping algorithm which enable IBS-QoL scores to be transformed into utility values for use in economic evaluation.

Various treatments are available for IBS patients, which are comparable in efficacy. An important determinant of an effective treatment strategy is to involve the patient in shared-decision making by inquiring their wishes and needs. Therefore, we performed health preference research in IBS patients to get more insight into their treatment preferences. In **Chapter 3** we aimed to assess the important aspects of treatment according to both IBS patients and physicians by means of semi-structured interviews and a survey. We also aimed to explore the differences between patients and practitioners. With the input of part of this research, we examined treatment preferences by performing a discrete choice experiment among patients with IBS in **Chapter 4**.

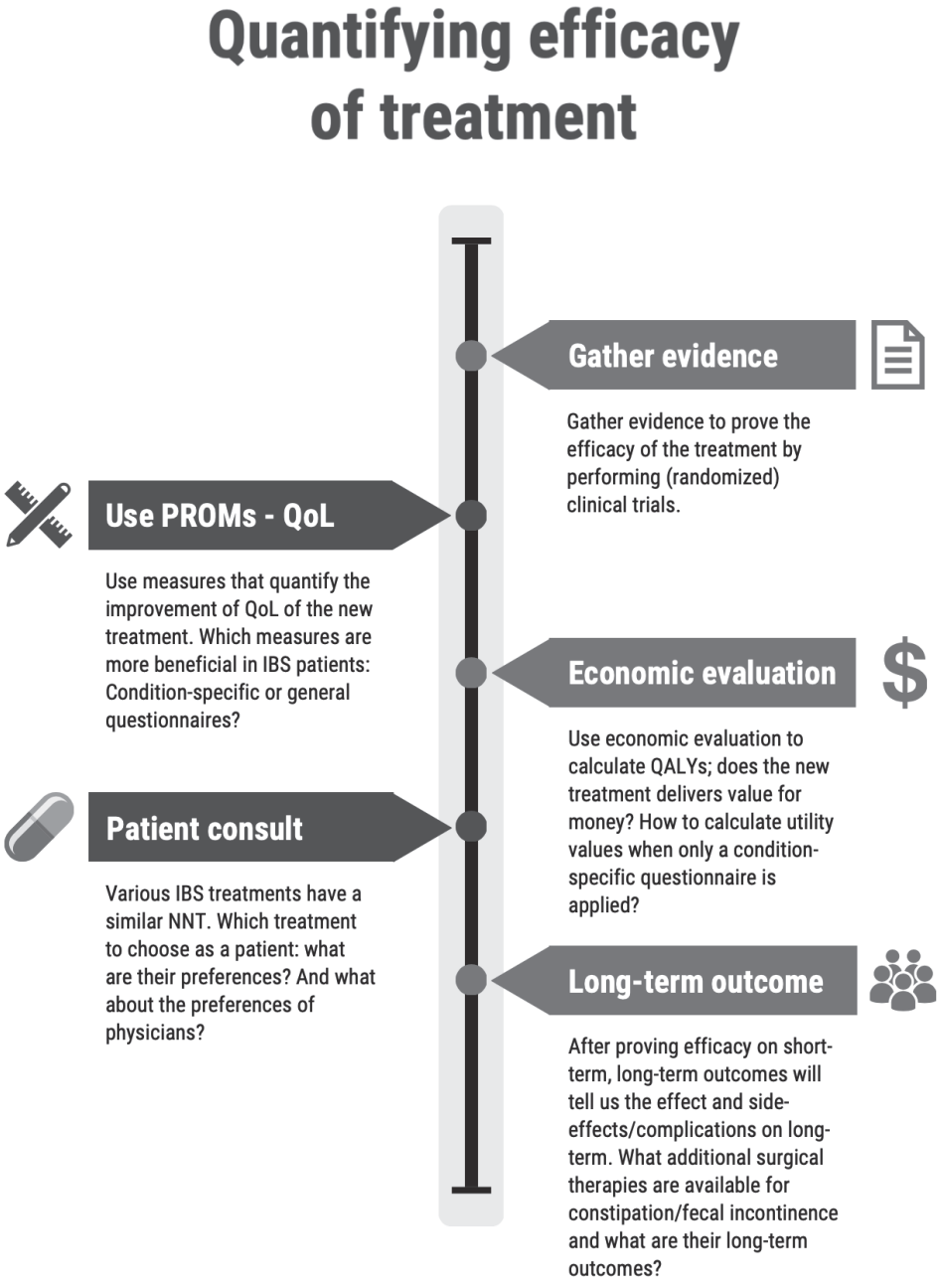


*Figure 5: Important steps of evaluating treatment outcome and implementation into health care practice.*

For patients with functional bowel disorders refractory to conservative treatment, several surgical options are available. The long-term effects, efficacy and complications, of surgical managements are still unknown. Therefore, in **Part II** we assessed the long-term outcomes of several surgical interventions available for patients with functional bowel disorders. In **Chapter 5** we aimed to assess the success rate, QoL- and morbidity scores of the MACE in patients with fecal incontinence or constipation. Long-term outcomes of sacral neuromodulation were investigated in functional constipation patients in **Chapter 6**. In **Chapter 7** we aimed to explore the long-term outcomes of the artificial bowel sphincter (ABS) in patients with refractory fecal incontinence.

Finally, in **Part III**, the main results of all studies presented in this thesis will be summarized and discussed. In **Chapter 8** directions for further research and future perspectives are suggested in relation to our studies. A summary of all main findings is available in **Chapter 9**.

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# Part 1

## QUALITY OF LIFE AND TREATMENT PREFERENCES IN IBS PATIENTS

# Chapter 2

## THE ESTIMATION OF A PREFERENCE-BASED SINGLE INDEX FOR THE IBS-QOL BY MAPPING TO THE EQ-5D-5L IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

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## ABSTRACT

Purpose

The Irritable Bowel Syndrome Quality of Life (IBS-QoL) questionnaire is a commonly used and validated IBS-specific QoL instrument. However, this questionnaire is in contrast to the EQ-5D-5L, not preference-based and as such does not allow calculation of QALYs. The objective of this study was to describe the convergent- and known-group validity of both questionnaires and to develop a mapping algorithm from EQ-5D-5L which enable IBS-QoL scores to be transformed into utility scores for use in economic evaluations.

Methods

We used data from two multicenter randomized clinical trials, which represented the estimation- and external validation dataset. The convergent validity was investigated by examining correlations between the EQ-5D-5L and IBS-QoL and the known-group validity by calculating effect sizes. Ordinary least squares (OLS), censored least absolute deviations (CLAD), and mixture models were used in this mapping approach.

Results

283 IBS patients were included (N = 189 vs. N = 84). Mean IBS-QoL score was 71.13 (SD 15.66) and mean EQ-5D-5L utility score was 0.73 (SD 0.19). The overall sensitivity of the IBS-QoL and EQ-5D-5L to discriminate between patient and disease characteristics was similar. CLAD model 4, containing the total IBS-QoL score and squared IBS-SSS (IBS severity scoring system), was chosen as the most appropriate model to transform IBS-QoL scores into EQ-5D-5L utility scores.

Conclusion

This study reports the development of an algorithm where the condition-specific questionnaire IBS-QoL can be used to calculate utility values for use in economic evaluations. Including a clinical measure, IBS-SSS, in the model improved the performance of the algorithm.

# INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic disorder of the gut-brain interaction characterized by altered bowel habits (constipation, diarrhea or mixed pattern) and abdominal pain. IBS affects a large number of people worldwide, 4.4-4.8% according to the Rome IV criteria.[1] These symptoms have a substantial impact on patients' quality of life (QoL) and are associated with considerable use of healthcare resources and secondary significant economic impact on individuals, healthcare systems and society. Between 15% and 50% of patients with IBS report absenteeism (work time missed) due to their symptoms and up to 34% report presenteeism (impairment while at work).[2,3] To accomplish symptom control to improve quality of life (QoL), various treatments for IBS are available nowadays. These include diets, psychological interventions and several types of pharmacological agents.[4,5]

The cost-effectiveness of these treatments is generally examined using cost-utility analysis.[6,7] In health care decision making and reimbursement procedures, the outcome of a cost utility analysis is known as quality-adjusted life years (QALY) which is used to determine whether a new therapy delivers value for money.[8] The quality of life side of the QALY can be assessed with a generic questionnaire, such as the frequently used EQ-5D (European Quality of Life Five Dimension questionnaire), which is designed to cover the core dimensions of health that are relevant across all medical conditions and to allow comparisons between patient groups.[9,10] In order to capture the impact of IBS on QoL, patients complete the EQ-5D-3L or the recently developed 5-level questionnaire after which a value set is applied to generate utility values. For example, mean-utility values in IBS patients range between 0.50 – 0.75, where 1 is equivalent to perfect health and 0 is death.[3,8,11–14] The utility scores are subsequently used to calculate QALYs.[8] However, in clinical studies a non-preference-based condition-specific questionnaire is often preferred because they capture more disease-specific or relevant aspects of the disease from a clinical and patients' perspective. The Irritable Bowel Syndrome Quality of Life questionnaire (IBS-QoL) is a condition-specific instrument for IBS patients which incorporates specific subdomains such as food avoidance, bowel habits and the effect on the social/sexual relationships.[15] EuroQoL-5D and IBS-QoL have both been proven to be valid for assessing QoL in IBS patients.[3,8] However, previous studies, in which different disease populations were examined, have suggested that condition-specific measures are more responsive than the generic measure with regards to capturing changes in health.[16–19] The involvement of the psychological domain in QoL questionnaires is relevant for IBS patients, due to the high prevalence of anxiety and depression disorders among these category of patients which has a significant impact on the disease course and the choice of therapy.[2,12,20–23] The EQ-5D-5L has one Anxiety/

Depression dimension, where IBS-QoL has several domains containing psychological questions. Whether the general EQ-5D and the condition-specific IBS-QoL are both sensitive enough to capture (mental) health changes is not yet investigated in IBS patients. Therefore, the difference in responsiveness of both the EQ-5D-5L and IBS-QoL should be further explored.

Because the IBS-QoL is specifically designed for IBS patients and uses aspects that are salient to this specific patient group, the IBS-QoL is often preferred in clinical studies. Up to now however, there is no proper method available to convert IBS-QoL scores into utilities to calculate QALYs. A mapping approach for the IBS-QoL to the EQ-5D-5L would be highly valuable to enable prediction of utility scores for modeling studies in which evidence is used from trials where in the past only the IBS-QoL questionnaire is included.[24] Mapping is recognized by the National Institute for Health and Clinical Excellence (NICE) for generating utility information for non-preferences based measures and the ISPOR(International Society for Pharmacoeconomics and Outcomes Research) guidelines have provided recommendations about this composed algorithm between a base measure and a target measure.[25–27]

To the best of our knowledge, no study thus far has performed a mapping approach to predict utility values for the condition-specific measure IBS-QoL for use in IBS patients. The goal of this study is to examine the convergent- and known-group validity between the EQ-5D-5L and the IBS-QoL and use empirical mapping to predict EQ-5D-5L utility values from the non-preference-based measure IBS-QoL scores in IBS patients.

## METHODS

Datasets

Two studies were included for this mapping approach. The first study (N = 189) is a three-armed multicenter placebo-controlled randomized controlled trial where the efficacy of peppermint oil was assessed, the PERSUADE study (NCT02716285).[28] Patient inclusion took place in the Netherlands from August 2016 through March 2018. This study was used as estimation data set to create the mapping algorithm. The second study (N = 84) is a three-armed multicenter randomized controlled non-inferiority trial where the efficacy of online hypnotherapy versus face-to face hypnotherapy is compared with online psychoeducation as control condition (FORTITUDE NCT03899779). Patient inclusion commenced in the Netherlands in July 2019 and is still ongoing. This trial was used as study data set to test the algorithm for external validation.

Inclusion criteria were similar in both studies. Subjects were included between age 16 and 75 years, diagnosed with IBS according to the Rome IV criteria and had no history of other causes for the abdominal complaints, such as Crohn's disease and coeliac disease.[29] They were both recruited via primary and secondary/tertiary healthcare. There was a slight difference in the age limits for inclusion between both studies; in the estimation data set subjects between 18-75 years of age are included, in the validation set subjects were included with 16-65 years of age. This is due to the changed age limit by the Dutch Medical Research Involving Human Subjects Act in august 2016 where research is allowed with subjects from 16 years and older.[30] The upper limit of age was adjusted due to involvement of online therapies. Exclusion criteria of both trials included insufficient command of the Dutch language, major surgery to the lower gastrointestinal tract, current pregnancy or lactation, and respectively peppermint oil usage or hypnotherapy in the last 3 months prior to inclusion. Patients with a positive screening for anxiety and depression (score $^{3}$10 of GAD-7 and PHQ-9 respectively) in the validation dataset were interviewed by the researcher and only patients with clinically significant anxiety or depression were excluded. In the estimation dataset, these scores were not incorporated during patient screening.

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Both studies were reviewed and approved by the ethics committee at the Maastricht University Medical Center (METC 162009; METC 18-037). Informed consent was obtained from all patients prior to being included in the study.

Questionnaires

Both the EQ-5D-5L and IBS-QoL were completed in these studies. The EQ-5D-5L is a preference-based measure and consists of five-dimensions mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with five severity levels (no, slight, moderate, severe, extreme problems).[10,31] This questionnaire is validated for use in IBS-patients.[3,8] In the Netherlands, it is recommended by the National Health Care Institute (ZIN) for use in cost-utility analyses and a Dutch Tariff for the EQ-5D-5L is applied to create the utility values.[32]

The IBS-QoL is a condition-specific instrument that is used to assess the impact of IBS and effects of treatment. It consists of 34 questions which covers eight domains including: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual and relationships.[15,33] Each item has a five-point response scale (not at all, slightly, moderately, quite a bit, extremely). The responses are summed and averaged for a total score and transformed to a scale between 0-100; higher scores indicating better IBS specific QoL. The Generalized Anxiety Disorder-7 (GAD-7)[34] and Patient Health Questionnaire-9 (PHQ-9)[35,36] were completed to screen for anxiety disorders respectively depressive disorders. A score of 10 or higher in both questionnaires was considered as cut-off point for (possible) diagnosis of the specific disorder, generalized anxiety or depression disorder, and further examination to confirm diagnosis is recommended at that point. The Irritable Bowel Syndrome Severity Scoring System (IBS-SSS) was completed to measure the severity of the symptoms (0-500).[37] It consists of five items with a maximum score of 100; higher scores indicate more severe symptoms.

Statistical Analysis

Descriptive analyses were performed for patient characteristics. Whether the IBS-QoL and EQ-5D-5L are sensitive to discriminate between relevant disease or patient characteristics was examined by comparing the mean values using paired t tests.[38] We hypothesized that both questionnaires would show similar levels of discriminatory power with regard to patient characteristics (age, gender and BMI). In addition, we hypothesized that the IBS-QoL would have greater discriminatory power for disease characteristics (IBS severity, depression and anxiety) compared to EQ-5D-5L.

The known-group validity was analyzed using standardized effect sizes, dividing the difference in means by the standard deviation. We used Cohen's d to calculate the effect size by using the pooled standard deviation of the population, where 0.2 was considered as a small effect, 0.5 a medium effect and 0.8 a large size.[39] If the sample size was small (<20), Hedges' g was used to describe the effect size.[40] Glass' delta was chosen if the variance in both groups significantly differed.[41]

The data from both trials were used to estimate a direct response mapping algorithm between IBS-QoL and EQ-5D-5L. The mapping approach was conducted following the principle described by Brazier *et al.*[42] and the ISPOR guidelines[27]. One of the criteria of mapping is the essential of overlap between the start and target measure to cover the important aspects of HRQoL. Mapping would be unsuccessful if there is no conceptual overlap.[26] At first, convergent validity was investigated by examining the correlations between the paired observations and their domains using Spearman correlation coefficients. Correlation coefficients of 0.10, 0.10-0.50, and >0.50 were considered as weak, moderate, and strong associations, respectively.[43] Second, different types of regression models were estimated with increasing complexity. As recommended by Brazier *et al.* our initial analysis included a simple model where the regression consists of the target measure onto the total score of the starting measure (IBS-QoL).[42] Afterwards the domain scores of the IBS-QoL, whether or not combined with covariates, were added to the algorithm.[42] We tested whether the models improved when including clinical covariates (age, BMI, sex, IBS-subtype, IBS-SSS).[27] Only age and the clinical variable IBS-SSS significantly improved the models ($p \leq 0.05$). These two variables were therefore included in the final models, as shown below.

The included models were specified as the following equations:
EQ-5D-5L is the EQ-5D-5L utility score; IBS-QoL is the IBS-QoL total score; Dysphoria score is the score of the domain Dysphoria of the IBS-QoL; Body Image score is the score of the domain Body Image of the IBS-QoL; the IBS-SSS score is the IBS Severity Score (0-500). Also, the squared term of the IBS-SSS is included in the models to capture non-linear effect. $b_0$ is a constant, $b_1$, $b_2$, $b_3$, are the coefficients to be estimated.

1. Total IBS-QoL score model
   $EQ\text{-}5D\text{-}5L = b_0 + b_1 * \text{IBS-QoL score}$
2. Total IBS-QoL score + IBS-SSS score model + age
   $EQ\text{-}5D\text{-}5L = b_0 + b_1 * \text{IBS-QoL score} + b_2 * \text{IBS-SSS score}$
3. Domain Dysphoria score + domain Body Image Score model
   $EQ\text{-}5D\text{-}5L = b_0 + b_1 * \text{Dysphoria score} + b_2 * \text{Body Image score}$
4. Total IBS-QoL score + Squared IBS-SSS score model
   $EQ\text{-}5D\text{-}5L = b_0 + b_1 * \text{IBS-QoL score} + b_2 * \text{IBS-SSS score}^2$
5. Dysphoria score + Body image score + Squared IBS-SSS score model + age
   $EQ\text{-}5D\text{-}5L = b_0 + b_1 * \text{Dysphoria score} + b_2 * \text{Body Image score} + b_3 * \text{IBS-SSS score}^2$

Overall, EQ-5D-5L utility score is the dependent variable in the different regression equations, while the IBS-QoL total score, the separate domains and the IBS-SSS score were used as predictors.

Three statistical approaches were used to estimate these five models. The first technique was the ordinary least squares (OLS) estimator, because it is the most widely used analysis and generates good estimate results, mostly better than the alternatives.[26,44] It estimates parameters by minimizing the sum of squared errors of data. However, because the utilities of the EQ-5D-5L in our population were censored (skewed left), we investigated the option for using estimators for censoring issues. The censored least absolute deviations (CLAD) estimator was chosen above the Tobit estimator, because CLAD is robust against departures of errors from homoskedasticity and normality.[45,46]

The Adjusted Limited Dependent Variable Mixture Model (ALDVMM) was used as third mapping model, which was developed to deal with the distributional features of the EQ-5D.[47] It accounts for the gap between 1 (full health) and the highest EQ-5D index value below 1 (truncation point). We used the command aldvmm in Stata to fit these models.[48] First, we estimated the mixture models with two to five components to determine that the model with 4 components has the best fit (highest Likelihood and the lowest BIC (Bayesian information criterion)). Models were conducted with and without inclusion of the truncation point. Model fit was better when the truncation point was included.

Models that were developed using data from one trial, were used to predict EQ-5D values in the other trial (external validation). Model fit was assessed by comparing the mean absolute error (MAE) and the root-mean-square error (RMSE) in this sample.[27] The lower the MAE/RMSE, the better the predictive accuracy of the model. A scatter plot of observed and predicted values in the estimation sample was provided of the best model. The best fitting model was selected by the value of MAE/RMSE, the predictive performance and by the convenience of the algorithm (simplicity e.g.) for usage in clinical practice.[49] Greater complexity of the algorithm by including more clinical and demographic characteristics does not always seem to be beneficial.[42] A significance level of $p<0.05$ was applied for all analysis. All analyses were performed in Stata version 14.1 (Stata Corp., College Station, Texas, USA) and IBM SPSS Statistics version 27.0 (Armonk, NY: IBM Corp.).

## RESULTS

Baseline characteristics of the population

In total 273 IBS patients were included in this mapping approach. The estimation data set consisted of 189 IBS patients. The external validation data set consisted of 84 patients. The baseline patient characteristics are shown in table 1. The mean age of the population was 35.07 years and 76.20% was female. The mean IBS-SS score was 278.17 (SD 76.17) which implies a moderate severity of IBS symptoms. The mean quality of life (QoL) according to the general questionnaire EQ-5D-5L was 0.73 (SD 0.20) and the mean QoL according to the condition-specific questionnaire IBS-QoL was 71.13 (SD 15.66).

*Table 1: Baseline characteristics of the population*

| | Estimation dataset N = 189 | Validation Dataset N = 84 | Total N = 273 |
|---|---|---|---|
| Mean age, years (SD) | 34.01 (13.29) | 37.44 (13.42) | 35.07 (13.39) |
| Female sex, n (%) | 147 (77.80) | 61 (72.60) | 208 (76.20) |
| Median BMI (kg/m$^2$) (SD) | 25.57 (5.35) | 24.75 (4.73) | 25.32 (5.17) |
| IBS subtype | | | |
| - Diarrhea (IBS-D), n (%) | 83 (43.90) | 27 (32.10) | 110 (40.30) |
| - Constipation (IBS-C), n (%) | 42 (22.20) | 23 (27.40) | 65 (23.80) |
| - Mixed (IBS-M), n (%) | 40 (21.20) | 19 (22.60) | 59 (21.60) |
| - Undefined (IBS-U), n (%) | 24 (12.70) | 15 (17.90) | 39 (14.30) |
| Mean IBS-SSS score (SD)[a] | 276.48 (71.95) | 281.98 (85.25) | 278.17 (76.17) |
| Severity of IBS (IBS-SSS)[a] | | | |
| - Mild IBS, n (%) | 15 (7.90) | 8 (9.50) | 23 (8.40) |
| - Moderate IBS, n (%) | 100 (52.90) | 34 (40.50) | 134 (49.10) |
| - Severe IBS, n (%) | 74 (39.20) | 42 (50.00) | 116 (42.50) |
| Mean total IBS-QoL score (SD) | 73.02 (15.15) | 66.88 (16.05) | 71.13 (15.66) |
| Mean total EQ-5D-5L score (SD) | 0.73 (0.19) | 0.72 (0.21) | 0.73 (0.20) |
| Mean depression score (PHQ-9) (SD)[b] | 6.77 (4.55) | 5.83 (3.93) | 6.48 (4.38) |
| Depression (PHQ-9)[b] | | | |
| - Minimal symptoms, n (%) | 75 (39.70) | 38 (45.20) | 113 (41.40) |
| - Mild depression, n (%) | 77 (40.70) | 30 (35.70) | 107 (39.40) |
| - Moderate depression, n (%) | 20 (10.60) | 13 (15.50) | 33 (12.10) |
| - Moderately severe depression, n (%) | 14 (7.40) | 3 (3.60) | 17 (6.20) |
| - Severe depression, n (%) | 3 (1.60) | 0 | 3 (1.10) |
| Mean anxiety score (GAD-7) (SD)[c] | 5.39 (4.35) | 4.92 (3.74) | 5.25 (4.17) |

*Table 1: Continued*

| | Estimation dataset N = 189 | Validation Dataset N = 84 | Total N = 273 |
|---|---|---|---|
| Anxiety (GAD-7)[c] | | | |
| - Minimal symptoms, n (%) | 91 (48.10) | 41 (48.80) | 132 (48.40) |
| - Mild anxiety, n (%) | 69 (36.50) | 32 (38.10) | 101 (37.00) |
| - Moderate anxiety, n (%) | 17 (9.00) | 10 (11.90) | 27 (9.90) |
| - Severe anxiety, n (%) | 12 (6.30) | 1 (1.20) | 13 (4.80) |

[a] The IBS-SSS, IBS symptom severity score, consists of 5 items with a maximum score of 100; a higher score indicates severe IBS symptoms. The total score (range 0-500) can be categorized as: Mild IBS (score < 175), Moderate IBS (175-300) and Severe IBS (300-500)

[b] The PHQ-9, Patient Health Questionnaire-9, is a 9 item questionnaire to screen for a depressive disorder. The total score (range 0-27) can be categorized as: Minimal symptoms (score 0-4), Mild depression (5-9), Moderate depression (10-14), Moderately severe depression (15-19), Severe depression (20-27).

[c] The GAD-7, Generalized Anxiety Disorder-7, is a 7 item questionnaire to screen for an anxiety disorder. The total score (range 0-21) can be categorized as: Minimal symptoms (score 0-4), Mild anxiety (5-9), Moderate anxiety (10-14), Severe anxiety (15-21).

Convergent- and known-group validity

The convergent validity between the IBS-QoL instrument and the EQ-5D-5L were investigated by Spearman's correlation coefficient and results are available in table 2. The correlation between these two instruments for the total score showed a moderately strong significant correlation (0.472). The majority (57.50%) of the correlations between the subscores of the IBS-QoL and the subscores of the EQ-5D-5L were statistically significant. All subscores of the IBS-QoL were positively significantly correlated with the total EQ-5D-5L scores. The subdomains dysphoria (0.420*) and body image (0.438*) of the IBS-QoL reached the strongest significant correlation with the total EQ-5D-5L score.

The analysis of the known-group validity of both HRQoL instruments is shown in table 3. Both the IBS-QoL and the EQ-5D-5L revealed a similar (very) small non-significant difference in QoL score or utility value with respect to gender (in the estimation set males have lower health state scores/values, whereas in the validation set females have lower health state scores/values). Patients younger than 40 years old showed lower quality of life scores or utility values and this effect was significant in the validation set. Greater effect sizes were seen in the validation set compared to the estimation set. This is probably due to a higher mean level of age and the presence of a greater percentage of the subgroup of patients aged $^{3}$ 40 years in the validation dataset. The IBS-QoL score

and EQ-5D-5L value were both lower in patients with severe IBS symptoms compared to patients with mild/moderate symptoms (all were significant). The difference in effect sizes between both datasets could be explained by the greater percentage of patients included with mild/moderate symptoms in the estimation dataset compared to the validation dataset. This observation is therefore reflected in the different effect sizes of the depression and anxiety subgroups, whereby patients with more severe symptoms have often more psychopathology. Patients with a depression had significantly lower health scores and values, both according to IBS-QoL and EQ-5D-5L in the validation set. Patients with anxiety also had lower health-related quality of life, according to both instruments. The IBS-QoL reported greater effect sizes compared to EQ-5D-5L with respect to the characteristics gender (male vs female), age (<40 vs >40 years old) and the severity of symptoms according to the IBS-SSS (mild/moderate symptoms vs severe symptoms) and is therefore more sensitive to discriminate here. The discriminatory power of the IBS-QoL and EQ-5D-5L is similar for the BMI score and the presence of depression, but for anxiety the EQ-5D-5L is slightly more sensitive.

*Table 2: Spearman's correlation coefficients between IBS-QoL values and EQ-5D-5L values*

| | EQ-5D mobility | EQ-5D selfcare | EQ-5D usual activities | EQ-5D pain | EQ-5D anxiety and depression | Total EQ-5D score |
|---|---|---|---|---|---|---|
| IBS-QoL Dysphoria | -0.061 | 0.080 | -0.389* | -0.204* | -0.429* | 0.420* |
| IBS-QoL interference with activity | -0.142 | -0.058 | -0.459* | -0.159* | -0.323* | 0.378* |
| IBS-QoL body image score | -0.106 | -0.012 | -0.354* | -0.322* | -0.377* | 0.438* |
| IBS-QoL health worry score | -0.041 | 0.080 | -0.277* | -0.231* | -0.221* | 0.307* |
| IBS-QoL food avoidance score | -0.021 | -0.012 | -0.371* | -0.165* | -0.258* | 0.275* |
| IBS-QoL social reaction score | 0.055 | 0.154* | -0.312* | -0.140 | -0.277* | 0.280* |
| IBS-QoL Sexual score | -0.097 | -0.033 | -0.226* | -0.130 | -0.185* | 0.224* |
| IBS-QoL Relationships | -0.059 | 0.031 | -0.290* | -0.089 | -0.328* | 0.317* |
| IBS-QoL overall score | -0.072 | 0.040 | -0.482* | -0.239* | -0.425* | 0.472* |

** Significance level p<0.05*

*Table 3: Differences in baseline health state values with corresponding effect sizes according to patient and disease characteristics*

| | | Estimation dataset (N = 189) | | |
|---|---|---|---|---|
| | | IBS-QoL | | |
| | No. (N =) | Mean | *r value* | Effect size |
| Male | 42 | 71.219 | *0.458* | -0.165 |
| Female | 147 | 73.529 | | |
| Aged < 40 | 130 | 72.115 | *0.226* | -0.191 |
| Aged ³ 40 | 59 | 75.000 | | |
| BMI < 25 | 101 | 71.717 | *0.229* | -0.177 |
| BMI ³ 25 | 88 | 74.392 | | |
| Mild/moderate symptoms (IBS-SSS <300) | 115 | 76.113 | *0.001** | 0.473 |
| Severe symptoms (IBS-SSS>300) | 74 | 68.204 | | |
| Depression (PHQ-9 ³10) | 37 | 75.219 | *0.325* | -0.181 |
| No depression (PHQ-9 <10) | 152 | 72.479 | | |
| Anxiety (GAD-7 ³10) | 29 | 72.978 | *0.936* | -0.016 |
| No anxiety (GAD-7 <10) | 160 | 73.225 | | |

** Significance level p<0.05*

Mapping results

Data of IBS-QoL and EQ-5D-5L in the estimation dataset were both left-skewed, where the EQ-5D-5L values were bimodally distributed. The EQ-5D-5L values were distributed as follows: 25% of the observations were between -0.02 and 0.68, 25% were between 0.68 and 0.82, 25% were between 0.82 and 0.86 and 25% were between 0.86 and 1.00 (full health). The truncation point for EQ-5D-5L is 0.92.

The goodness of fit results of the five models are shown in table 4. The MAE ranged from 0.117 to 0.118 and the RMSE from 0.166 to 0.171 for the OLS mapping functions. OLS model 4 performed best, containing the lowest MAE and RMSE. The MAE ranged from 0.111 to 0.114 and the RMSE from 0.168 to 0.191 for the CLAD mapping functions. CLAD model 4 performed best, containing the lowest MAE and RMSE. The MAE ranged from 0.118 to 0.123 and the RMSE from 0.169 and 0.175 for ALDVMM mapping functions. ALDVMM model 4 performed best with the lowest MAE and RMSE.

| | | | | Validation dataset (N = 84) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| EQ-5D-5L | | | | IBS-QoL | | | EQ-5D-5L | | |
| Mean | *r value* | Effect size | No. (N =) | Mean | *r value* | Effect size | Mean | *r value* | Effect size |
| 0.713 | *0.423* | -0.140 | 23 | 69.885 | *0.294* | 0.252 | 0.723 | *0.951* | 0.015 |
| 0.741 | | | 61 | 65.743 | | | 0.720 | | |
| 0.736 | *0.847* | 0.030 | 52 | 63.108 | *0.003** | -0.783 | 0.685 | *0.032** | -0.570 |
| 0.730 | | | 32 | 73.001 | | | 0.779 | | |
| 0.744 | *0.623* | 0.072 | 51 | 67.200 | *0.868* | 0.038 | 0.737 | *0.390* | 0.195 |
| 0.730 | | | 32 | 66.590 | | | 0.696 | | |
| 0.779 | *0.001** | 0.464 | 42 | 74.265 | *<0.001** | 1.032 | 0.805 | *<0.001** | 0.861 |
| 0.666 | | | 42 | 59.489 | | | 0.637 | | |
| 0.749 | *0.624* | -0.090 | 16 | 55.882 | *0.002** | 0.884 | 0.559 | *<0.001** | 1.001 |
| 0.731 | | | 68 | 69.464 | | | 0.759 | | |
| 0.699 | *0.306* | 0.207 | 11 | 59.492 | *0.102* | 0.530 | 0.548 | *0.074* | 0.609 |
| 0.741 | | | 73 | 67.989 | | | 0.747 | | |

The regression coefficients for all models are reported in Supplementary Table 1, 2 and 3. The predicted EQ-5D utilities nearly reached the value of 1 (full health), of which CLAD model 4 was closest to 1 with maximum values of 0.940. Figure 1 shows scatter plots from the observed and predicted utility values for model 4 from all three mapping models. The OLS model shows that the prediction is good at the upper end of the EQ-5D-5L, but worsens when the QoL is at the lower end. The CLAD model shows a good prediction for the higher QoL scores (>0.7), where the predicted values are equal to the expected values in some cases. However, when the QoL is at the lower end of EQ-5D-5L, the prediction is worse. A large proportion of the observations are present below the truncation point; 0.7 and 0.9. The ALDVMM tends to underestimate good health and overestimate poor health, but observations near the mean are well predicted.

*Table 4: Goodness-of-fit results for mapping from IBS-QoL to EQ-5D-5L score*

| | Observed EQ-5D utility | Predicted EQ-5D utilities<br>*Total IBS-QoL score*<br><br>OLS Model 1 |
|---|---|---|
| Mean (SE) | 0.734 (0.014) | 0.734 (0.008) |
| Minimum | -0.02 | 0.387 |
| Maximum | 1.00 | 0.916 |
| MAE | | 0.118 |
| RMSE | | 0.170 |
| Adjusted $R^2$ | | 0.271 |
| | | CLAD Model 1 |
| Mean (SE) | 0.734 (0.014) | 0.791 (0.004) |
| Minimum | -0.02 | 0.591 |
| Maximum | 1.00 | 0.896 |
| MAE | | 0.114 |
| RMSE | | 0.185 |
| Pseudo $R^2$ | | 0.148 |
| | | ALDVMM Model 1 |
| Mean (SE) | 0.734 (0.014) | 0.744 (0.005) |
| Minimum | -0.02 | 0.515 |
| Maximum | 1.00 | 0.865 |
| MAE | | 0.120 |
| RMSE | | 0.174 |
| Log likelihood | | 144 |

When assessing the goodness of fit results from the validation analysis, by using the constructed models from the estimation data set, OLS model 5 showed the lowest MAE of 0.124 and the lowest RMSE of 0.165 of all OLS mapping functions. The CLAD model 4 reported the lowest MAE of 0.124 and RMSE 0.169 of all CLAD mapping functions. The ALDVMM model 4 reported the lowest MAE of 0.128 and RMSE of 0.172 of all mixture functions. These goodness of fit results from the validation analysis are reported in table 5.

| *Total IBS-QoL score + IBS-SSS + age* | *Dysphoria score + Body image score* | *Total IBS-QoL score + squared IBS-SSS* | *Dysphoria score + Body image score + squared IBS-SSS + age* |
|---|---|---|---|
| OLS Model 2 | OLS Model 3 | OLS Model 4 | OLS Model 5 |
| 0.734 (0.008) | 0.734 (0.008) | 0.734 (0.008) | 0.734 (0.008) |
| 0.377 | 0.392 | 0.360 | 0.381 |
| 0.936 | 0.884 | 0.925 | 0.914 |
| 0.118 | 0.118 | 0.117 | 0.117 |
| 0.168 | 0.171 | 0.166 | 0.168 |
| 0.296 | 0.270 | 0.306 | 0.295 |
| CLAD Model 2 | CLAD Model 3 | CLAD Model 4 | CLAD Model 5 |
| 0.777 (0.006) | 0.784 (0.006) | 0.763 (0.007) | 0.797 (0.004) |
| 0.517 | 0.507 | 0.415 | 0.586 |
| 0.925 | 0.898 | 0.940 | 0.887 |
| 0.111 | 0.112 | 0.113 | 0.114 |
| 0.175 | 0.179 | 0.168 | 0.191 |
| 0.155 | 0.154 | 0.153 | 0.163 |
| ALDVMM Model 2 | ALDVMM Model 3 | ALDVMM Model 4 | ALDVMM Model 5 |
| 0.741 (0.004) | 0.742 (0.005) | 0.745 (0.006) | 0.738 (0.006) |
| 0.564 | 0.485 | 0.481 | 0.510 |
| 0.851 | 0.852 | 0.879 | 0.881 |
| 0.123 | 0.121 | 0.118 | 0.123 |
| 0.175 | 0.174 | 0.169 | 0.172 |
| 143.28 | 149.26 | 148.11 | 151.71 |

Given the ease and straightforwardness of the algorithm, the good prediction of the mean and minimum/maximum and a high adjusted/pseudo $R^2$, model 4 was identified as most appropriate model. Given the lower MAE/RMSE for CLAD model 4 compared to OLS Model 4 and ALDVMM model 4 in the validation sample, the best mapping function would be CLAD model 4, i.e., EQ-5D utility estimate based on total IBS-QoL score + squared IBS-SSS.

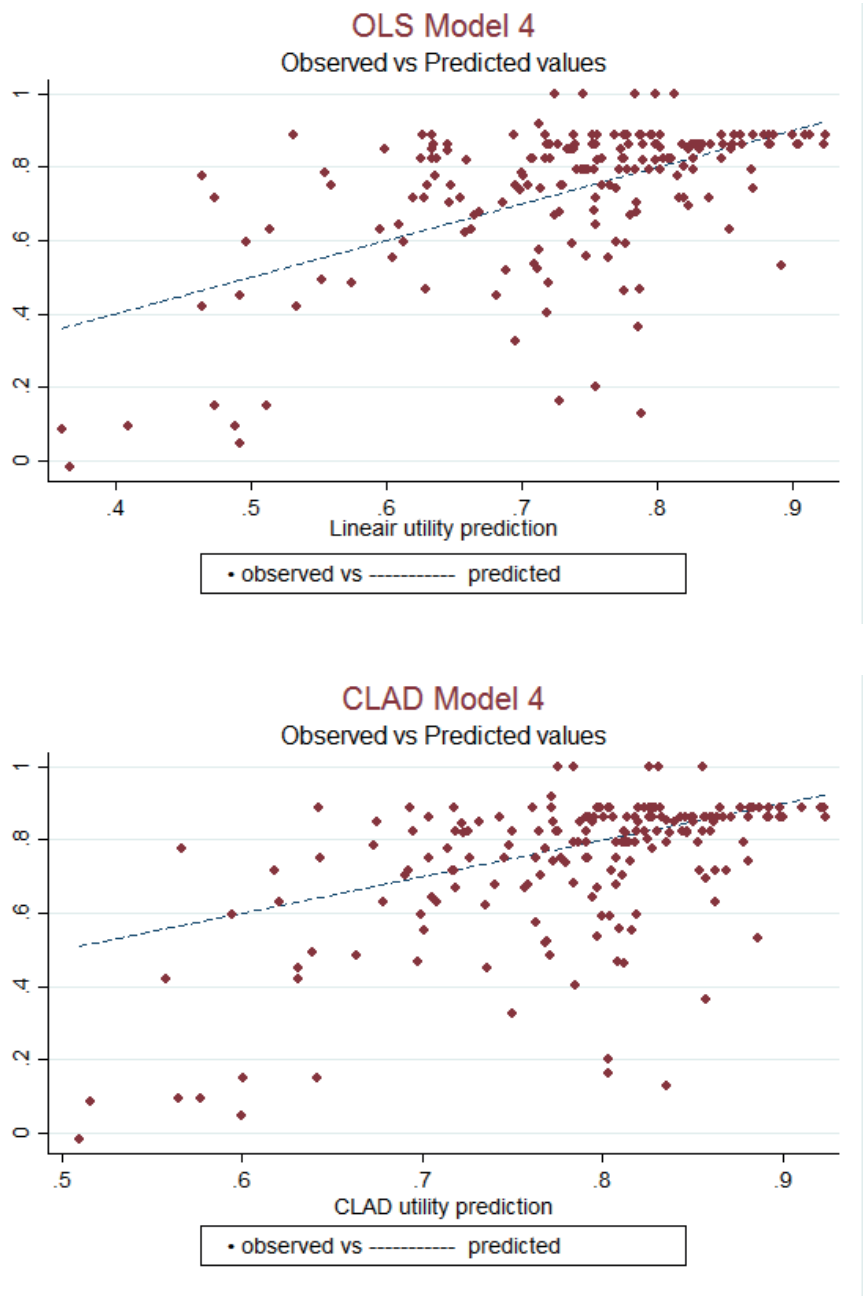


*Figure 1: Scatter plots of observed vs predicted EQ-5D-5L utility values for Model 4 (OLS, CLAD, ALDVMM).*

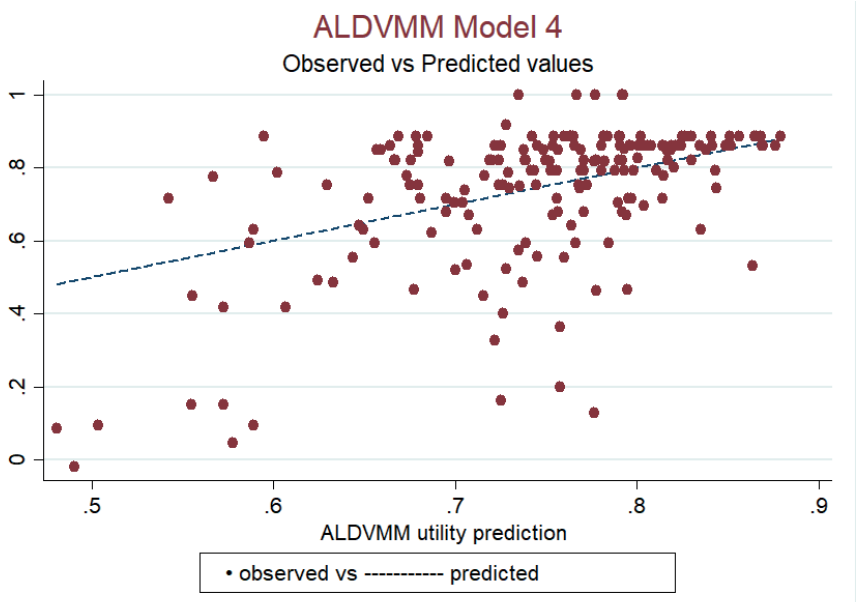


*Figure 1: Continued*

*Table 5: Summary of observed and predicted values for all models in the external validation dataset (N = 84)*

| | Observed EQ-5D utility | Predicted EQ-5D utilities<br>*Total IBS-QoL score*<br><br>OLS Model 1 |
|---|---|---|
| Mean (SE) | 0.72 (0.023) | 0.692 (0.111) |
| Minimum | -0.01 | 0.422 |
| Maximum | 1.00 | 0.901 |
| MAE | | 0.135 |
| RMSE | | 0.178 |
| | | CLAD Model 1 |
| Mean (SE) | 0.72 (0.023) | 0.767 (0.007) |
| Minimum | -0.01 | 0.611 |
| Maximum | 1.00 | 0.888 |
| MAE | | 0.134 |
| RMSE | | 0.189 |
| | | ALDVMM Model 1 |
| Mean (SE) | 0.72 (0.023) | 0.716 (0.008) |
| Minimum | -0.01 | 0.537 |
| Maximum | 1.00 | 0.855 |
| MAE | | 0.134 |
| RMSE | | 0.181 |

| *Total IBS-QoL score + IBS-SSS + age* | *Dysphoria score + Body image score* | *Total IBS-QoL score + squared IBS-SSS* | *Dysphoria score + Body image score + squared IBS-SSS + age* |
|---|---|---|---|
| OLS Model 2 | OLS Model 3 | OLS Model 4 | OLS Model 5 |
| 0.691 (0.012) | 0.699 (0.011) | 0.693 (0.014) | 0.698 (0.013) |
| 0.410 | 0.424 | 0.400 | 0.412 |
| 0.991 | 0.884 | 0.955 | 0.916 |
| 0.132 | 0.125 | 0.129 | 0.124 |
| 0.173 | 0.169 | 0.171 | 0.165 |
| CLAD Model 2 | CLAD Model 3 | CLAD Model 4 | CLAD Model 5 |
| 0.742 (0.009) | 0.754 (0.009) | 0.723 (0.012) | 0.776 (0.010) |
| 0.542 | 0.529 | 0.449 | 0.605 |
| 0.939 | 0.898 | 0.964 | 0.889 |
| 0.128 | 0.125 | 0.124 | 0.132 |
| 0.179 | 0.178 | 0.169 | 0.171 |
| ALDVMM Model 2 | ALDVMM Model 3 | ALDVMM Model 4 | ALDVMM Model 5 |
| 0.717 (0.007) | 0.721 (0.008) | 0.716 (0.010) | 0.717 (0.006) |
| 0.580 | 0.527 | 0.510 | 0.536 |
| 0.869 | 0.852 | 0.904 | 0.887 |
| 0.136 | 0.131 | 0.128 | 0.129 |
| 0.182 | 0.178 | 0.172 | 0.173 |

## DISCUSSION

This is the first study to present an algorithm to predict utility values in IBS patients from the condition-specific IBS-QoL questionnaire. Results of our mapping approach showed that CLAD model 4, containing the total IBS-QoL score and the squared IBS-SSS score is the most appropriate model to enable prediction of health state utilities. This algorithm was chosen because of its simplicity, the low MAE/RMSE and the small range to the predicted mean, minimum and maximum. The mapping from the IBS-QoL to the EQ-5D-5L provide utility scores that can be converted into QALY which is increasingly important in the current health society where economic evaluations are necessary to design reimbursement rules for drugs and medical services.

The reported mean IBS-QoL score in our study from 283 patients was 71.1. These results are similar to those reported in other IBS studies (baseline). In literature, IBS-QoL scores vary between 61.4 and 71.2. [3,12,15,33,50,51] Therefore, our patients sample used to derive and validate mapping algorithm covers the most commonly observed IBS-QoL data in clinical practice. Subdomains "Sexual Function" and "Relationships" were least affected in our cohorts in total QoL score. This finding is also in line with earlier studies.[33,51–53] Patients in our cohorts were most affected by the scores on the subdomain "Food Avoidance" (estimation set 58.5; validation set 47.9). This finding was also confirmed by other studies in IBS patients.[33,51] In both datasets the second most affected subdomain was "Health Worry" (estimation set 70.19; validation set 64.19), which reflects the impact of IBS on a psychological level.

The total IBS-QoL score in the validation set was lower than reported in the estimation set (66.88 and 73.02 respectively). This is probably caused by the higher prevalence of moderate depression and mild- and moderate anxiety among the IBS patients in the validation set due to offering psychological therapies in this trial. The domains, "dysphoria" and "body image", of the IBS-QoL, were strongly correlated with the EQ-5D-5L total utility score which highlights the relevance of these domains for IBS patients. Other disease-specific domains such as "food avoidance", "social reaction", "sexual" and "relationships" were less correlated with the total EQ-5D-5L scores and are not represented in the generic questionnaire EQ-5D-5L. Still, these domains are specific and important for the psychological well-being among IBS patients.[53] The overall known-group validity of the IBS-QoL and EQ-5D-5L was quite similar. The IBS-QoL had a greater discriminatory power with regard to age and gender and the severity of symptoms (IBS-SSS). But the EQ-5D-5L had a favorable discriminative power with regard to the presence of anxiety. Both questionnaires showed comparable discriminative power with regard to BMI and the presence of depression. Therefore, our initial hypothesis

has to be rejected, because the IBS-QoL is not more sensitive to discriminate between disease characteristics compared to the EQ-5D-5L. However, the condition-specific questionnaire IBS-QoL could be more favorable when different aspects of the disease are required to be addressed during a clinical study.

Other condition-specific measures intended for patients who suffer from epilepsy and cancer, had a similar sensitivity in comparison to the general EQ-5D.[54,55] However, in studies involving patients with asthma and urinary incontinence, construct validity of EQ-5D was not as strong as the condition-specific measures.[56,57]

For the final mapping algorithm, we not only included age but also the symptom severity score (IBS-SSS). According to the ISPOR guidelines, including covariates, such as sociodemographic variables and disease characteristics, should be explored to avoid mis-specification of the model.[27] The prediction of the utility values will be more accurate in that way. A recent review of mapping studies showed that age was included in 51% in the algorithm and gender was included in 55%.[44] Clinical measures, such as BMI, were included in the analysis in only 20% of the reports. When performing a mapping study, inclusion of covariates in the algorithm should be explored more extensively in the future to enhance performance.

This is the first study to enable the estimation of utility values from IBS-specific questionnaire scores. A strength of this study includes the applicability to other study IBS populations. The current study population was representable for IBS populations in general because our IBS population have comparable basic patient characteristics (i.e., age, gender) and includes the full range of IBS patient disease severity (range 44-445)[3,58,59]. The mean IBS symptom severity score of 278.17 in this study is similar to previous studies (range 259.45-290).[51,58,60,61] The two data sets used had similar inclusion criteria and the population had similar baseline characteristics, which facilitates the development of a valid mapping approach. Another strength of this study is that a different data set was used for external validation of the models and the model performance was reported by assessing the MAE and the RMSE.[42].

A limitation of the present study is that our predicted EQ-5D-5L utilities did not capture the full range of observed EQ-5D-5L utilities. The overprediction of the lowest utilities and the under-prediction of the highest utilities may result in an underestimation of the utility gain. This is a general problem with mapping studies, especially when using linear regression.[42,62] Therefore, the model fit of both CLAD and ALDVMM outperformed OLS functions. The CLAD Model 4 performed slightly better than ALDVMM Model 4, containing the lowest MAE/RMSE. The big proportion of observations in our dataset

was between 0.7 and 0.9. This is below the truncation point, which is an important feature of the ALDVMM, and could be an explanation for the fact that the CLAD model 4 performed better. ALDVMM could be a good option when data is differently distributed than in our dataset.

Furthermore, our algorithm is not directly applicable for usage in trial-based economic evaluations when a comparison with EQ-5D-3L data is requested. However, it is possible to use this data to generate 5L data by conducting a mapping function online.[63]

In conclusion, this study investigated a mapping approach where the condition-specific questionnaire IBS-QoL was estimated to EQ-5D-5L utility values. This algorithm is useful for modeling studies in which only the IBS-QoL is included and in trial-based economic evaluations to estimate QALYs. Including a clinical measure in the model, such as the severity score of the disease (IBS-SSS), will improve performance of the algorithm to predict utility values.

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# SUPPLEMENTARY MATERIAL

Supplementary Table 1
*Mapping equations from IBS-QoL score to EQ-5D-5L to IBS using OLS regression*

| Type of analysis | *Model 1*<br>*Total IBS-QoL score*<br>OLS | | *Model 2*<br>*Total IBS-QoL score + IBS-SSS + age*<br>OLS | |
|---|---|---|---|---|
| | Coeff. | SE | Coeff. | SE |
| Constant | 0.229 | 0.061** | 0.443 | 0.096** |
| IBS-QoL total score | 0.007 | 0.001** | 0.006 | 0.001** |
| IBS-SSS score | | | -0.00049 | 0.00018** |
| Age | | | -0.0008 | 0.0009 |
| IBS-QoL domain Dysphoria score | | | | |
| IBS-QoL domain Body Image score | | | | |
| Squared IBS-SSS score | | | | |

Coeff. = Coefficients, determined by regression analysis in STATA. SE: Standardized Error. Significance * p <0.05, ** p<0.01. IBS-QoL total score: Score between 0-100. IBS-SSS score: score between 0 and 500 defining the severity of IBS.

| | *Model 3*<br>*Two domains IBS-QoL: Dysphoria score + Body image score* | | *Model 4*<br>*Total IBS-QoL score + Squared IBS-SSS score* | | *Model 5*<br>*Dysphoria score + Body image score + squared IBS-SSS + age* | |
|---|---|---|---|---|---|---|
| | OLS | | OLS | | OLS | |
| | Coeff. | SE | Coeff. | SE | Coeff. | SE |
| | 0.297 | 0.054** | 0.385 | 0.077** | 0.449 | 0.076** |
| | | | 0.006 | 0.001** | | |
| | | | | | | |
| | | | | | -0.0005 | 0.001 |
| | 0.004 | 0.001** | | | 0.003 | 0.0007** |
| | 0.002 | 0.001** | | | 0.002 | 0.0008* |
| | | | -1.03E-6 | 3.24E-7** | 9.36e-07 | 3.32e-07** |

Supplementary table 2

*Mapping equations from IBS-QoL to EQ-5D-5L score using CLAD regression*

| | *Model 1* *Total IBS-QoL score* | | *Model 2* *Total IBS-QoL score + IBS-SSS + age* | |
|---|---|---|---|---|
| Type of analysis | Clad | | Clad | |
| | Coeff. | SE | Coeff. | SE |
| Constant | 0.408 | 0.114 | 0.511 | 0.114 |
| IBS-QoL total score | 0.005 | 0.001 | 0.005 | 0.001 |
| IBS-SSS score | | | -0.0002 | 0.0001 |
| Age | | | -0.001 | 0.0009 |
| IBS-QoL domain Dysphoria score | | | | |
| IBS-QoL domain Body Image score | | | | |
| Squared IBS-SSS score | | | | |

Coeff. = Coefficients, determined by CLAD analysis in STATA. SE: Standardized Error. IBS-QoL total score: Score between 0-100. IBS-SSS score: score between 0 and 500 defining the severity of IBS.

| | *Model 3*<br>*Two domains IBS-QoL: Dysphoria score + Body image score* | | *Model 4*<br>*Total IBS-QoL score + Squared IBS-SSS score* | | *Model 5*<br>*Dysphoria score + Body image score + squared IBS-SSS + age* | |
|---|---|---|---|---|---|---|
| | Clad | | Clad | | Clad | |
| | Coeff. | SE | Coeff. | SE | Coeff. | SE |
| | 0.451 | 0.108 | 0.471 | 0.099 | 0.482 | 0.098 |
| | | | 0.005 | 0.001 | | |
| | | | | | | |
| | | | | | -0.001 | 0.0008 |
| | 0.004 | 0.001 | | | 0.004 | 0.001 |
| | 0.001 | 0.001 | | | 0.001 | 0.001 |
| | | | -4.83E-7 | 3.59e-7 | 3.75e-07 | 3.11e-07 |

Supplementary table 3

*Mapping equations from IBS-QoL to EQ-5D-5L score using ALDVM models*

Model 1

| N_NLEQ5D5L_0 | Coef. | Std. Err. | z | P>\|z\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| Comp_1 | | | | | | |
| N_QOL_totalscore_0 | .0000188 | .0003018 | 0.06 | 0.950 | -.0005728 | .0006104 |
| _cons | .8745529 | .0223461 | 39.14 | 0.000 | .8307554 | .9183504 |
| Comp_2 | | | | | | |
| N_QOL_totalscore_0 | .0015819 | .0001953 | 8.10 | 0.000 | .0011991 | .0019646 |
| _cons | .7303442 | .0137961 | 52.94 | 0.000 | .7033044 | .7573841 |
| Comp_3 | | | | | | |
| N_QOL_totalscore_0 | .0084149 | .0015697 | 5.36 | 0.000 | .0053384 | .0114914 |
| _cons | -.0001242 | .1135621 | -0.00 | 0.999 | -.2227019 | .2224535 |
| Comp_4 | | | | | | |
| N_QOL_totalscore_0 | .0042495 | .0005319 | 7.99 | 0.000 | .0032071 | .0052919 |
| _cons | .470006 | .0404947 | 11.61 | 0.000 | .3906379 | .5493742 |
| Prob_C1 | | | | | | |
| _cons | -.7988692 | .375672 | -2.13 | 0.033 | -1.535173 | -.0625656 |
| Prob_C2 | | | | | | |
| _cons | -.7903465 | .4026044 | -1.96 | 0.050 | -1.579437 | -.0012563 |
| Prob_C3 | | | | | | |
| _cons | .073574 | .289447 | 0.25 | 0.799 | -.4937318 | .6408798 |
| /lns_1 | -4.197175 | .1912816 | -21.94 | 0.000 | -4.57208 | -3.82227 |
| /lns_2 | -4.59725 | .2146898 | -21.41 | 0.000 | -5.018034 | -4.176466 |
| /lns_3 | -1.550841 | .0966175 | -16.05 | 0.000 | -1.740208 | -1.361474 |
| /lns_4 | -3.176991 | .1824914 | -17.41 | 0.000 | -3.534667 | -2.819314 |
| sigma1 | .015038 | .0028765 | | | .0103364 | .0218781 |
| sigma2 | .0100795 | .002164 | | | .0066175 | .0153527 |
| sigma3 | .2120695 | .0204896 | | | .1754839 | .2562827 |
| sigma4 | .041711 | .0076119 | | | .0291685 | .0596468 |
| pi1 | .1509586 | .0457759 | | | .0811292 | .2636463 |
| pi2 | .1522506 | .0479998 | | | .0797356 | .2712739 |
| pi3 | .361206 | .0521542 | | | .2663636 | .4682638 |
| pi4 | .3355848 | .0578582 | | | .2221847 | .4489848 |

Supplementary table 3 *Continued*

| Model 2 | | | | | | |
|---|---|---|---|---|---|---|
| N_NLEQ5D5L_0 | Coef. | Std. Err. | z | P>\|z\| | [95% Conf. | Interval] |
| Comp_1 | | | | | | |
| N_QOL_totalscore_0 | .0006314 | .0003847 | 1.64 | 0.101 | -.0001226 | .0013854 |
| N_SSS_Eindscore_0 | -.0000559 | .000079 | -0.71 | 0.479 | -.0002108 | .0000989 |
| N_LEEFTIJD_SCREENING | .0003033 | .0003325 | 0.91 | 0.362 | -.0003483 | .000955 |
| _cons | .8158511 | .0448087 | 18.21 | 0.000 | .7280278 | .9036745 |
| Comp_2 | | | | | | |
| N_QOL_totalscore_0 | .0044806 | .0017009 | 2.63 | 0.008 | .0011469 | .0078144 |
| N_SSS_Eindscore_0 | -.0008834 | .0004141 | -2.13 | 0.033 | -.0016951 | -.0000717 |
| N_LEEFTIJD_SCREENING | -.0020032 | .0029254 | -0.68 | 0.493 | -.0077368 | .0037303 |
| _cons | .3346758 | .1909066 | 1.75 | 0.080 | -.0394943 | .7088459 |
| Comp_3 | | | | | | |
| N_QOL_totalscore_0 | .0037621 | .0008812 | 4.27 | 0.000 | .002035 | .0054892 |
| N_SSS_Eindscore_0 | -.000677 | .0002355 | -2.87 | 0.004 | -.0011386 | -.0002154 |
| N_LEEFTIJD_SCREENING | .0009462 | .0011221 | 0.84 | 0.399 | -.0012531 | .0031455 |
| _cons | .4824217 | .0917241 | 5.26 | 0.000 | .3026457 | .6621977 |
| Comp_4 | | | | | | |
| N_QOL_totalscore_0 | .0048154 | .0006595 | 7.30 | 0.000 | .0035229 | .006108 |
| N_SSS_Eindscore_0 | -.0000119 | .0001199 | -0.10 | 0.921 | -.0002469 | .0002231 |
| N_LEEFTIJD_SCREENING | -.001631 | .0007988 | -2.04 | 0.041 | -.0031965 | -.0000654 |
| _cons | .4859942 | .0723942 | 6.71 | 0.000 | .3441041 | .6278843 |
| Prob_C1 | | | | | | |
| _cons | -.2671206 | .3125627 | -0.85 | 0.393 | -.8797323 | .3454911 |
| Prob_C2 | | | | | | |
| _cons | -1.500278 | .3521834 | -4.26 | 0.000 | -2.190544 | -.8100108 |
| Prob_C3 | | | | | | |
| _cons | -1.194805 | .3717771 | -3.21 | 0.001 | -1.923474 | -.466135 |
| /lns_1 | -3.542181 | .1635771 | -21.65 | 0.000 | -3.862786 | -3.221576 |
| /lns_2 | -2.225104 | .2644117 | -8.42 | 0.000 | -2.743341 | -1.706866 |
| /lns_3 | -3.002799 | .2428768 | -12.36 | 0.000 | -3.478829 | -2.526769 |
| /lns_4 | -2.908221 | .1343496 | -21.65 | 0.000 | -3.171541 | -2.6449 |
| sigma1 | .0289501 | .0047356 | | | .0210094 | .0398921 |
| sigma2 | .1080562 | .0285713 | | | .064355 | .1814334 |
| sigma3 | .0496479 | .0120583 | | | .0308435 | .0799168 |
| sigma4 | .0545727 | .0073318 | | | .0419389 | .0710124 |
| pi1 | .3341087 | .0601875 | | | .2279561 | .4602263 |
| pi2 | .0973497 | .0284185 | | | .0541212 | .1689392 |
| pi3 | .1321295 | .0389786 | | | .0725284 | .2286346 |
| pi4 | .4364121 | .0654839 | | | .3080661 | .5647582 |

Supplementary table 3 *Continued*

Model 3

| N_NLEQ5D5L_0 | Coef. | Std. Err. | z | P>\|z\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| Comp_1 | | | | | | |
| N_QOL_dysphoriascore_0 | -.0005819 | .000115 | -5.06 | 0.000 | -.0008074 | -.0003564 |
| N_QOL_bodyimagescore_0 | -.0000496 | .0001116 | -0.44 | 0.657 | -.0002683 | .0001692 |
| _cons | .9170211 | .0102278 | 89.66 | 0.000 | .896975 | .9370672 |
| Comp_2 | | | | | | |
| N_QOL_dysphoriascore_0 | .0011631 | .000322 | 3.61 | 0.000 | .0005321 | .0017941 |
| N_QOL_bodyimagescore_0 | .0008845 | .0003775 | 2.34 | 0.019 | .0001447 | .0016243 |
| _cons | .6758889 | .0239743 | 28.19 | 0.000 | .6289001 | .7228777 |
| Comp_3 | | | | | | |
| N_QOL_dysphoriascore_0 | .0041291 | .0032791 | 1.26 | 0.208 | -.0022978 | .010556 |
| N_QOL_bodyimagescore_0 | -.0007499 | .0037602 | -0.20 | 0.842 | -.0081198 | .0066199 |
| _cons | .0353644 | .1584959 | 0.22 | 0.823 | -.2752819 | .3460106 |
| Comp_4 | | | | | | |
| N_QOL_dysphoriascore_0 | .002492 | .0008917 | 2.79 | 0.005 | .0007443 | .0042396 |
| N_QOL_bodyimagescore_0 | .0049927 | .0010213 | 4.89 | 0.000 | .0029911 | .0069944 |
| _cons | .1497876 | .076893 | 1.95 | 0.051 | -.0009198 | .3004951 |
| Prob_C1 | | | | | | |
| _cons | -1.283383 | .3513122 | -3.65 | 0.000 | -1.971942 | -.5948238 |
| Prob_C2 | | | | | | |
| _cons | -.1486043 | .2744568 | -0.54 | 0.588 | -.6865298 | .3893212 |
| Prob_C3 | | | | | | |
| _cons | -1.804801 | .5771771 | -3.13 | 0.002 | -2.936047 | -.6735544 |
| /lns_1 | -5.028607 | .3262587 | -15.41 | 0.000 | -5.668062 | -4.389152 |
| /lns_2 | -3.368456 | .1562448 | -21.56 | 0.000 | -3.67469 | -3.062222 |
| /lns_3 | -2.038223 | .4138256 | -4.93 | 0.000 | -2.849306 | -1.22714 |
| /lns_4 | -2.215607 | .1348761 | -16.43 | 0.000 | -2.479959 | -1.951254 |
| sigma1 | .0065479 | .0021363 | | | .0034546 | .0124113 |
| sigma2 | .0344428 | .0053815 | | | .0253573 | .0467836 |
| sigma3 | .13026 | .0539049 | | | .0578845 | .2931298 |
| sigma4 | .1090873 | .0147133 | | | .0837467 | .1420957 |
| pi1 | .1202936 | .0367355 | | | .0647648 | .2126091 |
| pi2 | .3741716 | .0609985 | | | .2640711 | .4990479 |
| pi3 | .0714157 | .035977 | | | .0258704 | .1821514 |
| pi4 | .4341191 | .0601545 | | | .3162184 | .5520197 |

Supplementary table 3 *Continued*

| Model 4 | | | | | | |
|---|---|---|---|---|---|---|
| N_NLEQ5D5L_0 | Coef. | Std. Err. | z | P>\|z\| | [95% Conf. | Interval] |
| Comp_1 | | | | | | |
| N_QOL_totalscore_0 | .0000459 | .0002847 | 0.16 | 0.872 | -.0005122 | .000604 |
| Squared_IBSSSS_score | -9.98e-09 | 7.97e-08 | -0.13 | 0.900 | -1.66e-07 | 1.46e-07 |
| _cons | .8686046 | .0245751 | 35.34 | 0.000 | .8204382 | .916771 |
| Comp_2 | | | | | | |
| N_QOL_totalscore_0 | .006668 | .0014618 | 4.56 | 0.000 | .003803 | .0095329 |
| Squared_IBSSSS_score | -1.99e-06 | 5.91e-07 | -3.36 | 0.001 | -3.14e-06 | -8.28e-07 |
| _cons | .3048719 | .1311956 | 2.32 | 0.020 | .0477333 | .5620106 |
| Comp_3 | | | | | | |
| N_QOL_totalscore_0 | .0016212 | .0004181 | 3.88 | 0.000 | .0008018 | .0024406 |
| Squared_IBSSSS_score | -3.77e-07 | 1.74e-07 | -2.16 | 0.031 | -7.18e-07 | -3.53e-08 |
| _cons | .7440232 | .0416033 | 17.88 | 0.000 | .6624822 | .8255643 |
| Comp_4 | | | | | | |
| N_QOL_totalscore_0 | .0042949 | .0003908 | 10.99 | 0.000 | .0035291 | .0050608 |
| Squared_IBSSSS_score | -5.37e-07 | 1.63e-07 | -3.28 | 0.001 | -8.57e-07 | -2.16e-07 |
| _cons | .499726 | .0336493 | 14.85 | 0.000 | .4337746 | .5656775 |
| Prob_C1 | | | | | | |
| _cons | -.0515761 | .3618687 | -0.14 | 0.887 | -.7608258 | .6576736 |
| Prob_C2 | | | | | | |
| _cons | .6374391 | .3091973 | 2.06 | 0.039 | .0314235 | 1.243455 |
| Prob_C3 | | | | | | |
| _cons | -.1170029 | .441314 | -0.27 | 0.791 | -.9819625 | .7479567 |
| /lns_1 | -4.141698 | .156953 | -26.39 | 0.000 | -4.44932 | -3.834076 |
| /lns_2 | -1.666758 | .0912376 | -18.27 | 0.000 | -1.845581 | -1.487936 |
| /lns_3 | -3.817968 | .2821738 | -13.53 | 0.000 | -4.371019 | -3.264918 |
| /lns_4 | -3.741095 | .2098454 | -17.83 | 0.000 | -4.152385 | -3.329806 |
| sigma1 | .0158958 | .0024949 | | | .0116865 | .0216213 |
| sigma2 | .1888583 | .017231 | | | .1579335 | .2258383 |
| sigma3 | .0219724 | .0062 | | | .0126384 | .0382001 |
| sigma4 | .0237281 | .0049792 | | | .0157269 | .0358001 |
| pi1 | .2007488 | .047818 | | | .1228469 | .3105607 |
| pi2 | .399842 | .0479099 | | | .3105752 | .4962963 |
| pi3 | .1880349 | .0554494 | | | .1020503 | .320601 |
| pi4 | .2113743 | .0499524 | | | .1134693 | .3092792 |

Supplementary table 3 *Continued*

Model 5

| N_NLEQ5D5L_0 | Coef. | Std. Err. | z | P>\|z\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| Comp_1 | | | | | | |
| N_QOL_dysphoriascore_0 | .0008095 | .0002873 | 2.82 | 0.005 | .0002465 | .0013726 |
| N_QOL_bodyimagescore_0 | .0008299 | .0002968 | 2.80 | 0.005 | .0002481 | .0014117 |
| Squared_IBSSSS_score | 1.83e-08 | 1.35e-07 | 0.14 | 0.892 | -2.46e-07 | 2.83e-07 |
| N_LEEFTIJD_SCREENING | -.0000816 | .0003741 | -0.22 | 0.827 | -.0008149 | .0006517 |
| _cons | .7203127 | .0334533 | 21.53 | 0.000 | .6547454 | .7858799 |
| Comp_2 | | | | | | |
| N_QOL_dysphoriascore_0 | .0016245 | .0005256 | 3.09 | 0.002 | .0005943 | .0026546 |
| N_QOL_bodyimagescore_0 | .0030349 | .0005886 | 5.16 | 0.000 | .0018812 | .0041886 |
| Squared_IBSSSS_score | -1.09e-06 | 2.28e-07 | -4.78 | 0.000 | -1.53e-06 | -6.42e-07 |
| N_LEEFTIJD_SCREENING | -.0041577 | .0006712 | -6.19 | 0.000 | -.0054733 | -.0028421 |
| _cons | .6180535 | .0582951 | 10.60 | 0.000 | .5037972 | .7323099 |
| Comp_3 | | | | | | |
| N_QOL_dysphoriascore_0 | -.0001995 | .0019624 | -0.10 | 0.919 | -.0040458 | .0036468 |
| N_QOL_bodyimagescore_0 | .0029985 | .0023042 | 1.30 | 0.193 | -.0015176 | .0075146 |
| Squared_IBSSSS_score | -3.72e-06 | 9.38e-07 | -3.96 | 0.000 | -5.55e-06 | -1.88e-06 |
| N_LEEFTIJD_SCREENING | -.0032107 | .0023475 | -1.37 | 0.171 | -.0078118 | .0013904 |
| _cons | .4602395 | .1310278 | 3.51 | 0.000 | .2034297 | .7170493 |
| Comp_4 | | | | | | |
| N_QOL_dysphoriascore_0 | .002216 | .0009035 | 2.45 | 0.014 | .0004451 | .0039869 |
| N_QOL_bodyimagescore_0 | .0003956 | .0015278 | 0.26 | 0.796 | -.0025988 | .0033899 |
| Squared_IBSSSS_score | -3.39e-06 | 5.84e-07 | -5.81 | 0.000 | -4.53e-06 | -2.25e-06 |
| N_LEEFTIJD_SCREENING | .0035879 | .0026005 | 1.38 | 0.168 | -.0015089 | .0086847 |
| _cons | .5415439 | .095222 | 5.69 | 0.000 | .3549122 | .7281755 |
| Prob_C1 | | | | | | |
| _cons | .939732 | .2758325 | 3.41 | 0.001 | .3991103 | 1.480354 |
| Prob_C2 | | | | | | |
| _cons | .2276444 | .3204753 | 0.71 | 0.477 | -.4004757 | .8557644 |
| Prob_C3 | | | | | | |
| _cons | -1.469592 | .4699436 | -3.13 | 0.002 | -2.390664 | -.5485192 |
| /lns_1 | -3.224936 | .0993751 | -32.45 | 0.000 | -3.419707 | -3.030164 |
| /lns_2 | -3.306219 | .1707842 | -19.36 | 0.000 | -3.64095 | -2.971488 |
| /lns_3 | -2.794877 | .3660135 | -7.64 | 0.000 | -3.51225 | -2.077504 |
| /lns_4 | -2.45808 | .2144867 | -11.46 | 0.000 | -2.878466 | -2.037693 |
| sigma1 | .0397583 | .003951 | | | .032722 | .0483077 |
| sigma2 | .0366545 | .00626 | | | .0262274 | .051227 |
| sigma3 | .0611224 | .0223716 | | | .0298297 | .1252425 |
| sigma4 | .0855992 | .0183599 | | | .056221 | .130329 |
| pi1 | .5072981 | .053683 | | | .4032931 | .6106752 |
| pi2 | .2488901 | .0483327 | | | .1664119 | .3548452 |
| pi3 | .045594 | .0171066 | | | .0216299 | .0935688 |
| pi4 | .1982179 | .0415872 | | | .1167086 | .2797272 |

# Chapter 3

## DO PATIENTS' AND PHYSICIANS' PERSPECTIVES DIFFER ON PREFERENCES FOR IRRITABLE BOWEL SYNDROME TREATMENT? ATTRIBUTES FOR QUANTITATIVE PREFERENCE ELICITATION

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*Submitted*

## ABSTRACT

Objectives

Irritable bowel syndrome (IBS) is a highly prevalent disorder of the gut-brain interaction and poses a significant burden to patients. Pharmacotherapy, diet and psychotherapy all have largely comparable clinical efficacy. Therefore, factors outside efficacy can have important impact in determining preferences for a specific therapeutic entity. The aim of this study was to select important treatment factors, next to efficacy, to determine preferences for a specific therapeutic entity and to compare perspectives of both patients and physicians regarding the management of IBS.

Methods

Semi-structured interviews were performed among IBS patients (N = 8), fulfilling the Rome IV criteria, and surveys were sent to physicians involved in IBS care (N = 15). To identify most relevant treatment aspects, the level of importance was ranked for each attribute. Final definitions and levels were set during an expert opinion meeting.

Results

The survey and interviews took place between June and September 2020. Nine potential attributes for use in DCE were revealed: effectiveness, time until response, cessation of response, side effects, location, waiting period, treatment burden, frequency of healthcare appointments and willingness to pay. Effectiveness, duration of response, side effects and treatment burden were all scored as important by patients and physicians. Time to response, location and waiting time were less important for patients compared to physicians.

Conclusions

This study assessed potential attributes and levels regarding preferences for IBS treatments by qualitative research. These data could be applied in quantitative preference elicitation to help individualize IBS treatment.

# INTRODUCTION

Irritable bowel syndrome (IBS) is a highly prevalent disorder of the gut-brain interaction. It is characterized by recurrent abdominal pain and altered bowel habits and is diagnosed according to the Rome IV criteria.[1,2] Prevalence ranges from 4-14% worldwide. Symptoms may occur at every age but are more present in younger individuals (<age 50 years) and among women.

IBS bears a negative impact on quality of life of patients and therefore IBS imposes a significant burden to the health care system.[3] It is therefore imperative to employ effective management strategies that not only reduce symptom burden but also increase quality of life.[4] Nowadays, a substantial number of therapeutic options are available for treating IBS. These therapeutic modalities include diets, psychologic therapy and pharmacotherapy.[5,6] Dietary interventions vary from standardized dietary advice to elimination diets (i.e. low-FODMAP-diet). Pharmacological options include peppermint oil capsules, antidepressants and antispasmodics. Psychologic therapies include cognitive behavioral therapy and hypnotherapy.[7] All therapies mentioned above have comparable efficacy with a number needed to treat (NNT) from 4 to 5.[5]

Although various therapeutic options are available, treating IBS symptoms remains challenging. IBS patients constitute a clinical heterogeneous population and no single treatment will suit all patients. Tailored approaches are necessary. Therefore, apart from the efficacy, other characteristics of the therapy are important in recommending a specific treatment. This includes for example, the risk of side effects, the method of administration, length of therapy or treatment burden. By analyzing and determining which factors are important in the management of IBS to patients, the treatment efforts can be tailored to individual needs and preferences. For instance, in a previous study among young women suffering from diarrhea-predominant IBS (IBS-D), patients were shown to be willing to accept higher risks of serious adverse effects of the therapy, if their symptoms improved.[8,9] Besides, they were willing to pay significant monthly costs.[10]

Quantitative studies of such kind examining preferences of patients or professionals for different treatment or service options, necessitate adequate qualitative research as input prior to performing such a study. Because qualitative studies reveal the social context and identify patients' perceptions, this type of research becomes more relevant.[11] Qualitative research also has gained attention within the field of gastroenterology and in IBS patients, specifically.[12–17] Guidelines have recently been developed for the

methodological development process of quantitative health preference research in order to improve quality.[18] These guidelines recommend investigating the most salient aspects related to preference, i.e. attributes and their respective levels, by performing semi-structured cognitive and/or focus groups interviews.[19]

Previous studies have not yet addressed the question of treatment preferences and their specific characteristics in IBS according to the above-mentioned methodology, neither from patients' nor from physicians' perspective. Therefore, in this qualitatively driven study we examine from both a patient and professional perspective which treatment characteristics of IBS are considered important. Their different perspectives will be compared and can be used as input for a discrete choice experiment (DCE) among patients in the future in order to quantify their preferences and examine for example trade-offs between efficacy and side effects.

## METHODS

Study population

Patients diagnosed with IBS, fulfilling the Rome IV criteria, were recruited from the outpatient clinics of the division of Gastroenterology and Hepatology of Maastricht University Medical Center+ (MUMC+). This is an academic hospital with a combined secondary and tertiary care function. Patients between 18 and 75 years of age were included in this study. They had a good understanding of the Dutch language and were able to participate in an interview. Treatment-naïve patients were not included as we considered that these patients might be less able to judge multiple treatment entities. Patients who had been diagnosed with disorders involving the abdomen other than IBS, for example colon cancer or inflammatory bowel disease (IBD), were excluded from this study.

The recruited clinical experts were registered gastroenterologists all over the Netherlands, both from academic and non-academic teaching hospitals, specialized in the field of neurogastroenterology and were all members of the Neurogastroenterology Committee of the Dutch Association for Gastroenterologists (n = 16). Also, general practitioners (GP) from South-Limburg participated in this research based on the network of clinical experiences of the investigators (N = 3). All clinicians were currently treating patients with IBS.

All procedures that followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. The study was reviewed and approved by the ethics committee at the Maastricht University Medical Center (2020-2212). Written informed consent (for audio recording as well) was obtained from all patients prior to being included in the study.

Interviews

Semi-structured interviews were performed with patients to assess the patient preferences for the choice of treatment in IBS. This qualitative method was chosen to enable more time for in-depth exploration of the IBS treatment options and previous experiences. Moreover, an advantage of one-on-one interviews is that participants are more willing to talk about sensitive subjects involving bowel movements.

Prior to the interviews, a screening of the literature was performed to select possible attributes and levels regarding treatment preferences (See Supplementary material online 1 for details about the Literature Screening). In particular, former DCE articles

involving treatment preferences and qualitative studies involving IBS patients and discussing their treatment, were used to extract this information. All possible attributes were discussed within the research team. The result from this literature screening was used to develop the patient and physician (interview) topic guide (See Supplementary material online 2 for the Topic Guide for patients).[20–26] The topic guide was used to provide consistency between interviews.

Before the interviews, participants were asked to fill in the irritable bowel syndrome symptom severity scale (IBS-SSS) questionnaire to assess the severity of their symptoms.[27]

All individual interviews were conducted by the primary investigator (RS) and were audio recorded. This investigator had received training and masterclasses in qualitative research and how to conduct interviews. There was no treatment relationship between this investigator and the participants. These interviews were performed either in the hospital or digitally (due to the COVID 19 outbreak). The final location was chosen by the participant.

Process of the interview

At the start of the semi-structured interview, the Rome IV criteria were assessed and the IBS subtype was defined.[2,28] The participants answered open questions about time of diagnosis, type of symptoms, effect on daily life, previous treatment experiences and treatment preferences in the first part of the interview. Participants described what they considered important aspects of a treatment, including likes and dislikes and their view of an ideal therapy. Also, the clinical acceptable properties of each treatment characteristic were discussed with the patient. In the second part, participants were asked to rank the aspects of treatment on level of importance, using a pre-defined list derived from the literature and treatment aspects suggested by the participants during the interview. The discussed items are shown in the topic guide (Supplementary material online 2). During the second part of the interview, the level of importance of each characteristic was ranked by selecting the number of the Likert scale (1-5), reaching from respectively very unimportant to very important.[29]

The overall sample size of the interviews was determined by saturation point, as per guideline recommendations.[21,30] The saturation point was achieved when no new information was derived from the interviews although two additional interviews were then performed to confirm saturation. Therefore, analysis and data collection were conducted concurrently, until all attributes were clearly described and no new information emerged.

Clinician surveys

To investigate the important characteristics of physicians' preference in advising a therapy for IBS patients, a survey was sent to them by email. To identify several perspectives of physicians, both gastroenterologists and general practitioners were invited to participate. Participants were given one month to respond, with a reminder sent out after two weeks. This electronic survey consisted of two parts, in total consisting of 15 questions. The first part consisted of six open questions about the work experience of the clinical expert and their perspective on different characteristics of therapy. In the second part a table was listed consisting of eight treatment characteristics derived from the literature. This literature screening is also available in Supplementary material online 1. The discussed aspects were: effectiveness on predominant symptom of patient, speed of effectiveness, risk of recurrence, side effects, location of treatment, waiting time to start treatment, effect on daily life of therapy, ability and willingness to pay for a therapy. The level of importance of each characteristic was ranked using the Likert scale (1-5). The survey was pretested by two physicians and assessed on accuracy and clarity.

Data Analysis

Interviews were audio-recorded and transcribed. Qualitative analyses of the interview data were performed by using a qualitative analysis software tool, NVivo Release 1.2 QSR International. These data were coded to reflect the interviews in an iterative process. Codes were selected in groups of themes and subthemes. This process was checked among the investigators and disagreements were discussed in detail to enhance reliability. Both the frequency in which aspects of treatment arose and the relative importance to the participant were acquired. The collected data of the sample were reviewed multiple times to evaluate the analysis process on reliability and the extracted attributes and levels were discussed within the research team. The phrasing and definitions of the final attributes and levels for both patients and physicians were finally set during an expert opinion meeting with three gastroenterologists specialized in IBS care from the MUMC+.

Descriptive statistics were used to analyze the background characteristics of the sample and to determine the severity of IBS symptoms by using the IBS-SS score (0-500). The median was used to calculate central tendency for the Likert scale data, because of the categorial data and the non-normal distribution.[31] Software program IBM SPSS Statistics version 27.0 for Macintosh (SPSS Inc., Chicago, Illinois, USA) was used.

# RESULTS

Patient characteristics

In total 8 patients were included between August and September 2020. Mean age was 44.0 years (SD 18.18) and 6 out of 8 were female. All patients met the Rome IV criteria for IBS. The majority of them had IBS subtype diarrhea (IBS-D; n = 5), one patient had subtype constipation (IBS-C) and two patients had mixed type (IBS-M). The mean IBS-SSS was 256.25 (SD 69.68), indicating a moderate severity of IBS. All patient characteristics are shown in table 1.

*Table 1: Baseline patient characteristics*

| | Patients (n = 8) |
|---|---|
| Mean age, years (SD) | 44.00 (18.18) |
| Female sex, n (%) | 6 (75.00) |
| IBS subtype | |
| - Diarrhea (IBS-D), n (%) | - 5 (62.50) |
| - Constipation (IBS-C), n (%) | - 1 (12.50) |
| - Mixed (IBS-M), n (%) | - 2 (25.00) |
| Mean IBS-SS score (SD) | 256.25 (69.68) |
| - Mild (75-175), n (%) | - 0 (0.00) |
| - Moderate (175-300), n (%) | - 7 (87.50) |
| - Severe (>300), n (%) | - 1 (12.50) |
| Mean length of IBS diagnosis, years (SD) | 9.56 (6.73) |
| Ever received this treatment, n (%) | |
| - Bulk-forming laxatives | 1 (12.50) |
| - Psyllium fiber | 4 (50.00) |
| - Enema | 1 (12.50) |
| - Anti-diarrhea drugs | 1 (12.50) |
| - Scopolamine butylbromide | 2 (25.00) |
| - Probiotics | 4 (50.00) |
| - Peppermint oil | 6 (75.00) |
| - Antidepressants | 2 (25.00) |
| - Low-FODMAP diet | 2 (25.00) |
| - Other diet (elimination diet i.e.) | 4 (50.00) |
| - Psychotherapy | 1 (12.50) |
| - Mindfulness | 1 (12.50) |

SD = Standard deviation

The mean duration of the interviews was 27 minutes. One interview was digital, the others were face-to-face. Saturation was reached after six interviews, after which two more interviews were conducted for confirmation. No new relevant treatment aspects were reported. All discussed IBS (sub)themes and sample patient quotations are shown in table 2.

*Table 2: Sample patient quotations about patients' experiences of living with IBS*

| Themes | Subthemes | Sample quotations |
|---|---|---|
| Diagnosis | *Different tests* | "Multiple tests were completed; stool and laboratory analysis. This was normal. After these tests, I was referred to this hospital and a coloscopy was performed where no abnormalities were found. IBS was the remaining diagnosis." (Female, 34 years old) |
| | *Multiple colonoscopies* | "One year ago, I went to the hospital again because the symptoms were worsening. The symptoms felt different than before. That's what worried me. Isn't it something serious after all? Eventually after some tests, the diagnosis was still IBS. Eventually, you go home relieved it is still IBS and not something else." (Male, 64 years old) |
| Symptoms | *Stress and diet* | "Since the level of stress is decreased in my life, I experience less abdominal pain. Also, dietary changes helped me a lot. I have learnt a lot about my illness over the years." (Female, 61 years old) |
| | *Different predominant symptom over time* | "In the past the abdominal pain was the main symptom. Now, it is the abdominal bloating and constipation. The abdominal pain is more present during periods with more stress in my life. The pain is present from time to time, at random moments." (Female, 22 years old) |
| Daily life functioning | *Sudden urges to have bowel movement* | "It was especially annoying that you had to make sure at a sudden moment that you found a toilet in the area. This was always unpredictable. Everywhere you go, first you will search for an available toilet. It makes you doubt whether you should go to a certain event or not." (Female, 34 years old)<br>"Because of these symptoms, I am staying home more often. When I have an appointment, I will bring extra-large sanitary towels and an extra pair of underwear." (Female, 28 years old) |
| | *Impact on self-image* | "The constipation negatively affects my self-image, because of the abdominal distension. It looks like I am two-months pregnant." (Female, 22 years old) |

*Table 2: Continued*

| Themes | Subthemes | Sample quotations |
|---|---|---|
| Anxiety & Depression | *Anxiety* | "I sometimes have anxiety due to the disorder. Will it get better? Will they find the right treatment? Because I already had many treatments." (Female, 28 years old)<br>"At the beginning of my symptoms, I worried a lot. I thought it might be cancer, for example from the stomach or the large intestine. Finally, I managed to get past this." (Male, 64 years old) |
| | *Depressed feelings* | "It amplifies, back and forth. If you become more depressed, the abdominal symptoms will get worse. If the symptoms will get worse, you will feel more down. This arranges that you will end up in a vicious circle which is difficult to break." (Male, 64 years old) |
| Treatment | *Peppermint oil* | "Peppermint oil helped in diminishing my symptoms, but the heartburn and burps were impractical. The side effects and costs were not worth it. At that time, I was still a student." (Female, 22 years old)<br>"I take peppermint oil when I develop symptoms again. I will use it for a couple of weeks until the symptoms resolve. After completing the therapy, the symptoms do not return immediately." (Male, 64 years old) |
| | *Low-FODMAP diet* | "I did not like the low-FODMAP diet. You are allowed to eat only a few dietary products. It was also time-consuming. But I found the nutrients which trigger my symptoms. But with some products, I know it could give me complaints but sometimes I take that for granted." (Female, 26 years old) |
| | *Psychological therapy* | "They tell you where to pay attention to, how to deal with your complaints. I already know a lot. It is also time-consuming... I personally don't believe in psychotherapy. Because I believe it is clearly a physical disorder." (Female, 63 years old)<br>"Mindfulness did not decrease my symptoms. I am too down to earth for this treatment. I followed a couple of sessions, five or six. I didn't like these group sessions, I prefer individual therapy because of a safe environment and of encouraging self-exploration." (Female, 26 years old) |
| | *Ideal therapy* | "It would be a comprehensive treatment. Something broad in psychological way. Also, dietary therapy would be involved. Not only focus on the symptoms but on the whole patient. Patients may need to adjust their lifestyle." (Female, 61 years old) |

*Table 2: Continued*

| Themes | Subthemes | Sample quotations |
|---|---|---|
| Health-professional relationship | *Guidance* | "I only had one physical consultation with the dietician. There were no other appointments. I would expect a more active role from the practitioner." (Female, 34 years old) |
| | *The same doctor during treatment* | "I think it is a pity that you get different doctors during a treatment. Because then the doctor gained confidence and you've built a good patient-doctor relationship. Then you have to tell your whole story of symptoms again." (Female, 28 years old) |
| Preferences therapy | *Type of therapy* | "If the complaints disappear as a result of the therapy, I am open to any form of therapy." (Female, 34 years old)<br>"I think it's important which kind of therapy I choose, because I personally don't believe in psychotherapy. I think the symptoms are physical." (Female, 63 years old) |
| | *Confidence in therapy* | "If you don't have faith in the therapy, it's not going to work." (Female, 63 years old) |

Diagnosis

The mean length of IBS diagnosis was 9.56 years (SD 6.73). In all patients, IBS was diagnosed by general practitioners. After diagnosis, 3 of 8 patients (37.5%) were immediately referred to a gastroenterologist in the hospital. The other patients were referred after treatment prescribed by the GP. According to patients, reasons for referral to a specialist were the absence of improvement or worsening of symptoms. Two patients reported suffering from abdominal pain since childhood. Their diagnosis of IBS was confirmed during teenage years. One of the eight patients, subtype constipation, had no additional investigations in the hospital and received only treatment. The patient was comfortable with this approach. Besides laboratory- and stool tests, 6 of the 8 patients underwent a coloscopy. Some of them had multiple colonoscopies, due to worsening complaints over the time (see table 2 for sample quotations).

Symptoms

In five patients the predominant symptom was abdominal pain. In two patients, diarrhea was the most bothersome symptom of IBS and one patient reported the combination of abdominal bloating and constipation to be the most bothersome symptom. Three patients reported stress to be an important factor in the severity of symptoms. Four patients experienced a clear relationship between the symptoms and certain dietary products.

Daily life functioning

All patients experienced that their symptoms were interfering with daily life functioning, but only one of them occasionally cancelled social gatherings. Two patients had very frequent loose stools, up to six times a day. These patients reported to have sudden urges to use the bathroom. One patient with IBS-D and fecal incontinence took precautionary measures when leaving her house. One patient mentioned the big impact of her symptoms on her level of self-confidence.

Anxiety and depression

One of the patients still experienced anxiety recently due to IBS symptoms. This patient worried about the future with the disorder. In total, 3 out of 8 patients experienced anxiety in the past. They were all worried about the cause of the abdominal pain. Some of them feared it was a malignancy. This often led to experiencing more abdominal pain in these patients.

None of them felt down or depressed lately. Three of them experienced depressive symptoms in the past. Comparable to anxiety, among the patients more symptoms were present when depressed feelings were present.

Treatment experiences

Most of the patients had received multiple IBS therapies. Mean amount was 3.63 (SD 1.51) therapies per patient. All therapies these patients ever received, are summarized in table 1.

The majority of the patients was advised about the most appropriate treatment by the gastroenterologist, one patient by the GP. One patient tried successfully to adjust her diet herself. All treatments were advised according to the patient's preferences.

Six patients were not using IBS treatment currently. Two other patients were using some form of treatment at the time of the interview: one patient was receiving psychotherapy and one used probiotics on a daily basis.

Peppermint oil was the most frequently used pharmacological treatment in this study (6 out of 8 patients used this). Three out of 6 patients reported peppermint oil to be effective in reducing their symptoms. In the other three patients no symptom reduction was achieved.

Three patients reported side effects related to the use of peppermint oil: two patients experienced heartburn and one patient experienced stomach cramps and a headache. One patient finished therapy because of the heartburn and costs. One patient used peppermint oil whenever symptoms worsen.

Four patients had ever used probiotics. Two of them reported probiotics to be unsuccessful. One patient experienced only a short-term positive effect on diarrheal symptoms when using it on a daily basis. One patient reported probiotics to be effective and she used it on a daily basis. Both patients used probiotics for several months.

Two patients used antidepressants in the past (both citalopram; SSRI). One patient outlined that the pharmacological agent was not effective and she suffered from severe headache as a side effect. In the other patient the abdominal pain resolved completely, only the irregular stool was still present.

Six of the eight patients followed a type of diet in order to diminish their IBS symptoms. Two followed the Low-FODMAP diet, two the elimination diet and the other two patients followed a gluten-free diet and her own diet plan. They all reported the therapy to be effective. The low-FODMAP diet was difficult to adhere to according to one patient.

Only two patients followed psychological therapy, one psychotherapy and one mindfulness. Psychotherapy was followed online. This patient was not that satisfied with the treatment and she reported the therapy to be ineffective. Mindfulness therapy was also not effective for this one patient.

Ideal therapy

All patients described their ideal treatment for IBS. All patients would like to have an effective therapy. Four patients mentioned the therapy should possess none/few minor side effects. One mentioned additionally a preference toward low costs. One patient mentioned the ideal therapy not to be time-consuming but it should be easy to complete with minimal effort. Two patients reported the need of sufficient guidance and sufficient number of healthcare appointments. One patient wished for a therapy with a quick response. One patient had specific ideas about the content of the therapy and would like a combined therapy of diet intervention and psychotherapy.

Health professional-patient relationship

The length of practice time of the health care professional was not important to patients; median score of 2.00 (1-3). One patient was discontented with the lack of guidance of the health care professional during her diet therapy. She would prefer more one-on-one contact with her healthcare professional during her treatment. Patients preferred a professional who pays enough attention and listens carefully.

Patients would like to gather enough information about the different available therapies from the professional. A few patients mentioned 'trust' to be an important feature in the professional-patient relationship. Also, one patient preferred one doctor during the whole treatment, not several doctors. Other patients did not report any point for improvement regarding the physician-patient relationship.

Preferences for type of therapy

The prescribed modality of the treatment in IBS (diet or pharmacological therapy or psychotherapy) was slightly important to patients. The median score of this item was 3.50 (range 1-5) on the Likert scale. Some of the patients had no preference for a therapy modality (N = 3). Two patients wished for a pharmacological agent. Two patients favored diet therapy and one preferred psychological therapy. Also, the aspect "having confidence in therapy" was scored and rated as important to very important (median score as 4.50 (range 2-5)).

Results survey physicians

In total 19 experts were contacted to take part in this survey. The response rate was 78.9% (n = 15). Twelve gastroenterologists and three general practitioners completed the survey. The mean practice time treating IBS patients was 20.4 years (S.D. 8.95). The number of prescribed therapies and therapies physicians deemed to be effective, are summarized in table 3. The majority of physicians believed in the effectiveness of the low-FODMAP diet, hypnotherapy, tricyclic antidepressants and bulk-forming laxatives (>80%). The most prescribed therapies include bulk-forming laxatives, anti-diarrhea drugs, peppermint oil, tricyclic antidepressants, low-FODMAP diet and hypnotherapy (>80%). Ineffectiveness, adverse effects, too much time for a response to occur, high costs, high treatment burden, distant location of therapy, were all reported as reasons to discontinue therapy for patients, according to the perception of physicians. Besides the important treatment characteristics (attributes), their preferences for therapy depended on the IBS subtype of the patient, the opinion of the patients about the treatment options, experience with previous treatment and additional psychological complaints.

Ranked Attributes by patients and physicians

The predefined therapy characteristics were scored by both the patients and physicians using the Likert Scale (1-5) to rank the level of importance. These scores are shown in figure 1.

According to patients, the important characteristics of treatment (scored as ≥ 4) were effectiveness, duration of response, side effects and treatment burden. Waiting period and location of therapy were classified as 'not important' to patients.

*Table 3: Opinion of physicians about the different therapy modalities (n = 15)*

| Types of therapy | Believe in effectiveness of therapy (n (%)) | Ever prescribed therapy (n (%)) |
|---|---|---|
| Bulk-forming laxatives | 13 (86.7) | 13 (86.7) |
| Anti-diarrhea drugs | 10 (66.7) | 12 (80.0) |
| Antispasmodics | 5 (33.3) | 11 (73.3) |
| Probiotics | 4 (26.7) | 6 (40.0) |
| Peppermint oil | 9 (60.0) | 15 (100) |
| Linaclotide | 11 (73.3) | 11 (73.3) |
| Antidepressants - SSRI | 6 (40.0) | 6 (40.0) |
| Antidepressants - TCAs | 13 (86.7) | 13 (86.7) |
| Low-FODMAP diet | 14 (93.3) | 15 (100) |
| Hypnotherapy | 14 (93.3) | 14 (93.3) |
| Pelvic floor therapy | 7 (46.7) | 8 (53.3) |
| Psychological therapy (cognitive behavioral therapy) | 10 (66.7) | 10 (66.7) |
| Other therapy | Ebastine – 1 (6.7) | Colesevelam – 1 (6.7)<br>Ebastine – 1 (6.7) |

TCAs Tricyclic antidepressants; SSRI Selective serotonin reuptake inhibitor

According to physicians, important characteristics of treatment were effectiveness, duration of response, side effects, treatment burden and willingness-to-pay. None of the characteristics were reported as 'not important' to physicians.

Treatment attributes and levels

The attributes and levels of the IBS treatment were acquired from both the literature screening as well as the interviews with patients and the completed survey by physicians. After analyzing the survey and patient interviews, these potential attributes and corresponding levels were discussed during an expert opinion meeting to obtain correct definitions and define the range of the levels. The final attributes, their definitions and levels are summarized in table 4. In addition, this table contains references of literature, which were used to define the levels of the attributes. Table 5 shows sample patient quotations about the different treatment attributes.

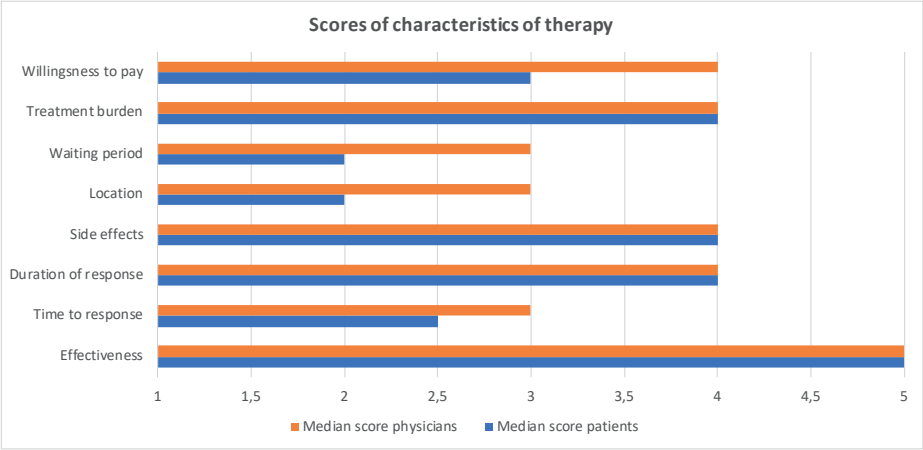


*Figure 1: The bars represent the median scores of level of importance* of the treatment aspects, among physicians and patients.*

* The Likert scale is a five-point scale (1-5) to rank the level of importance, where 1 displays very unimportant, 2 not important, 3 neutral, 4 important and 5 very important.

Attribute: Effectiveness

Effectiveness was scored as very important by both the physicians and patients. The majority of the patients reported effectiveness to be the most important attribute (see table 5 and figure 1). The attribute effectiveness can be quantified by using the IBS-SSS, which is an outcome measure that has broadly been used in IBS studies assessing dietary, pharmacological and psychological interventions. On the IBS-SSS, a decrease of 50 points corresponds to Minimal clinically important difference (MCID) [27]. Such attribute levels can be used for physicians who are accustomed for using such instruments to evaluate efficacy. For patients, the definition of the attribute effectiveness reflects the percentage of symptom reduction.[32] This description of the attribute effectiveness also emerged during the interviews.

Attribute: Time until response

The time until response occurs after starting a treatment was an important aspect of therapy according to the physicians, but was not that important for patients. The main reason could be that patients have been experiencing symptoms for several years. Levels were described as the period of time until response occurred of the treatment, which was based on the interviews and the literature.

Attribute: Cessation of response

Cessation of response following discontinuation of therapy or completing the therapy, was scored as important by both patients as physicians. The levels were described by the period of time from the discontinuation of therapy until the moment of termination of response. The description of the levels was based on the patient interviews and the literature.

Attribute: Side effects

Side effects were important to patients and scored as neutral in physicians. Patients were not willing to accept all side effects even if the therapy is fully effective. Generally, patients were willing to accept mild side effects. To make the levels of the attribute side effects more realistic, examples and risk percentages were described. The description of examples of side effects was emerged from the patients' interviews, because it helped in the clarification of this attribute. Risk percentages were extracted from the literature.

Attribute: Treatment burden

The treatment burden was scored by both the physicians as the patients as an important aspect of treatment. The treatment burden covers the effort to complete the whole therapy, like the time of the therapy itself, dietary instructions, homework etc. The maximum time patients would like to spend on a therapy differed among these patients. This amount ranged from 1 hour per week to 2 hours per day. Levels were defined as the number of hours per week spent on a therapy, which was based on the literature and the input from patients.

Attribute: Waiting period

The waiting period comprises the period of waiting to start a therapy after being referred. This aspect was not important to patients. They felt comfortable with waiting a few months until their therapy is available. Physicians scored this item as neutral. Levels were defined based on the content of the interviews and literature.

Attribute: Location of therapy

Location of therapy was scored as not important to patients. Physicians scored neutral. Most of the patients would not mind to travel 20-30km every week by car to join therapy. Levels were described as the travel distance from home to the therapy session (hospital or office). The levels were based on the literature and the interviews.

*Table 4: Final attributes and levels for the management of irritable bowel syndrome*

| Attributes | Definition |
|---|---|
| Effectiveness | Physicians: Reduction of 50 points on the IBS-SS score (Minimal clinically important difference (MCID))<br><br>Patients: Percentage of symptom reduction |
| Time until response to occur | Response = Reduction of 50 points on the IBS-SS score |
| Cessation of response following discontinuation of therapy | Response = Reduction of 50 points on the IBS-SS score |
| Side effects | |
| Treatment burden | Effort to complete the therapy |
| Waiting period | Waiting period to start therapy after being referred |
| Location | Distance to location of therapy |
| Willingness to pay (monthly costs) | The maximum price a patient wants to pay for the therapy |
| Frequency of healthcare appointments | Amount of contact moments with the healthcare professional during and/or after the therapy (including evaluation) |

| | Levels | References |
|---|---|---|
| | Physicians (Average score of 250 points):<br>- Reduction of 50 points on the IBS-SS score<br>- Reduction of 100 points on the IBS-SS score<br>- Reduction of 150 points or more on the IBS-SS score<br><br>Patients:<br>- Symptom reduction of 25%<br>- Symptom reduction of 50%<br>- Symptom reduction of 75%<br>- Symptom reduction of 100% | [27,32,33] |
| | - 2 weeks<br>- 4 weeks<br>- 8 weeks<br>- 12 weeks | [34–39] |
| | - Immediately<br>- 2 months<br>- 6 months<br>- 12 months or longer | [37–41] |
| | - None<br>- Mild (heartburn, dry mouth, drowsiness; risk 10%)<br>- Severe (heart rhythm disturbance, risk 0.01%) | [5,6,34,36, 42–44] |
| | - No/barely effort<br>- 1-hour weekly<br>- 2-hours weekly | [42,45,46] |
| | - No waiting time<br>- 2 weeks<br>- 4 weeks | [38] |
| | - At home<br>- Distance <10km<br>- Distance <30km | [38] |
| | - No costs, € 0,00<br>- Up to € 20,00<br>- Up to € 50,00<br>- Up to € 100,00 or more | [42,47] |
| | - A single appointment, no follow up<br>- Every 2 weeks<br>- Every month<br>- Every 2 months | [38, 48–51] |

*Table 5: Sample patient quotations about the different treatment attributes*

| Attributes | Sample quotations |
|---|---|
| Effectiveness | "Effectiveness is the most important to me. That's the first thing I inspect when choosing a therapy." (Male, 64 years old)<br>"If the therapy will provide 50% symptom reduction, then I already think it is worth to try. The therapy must ensure a significant difference in symptom reduction." (Female, 63 years old) |
| Time until response | "I have been dealing with bowel problems for years, so it doesn't matter if the treatment takes months to work". (Female, 28 years old)<br>"I would invest up to a year in the therapy, if the treatment is effective" (Female, 26 years old) |
| Cessation of response | "This aspect is very important to me. Because I have been dealing with the complaints for several years, it is important to me that the effects are long-term. This period should be at least two months." (Female, 26 years old) |
| Side effects | "It is very important to choose a treatment with few side effects." (Female, 28 years old)<br>"Side effects are more important than the effectiveness when choosing a therapy. Imagine having a constant headache as a side effect, I wouldn't choose that therapy. It's the balance between these two aspects, that is important" (Female, 63 years old)<br>"Minor side effects are no issue at all." (Male, 64 years old)<br>"There may be side effects, but they should not cause any harm. They must be reversible." (Male, 54 years old) |
| Treatment burden | "Maximum time I would like to spend on a therapy would be one or two hours per week. This time would be more if my complaints were worse." (Female, 22 years old)<br>"One hour per day would be acceptable for me." (Female, 63 years old)<br>"Eight hours or one day a week would be okay for me to spend on therapy sessions, including homework." (Male, 54 years old) |
| Waiting period | "I don't mind waiting a few months, because I know that these symptoms are long term that will continue my whole life." (Female, 22 years old) |
| Location of therapy | "The maximum distance I would like to travel to therapy depends on the frequency of the therapy session. If the therapy is weekly, then 40 km is the maximum distance I would like to travel. If the therapy is once in six weeks, then 200km is acceptable." (Female, 26 years old)<br>"The location of therapy is not important to me. It doesn't matter to me if I have to travel 30km to the location every two weeks during six months. If the therapy is effective, then it's worth the effort." (Male, 54 years old) |
| Willingness to pay | "I earlier paid €30,00 per month, that was okay for me. Because I am a student, I am not able to pay more for a treatment." (Female, 22 years old)<br>"If the therapy is effective for my bowel pain, then I am willing to pay € 200-400 euros per month for a therapy." (Female, 63 years old) |

*Table 5: Continued*

| Attributes | Sample quotations |
|---|---|
| Frequency of healthcare appointments | "I would like to have more doctor visits during therapy for guidance. Once in six weeks would be optimal." (Female, 26 years old)<br>"Regular telephone contacts with the doctor of therapist would be important to me. Five or ten minutes will be enough." (Female, 34 years old) |



Attribute: Willingness to pay

Willingness to pay (WTP) was scored as important to physicians when prescribing a therapy and neutral to patients. The maximum price the patients were willing to pay differed and depended on the economic status of the patient. The median amount among the eight participants was € 50.00 euro per month (range 30-300 euros). Definition of willingness to pay is set as the maximum price a patient is willing to pay for the therapy; this includes the out-of-pocket cost and a part of the mandatory deductible amount which is present in the Dutch health insurance.

Supplementary to the predefined healthcare characteristics, one new attribute was extracted from the patient interviews. Evaluation of the survey for physicians showed no new attribute.

Attribute: Frequency of healthcare appointments

Patients preferred frequent healthcare appointments with their physicians or therapist/dietarian during their treatment. This aspect is defined as the amount of contact moments with the healthcare professional during and/or after the therapy (including evaluation). Three out of the eight patients introduced this aspect as important when choosing a therapy.

## DISCUSSION

In this study we performed semi-structured interviews with IBS patients and a survey was completed by physicians in order to explore which potential attributes and levels are related to preferences for an IBS treatment. These findings not only provide insight into the difference in perspective on treatment between patients and physicians but can also be used in the future for further quantitative preference research.

Effectiveness of treatment appears to be the most important factor with regards to treatment preference, as described by both patients and physicians. Duration of response, side effects and treatment burden were scored by patients and physicians as important, too. Time to response, location and waiting time for an appointment were not important for patients (scored as not important) compared to physicians (scored as neutral). Patients reported these aspects to be minor details during the interviews, because they were suffering from these symptoms for many years and were therefore willing to wait for a treatment to start and response to occur. Physicians believed that the willingness to pay or costs of a treatment is an important attribute for patients. However, patients valued this as less important (scored as neutral). Interviews with patients revealed a further attribute that was not yet identified based on the literature search, i.e. the frequency of appointments with the healthcare professional. No differences in results were seen between male or female and the level of education of the patients. In total, the interviews and surveys revealed nine potential important treatment attributes. Previous studies that focused on the development of quantitative preference elicitation in both physicians and patients, showed similar attributes for treatment choices. A treatment that would result in symptom relief, speed of action, duration of relief and ease of use were important aspects to asthma and COPD patients.[22] Clinical experts considered a long duration of effect and reliability of symptom control as important.[22] Also, patients with degenerative disc diseases of the spine, described effectiveness and duration of symptoms important in choice of therapy; this was similar to their doctors.[26] A majority of the attributes identified in the current study therefore appears generic across different diseases. These diseases have in common that they are of chronic nature and have frequent relapses/exacerbations because no complete cure is available. Therefore, the treatment is mainly focused on symptom relief.

The ideal therapy, according to the IBS patients interviewed in our study, would consist of a therapy that is effective, contains no or few side effects and includes frequent appointments with the healthcare professional for guidance. Generally, patients in our study were willing to take mild side effects for granted if the therapy was effective. Two previous studies, both involving a standard gamble between willingness to

accept medication risk and symptom relief, showed that IBS patients are willing to take substantial medications risks for symptom relief.[9,33] Patients would even accept a mean risk of 10.2% of sudden death for a 99% chance of cure.[9] Our study shows that indeed risk of side effects and symptom relief are considered important. However, for estimating the trade-offs between these and other additional relevant attributes, quantitative research such as a DCE is necessary. In a DCE survey, patients are offered series of hypothetic choices of two or more medical intervention alternatives with each different combinations of attribute levels. The characteristics of an intervention can be described as attributes with corresponding levels to illustrate the individual's preference.[19,34] This study is the first part of the development of the DCE where attributes and levels were constructed by performing semi-structured interviews and a survey. Therefore, the most paramount attributes identified in this current study could be used to perform a DCE in the future to ascertain treatment preferences for IBS in a more quantifiable manner.

To give insight in living and dealing with IBS, different qualitative studies have been previously performed in IBS patients.[12,13,35] In these studies, the perspective of the IBS patient was explored regarding a specific kind of therapy. In our study, the perspective of IBS patients was enlightened of the whole management of IBS and all treatment characteristics were ranked on level of importance. Also, the view of physicians was explored about the important factors of IBS treatment. Our findings reveal the difference in perspective on treatment between physicians and patients. This discrepancy will address the gap between patient and providers and is relevant for shared-decision making during consultation. By involving patient' needs and preferences in the management, the treatment could be better individualized. This will contribute to a better treatment adherence, which is crucial for management success.[36,37]

A strength of this study is that it used most recent reporting standards. In recent studies the importance of performing a structured and in detail reported method for designing a DCE was emphasized.[18,30,38] To avoid underreporting, guidelines were recently published for qualitative studies that support development of quantitative preference study protocols and survey instruments.[18] These are derived from already existing guidelines on the Standards for Reporting Qualitative Research (SRQR) and the Consolidated Criteria for Reporting Qualitative Research (COREQ).[38,39]

These published guidelines consist of best practices for reporting all items of a research article. The qualitative method used in this study was based on these guidelines and is congruent with those reported in other qualitative DCE development studies.[20,22,23,40,41] A predefined list of attributes derived from a broad screening in literature, the use of a

topic guide, approach and reporting of iterations when discussing attributes and their levels, are all examples of the detailed reported method of this study. Transcription and iterative coding were performed using the software tool NVivo which is a well-established tool to complete qualitative evidence synthesis.[42] Another strength of this study includes the novelty of the collected information about the factors that patients and clinical experts consider important in the treatment of IBS, specifically.

Our study also has limitations. Patients were recruited from outpatient clinics in an academic hospital which has a combined secondary and tertiary care function. No patients from primary care were included. This could have resulted in a selection bias, because these patients do not necessarily represent the whole IBS population. However, these patients have often experienced different therapies and are more able to describe their perspective on IBS therapies and will be more suitable to participate in this study than treatment-native patients. Also, all three subtypes of IBS were represented during the interviews, but a more equal distribution would have been more preferable. The majority of our patients had IBS-D. In addition, the number of patients included (N = 8) may appear limited. However, sample size in qualitative research is determined by the saturation point. Saturation in our study was reached after six interviews which means that no new information was discovered. However, two more interviews were conducted to assure no additional content was missed. As for the physicians, the form of survey was chosen for reasons of practicality. Due to schedule difficulties and time investment, in-person meetings were not found suitable. In-depth interviews with physicians may have provided us more detailed information but was not considered feasible.

In conclusion, this study provides the important aspects and context of preferences related to the management of IBS according to both patients and physicians. The precise description of our methods will help to provide better quality and transparency of the designs for informing attribute and attribute-level selection. The collected attributes and levels can be used to further explore the IBS treatment preferences in future quantitative research within the framework of a discrete choice experiment. This will further pave the way for personalized treatment efforts tailed towards individual needs in IBS patients.

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# Chapter 4

## DISCRETE CHOICE EXPERIMENT REVEALS STRONG PREFERENCE FOR DIETARY TREATMENT AMONG PATIENTS WITH IRRITABLE BOWEL SYNDROME

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## ABSTRACT

Background & Aims

Irritable Bowel Syndrome (IBS) is a highly prevalent, chronic disorder of the Gut-brain interaction which significantly affects quality of life. Several treatments, with comparable clinical efficacy, are available. Patient preferences can therefore be an important determinant of an effective management strategy. Treatment preferences of patients regarding decision-making remain unclear. We aimed to examine these preferences and estimate trade-offs between different attributes.

Methods

427 patients from the Maastricht IBS cohort were invited to participate. A labeled discrete choice experiment (DCE) survey, containing 9 scenarios with each three alternatives (medication, diet, psychotherapy), was developed in order to estimate preferences. The treatment scenarios were based on six attributes: effectiveness, time to response, time until recurrence, side effects, time required and frequency of appointments. The preference weights and relative importance were analyzed using a mixed logit model.

Results

A total of 185 (43.3%) of 427 potential respondents completed the questionnaire (mean age 49.51 years, 69.2% female). The most-preferred treatment was dietary intervention (48.1%), subsequently pharmacotherapy (29.2%) and psychotherapy (22.7%). IBS patients preferred a higher effectiveness, shorter time interval to response, longer time interval until recurrence, no severe side effects and frequent appointments when attending psychotherapy. Younger patients (£50 years) preferred dietary interventions and a long period until recurrence, whereas older patients (>50 years) were more inclined to choose pharmacotherapy and the period until recurrence was not important.

Conclusions

Dietary interventions were the most-preferred IBS therapy. Identifying patients' treatment preferences during shared decision-making, will provide more optimal management strategies and could be the best approach to diminish disease burden.

# INTRODUCTION

Irritable bowel syndrome (IBS) is a prevalent disorder of the Gut-Brain interaction in which recurrent abdominal pain is associated with disordered bowel habits.[1] The prevalence of IBS is around 4.6% worldwide, according to the Rome IV criteria.[2] IBS symptoms greatly affect individuals' quality of life (QoL), which contributes to a considerable burden on work absenteeism and presenteeism and forces increased demands of healthcare facilitations. Therefore, efficient management strategies for IBS are essential to improve the QoL of these patients and reduce overall healthcare costs.[3]



The management of IBS remains challenging, due to the clinical heterogeneity and the absence of a single effective therapy. Currently, all available treating options for IBS include dietary intervention (i.e., standardized dietary advice, low-FODMAP-diet), pharmacotherapy (i.e., antispasmodics, antidepressants) and psychotherapy (i.e., cognitive behavioral therapy, hypnotherapy). Although trial design and definitions of outcome measures differ substantially, IBS treatments generally have comparable efficacy with a number needed to treat (NNT) from 4 to 5, based on meta-analysis.[3] Therefore, other aspects besides efficacy are important when making IBS treatment decisions. Identifying patients' wishes about other treatment aspects, such as the risk of severe side effects or process related characteristics, will affect compliance to treatment and is therefore highly valuable to successfully complete a treatment. Establishing and retaining effective treatment is only possible if clinicians understand which treatment factors are important to patients. Previous research showed that this contributes to a better patient-centered care and a higher compliance to treatment.[4] Addressing these preferences of patients during consultation, will assist in bridging the communication gap between health care providers and IBS patients and ultimately will provide more patient satisfaction with the current IBS health care.[5]

One study showed that tablets and lifestyle changes (diet, yoga) were the most preferred therapies.[6] Regarding the risk of side effects, two previous studies showed that patients with diarrhea-predominant IBS are willing to take substantial medications risks for symptom relief.[7,8] Patients would accept a mean risk of 10.2% of sudden death for a 99% chance of cure and were willing to tolerate a 2.65% increase in impacted-bowel risk. Still, the effects of other treatment aspects on treatment decision in IBS patients remain unclear. We therefore aimed to perform a quantitative preference study by using a discrete choice experiment involving different treatment aspects and all current IBS treatment options.

## METHODS

Study population

Participants in this study where patients from the Maastricht IBS (MIBS) cohort. This cohort consists of patients with IBS between 18 and 75 years of age and were recruited via the outpatient clinic of the Gastroenterology-Hepatology division of the Maastricht University Medical Center+ (MUMC+) in the Netherlands or via general practitioners in the area of South Limburg. All patients fulfilled the Rome III criteria at moment of inclusion in the MIBS cohort. IBS subtypes were applied and questionnaires were completed about their (comorbid) symptoms, lifestyle, general quality of life at inclusion in the MIBS cohort.[9] Patients who approved invitation for follow-up were invited to participate in this study (n = 427). All participants resided in the Netherlands at the time of the survey and were able to read and understand Dutch to provide informed consent and complete the survey.

All procedures that followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. The study was reviewed and approved by the ethics committee at the Maastricht University Medical Center (NL24160.068.08 / 08-2-066). Written informed consent was obtained from all patients prior to being included in the MIBS cohort.

Identifying and selection of attributes and levels

A popular and valid instrument in health care to extract patient preferences regarding treatment choices and decision making, is to perform a discrete choice experiment.[10] This is a quantitative method where patients are offered series of hypothetic choices of two or more medical intervention alternatives with each choice including different combinations of attribute levels. The attributes serve as the characteristics of an intervention, where the different levels illustrate their values. Based on the choice variation, the preferences of the respondents are analyzed. Before designing a discrete choice experiment, qualitative research to identify and select appropriate attributes and levels is important for enhancing valid results.[11] Several guidelines were followed during the development of the DCE.[10,12] We first developed a topic guide by performing a literature screen to select possible relevant characteristics of IBS treatment. This topic guide was used as input for the qualitative research in which interviews were conducted with IBS patients (n = 8). These interviews were semi-structured and performed to identify which characteristics were considered important for IBS treatment. The interviews consisted of open questions about diagnosis, symptoms, previous treatment experiences and their opinion about important treatment aspects.

At the end of the interview, patients completed a ranking assignment where the possible relevant treatment characteristics from the literature screen were scored on level of importance. In the next phase, the derived attributes and levels from the semi-structured interviews and literature were discussed in the research group (consisting of all authors) and an expert opinion meeting with three other gastroenterologists. Final attributes, levels and their definitions were set during this expert opinion meeting. In total, six final attributes and their levels were included, as shown in table 1. We chose to include three clinically relevant treatment options in our DCE: pharmacotherapy, dietary intervention and psychotherapy. Respondents were thus presented with three labelled therapies, each characterized by various levels of the six attributes. A labeled design was chosen to represent the clinical practice more realistically, which adds to the validity of the results.[13]



Design of DCE

A D-efficient fractional factorial design was created in Ngene software (v 1.1.1, Choice Metrics Pty. Ltd.) with 3 blocks of each eight choice sets. The order of the attributes varied over these 3 versions to control for a potential attribute-ordering effect. Patients were randomly assigned to one block of eight questions. Effectiveness and time to response were treated as generic attributes, meaning all levels were applicable for each treatment. Pharmacotherapy included a treatment specific attribute side-effects. All treatments shared the same attributes recurrence and frequency of appointment but with alternative specific levels while dietary interventions and psychotherapy also included the attribute time required. The categorical parameter, side effects, was effect coded.[14] The other attributes were treated as continuous parameters.

A pilot study was conducted to analyze the accuracy and comprehensibility of the survey. The survey was clear and comprehensible to all IBS patients (n = 7). The design was updated with priors from the pilot to a Bayesian design. Details of the sample size calculation are available in Supplementary material.

Questionnaires

Patients were invited by mail or by post, after 3 and 6 weeks a reminder was sent. To test the rationality of choice behavior, a nineth question was applied as a dominance test.[15] The option dietary intervention was logically preferable here because the levels of all attributes were better compared to the other treatments.

*Table 1: Attributes and levels of the discrete choice experiment*

| Attributes | *Alternative specific levels* |
|---|---|
| | Medication |
| Effectiveness | - Symptom reduction of 25%<br>- Symptom reduction of 50%<br>- Symptom reduction of 75%<br>- Symptom reduction of 100% |
| Time until response | - 4 weeks<br>- 8 weeks<br>- 12 weeks |
| Time until recurrence | - Immediately<br>- 2 months<br>- 6 months<br>- 12 months or longer |
| Side effects | - None<br>- Mild (heartburn, dry mouth, drowsiness; risk 10%)<br>- Severe (heart rhythm disturbance, risk 0.01%) |
| Time required | - No |
| Frequency of healthcare appointments | - A single appointment<br>- Every two weeks<br>- Every month<br>- Every 2 months |

In total, every survey consisted of nine DCE scenarios. A sample choice set of the DCE is found in figure 1. The survey is available in Supplementary material. Basic characteristics of the cohort were additionally measured by completing the following questionnaires: the diagnostic Rome III[16] and IV criteria[1], general quality of life (QoL) (EQ-5D-5L)[17], the PHQ-9 (diagnostic tool to screen for a depressive disorder)[18], the GAD-7 (diagnostic tool to screen for an anxiety disorder)[19] and the severity of IBS-symptoms (IBS-SSS)[20]. The average time to complete the survey was fifteen minutes. Participants received no honorarium when completing the survey.

Statistical analysis

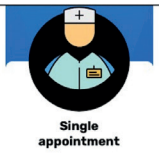
Treatment preferences of respondents were evaluated by a multinominal choice model and a mixed logit model with the use of Nlogit software, version 6, 2016 (Econometric Software Inc.). All data of all participants, except for the answer of dominance test

| Diet | Psychotherapy |
|---|---|
| - Symptom reduction of 25%<br>- Symptom reduction of 50%<br>- Symptom reduction of 75%<br>- Symptom reduction of 100% | - Symptom reduction of 25%<br>- Symptom reduction of 50%<br>- Symptom reduction of 75%<br>- Symptom reduction of 100% |
| - 4 weeks<br>- 8 weeks<br>- 12 weeks | - 4 weeks<br>- 8 weeks<br>- 12 weeks |
| - Immediately<br>- 2 months<br>- 6 months<br>- 12 months or longer | - 2 months<br>- 6 months<br>- 12 months or longer |
| - None | - None |
| - 1-hour weekly<br>- 2-hours weekly | - 1-hour weekly<br>- 2-hours weekly |
| - A single appointment<br>- Every two weeks<br>- Every month<br>- Every 2 months | - Every 2 weeks<br>- Every month<br>- Every 2 months |



itself, were included in the final analysis. Our a priori hypothesis is that next to efficacy, patients wish a fast responding and long-lasting therapy. Variation in preferences in IBS patients could be present depending on level of symptom severity and presence of psychological comorbidity.

Therefore, subgroup analysis was performed for various covariables which could be important for assessing patients' preferences according to either the clinicians' perspective or based on significant interactions: age (≤50 years and >50 years based on median value), symptom severity, IBS subtype and psychological comorbidity (depression and anxiety according to the PHQ-9 and GAD-7 score). Details of statistics can be found in Supplementary material.

| | Medication | Diet | Psychotherapy |
|---|---|---|---|
| Symptom reduction |   |   |   |
| Time until response | 8 weeks | 12 weeks | 4 weeks |
| Period of time after symptoms return after completing therapy |   |   |   |
| Side effects | None | None | None |
| Frequency of healthcare appointments |   |   |   |
| Time required | No/barely effort | 1-hour weekly | 1-hour weekly |

Which treatment would you prefer?

- Medication
- Diet
- Psychotherapy

*Figure 1: Discrete choice experiment choice sets: Patients were represented with nine different DCE choice sets (with choice set nine as a dominant choice set). Each choice set consisted of three treatment options (medication, diet and psychotherapy). Every option was characterized by various levels of the six attributes. Looking at the properties of each treatment, patients were asked which treatment they preferred.*

## RESULTS

Recruitment and baseline characteristics

427 patients from the Maastricht IBS cohort were assessed for eligibility of this study. Twelve patients were excluded due to lost to follow-up after inclusion in the MIBS, decease or refusal to participate in the study. The survey was sent to 415 patients in total. The response rate was 43.33%; 185 respondents completed the survey. Details of inclusion are shown in figure 2.

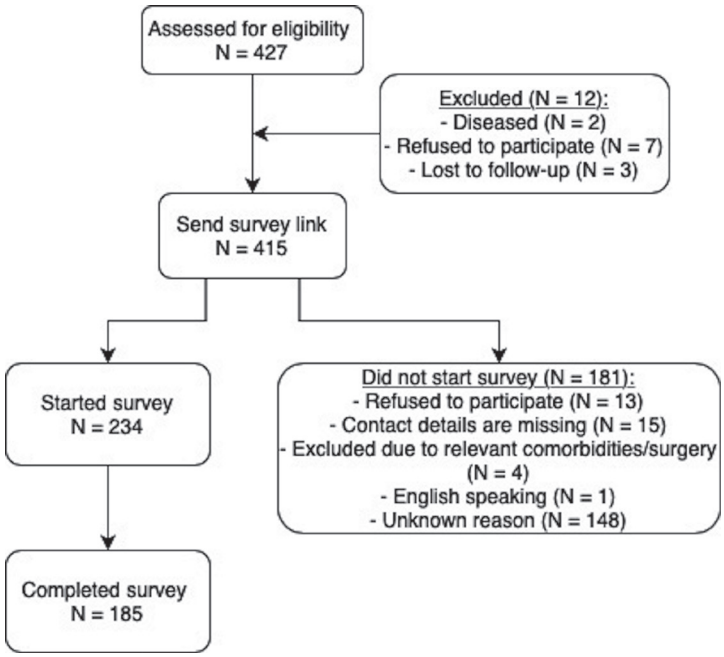



*Figure 2: Flow chart of patient inclusion of the Maastricht IBS cohort*

The mean age of the respondents was 49.51 years (SD 14.85). 69% was female and the majority of the respondents was highly educated (46%). The mean duration of IBS symptoms was 22.37 (SD 13.42) years. 88.10% of the respondents fulfilled the Rome III criteria at follow-up and 52.40% of the respondents fulfilled the Rome IV criteria. The mean IBS-SSS was 187.94 (SD 118.09), which correspondents with a moderate severity of IBS symptoms (175-300). 74% had ever received IBS treatment. All characteristics are reported in table 2. The demographics of the total MIBS-cohort is shown in Supplementary material.

*Table 2: Demographical and clinical characteristics of IBS-cohort*

| *Characteristics* | IBS cohort responses, N = 185 |
|---|---|
| Mean age, years (SD) | 49.51 (14.85) |
| Gender, n (%) | |
| - Female | - 128 (69.2) |
| - Male | - 57 (30.8) |
| Mean BMI (kg/m$^2$) (SD) | 25.87 (5.30) |
| Educational level, n (%) | |
| - Low | - 34 (18.4) |
| - Moderate | - 66 (35.7) |
| - High | - 85 (45.9) |
| Employment status, n (%) | |
| - Currently studying | - 5 (2.7) |
| - Employed, full-time or part-time | - 120 (64.9) |
| - Unemployed | - 6 (3.2) |
| - Incapacitated for work | - 18 (9.7) |
| - Homemaker | - 9 (4.9) |
| - Retired | - 33 (17.8) |
| Comorbidities, n (%) | |
| - IBD | - 9 (4.9) |
| - Coeliac disease | - 1 (0.5) |
| - Cardiovascular disease | - 11 (5.9) |
| - Respiratory disease | - 11 (5.9) |
| - Hypertension | - 12 (6.5) |
| - Diabetes | - 3 (1.6) |
| - Kidney disease | - 3 (1.6) |
| - Liver disease | - 3 (1.6) |
| - Hematologic disease | - 1 (0.5) |
| - Oncologic disorder | - 6 (3.2) |
| - Arthrosis | - 32 (17.3) |
| - Depression | - 17 (9.2) |
| - Back pain | - 45 (24.3) |
| - Fibromyalgia | - 31 (16.8) |
| - Chronic fatigue syndrome | - 6 (3.2) |
| - Thyroid disease | - 13 (7.0) |
| - Hypercholesterolemia | - 19 (10.3) |
| Mean duration IBS symptoms, years (SD) | 22.37 (13.42) |
| Mean severity IBS-SSS, (SD) | 187.94 (118.09) |

*Table 2: Continued*

| *Characteristics* | IBS cohort responses, N = 185 |
|---|---|
| Severity of IBS (IBS-SSS), n (%) | |
| - IBS in remission | - 32 (17.3) |
| - Mild IBS | - 60 (32.4) |
| - Moderate IBS | - 56 (30.3) |
| - Severe IBS | - 37 (20.0) |
| Fulfilled Rome III-criteria at follow-up, n (%) | 163 (88.1) |
| Fulfilled Rome IV-criteria at follow-up, n (%) | 97 (52.4) |
| IBS subtype according to Rome IV | |
| - Diarrhea (IBS-D), n (%) | - 30 (16.2) |
| - Constipation (IBS-C), n (%) | - 18 (9.7) |
| - Mixed (IBS-M), n (%) | - 20 (10.8) |
| - Undefined (IBS-U), n (%) | - 29 (15.7) |
| IBS subtype according to stool pattern (including patients who did not fulfilled Rome IV-criteria) | |
| - Diarrhea (IBS-D), n (%) | - 54 (29.2) |
| - Constipation (IBS-C), n (%) | - 37 (20.0) |
| - Mixed (IBS-M), n (%) | - 38 (20.5) |
| - Undefined (IBS-U), n (%) | - 56 (30.3) |
| Ever received IBS treatment, n (%) | |
| - None | - 49 (26.5) |
| - Dietary advice | - 92 (49.7) |
| - Referral to dietitian | - 62 (33.5) |
| - FODMAP-diet | - 28 (15.1) |
| - Antidepressants | - 41 (22.2) |
| - Diarrhea inhibitors | - 22 (11.9) |
| - Laxatives | - 36 (19.5) |
| - Scopolamine butylbromide | - 32 (17.3) |
| - Antispasmodic | - 7 (3.8) |
| - Peppermint oil | - 34 (18.4) |
| - Psyllium fiber | - 31 (16.8) |
| - Probiotics | - 40 (21.6) |
| - Pelvic floor therapy | - 22 (11.9) |
| - Hypnotherapy | - 9 (4.9) |
| - Cognitive behavioral therapy | - 7 (3.8) |
| - Other | - 14 (7.6) |
| Received IBS treatment by | |
| - General practitioner | - 53 (28.6) |
| - Gastroenterologist | - 132 (71.4) |
| Mean total EQ-5D-5L score (SD) | 0.78 (0.22) |
| Mean depression score (SD) | 5.50 (4.86) |

*Table 2: Continued*

| *Characteristics* | IBS cohort responses, N = 185 |
|---|---|
| Depression (PHQ-9) | |
| - Minimal symptoms, n (%) | - 96 (51.9) |
| - Mild depression, n (%) | - 55 (29.7) |
| - Moderate depression, n (%) | - 25 (13.5) |
| - Moderately severe depression, n (%) | - 4 (2.2) |
| - Severe depression, n (%) | - 5 (2.7) |
| Mean anxiety score (SD) | 4.20 (4.33) |
| Anxiety (GAD-7) | |
| - Minimal symptoms, n (%) | - 116 (62.7) |
| - Mild anxiety, n (%) | - 52 (28.1) |
| - Moderate anxiety, n (%) | - 11 (5.9) |
| - Severe anxiety, n (%) | - 6 (3.2) |

Discrete choice experiment analysis

None of the questionnaires had missing data. The most-preferred treatment was dietary intervention which was chosen 712 times (48.10%). Pharmacotherapy was chosen in 29.20% of the cases and psychotherapy in 22.70%. Older patients (>50 years old) chose less often for psychotherapy (15.58%) compared to younger patients (£50 years old; 26.42%), whilst the percentage of patients who chose pharmacotherapy was equal. 79.50% of respondents chose the dominant option of the rationality test.

Multinominal logit (MNL) model

The results of the multinominal logit model for IBS treatment preferences are shown in table 3. Effectiveness, time to response, time until recurrence for pharmacotherapy and diet, showed a significant impact on the choice for a therapy. In addition, severe side effects for pharmacotherapy and the frequency of appointments for psychotherapy were also statistically significant. The signs of the coefficients confirm the validity of the results and show that patients prefer a therapy with a higher effectiveness, less time to response, longer period until recurrence of the symptoms after finalizing therapy when choosing pharmacotherapy and diet. Furthermore, they prefer no severe side effects for pharmacotherapy and frequent appointments when choosing psychotherapy. Mild side effects, time required and the frequency of appointments for pharmacotherapy and dietary interventions were not significant. The two significant alternative specific constants reveal that there is a labeling effect of both pharmacotherapy and diet compared to psychotherapy, which means that patients chose the label pharmacotherapy and diet over psychotherapy regardless of the presented levels of the attributes.

*Table 3: Results of the Discrete Choice Multinominal Logit Model for IBS treatment preferences (N = 185)*

| Attributes | Coefficient | P-value | 95% Confidence Interval | |
|---|---|---|---|---|
| Effectiveness | 0.017* | <0.01 | 0.015 | 0.021 |
| Time to response | -0.026* | 0.018 | -0.048 | -0.005 |
| Time until recurrence (medication and diet) | 0.025* | <0.01 | 0.010 | 0.039 |
| Time until recurrence psychotherapy | 0.027 | 0.143 | -0.009 | 0.063 |
| Mild side effects | 0.125 | 0.185 | -0.059 | 0.309 |
| Severe side effects | -0.231* | 0.009 | -0.405 | -0.058 |
| Time required | -0.032 | 0.686 | -0.188 | 0.124 |
| Frequency appointments medication | -0.015 | 0.058 | -0.031 | 0.001 |
| Frequency appointments diet | -0.008 | 0.294 | -0.023 | 0.007 |
| Frequency appointments psychotherapy | 0.025* | 0.025 | 0.003 | 0.047 |
| ASC_medication | 0.993* | 0.001 | 0.399 | 1.586 |
| ASC_diet | 1.48* | <0.01 | 0.929 | 2.036 |

Number of observations = 1480 (no missing values) Log Likelihood = -1396.91
ASC = alternative specific constant
*$r$ <0.05



Mixed logit model & relative importance

As shown in table 4, a higher effectiveness and a longer time interval until recurrence, has a significant positive impact, while severe side effects and a higher frequency of appointments were seen as negative when choosing pharmacotherapy. Time to response, mild side effects, time required and the frequency of appointment when attending dietary therapy and psychotherapy were not significant. Again, a labeling effect of both pharmacotherapy and diet towards psychotherapy was seen. When choosing pharmacotherapy, the most important attribute was effectiveness with a relative importance of 55.86%. Next the frequency of appointments (21.89%) and severe side effects (16.82%) were considered important in decision-making. Time until recurrence had the smallest relative importance of the four significant attributes (6.46%). When choosing dietary interventions or psychotherapy, effectiveness was the most important (89.64%; 91.22% respectively), next to time until recurrence (10.36%; 8.78% respectively).

The estimated standard deviations were significant for the attributes 'effectiveness' and 'time until recurrence for mediation and diet,' which indicates heterogeneity. Interaction analysis with age, symptom severity and depression/anxiety showed that two interactions were significant: between effectiveness and age, and between effectiveness and anxiety. No interactions were significant between the attribute 'recurrence' and other covariates.

*Table 4: Results from the Discrete Choice Mixed Logit Model and relative importance*

| Attributes | | Coefficient | P-value |
|---|---|---|---|
| *Random parameters in utility functions* | | | |
| Effectiveness | Mean | 0.036* | 0.0001 |
| | s.d. | 0.029** | 0.016 |
| Time to response | Mean | -0.034 | 0.122 |
| | s.d. | 0.026 | 0.923 |
| Time until recurrence (medication and diet) | Mean | 0.026 | 0.155 |
| | s.d. | 0.296** | 0.008 |
| ASC_medication | Mean | 1.406* | 0.004 |
| | s.d. | 0.059 | 0.949 |
| ASC_diet | Mean | 1.963* | 0.0001 |
| | s.d. | 1.589 | 0.066 |
| *Nonrandom parameters in utility functions* | | | |
| Mild side effects | | 0.266 | 0.140 |
| Severe side effects | | -0.547* | 0.017 |
| Time required | | 0.033 | 0.806 |
| Time until recurrence psychotherapy | | 0.029 | 0.267 |
| Frequency appointments medication | | -0.046* | 0.028 |
| Frequency appointments diet | | -0.026 | 0.111 |
| Frequency appointments psychotherapy | | 0.011 | 0.532 |

Number of observations = 1480 (no missing values). Halton draws with 2000 simulations.
Log Likelihood = -1390.43; McFadden Pseudo R-squared 0.145; AIC/N = 1.903
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific

Subgroup analysis

All subgroup analyses are shown in Supplementary material. Subgroup analysis with age revealed that for respondents £50 years, a higher effectiveness, a longer period until recurrence and no severe side effects were valued as important when choosing therapy. Dietary interventions were reported as significant, although pharmacotherapy was no longer important in this subgroup of patients. For respondents older than 50 years, a higher effectiveness was also considered important but there was preference variation as shown by the significant standard deviation. In addition, both the labels for dietary interventions, as well as pharmacotherapy, were significant. Severe side-effects were negatively valued.

| 95% CI | | Relative importance (%) | | |
|---|---|---|---|---|
| | | *M* | *D* | *P* |
| 0.018 | 0.054 | 55.86 | 89.64 | 91.22 |
| 0.005 | 0.053 | | | |
| -0.077 | 0.009 | | | |
| -0.499 | 0.551 | | | |
| -0.009 | 0.062 | 6.46 | 10.36 | 8.78 |
| 0.076 | 0.518 | | | |
| 0.441 | 2.369 | | | |
| -1.745 | 1.864 | | | |
| 0.997 | 2.929 | | | |
| -0.106 | 3.283 | | | |
| | | | | |
| -0.088 | 0.620 | | | |
| -0.997 | -0.097 | 16.82 | | |
| -0.229 | 0.295 | | | |
| -0.022 | 0.081 | | | |
| -0.086 | -0.005 | 21.89 | | |
| -0.057 | 0.006 | | | |
| -0.023 | 0.044 | | | |

constant, Relative importance; M = medication/pharmacotherapy, D = dietary interventions, P = psychotherapy.

* $r$ <0.05; ** significant standard deviation indicates preference heterogeneity

Patients with mild/moderate symptoms (IBS-SSS<300) showed a preference towards a higher effectiveness. When choosing pharmacotherapy, patients preferred fewer appointments and no severe side effects. Both the labels pharmacotherapy and dietary interventions were significant. However, patients with severe symptoms (IBS-SSS>300) showed no significant preferences and the labelled effect of pharmacological options, as well as for dietary interventions, was no longer present.

Patients without an indication of a depressive disorder (PHQ<10) reported a higher effectiveness and severe side effects to be important during decision-making. Moreover, they preferred both pharmacotherapy and dietary interventions over psychotherapy. However, patients with a possible comorbid depressive disorder reported no attributes or therapy as significant.

Subgroup analysis of patients without indications of an anxiety disorder (GAD <10) showed preferences for a therapy with a higher effectiveness, shorter interval of time until the therapy responses, a longer period until recurrence and few appointments and no severe side effects when choosing medication. They also highly valued pharmacotherapy or dietary interventions. However, patients with possible comorbid anxiety disorder preferred only a dietary intervention and not pharmacotherapy. Other attributes were not reported as significant. No significant preferences for a certain therapy or attributes were seen between the different IBS subtypes.

## DISCUSSION

When examining IBS patients' preferences using a discrete choice experiment, patients overwhelmingly prefer dietary interventions in the first place, followed by pharmacotherapy and psychotherapy. When choosing a therapy, patients valued a higher effectiveness, a shorter time to response, a longer time until recurrence and no severe side effects as significant attributes. Heterogeneity between patients was found in the attributes 'effectiveness' and 'time until recurrence', which could only be partially explained by age and the potential presence of anxiety among the participants. These results and the subgroup analysis provide insight to advise a more personalized treatment for the IBS patient.



The most-preferred treatment in our study was dietary intervention (48%) in our study, above pharmacotherapy (29%) and psychotherapy (23%). In contrast, a previous study that explored the acceptability of multiple IBS treatments by means of a questionnaire, showed that 84% of the patients reported pharmacotherapy to be the most acceptable, followed by lifestyle changes (diet 82%; yoga 77%) and hypnotherapy (64%).[6] The authors suggest that lifestyle changes may be popular because of the fewer risks and side effects and the ability for patients to retain greatest control. Our study was performed more than ten years later and the ongoing promotion of a healthy lifestyle, where nutritional interventions gained more attention, could also have contributed to our result.

Furthermore, that study showed that younger people (<55 years old) were more likely to accept other treatment forms as hypnotherapy. This is in line with our study, where younger patients (<50 years old) more often preferred psychotherapy (26%) than older patients (16%). Nonetheless, the methodology used in Harris *et al.,* is difficult to compare to our design. The questionnaire involved a list of treatments and patients were asked whether they would consider each of these treatments as options. However, our questionnaire included a discrete choice experiment where choice sets are described with treatments containing different characteristics and levels. This requires a trade-off between the benefits and potential disadvantages because the respondent can only choose one option each time a choice is offered.

Based on the relative importance, the attribute effectiveness was found to be the most important one relative to others. This is also in line with an earlier performed unlabeled conjoint analysis including only pharmacological options, where IBS patients choose a therapy for breakthrough pain.[21] Patients wished also to avoid nausea as a side effect of acute pain treatment, but the different design, attributes and patient characteristics

(multiple patients had >4 pain attacks per month) of this study makes it difficult to compare with our findings. In our study, patients secondly preferred few appointments and no severe side effects when choosing for medication, but minor side effects were not considered that important. In contrast, other studies showed that IBS patients were willing to take risks involving possible complications of therapy.[7,8] A stated-choice survey reported that women with IBS-D (mostly moderate symptoms) were willing to tolerate a 2.65% increase in impacted-bowel risk and a 1.34% increase in perforated-bowel risk to facilitate complete symptom relief.[8] Other DCE studies of patients with chronic disorders, such as ulcerative colitis and chronic back pain, showed similar preferences of a high effectiveness and a short time interval to symptom improvement.[22,23]

Subgroup analysis revealed treatment preferences of certain populations which can be used during shared decision-making during medical consultation. Younger patients generally preferred dietary intervention and preferred a long duration until recurrence of symptoms, whereas older patients tend to be more willing to choose for pharmacotherapy. Patients with a potential anxiety disorder preferred a dietary intervention and no pharmacologic options, whereas patients with a potential depressive disorder had no clear preferences.

Subgroup analysis between all different IBS subtypes showed no significant preferences. However, the size of the subgroups was small and should therefore be interpreted with appropriate caution. Future research could address these treatment preferences in IBS patients with different subtypes.

These identified patient preferences might be used during the consultation of an IBS patient. Earlier research showed that revealing patient preferences, contributes to a better management of patient' symptoms by providing a better compliance with prescribed treatments.[5] Identifying treatment preferences should therefore be part of the consultation strategy. The results from this cohort study provide guidance for which aspects of management could be discussed with your treatment-seeking patient to pursue the optimal personalized management.

This study has several strengths. We included patients from a population-based cohort, recruited via outpatient clinics or the general practitioner, with varying length of IBS symptoms and severity of symptoms. We therefore believe that this cohort is representative for IBS populations seeking care for their symptoms. Another strength is the inclusion of all possible treatment options in the design, pharmacological and non-pharmacological therapies. The attributes and levels were extracted from explicit in-depth qualitative interviews, a literature screening and an expert opinion

level, according to the current guidelines.[12] We used a labeled design to make the IBS treatment options more realistic. Therefore, the validity of our results may be improved, because individual feelings and knowledge for specific therapies are considered during decision making.[13] Otherwise, using an unlabeled design would be less appropriate because some of the attributes are specific for a certain alternative and are not applicable for other alternatives, for instance side effects is only relevant to drug usage. Unrealistic choices may also reduce respondents' interest and involvement with answering the choice sets.[24] However, this labeled design also has limitations. Our analysis showed that there was a labeled effect for both pharmacotherapy and dietary interventions when choosing a therapy. This means that patients choose their preferred therapy regardless of what the presented levels of the attributes tell them about this therapy. This could be related to strong beliefs about specific therapeutic entities. Due to this labeled effect, it is possible that patients were not always trading the levels of the different attributes when choosing a treatment. It is also possible that order bias might have played a role because we did not change the order of the treatments (pharmacotherapy, diet and psychotherapy were always presented from left to right). Patient engagement may not be fully enclosed in the DCE, although we included the attribute 'time to invest in treatment' which could be seen as a potential proxy for commitment. However, when analyzing the DCE, this attribute was not significant, so time investment seems not to be a major hurdle for patients. We believe that commitment is inherent to following a therapy and is not part of treatment choice.



It may be possible that patients choose differently in real-world choices than in this DCE, however previous studies have reported that the external validity of DCEs is satisfactory to predict actual healthcare choices.[25] Patients may have considered other aspects of therapy as important during decision-making which may additionally explain the significant label effect. These include costs, availability of treatments, and prior knowledge, beliefs and misconceptions of IBS treatments, which were not included in the current analyses in order to limit patient burden related to the completion of the survey. Moreover, the local availability and customs and traditions may vary by region in the world and may affect treatment preferences. A selection bias might be present because not all patients from the MIBS cohort completed this questionnaire. However, there was no significant difference in gender and age between the survey responders and non-responders.

In conclusion, this study reveals how IBS patients prioritize their preferences about management and this is crucial for all health care decision-makers and developers of novel therapies. Exploring patients' treatment preferences and establishing personalized treatment during shared decision-making, would provide more optimal management strategies.

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# SUPPLEMENTARY MATERIAL
# FILE 1: STATISTICAL ANALYSIS

Sample size

Sample size calculation for stated-preference studies is difficult as it depends on the true values of the unknown parameters estimated in the DCE. *Lancsar and Louviere*[1] described that based on empirical experience, one rarely requires more than 20 respondents per questionnaire version to estimate reliable models, but undertaking significant post hoc analysis to identify and estimate co-variate effects invariably requires larger sample size. From a clinical perspective, we decided to examine the preferences of subgroups based on symptom severity, type of IBS subgroup and psychological comorbidity. Hence, we ultimately included 185 patients.

Questionnaires

To clarify the discrete choice experiment, the survey consisted of an introduction, instruction and an explanation of the therapies and all attributes. Also, a sample choice set was presented and explained. Infographics were added to the choice sets to make the questions more clearly.

Statistical Analysis

Descriptive analysis of baseline characteristics was performed in IBM SPSS Statistics version 27.0 for Macintosh (SPSS Inc., Chicago, Illinois, USA). Nlogit software (Econometric Software, Inc., Plainview, NY, USA) version 6.0 was used to analyze the patients' choices. The preferences of respondents were evaluated according the random utility theory[2]. This theory assumes that a respondent derives utility (benefit) from the attributes of a product or intervention etc.[3] The relative utility score patients derive from a treatment is expressed by a constant and different coefficients, reflecting the effect of a particular attribute level on the utility score. The two constants describe the label effect for a specific treatment (medication or diet therapy), compared to psychotherapy regardless of the levels of the attributes. The sign of a coefficient shows whether an attribute has a positive or negative effect on utility. A p-value of $<0.05$ was considered as statistically significant.

First, a simple multinominal choice model was conducted to assess patients' preferences for IBS treatment. Second, a more advanced model, the mixed logit model, was conducted to examine heterogeneity in preferences between patients by analyzing the effect of the standard deviation.[4] The attributes effectiveness, time to response, time until recurrence and the two alternative specific constants were initially set as random-specified parameters in this model with a normal distribution.

The random parameters with statistically insignificant standard deviations (i.e.$p > 0.05$) were included as fixed parameters and the model was re-estimated until a final mixed logit model was achieved. This model included effectiveness as generic attribute and time to recurrence of symptoms for medication and diet as random parameters with significant heterogeneity. Subsequently, the following covariables were included to examine heterogeneity: severity of IBS symptoms, indication of depression/anxiety (based on screening with PHQ or GAD) and age (older/younger than 50 years old). Two interactions turned out to be significant: between effectiveness/anxiety and effectiveness / age. A mixed logit model including these interactions was re-estimated and chosen as final model. The model fit was based on the normalized Akaike's Information Criterion (AIC/N).



Estimation of the mixed logit models was carried out using Halton draws, with 2000 simulations. The relative importance of the attributes was then calculated by using the estimated coefficients and the range of the best- and worst levels of the attributes.[4] Subgroup analysis was performed for various covariables which would be important for patients' preferences according to clinicians' perspective or based on significant interaction analysis: age, symptom severity, IBS subtype, and psychological comorbidity (depression and anxiety). Age was divided in two categories: £50 years and >50 years, based on the median value. Severity of symptoms was split into patients with mild/moderate symptoms (IBS-SSS<300) and patients with severe symptoms (IBS-SSS>300). The indication of depression or anxiety disorder was used for the last subgroups (PHQ-9 and GAD-7; score >10). IBS subtype was classified in the four subtypes: IBS-D, IBS-C, IBS-M and IBS-U.

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# FILE 2: THE INTRODUCTION OF THE DCE SURVEY

Instruction
By means of this questionnaire we would like to get insight into the preferences of patients with regard to the treatment of irritable bowel syndrome (IBS). We would like to examine which aspects of a treatment patients find most important when choosing a treatment. For example, in addition to the effectiveness of the treatment, other aspects can also be important; such as side effects, time until response of the treatment, the effort necessary to complete the therapy.



This questionnaire contains 9 hypothetical (imaginary) choice sets: each choice set always contains the same three treatment options (pharmacotherapy, diet and psychotherapy).

The underlying properties of these treatments are different during each choice task. First, we would like you to look at all the properties of each treatment and then decide which treatment you prefer. For each choice set you can indicate which treatment you prefer: Option 1 (medication), Option 2 (diet), Option 3 (psychotherapy).

Completing this questionnaire will take approximately 5-10 minutes.
On the next page you will find an explanation of the different treatment characteristics and its properties and the three types of treatment (medication, diet, psychotherapy). Read all of this carefully.

Explanation treatment characteristics

| Characteristics | Definition | Options |
|---|---|---|
| *Symptom reduction* | This is the percentage reduction of complaints after the start of the treatment. Assume moderately severe symptoms of irritable bowel syndrome at the start of therapy.<br>Example: You have moderately severe complaints and you start a therapy. Due to the treatment, you have 50% fewer complaints; this means that you still have mild complaints. | - 25% reduction in complaints (From moderately severe to moderate complaints)<br>- 50% reduction in complaints (moderately severe to mild complaints)<br>- 75% reduction in complaints (from moderately severe to very mild complaints)<br>- 100% complaints reduction (from moderately severe to no complaints) |

Explanation treatment characteristics (Continued)

| Characteristics | Definition | Options |
|---|---|---|
| *Period after treatment works* | This is the period from the start of treatment until you start to notice the effect of the therapy.<br>Example: It takes 12 weeks before you start to notice the effect of the treatment on the complaints. This is the beginning of the effect, this does not mean that this is the maximum effect of the treatment (complaint reduction may increase in the subsequent period). | - 4 weeks<br>- 8 weeks<br>- 12 weeks |
| *Period after symptoms return after completing of treatment* | This is the period after your symptoms return, after you have stopped or completed the treatment.<br>Example:<br>Your complaints will return after 6 months, after you have completed the treatment. | - Immediately<br>- 2 months<br>- 6 months<br>- 12 months or longer |
| *Side effects during treatment* | These are side effects that might arise as a result of the treatment. These are temporary side effects that disappear once you have stopped or completed the treatment.<br>Example:<br>The treatment will give you mild side effects; eg. heartburn, dry mouth, or drowsiness. The chance of this happening is 10% (1 in 10). | - No<br>- Mild: 1 in 10 patients will experience a mild side effect (e.g. heartburn, dry mouth, sleepiness)<br>- Severe: 1 in 10,000 patients will experience a serious side effect (e.g. heart rhythm disorder) |
| *Frequency of appointments with care provider* | This is the number of appointments with the doctor/therapist during treatment.<br>Example:<br>You see the therapist every 2 weeks for this treatment. | - A single appointment<br>- Every two weeks<br>- Every month<br>- Every 2 months |
| *Time required* | The time you need to invest in this treatment.<br>Example:<br>You need 2 hours per week for this treatment (e.g. a psychological treatment with 1 session per week of 1 hour and 1 hour of homework per week) | - None<br>- 1 hour per week<br>- 2 hours a week |

Explanation of treatments:

- Medication: Think of antidepressants and peppermint oil tablets. This is advised and, if necessary, prescribed by your GP or gastroenterologist. This treatment is easy to use because all you have to do is take the medicine.
- Diet: Think of standard dietary advice about nutrition, but also of the special FODMAP diet (avoiding certain sugary substances in food that can cause complaints). You will go to a dietician for this treatment after a referral from your general practitioner or gastroenterologist. In addition to a consultation for advice, you also have to delve into the diet yourself and sometimes purchase special diet products.
- Psychotherapy: Think of a treatment by a psychologist to deal with the complaints (eg cognitive behavioral therapy) and hypnotherapy (combination talk therapy and hypnosis. Hypnosis is a deep form of relaxation). For this you go to a psychologist or a specially trained therapist after referral from your general practitioner or gastroenterologist. In addition to the (bi-)weekly sessions with the healthcare provider, you often also have to do exercises at home.

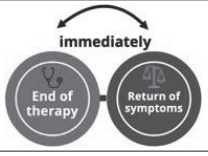
On the next page you will find an example of what a choice set looks like and how to answer the question. You do not need to answer this sample question.

# SAMPLE QUESTION:

Which treatment do you prefer?
- Medication
- Diet
- Psychotherapy

*Here you fill in your treatment preference: Option 1 Medication, Option 2 Diet, Option 3 Psychotherapy.*

*These are the three options you can choose from for each question. Each column represents a different treatment.*

| | Medicatie | Dieet | Psychotherapie |
|---|---|---|---|
| Symptom reduction |   |   |   |
| Time until response | 8 weeks | 12 weeks | 4 weeks |
| Period of time when symptoms return after completing of treatment |   |   |   |
| Side effects | 1 in 10 patients will experience a mild side effect (e.g. heartburn, dry mouth, sleepiness) | None | None |
| Frequency of healthcare appointments |   |   |   |
| Time required | None | 1 hour weekly | 1 hour weekly |

*The properties of the treatments are shown here. These are listed by default for each question.*

*In this column you will find the properties of the treatment "diet" for this question. These properties differ for each question for each treatment (including medication and psychotherapy). Look at all the properties of each treatment and determine which treatment you prefer.*
*For example: In this question, this diet contains the following properties:*
- *25% reduction in complaints (From moderately severe to moderate complaints)*
- *Works after 12 weeks after starting treatment*
- *Retains its effect for 12 months or longer a long time after completing treatment*
- *Has no side effects*
- *You will see a doctor/dietitian once every 2 months*
- *You need to invest 1 hour per week for this treatment*

# **FILE 3:** THE NINE DCE SCENARIOS THAT WERE INCLUDED IN THE QUESTIONNAIRE

Version 1

Choice set 1

| | **Medication** | **Diet** | **Psychotherapy** |
|---|---|---|---|
| Symptom reduction |  |  |  |
| Time until response | 8 weeks | 4 weeks | 12 weeks |
| Period of time when symptoms return after completing therapy |  |  |  |
| Side effects | 1 in 10.000 patients will experience a serious side effect (e.g. heart rhythm disorder) | None | None |
| Frequency of healthcare appointments |  |  |  |
| Time required | No effort | 1 hour weekly | 2 hours weekly |

Which treatment would you prefer?

- Medication
- Diet
- Psychotherapy

Choice set 2

| | Medication | Diet | Psychotherapy |
|---|---|---|---|
| Symptom reduction |  |  |  |
| Time until response | 12 weeks | 4 weeks | 4 weeks |
| Period of time when symptoms return after completing therapy |  |  |  |
| Side effects | None | None | None |
| Frequency of healthcare appointments |  |  |  |
| Time required | No effort | 2 hours weekly | 1 hour weekly |

Which treatment would you prefer?

- Medication
- Diet
- Psychotherapy

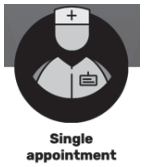
Choice set 3

| | Medication | Diet | Psychotherapy |
|---|---|---|---|
| Symptom reduction |  |  |  |
| Time until response | 4 weeks | 8 weeks | 8 weeks |
| Period of time when symptoms return after completing therapy |  |  |  |
| Side effects | None | None | None |
| Frequency of healthcare appointments |  |  |  |
| Time required | No effort | 1 hour weekly | 2 hours weekly |

Which treatment would you prefer?

- Medication
- Diet
- Psychotherapy

Choice set 4

| | Medication | Diet | Psychotherapy |
|---|---|---|---|
| Symptom reduction |  |  |  |
| Time until response | 12 weeks | 12 weeks | 8 weeks |
| Period of time when symptoms return after completing therapy |  |  |  |
| Side effects | 1 in 10.000 patients will experience a serious side effect (e.g. heart rhythm disorder) | None | None |
| Frequency of healthcare appointments |  |  |  |
| Time required | No effort | 2 hours weekly | 1 hour weekly |

Which treatment would you prefer?

- Medication
- Diet
- Psychotherapy

Choice set 5

| | Medication | Diet | Psychotherapy |
|---|---|---|---|
| Symptom reduction |  |  |  |
| Time until response | 8 weeks | 8 weeks | 4 weeks |
| Period of time when symptoms return after completing therapy |  |  |  |
| Side effects | 1 in 10.000 patients will experience a serious side effect (e.g. heart rhythm disorder) | None | None |
| Frequency of healthcare appointments |  |  |  |
| Time required | No effort | 2 hours weekly | 1 hour weekly |

Which treatment would you prefer?

- Medication
- Diet
- Psychotherapy

Choice set 6

| | Medication | Diet | Psychotherapy |
|---|---|---|---|
| Symptom reduction |  |  |  |
| Time until response | 8 weeks | 8 weeks | 4 weeks |
| Period of time when symptoms return after completing therapy |  |  |  |
| Side effects | 1 in 10.000 patients will experience a serious side effect (e.g. heart rhythm disorder) | None | None |
| Frequency of healthcare appointments |  |  |  |
| Time required | No effort | 1 hour weekly | 2 hours weekly |

Which treatment would you prefer?

- Medication
- Diet
- Psychotherapy

Choice set 7

| | Medication | Diet | Psychotherapy |
|---|---|---|---|
| Symptom reduction |  |  |  |
| Time until response | 12 weeks | 4 weeks | 8 weeks |
| Period of time when symptoms return after completing therapy |  |  |  |
| Side effects | 1 in 10 patients will experience a mild side effect (e.g. heartburn, dry mouth, drowsiness) | None | None |
| Frequency of healthcare appointments |  |  |  |
| Time required | No effort | 2 hours weekly | 1 hour weekly |

Which treatment would you prefer?

- Medication
- Diet
- Psychotherapy

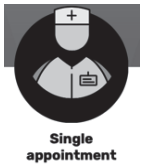
Choice set 8

| | Medication | Diet | Psychotherapy |
|---|---|---|---|
| Symptom reduction |  |  |  |
| Time until response | 8 weeks | 12 weeks | 8 weeks |
| Period of time when symptoms return after completing therapy |  |  |  |
| Side effects | None | None | None |
| Frequency of healthcare appointments |  |  |  |
| Time required | No effort | 1 hour weekly | 2 hours weekly |

Which treatment would you prefer?

- Medication
- Diet
- Psychotherapy

Choice set 9

| | Medication | Diet | Psychotherapy |
|---|---|---|---|
| Symptom reduction |  |  |  |
| Time until response | 12 weeks | 4 weeks | 8 weeks |
| Period of time when symptoms return after completing therapy |  |  |  |
| Side effects | 1 in 10.000 patients will experience a serious side effect (e.g. heart rhythm disorder) | None | None |
| Frequency of healthcare appointments |  |  |  |
| Time required | No effort | 1 hours weekly | 2 hours weekly |

Which treatment would you prefer?

- Medication
- Diet
- Psychotherapy

Supplementary Table 1:
Demographics of total MIBS-cohort, the survey responders and survey non-responders

| Characteristics | Survey responders (N = 185) | Survey non-responders (N = 242) | Total IBS cohort (N = 427) |
|---|---|---|---|
| Mean age, years (SD) | 49.51 (14.85) | 48.06 (14.61)[a] | 48.95 (14.75) |
| Gender, n (%) | | | |
| - Female | - 128 (69.2) | - 187 (77.30) | - 315 (73.80) |
| - Male | - 57 (30.8) | - 55 (22.70)[b] | - 112 (26.20) |

SD = standard deviation

[a] Difference in means between the responders and non-responders was not significant ($t$ (425) = -1.44, p = 0.151)

[b] Chi square test showed no significant difference in frequency of female and male among survey responders and non-responders ($\chi^2$ (1) = 3.54, p = 0.060).

Supplementary Table 2:
Results of the mixed logit analysis of all patients to see in which attribute heterogeneity was present

| Attributes | | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|---|
| *Random parameters in utility function* | | | | | |
| Effectiveness | Mean | 0.029* | <0.001 | 0.019 | 0.040 |
| | s.d. | 0.025** | 0.0048 | 0.007 | 0.042 |
| Time until recurrence (medication and diet) | Mean | 0.020 | 0.144 | -0.007 | 0.047 |
| | s.d. | 0.239** | 0.002 | 0.091 | 0.389 |
| *Nonrandom parameters in utility functions* | | | | | |
| Time to response | | -0.030 | 0.067 | -0.063 | 0.002 |
| Mild side effects | | 0.249 | 0.085 | -0.035 | 0.533 |
| Severe side effects | | -0.475* | 0.005 | -0.807 | -0.142 |
| Time required | | 0.044 | 0.682 | -0.165 | 0.252 |
| Time until recurrence psychotherapy | | 0.028 | 0.211 | -0.016 | 0.072 |
| Frequency appointments medication | | -0.035* | 0.017 | -0.063 | -0.006 |
| Frequency appointments diet | | -0.024 | 0.060 | -0.048 | 0.001 |
| Frequency appointments psychotherapy | | 0.009 | 0.504 | -0.019 | 0.039 |
| ASC_medication | | 1.242* | 0.0017 | 0.466 | 2.017 |
| ASC_diet | | 1.785* | <0.001 | 1.051 | 2.518 |

Number of observations = 1480 (no missing values). Halton draws with 2000 simulations.
Log Likelihood = -1391.29; McFadden Pseudo R-squared 0.144; AIC/N = 1.899
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific constant.
* $r$ <0.05; ** significant standard deviation indicates preference heterogeneity

Results of the interaction analysis

| Attributes | | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|---|
| *Random parameters in utility function* | | | | | |
| Effectiveness | Mean | 0.069* | <0.001 | 0.047 | 0.091 |
| | s.d. | 0.013 | 0.226 | -0.008 | 0.033 |
| Time until recurrence (medication and diet) | Mean | -0.026 | 0.533 | -0.109 | 0.057 |
| | s.d. | 0.204** | 0.004 | 0.090 | 0.317 |
| *Nonrandom parameters in utility functions* | | | | | |
| Time to response | | -0.026 | 0.076 | -0.055 | 0.003 |
| Mild side effects | | 0.213 | 0.106 | -0.045 | 0.471 |
| Severe side effects | | -0.401* | 0.007 | -0.691 | -0.110 |
| Time required | | 0.043 | 0.658 | -0.148 | 0.235 |
| Time until recurrence psychotherapy | | 0.031 | 0.140 | -0.010 | 0.073 |
| Frequency appointments medication | | -0.029* | 0.022 | -0.054 | -0.004 |
| Frequency appointments diet | | -0.020 | 0.064 | -0.042 | 0.001 |
| Frequency appointments psychotherapy | | 0.013 | 0.343 | -0.014 | 0.041 |
| ASC_medication | | 1.214* | 0.001 | 0.485 | 1.942 |
| ASC_diet | | 1.738* | <0.001 | 1.059 | 2.417 |
| *Heterogeneity in mean, Parameter:Variable* | | | | | |
| Effectiveness:Anxiety | | -0.012* | 0.037 | -0.023 | -0.001 |
| Effectiveness:Age | | -0.001* | <0.001 | -0.001 | -0.001 |
| Time until recurrence:Anxiety | | 0.027 | 0.461 | -0.045 | 0.100 |
| Time until recurrence:Age | | 0.001 | 0.285 | -0.001 | 0.002 |

Number of observations = 1480 (no missing values). Halton draws with 2000 simulations.
Log Likelihood = -1357.31; McFadden Pseudo R-squared 0.165; AIC/N = 1.859
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific constant.
* $r$ <0.05; ** significant standard deviation indicates preference heterogeneity

*Results of the mixed logit subgroup analysis for variable age (A), symptom severity (B), depression (C), anxiety (D), IBS subtypes (E), regarding treatment preferences of IBS patients*

A. Age

*Age £ 50 years (n = 88)*

| Attributes | | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|---|
| *Random parameters in utility function* | | | | | |
| Effectiveness | Mean | 0.024* | <0.001 | 0.019 | 0.029 |
| | s.d. | 0.000 | 0.991 | -0.035 | 0.036 |
| *Nonrandom parameters in utility functions* | | | | | |
| Time to response | | -0.029 | 0.080 | -0.061 | 0.004 |
| Time until recurrence (medication and diet) | | 0.038* | 0.001 | 0.016 | 0.061 |
| ASC_medication | | 0.576 | 0.181 | -0.268 | 1.419 |
| ASC_diet | | 0.896* | 0.26 | 0.105 | 1.687 |
| Mild side effects | | 0.076 | 0.595 | -0.203 | 0.354 |
| Severe side effects | | -0.261* | 0.048 | -0.519 | -0.002 |
| Time required | | -0.089 | 0.454 | -0.321 | 0.144 |
| Time until recurrence psychotherapy | | 0.012 | 0.637 | -0.039 | 0.064 |
| Frequency appointments medication | | -0.017 | 0.148 | -0.040 | 0.006 |
| Frequency appointments diet | | 0.001 | 0.985 | -0.022 | 0.023 |
| Frequency appointments psychotherapy | | 0.027 | 0.087 | -0.004 | 0.058 |

Number of observations = 704 (no missing values). Halton draws with 2000 simulations.
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific constant;
* $r < 0.05$; ** significant standard deviation indicates preference heterogeneity

*Age >50 years (n = 97)*

| Attributes | | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|---|
| *Random parameters in utility function* | | | | | |
| Effectiveness | Mean | 0.017* | <0.001 | 0.009 | 0.024 |
| | s.d. | 0.023** | 0.03 | 0.008 | 0.038 |
| *Nonrandom parameters in utility functions* | | | | | |
| Time to response | | -0.027 | 0.109 | -0.059 | 0.006 |
| Time until recurrence (medication and diet) | | 0.018 | 0.113 | -0.004 | 0.039 |
| ASC_medication | | 1.397* | 0.002 | 0.501 | 2.293 |
| ASC_diet | | 1.870* | <0.001 | 1.027 | 2.713 |
| Mild side effects | | 0.209 | 0.131 | -0.062 | 0.479 |
| Severe side effects | | -0.312* | 0.028 | -0.590 | -0.034 |
| Time required | | 0.035 | 0.780 | -0.213 | 0.284 |
| Time until recurrence psychotherapy | | 0.039 | 0.191 | -0.019 | 0.097 |
| Frequency appointments medication | | -0.021 | 0.091 | -0.045 | 0.003 |
| Frequency appointments diet | | -0.009 | 0.422 | -0.031 | 0.013 |
| Frequency appointments psychotherapy | | 0.005 | 0.809 | -0.033 | 0.042 |

Number of observations = 776 (no missing values). Halton draws with 2000 simulations.
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific constant;
* $r < 0.05$; ** significant standard deviation indicates preference heterogeneity

B. Symptom severity

*Mild/moderate symptoms (IBS-SSS <300) (n = 148)*

| Attributes | | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|---|
| *Random parameters in utility function* | | | | | |
| Effectiveness | Mean | 0.040* | 0.001 | 0.017 | 0.064 |
| | s.d. | 0.032 | 0.056 | -0.001 | 0.064 |
| Time to response | Mean | -0.052 | 0.094 | -0.112 | 0.009 |
| | s.d. | 0.018 | 0.913 | -0.298 | 0.334 |
| Time until recurrence (medication and diet) | Mean | 0.026 | 0.283 | -0.022 | 0.075 |
| | s.d. | 0.374** | 0.018 | 0.065 | 0.683 |
| ASC_medication | Mean | 1.626* | 0.009 | 0.402 | 2.849 |
| | s.d. | 0.012 | 0.990 | -1.917 | 1.941 |
| ASC_diet | Mean | 2.313* | 0.009 | 0.402 | 2.849 |
| | s.d. | 2.096** | 0.038 | 0.113 | 4.079 |
| *Nonrandom parameters in utility functions* | | | | | |
| Mild side effects | | 0.373 | 0.136 | -0.117 | 0.862 |
| Severe side effects | | -0.739* | 0.026 | -1.39 | -0.086 |
| Time required | | 0.005 | 0.978 | -0.330 | 0.339 |
| Time until recurrence psychotherapy | | 0.038 | 0.236 | -0.025 | 0.102 |
| Frequency appointments medication | | -0.060* | 0.035 | -0.117 | -0.004 |
| Frequency appointments diet | | -0.039 | 0.085 | -0.084 | 0.005 |
| Frequency appointments psychotherapy | | 0.010 | 0.634 | -0.031 | 0.051 |

Number of observations = 1184 (no missing values). Halton draws with 2000 simulations.
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific constant;
* $r < 0.05$; ** significant standard deviation indicates preference heterogeneity

*Severe symptoms (IBS-SSS>300) (n = 37)*

| Attributes | | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|---|
| *Random parameters in utility function* | | | | | |
| Effectiveness | Mean | 0.033 | 0.073 | -0.003 | 0.069 |
| | s.d. | 0.036 | 0.163 | -0.015 | 0.086 |
| Time to response | Mean | -0.021 | 0.641 | -0.109 | 0.067 |
| | s.d. | 0.038 | 0.949 | -1.129 | 1.205 |
| Time until recurrence (medication and diet) | Mean | 0.047 | 0.218 | -0.028 | 0.122 |
| | s.d. | 0.010 | 0.972 | -0.577 | 0.598 |
| ASC_medication | Mean | 0.399 | 0.728 | -1.845 | 2.642 |
| | s.d. | 2.494 | 0.334 | -2.566 | 7.555 |
| ASC_diet | Mean | 1.371 | 0.087 | -0.198 | 2.939 |
| | s.d. | 0.197 | 0.956 | -6.827 | 7.221 |
| *Nonrandom parameters in utility functions* | | | | | |
| Mild side effects | | 0.130 | 0.750 | -0.672 | 0.932 |
| Severe side effects | | -0.096 | 0.815 | -0.904 | 0.711 |
| Time required | | 0.157 | 0.622 | -0.468 | 0.782 |
| Time until recurrence psychotherapy | | 0.015 | 0.778 | -0.086 | 0.115 |
| Frequency appointments medication | | -0.015 | 0.671 | -0.084 | 0.054 |
| Frequency appointments diet | | 0.612D-04 | 0.998 | -0.467 D-01 | 0.469 D-01 |
| Frequency appointments psychotherapy | | 0.019 | 0.575 | -0.047 | 0.084 |

Number of observations = 296 (no missing values). Halton draws with 2000 simulations.
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific constant;
*$r < 0.05$; ** significant standard deviation indicates preference heterogeneity

C. Depression

*No depression (PHQ<10) (n = 151)*

| Attributes | | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|---|
| *Random parameters in utility function* | | | | | |
| Effectiveness | Mean | 0.261* | <0.001 | 0.016 | 0.036 |
| | s.d. | 0.022** | 0.013 | 0.004 | 0.039 |
| Time until recurrence (medication and diet) | Mean | 0.014 | 0.295 | -0.012 | 0.041 |
| | s.d. | 0.195** | 0.007 | 0.053 | 0.337 |
| *Nonrandom parameters in utility functions* | | | | | |
| Time to response | | -0.031 | 0.059 | -0.064 | 0.001 |
| Mild side effects | | 0.238 | 0.102 | -0.047 | 0.523 |
| Severe side effects | | -0.453* | 0.007 | -0.779 | -0.127 |
| Time required | | 0.074 | 0.518 | -0.149 | 0.296 |
| Time until recurrence psychotherapy | | 0.029 | 0.220 | -0.017 | 0.077 |
| Frequency appointments medication | | -0.023 | 0.085 | -0.051 | 0.003 |
| Frequency appointments diet | | -0.016 | 0.196 | -0.041 | 0.008 |
| Frequency appointments psychotherapy | | 0.012 | 0.461 | -0.019 | 0.042 |
| ASC_medication | | 1.255* | 0.002 | 0.449 | 2.061 |
| ASC_diet | | 1.759* | <0.001 | 1.003 | 2.516 |

Number of observations = 1208 (no missing values). Halton draws with 2000 simulations.
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific constant;
* $r < 0.05$; ** significant standard deviation indicates preference heterogeneity

*Depression (PHQ>10) (n = 34)*

| Attributes | | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|---|
| *Random parameters in utility function* | | | | | |
| Effectiveness | Mean | 0.058 | 0.074 | -0.005 | 0.123 |
| | s.d. | 0.054 | 0.202 | -0.029 | 0.137 |
| Time until recurrence (medication and diet) | Mean | 0.066 | 0.327 | -0.066 | 0.198 |
| | s.d. | 0.570 | 0.149 | -0.205 | 1.347 |
| *Nonrandom parameters in utility functions* | | | | | |
| Time to response | | -0.037 | 0.603 | -0.179 | 0.104 |
| Mild side effects | | 0.352 | 0.546 | -0.789 | 1.493 |
| Severe side effects | | -0.804 | 0.272 | -2.258 | 0.649 |
| Time required | | -0.143 | 0.674 | -0.081 | 0.525 |
| Time until recurrence psychotherapy | | 0.027 | 0.702 | -0.111 | 0.165 |
| Frequency appointments medication | | -0.110 | 0.116 | -0.248 | 0.027 |
| Frequency appointments diet | | -0.064 | 0.148 | -0.151 | 0.022 |
| Frequency appointments psychotherapy | | -0.006 | 0.915 | -0.107 | 0.096 |
| ASC_medication | | 1.356 | 0.319 | -1.313 | 4.025 |
| ASC_diet | | 2.154 | 0.106 | -0.460 | 4.768 |

Number of observations = 272 (no missing values). Halton draws with 2000 simulations.
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific constant;
* $r < 0.05$; ** significant standard deviation indicates preference heterogeneity

D. Anxiety

*No anxiety disorder (GAD<10) (n = 168)*

| Attributes | | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|---|
| *Random parameters in utility function* | | | | | |
| Effectiveness | Mean | 0.023* | <0.001 | 0.016 | 0.028 |
| | s.d. | 0.016 | 0.011 | 0.004 | 0.029 |
| *Nonrandom parameters in utility functions* | | | | | |
| Time to response | | -0.029* | 0.015 | -0.054 | -0.006 |
| Time until recurrence (medication and diet) | | 0.027* | 0.002 | 0.009 | 0.043 |
| ASC_medication | | 0.909* | 0.0048 | 0.277 | 1.540 |
| ASC_diet | | 1.315* | <0.001 | 0.719 | 1.911 |
| Mild side effects | | 0.164 | 0.118 | -0.042 | 0.370 |
| Severe side effects | | -0.338* | 0.002 | -0.553 | -0.123 |
| Time required | | -0.010 | 0.911 | -0.186 | 0.166 |
| Time until recurrence psychotherapy | | 0.019 | 0.336 | -0.020 | 0.059 |
| Frequency appointments medication | | -0.019* | 0.034 | -0.037 | -0.001 |
| Frequency appointments diet | | -0.004 | 0.621 | -0.021 | 0.012 |
| Frequency appointments psychotherapy | | 0.016 | 0.224 | -0.009 | 0.041 |

Number of observations = 1344 (no missing values). Halton draws with 2000 simulations.
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific constant;
* $r < 0.05$; ** significant standard deviation indicates preference heterogeneity

*Anxiety disorder (GAD>10) (n = 17)*

| Attributes | | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|---|
| *Random parameters in utility function* | | | | | |
| Effectiveness | Mean | 0.007 | 0.261 | -0.005 | 0.019 |
| | s.d. | 0.004 | 0.959 | -0.136 | 0.144 |
| *Nonrandom parameters in utility functions* | | | | | |
| Time to response | | -0.010 | 0.793 | -0.086 | 0.066 |
| Time until recurrence (medication and diet) | | 0.028 | 0.245 | -0.019 | 0.075 |
| ASC_medication | | 1.887 | 0.087 | -0.274 | 4.048 |
| ASC_diet | | 2.521* | 0.012 | 0.551 | 4.492 |
| Mild side effects | | 0.131 | 0.695 | -0.524 | 0.785 |
| Severe side effects | | -0.002 | 0.995 | -0.591 | 0.587 |
| Time required | | -0.097 | 0.713 | -0.613 | 0.419 |
| Time until recurrence psychotherapy | | 0.069 | 0.267 | -0.053 | 0.191 |
| Frequency appointments medication | | -0.014 | 0.636 | -0.069 | 0.043 |
| Frequency appointments diet | | -0.027 | 0.284 | -0.077 | 0.022 |
| Frequency appointments psychotherapy | | 0.057 | 0.169 | -0.024 | 0.138 |

Number of observations = 136 (no missing values). Halton draws with 2000 simulations.
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific constant;
* $r < 0.05$; ** significant standard deviation indicates preference heterogeneity

E. IBS subtype

*Subtype constipation (IBS-C) (n = 37)*

| Attributes | | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|---|
| *Random parameters in utility function* | | | | | |
| Effectiveness | Mean | 0.049 | 0.138 | -0.016 | 0.114 |
| | s.d. | 0.049 | 0.200 | -0.026 | 0.126 |
| Time to response | Mean | -0.004 | 0.939 | -0.109 | 0.101 |
| | s.d. | 0.169 | 0.512 | -0.336 | 0.674 |
| ASC_medication | Mean | 0.307 | 0.796 | -2.022 | 2.637 |
| | s.d. | 0.264 | 0.915 | -4.577 | 5.105 |
| ASC_diet | Mean | 2.015 | 0.142 | -0.672 | 4.703 |
| | s.d. | 3.314 | 0.291 | -2.834 | 9.463 |
| *Nonrandom parameters in utility functions* | | | | | |
| Time until recurrence (medication and diet) | | 0.091 | 0.202 | -0.048 | 0.230 |
| Mild side effects | | -0.197 | 0.717 | -1.261 | 0.867 |
| Severe side effects | | -0.435 | 0.453 | -1.569 | 0.701 |
| Time required | | 0.449 | 0.369 | -0.529 | 1.428 |
| Time until recurrence psychotherapy | | 0.048 | 0.513 | -0.097 | 0.194 |
| Frequency appointments medication | | -0.046 | 0.374 | -0.146 | 0.055 |
| Frequency appointments diet | | -0.021 | 0.605 | -0.100 | 0.058 |
| Frequency appointments psychotherapy | | 0.0167 | 0.714 | -0.072 | 0.105 |

Number of observations = 296 (no missing values). Halton draws with 2000 simulations.
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific constant;
* $r < 0.05$ ; ** significant standard deviation indicates preference heterogeneity

*Subtype diarrhea (IBS-D) (n = 54)*

| Attributes | | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|---|
| *Random parameters in utility function* | | | | | |
| Effectiveness | Mean | 0.031 | 0.367 | -0.037 | 0.099 |
| | s.d. | 0.001 | 0.995 | -0.047 | 0.047 |
| Time to response | Mean | -0.027 | 0.572 | -0.119 | 0.066 |
| | s.d. | 0.005 | 0.986 | -0.514 | 0.523 |
| ASC_medication | Mean | 1.623 | 0.294 | -1.409 | 4.656 |
| | s.d. | 2.346 | 0.598 | -6.369 | 11.062 |
| ASC_diet | Mean | 2.232 | 0.338 | -2.333 | 6.798 |
| | s.d. | 2.813 | 0.549 | -6.389 | 12.015 |
| *Nonrandom parameters in utility functions* | | | | | |
| Time until recurrence (medication and diet) | | 0.071 | 0.455 | -0.114 | 0.255 |
| Mild side effects | | 0.095 | 0.784 | -0.580 | 0.769 |
| Severe side effects | | -0.377 | 0.412 | -1.277 | 0.523 |
| Time required | | -0.361 | 0.459 | -1.317 | 0.595 |
| Time until recurrence psychotherapy | | -0.005 | 0.928 | -0.124 | 0.113 |
| Frequency appointments medication | | -0.054 | 0.463 | -0.199 | 0.091 |
| Frequency appointments diet | | -0.011 | 0.788 | -0.090 | 0.068 |
| Frequency appointments psychotherapy | | 0.055 | 0.429 | -0.081 | 0.191 |

Number of observations = 432 (no missing values). Halton draws with 2000 simulations.
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific constant;
* $r < 0.05$; ** significant standard deviation indicates preference heterogeneity

*Mixed subtype (IBS-M) (n = 38)*

| Attributes | | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|---|
| *Random parameters in utility function* | | | | | |
| Effectiveness | Mean | 0.060 | 0.072 | -0.005 | 0.125 |
| | s.d. | 0.024 | 0.677 | -0.090 | 0.138 |
| Time to response | Mean | -0.169 | 0.127 | -0.385 | 0.048 |
| | s.d. | 0.402 | 0.208 | -0.223 | 1.027 |
| ASC_medication | Mean | 2.544 | 0.124 | -0.697 | 5.785 |
| | s.d. | 0.083 | 0.961 | -3.258 | 3.424 |
| ASC_diet | Mean | 1.765 | 0.179 | -0.807 | 4.338 |
| | s.d. | 5.433 | 0.163 | -2.205 | 13.071 |
| *Nonrandom parameters in utility functions* | | | | | |
| Time until recurrence (medication and diet) | | 0.154 | 0.163 | -0.063 | 0.372 |
| Mild side effects | | 1.287 | 0.132 | -0.388 | 2.963 |
| Severe side effects | | -1.451 | 0.127 | -3.312 | 0.410 |
| Time required | | 0.912 | 0.165 | -0.376 | 2.199 |
| Time until recurrence psychotherapy | | 0.087 | 0.384 | -0.108 | 0.282 |
| Frequency appointments medication | | -0.062 | 0.267 | -0.171 | 0.047 |
| Frequency appointments diet | | -0.016 | 0.771 | -0.126 | 0.094 |
| Frequency appointments psychotherapy | | -0.026 | 0.633 | -0.134 | 0.082 |

Number of observations = 304 (no missing values). Halton draws with 2000 simulations.
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific constant;
* $r < 0.05$; ** significant standard deviation indicates preference heterogeneity

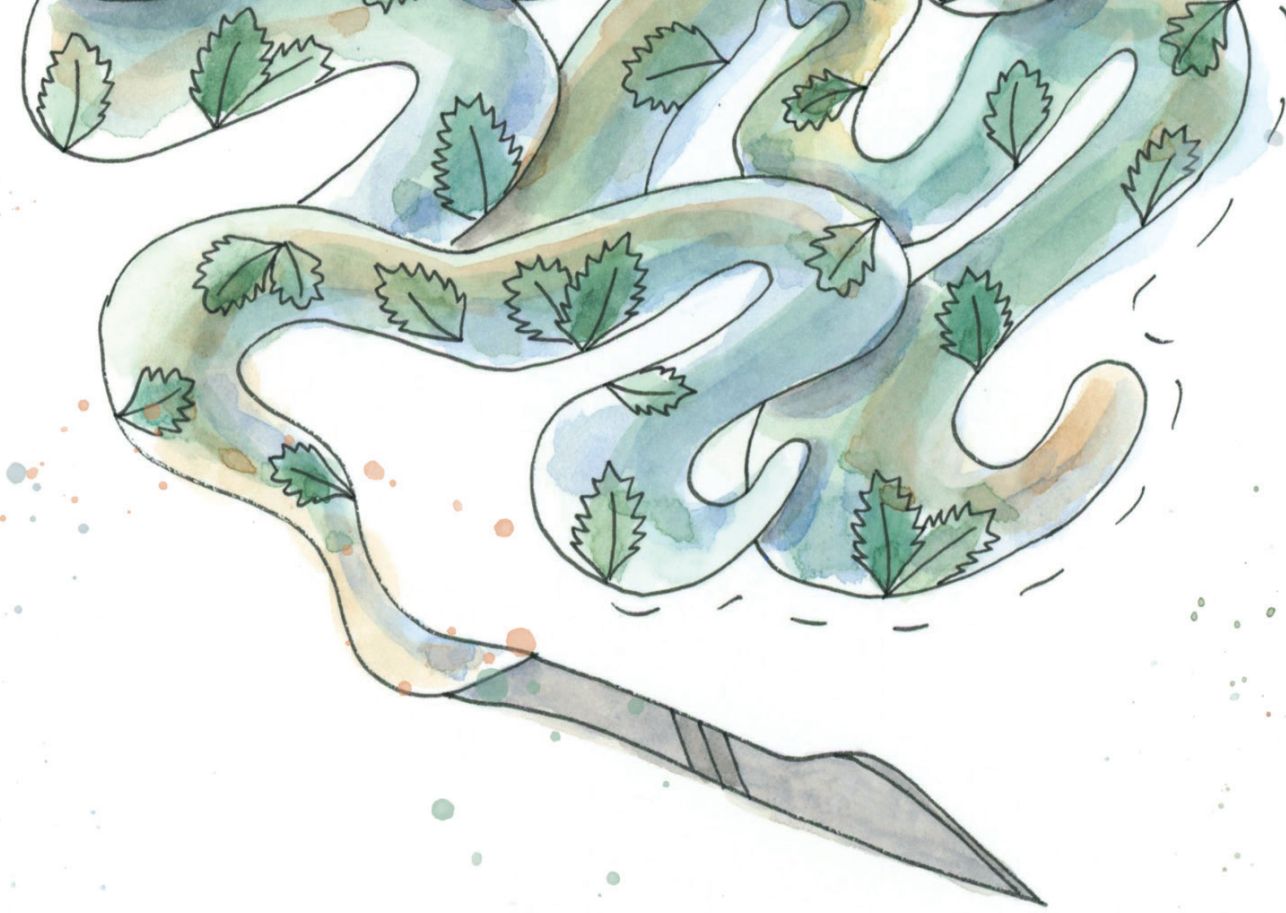
*Unspecified subtype (IBS-U) (n = 56)*

| Attributes | | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|---|
| *Random parameters in utility function* | | | | | |
| Effectiveness | Mean | 0.267 | 0.902 | -3.966 | 4.500 |
| | s.d. | 0.195 | 0.900 | -2.851 | 3.240 |
| Time to response | Mean | -0.371 | 0.903 | -6.355 | 5.613 |
| | s.d. | 1.255 | 0.904 | -19.067 | 21.577 |
| ASC_medication | Mean | -1.730 | 0.919 | -35.313 | 31.852 |
| | s.d. | 31.236 | 0.902 | -467.95 | 530.42 |
| ASC_diet | Mean | 11.122 | 0.902 | -165.35 | 187.60 |
| | s.d. | 14.625 | 0.903 | -221.63 | 250.88 |
| *Nonrandom parameters in utility functions* | | | | | |
| Time until recurrence (medication and diet) | | 0.149 | 0.903 | -2.249 | 2.549 |
| Mild side effects | | -2.879 | 0.905 | -49.977 | 44.219 |
| Severe side effects | | 0.435 | 0.936 | -10.223 | 11.094 |
| Time required | | -0.908 | 0.905 | -15.868 | 14.051 |
| Time until recurrence psychotherapy | | 0.157 | 0.907 | -2.496 | 2.811 |
| Frequency appointments medication | | 0.023 | 0.949 | -0.716 | 0.763 |
| Frequency appointments diet | | -0.216 | 0.902 | -3.646 | 3.215 |
| Frequency appointments psychotherapy | | 0.104 | 0.901 | -1.593 | 1.800 |

Number of observations = 448 (no missing values). Halton draws with 2000 simulations.
Abbreviations: CI = confidence interval, s.d. = standard deviation, ASC = alternative specific constant;
* $r < 0.05$; ** significant standard deviation indicates preference heterogeneity

# Part 2

## LONG-TERM OUTCOMES OF SURGICAL MANAGEMENT FOR FUNCTIONAL BOWEL DISORDERS



# Chapter 5

## LONG-TERM OUTCOMES OF A MALONE ANTEGRADE CONTINENCE ENEMA (MACE) FOR THE TREATMENT OF FECAL INCONTINENCE OR CONSTIPATION IN ADULTS

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## ABSTRACT

Purpose

The aim of the study was to assess the long-term outcome of a Malone Antegrade Continence Enema (MACE) procedure for fecal incontinence or constipation in adults.

Methods

This retrospective single center study assessed the long-term outcome and quality of life (QoL) of patients who underwent a MACE procedure between 2005 and 2014 at the Maastricht University Medical Centre. Success rate was quantified by using Malone's continence scale. Quality of life was assessed by validated questionnaires covering general quality of life (SF-36 and Karnofsky scale), current pain level (Visual Analogue Scale), fecal incontinence (Vaizey Incontinence Survey) or constipation (Cleveland Clinic Constipation Score).

Results

Based on patients' records, 22 out of 30 patients (73%; 95% CI 54 – 87%) were still using their MACE. Mean follow up was 43 months (S.D. 25.9) since time of surgery. According to the Malone continence scale, the overall success rate was 37% (95 % CI: 20.0 – 53.3). Nine patients developed a postoperative complication. Eighteen out of 22 patients (13 with constipation and 5 with fecal incontinence) returned the QoL questionnaires (82% response rate). Long-term quality of life of patients with a MACE did not differ from the general Dutch population.

Conclusions

In our cohort of patients with fecal incontinence or constipation, MACE resulted in a disappointed overall success rate of 37%. However, it may be indicated in patients who do not prefer more invasive surgical procedures or a definite stoma. The success- and morbidity rate should be thoroughly discussed with the patients preoperatively.

# INTRODUCTION

Idiopathic fecal incontinence and functional constipation im- pose a considerable burden on patients. Fecal incontinence is highly prevalent, ranging from 2.2 to 15% in the general population and up to 40% in nursing homes.[1-3] The treatment of fecal incontinence and constipation starts with conservative treatment like bulk agents, retrograde washouts, and pelvic floor therapy.[4] Sacral neuromodulation can be considered if conservative treatment in patients with fecal incontinence fails.[4] The next step after conservative treatment in constipated patients is often a stoma or a subtotal colectomy. This is a major, invasive, and irreversible procedure, which is associated with high morbidity, frequent adverse events, and highly variable outcome.[5-7] If the patient prefers to eschew such invasive procedures, a Malone stoma can be considered for antegrade colon irrigation. The Malone antegrade continence enema (MACE) was first described in 1990 by Malone *et al*.[8] They specified a new operative technique enabling antegrade washouts to accomplish production of stool. During this procedure, the appendix is attached to the anterior abdominal wall to serve as a continent stoma. If the appendix has been removed before, the procedure consists of a neoappendicostomy by using a segment of the terminal ileum or a cecal flap.[9] The MACE was first introduced in patients with fecal incontinence to become pseudo continent.[10-12] Later studies demonstrated that the MACE could also be effective in patients who suffer from constipation.[13-16]

The current literature is mainly focused on the success rate in children. In the adult population, data of long-term outcome and quality of life of the MACE show contradictory results.[12, 17-19] The median follow-up of these studies ranges between 6 and 75 months, covering cohorts of 5–80 patients. The aim of this study is to report long-term outcome and quality of life of eighteen adult patients with fecal incontinence or constipation treated with MACE.

## METHODS

This is a retrospective observational study in which we retrieved patient characteristics from hospital records and sent postal questionnaires to ascertain current functional outcome. All patients suffering from fecal incontinence or constipation who underwent a MACE procedure at Maastricht University Medical Centre between 1997 and 2014 were selected. Medical charts of these patients were reviewed and data regarding indication, history, previous surgery for fecal incontinence or constipation, surgical procedure, and peri- and postoperative complications and revisions were extracted. All patients who, according to their medical records, were still using MACE were contacted by mail to participate in the study. In case of no response, patients were reminded by telephone within 2 weeks.

### Surgical procedure

The MACE procedure is an operative technique to facilitate the administration of antegrade washouts to empty the colon by using the (neo-)appendix. The appendix is brought out to the abdominal wall in a non-refluxing manner as a continent stoma.[8] If the appendix was still in situ and suitable for fixation to the abdominal wall, a classical appendicostomy was performed. In all other cases, a neoappendicostomy was performed where a cecal flap was used to staple to the abdominal wall.[9] The procedure was performed both by laparotomy or laparoscopy. Antibiotics, cefazolin (INN), and metronidazole were administered to all patients preoperatively.

### Success rate

To evaluate the efficacy of the MACE procedure, Malone introduced a continence scale which was based on several criteria categorizing the success rate as full, partial, or failure.[17] Full success represents totally clean or minor rectal leakage on the night of the washout. Partial success represents clean but significant stomal or rectal leakage, occasional major leaks, still wearing protection, and perceived improvement by the parents or child. Failure represents regular soiling or constipation, no perceived improvement, or the procedure abandoned. According to the Malone continence scale, the overall success rate was calculated by combining the full and partial success rates, using the number of patients in the intention-to-treat group as denominator (n = 30).[18]

### Questionnaires

General quality of life was assessed using the SF-36.[19-22] The raw scores of the eight different domains were linearly transformed to scores ranging from 0 to 100; a higher score indicates a better health status. To assess the level of a patient's general well-being and activities in daily life, the Karnofsky Performance Status was used.[23,24] This

score is mostly used in patients with cancer and indicates the level of requirement of medical care on a scale from 0 to 100. Scores of 100, 70, 40, and 0 correspond with 'no complaints, no evidence of disease', 'cares for self, unable to carry out normal activity or to do active work', 'disabled, requiring special care and assistance', and 'dead', respectively.

The visual analog scale (VAS) provides information regarding the minimum and maximum levels of pain currently experienced by the patients. The score ranged from 0 to 10; a score of 0 corresponds with no pain, and scores of 1–3, 4–6, and 7–10 correspond to mild, moderate, and severe pain, respectively.[28-30]



The Vaizey survey was used in patients who suffered from fecal incontinence. Incontinence was scored from 0 to 24 and major incontinence was defined as a score of 7 or higher. Patients are asked to report on frequency of incontinence and alterations in life style, the need to wear pads or plugs, constipating medication, and the lack of ability to defer defecation for 15 min. The Vaizey survey has been validated for Dutch language.[25-27]

Constipation was assessed using the Cleveland Clinic Constipation Score.[25] With this questionnaire, patients are asked to report on the frequency of bowel movements, of painful, incomplete, and unsuccessful evacuation, of abdominal pain, time spent in lavatory and need for assistance, and duration of constipation. A score above 15 was considered as constipation.

Complication score

Complications were graded according to the Clavien-Dindo classification.[28] Minor complications are classified as grade I (deviation from normal postoperative course, not requiring intervention) or II (requiring pharmacological intervention) and major complications as grade III (requiring surgical, endoscopic, or radiological intervention) and IV (life threatening). A fatal adverse event is classified as grade V.

Statistics

Patient characteristics are presented as mean (standard deviation [SD]), median (interquartile range [IQR]), or absolute number (%), as appropriate. Homogeneity of variances was assessed using Levene's test. The outcome of the SF-36 was compared to the reference values of the general population.[22] This was analyzed using a two-tailed unpaired t test. A p value of $< 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS version 2

## RESULTS

Demographics

A flow chart of the process of inclusion is shown in figure 1. Thirty patients underwent a MACE procedure in the Maastricht University Medical Centre between 1997 and 2014. During the follow-up period, the MACE stoma was removed in 8 (26.7%) patients. Reasons for removal were lack of efficacy (n = 3), stoma leakage (n = 2), washouts were not feasible because of the worsened stage of multiple sclerosis (n = 1), and in two patients, the cause of failure was unknown. Six of these eight patients underwent a colostomy. One patient underwent an ileocecal resection, followed by a split ileo-/ascendostomy, and in another patient, a subtotal colectomy with ileorectal anastomosis was performed.

In total, 22 patients (73.3%) were still using the MACE after a maximum follow-up of 8.4 years. These patients were eligible for this study and 18 patients completed the questionnaires, resulting in a response rate of 81.8%. Thirteen patients had constipation and 5 (27.8%) had fecal incontinence. The characteristics of the 18 responders are described in Table 1. The etiology of the different causes of fecal incontinence and constipation is displayed in Table 2.

All patients underwent a prolonged period of failed conservative bowel management before the MACE procedure. The mean symptom duration before MACE was 10.9 years (SD 7.4). To treat constipation, patients used laxatives (n = 12), retrograde enemas (n = 13), and rectal suppositories (n = 7). To treat fecal incontinence, two patients used pelvic floor therapy and two used retrograde enemas. Twelve patients (66.7%) underwent previous surgery to treat the underlying cause of the fecal incontinence/constipation: sacral nerve stimulation (n = 9), rectovaginopexy (n = 2), recto-uteropexy (n = 1), and rectumextirpation with colo-anal anastomosis because of a malignancy (n = 1).

Surgical technique

Surgical procedure was open in 11 (61.1%) and laparoscopic in 7 (38.9%) patients. In 12 patients, an appendicostomy was performed, and in 6, a neoappendicostomy. Data regarding the MACE are shown in Table 4.

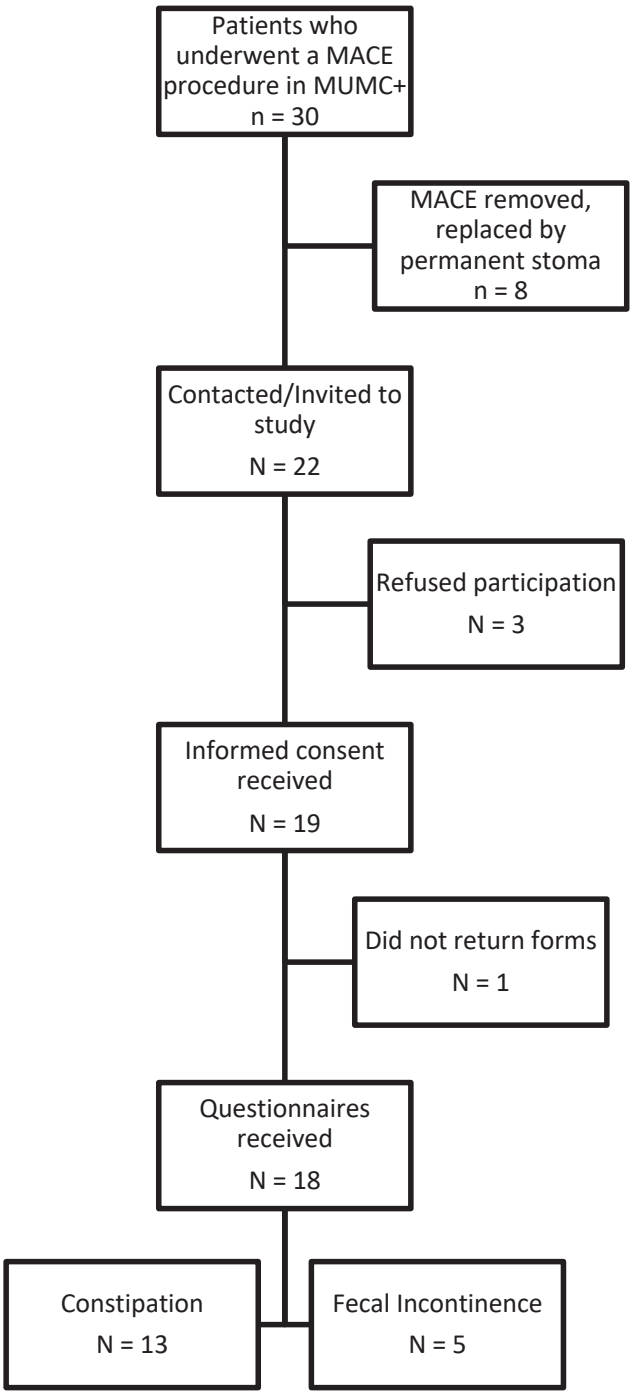


*Figure 1: Flow chart of patient inclusion*

*Table 1: Patients characteristics*

| | Constipation n = 13 | Fecal Incontinence n = 5 |
|---|---|---|
| *Female sex (n)* | 11 | 4 |
| *Mean age (SD)* | 39 (18.1 years) | 48 (19.9 years) |
| *Mean age at surgery (SD)* | 35 (19.3 years) | 46 (19.7 years) |
| *Mean follow-up duration (SD)* | 50.2 (26.4 months) | 23.1 (9.1 months) |
| *Mean symptom duration before appendicostomy (SD)* | 10.7 (7.6 years) | 11.4 (7.6 years) |
| *Median BMI (kg/m²)(SD)* | 23.5 (6.3) | 25.8 (5.9) |
| *Comorbidities (n)* | | |
| *- none* | 3 | 1 |
| *- Cardiovascular* | 2 | 3 |
| *- Respiratory* | 2 | 0 |
| *- Neurologic* | 3 | 0 |
| *- Inflammatory* | 1 | 0 |
| *- Urologic* | 2 | 1 |
| *Smoking status (n)* | | |
| - Never smoked | 8 | 2 |
| - Smoked in the past | 2 | 1 |
| - Current smoker | 3 | 2 |

*Table 2: Etiology of fecal incontinence and constipation in 18 patients*

| Etiology | Number of patients |
|---|---|
| Spina Bifida | 4 |
| Spinal cord lesion (including paraplegia, caudal equine lesion, spinal cord injury) | 3 |
| Rectocele | 3 |
| Idiopathic Slow-transit constipation | 2 |
| Psychological | 2 |
| Diabetic neuropathy | 1 |
| Multiple Sclerosis | 1 |
| Neoplasm (rectum) | 1 |
| Primary IgA immunodeficiency | 1 |

MACE usage

All patients used tap water to perform the antegrade washouts. The median duration of each washout was 38.5 min (range 15–60). The amount of fluid used ranged from 150 to 2000 cm3 (median 1500) for each antegrade continence enema administration. Thirteen (72.2%) patients performed washouts daily, one patient twice a day, one patient five times a week, and three patients less than five times a week. Most patients (n = 13) performed the washouts themselves. The washouts in the other patients were performed by parents (n = 3), care- givers (n = 1), or partner (n = 1). Nine patients (50%) reported leakage during antegrade washouts. Eight patients suffered from (some) pain during antegrade washouts. Soiling was reported by six of the patients ranging from once a day (2), twice a week (1), once a week (2), up to once a month (1).



Thirteen patients needed supplementary treatment to facilitate antegrade washouts: ten patients used laxatives, one patient used bulking agents, and two patients used spasmolytics.

Overall success rate

Using the Malone criteria, the procedure was successful in 11 of the intention-to-treat cohort (N = 30) (36.7%; 95% CI 20.0– 53.3). Full and partial success was reached in 4 and 7 patients (13%, 95% CI: 4 – 32 and 23% (95% CI: 11 – 43), respectively.

Success rate in patients with fecal incontinence (N = 5)

According to the Vaizey score and the presence of rectal or stomal leakage, none of the five patients with fecal incontinence reached full success, three reached partial success, and in two patients, the MACE failed.

Success rate in patients with constipation (n = 13)

According to the Cleveland Clinic Constipation Score, of the 13 included patients with constipation, 4 patients reached full success, 4 reached partial success and in 5 patients, the MACE failed due to regular constipation (score > 15).

Quality of life, general well-being, and pain

Results of the SF-36 questionnaire and of the Dutch general population are presented in Table 3 and figure 2. Patients who underwent a MACE procedure scored substantially lower on all SF-36 domains compared to a Dutch reference population, although none of these differences were statistically significant when taking multiple comparisons into account.

The mean Karnofsky score was 63.1 (SD 13.2) in the fecal incontinence group, indicating that patients were usually unable to carry out normal activities, but able to care for themselves.

The mean minimal pain level was 3.5 (SD 2.6) and the mean maximum level was 7.6 (SD 2.0) in patients with fecal incontinence, indicating moderate to severe pain.

In patients with constipation, the mean Karnofsky score was 68.0 (SD 16.4), indicating that patients were usually un- able to carry out normal activities, but able to care for them- selves. Mean minimum and maximum pain levels in these patients were 2.3 (SD 1.5) to 6.2 (SD 1.8), respectively, indicating mild to moderate pain.

*Table 3: Results of the SF-36 and norm-based scores*

| Subscale | MACE | General Population | p value |
|---|---|---|---|
| *Physical functioning* | 35.6 (35.2) | 83.0 (22.8) | 0.15 |
| *Role physical* | 43.1 (45.2) | 76.4 (36.3) | 0.38 |
| *Bodily pain* | 49.8 (27.2) | 74.9 (23.4) | 0.29 |
| *General Health* | 60.3 (9.3) | 70.7 (20.7) | 0.47 |
| *Vitality* | 50.3 (12.1) | 68.6 (19.3) | 0.24 |
| *Social functioning* | 45.1 (9.7) | 84.0 (22.4) | 0.051 |
| *Role emotional* | 87.0 (32.6) | 82.3 (32.9) | 0.87 |
| *Mental health* | 64.7 (6.2) | 76.8 (17.4) | 0.32 |

Values as mean (SD)

Complications

Postoperative complications were observed in all 5 patients with fecal incontinence and in 4 of the 13 patients (30.8%) with constipation. These complications are described in Table 4. Nine patients (50%) had one or more complications, with three patients having multiple complications. Six patients developed an infection, classified as a minor complication according to the Clavien-Dindo classification, which was treated with antibiotics. Six patients developed major complications such as washout leakage (n = 2), stomal stenosis (n = 2), and an abscess (n = 2). To treat the abscess, incision and drainage was performed and antibiotics were prescribed. Surgical revision of the MACE was necessary in two patients (11.1%) suffering from stenosis or leakage. In these cases, the MICK-KEY button was replaced.

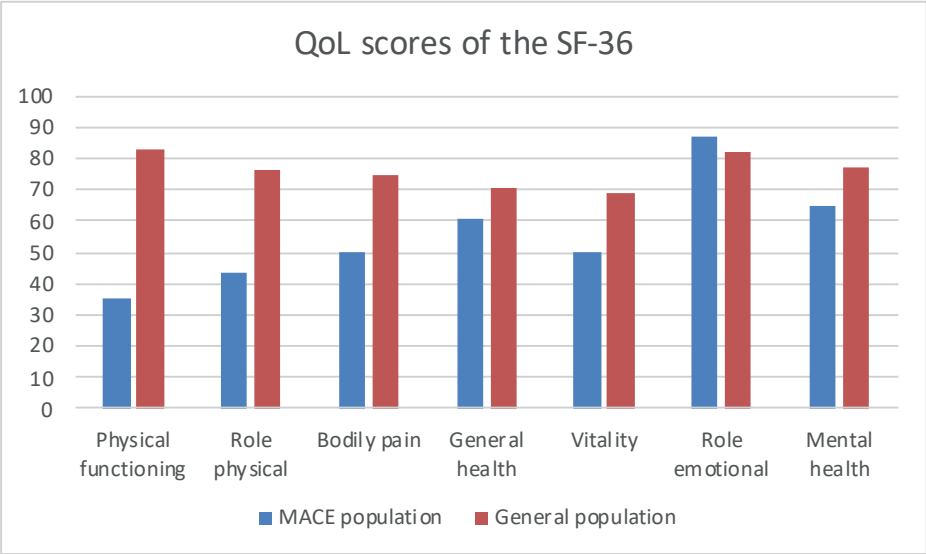


*Figure 2: Chart of the mean norm-based scores of the Short Form 36 questionnaires of the MACE population after surgery versus the quality of life of the Dutch population*

*Table 4: The surgical procedure and post-operative complications*

| | Constipation n = 13 | Faecal Incontinence n = 5 |
|---|---|---|
| *Surgical type (n)* | | |
| - Laparoscopic | 6 | 1 |
| - Open | 7 | 4 |
| *Surgical technique (n)* | | |
| - Appendicostomy | 9 | 3 |
| - Neo-appendicostomy | 4 | 2 |
| *Complication after surgery (n)* | 4 (30.8%) | 5 (100%) |
| - Clavien-Dindo Grade I | 0 | 0 |
| - Clavien-Dindo Grade II | 2 | 4 |
| - Clavien-Dindo Grade III | 2 | 1 |
| - Clavien-Dindo Grade IV | 0 | 0 |
| - Clavien-Dindo Grade V (death) | 0 | 0 |

## DISCUSSION

This study assessed the long-term outcome and QoL of adults who underwent a MACE procedure for the treatment of fecal incontinence or constipation. Using the Malone continence scale, we report an overall success rate of 36.7%. Six patients developed major complications and two patients needed surgical revision of the MACE. Quality of life of the patients with a MACE tended to be lower than in the general Dutch population, especially in the domains of physical and social functioning and bodily pain, although these differences failed to reach conventional levels of statistical significance (Figure 2).

Relatively few studies have reported long-term outcome after the MACE procedure in adults. Most of the studies used no validated criteria defining the success rate of the procedure. Many studies used the continued use of the MACE for their primary outcome and as definition of success during follow-up. The majority of studies did not use validated questionnaires to assess QoL post treatment.

These inconsistencies in definitions of 'successful use of the MACE' make it difficult to compare the different studies reporting on the outcome of the MACE procedure. This lack of consistency is also described in the recent published meta-analysis of *Chan and Delicata*.[29] They reported on the outcome of seventeen studies of MACE procedure in adults. They described a pooled success rate of 71.8%. This success rate was determined by continued use of the MACE at the end of follow-up or resolution of the symptoms. This rate is similar to our study, with 73% of the patients still using the MACE.

However, if you chose to use the Malone continence scale as primary endpoint, the success rates of the previous per- formed studies might be lower. Using this primary endpoint, we found an overall success rate of 36.7% in our study. To our knowledge, our study used the Malone success rate for the first time in adult patients. We think that the Malone continence scale reflects more the clinically relevant success rate of the MACE than the previous mentioned outcome 'continued used of the MACE at the end of follow-up or resolution of the symptoms'.

Two studies in children used also the Malone success rate as primary endpoint.[10,30] In one study, with 21 patients with a spina bifida, the success rate was 90% with a median follow-up of 75 months. The other study included 40 children, suffering from constipation with all different etiologies, and reported a success rate of 92% with a mean follow-up of 6.5 years.

Studies publishing about quality of life after a MACE in adults and using validated questionnaires are scarce. This topic is described more comprehensively in children.[16,31,32] Only three studies assessed the quality of life after MACE in adults using the SF-36.[12,33,34] These three studies reported the outcome of fecal incontinent patients and showed a good postoperative physical recovery and general health.

Our data suggest that at long-term follow-up, patients with a MACE struggle especially with physical and social functioning. This may be related to complications that can arise in the long run. The most common complications are the formation of granulation tissue, stomal infection, and leakage from the appendicostomy.[13] In some cases, the complications are so debilitating that patients prefer the MACE to be removed. Eight patients in our study chose to have the MACE removed for a lack of effectiveness or because of complications (stoma leakage, pain). This is in agreement with the results of Yardley *et al*.[35] Revision surgeries are often necessary in these patients to resolve the complications.[15,35]



Some limitations of our study have to be addressed. First of all, this is a retrospective study and preoperative values were not available. Besides we included a heterogeneous cohort of patients suffering from fecal incontinence or constipation with different etiology. The underlying diseases may interfere with the general health of the patient. This may have affected not only the results of the SF-36, but also the visual analog scale and the Karnofsky score.

MACE was developed to offer patients the prospect of resolving the problems associated with fecal incontinence or constipation, while avoiding more invasive surgery. Our results, adopting a more realistic definition of successful outcome and including considerations such as quality of life, general well-being, and pain, show that in the long run, the results are disappointing. This underscores, once more, the utmost importance of carefully informing patients and making sure that they hold realistic expectations of the various options.

## CONCLUSIONS

MACE was developed to offer patients the prospect of resolving the problems associated with fecal incontinence or constipation, while avoiding more invasive surgery. Our results, using the Malone success rate as primary endpoint, are disappointing. However, it may be indicated in patients who do not prefer more invasive surgical procedures or a definite stoma. The success and morbidity rate should be thoroughly discussed with the patients preoperatively.

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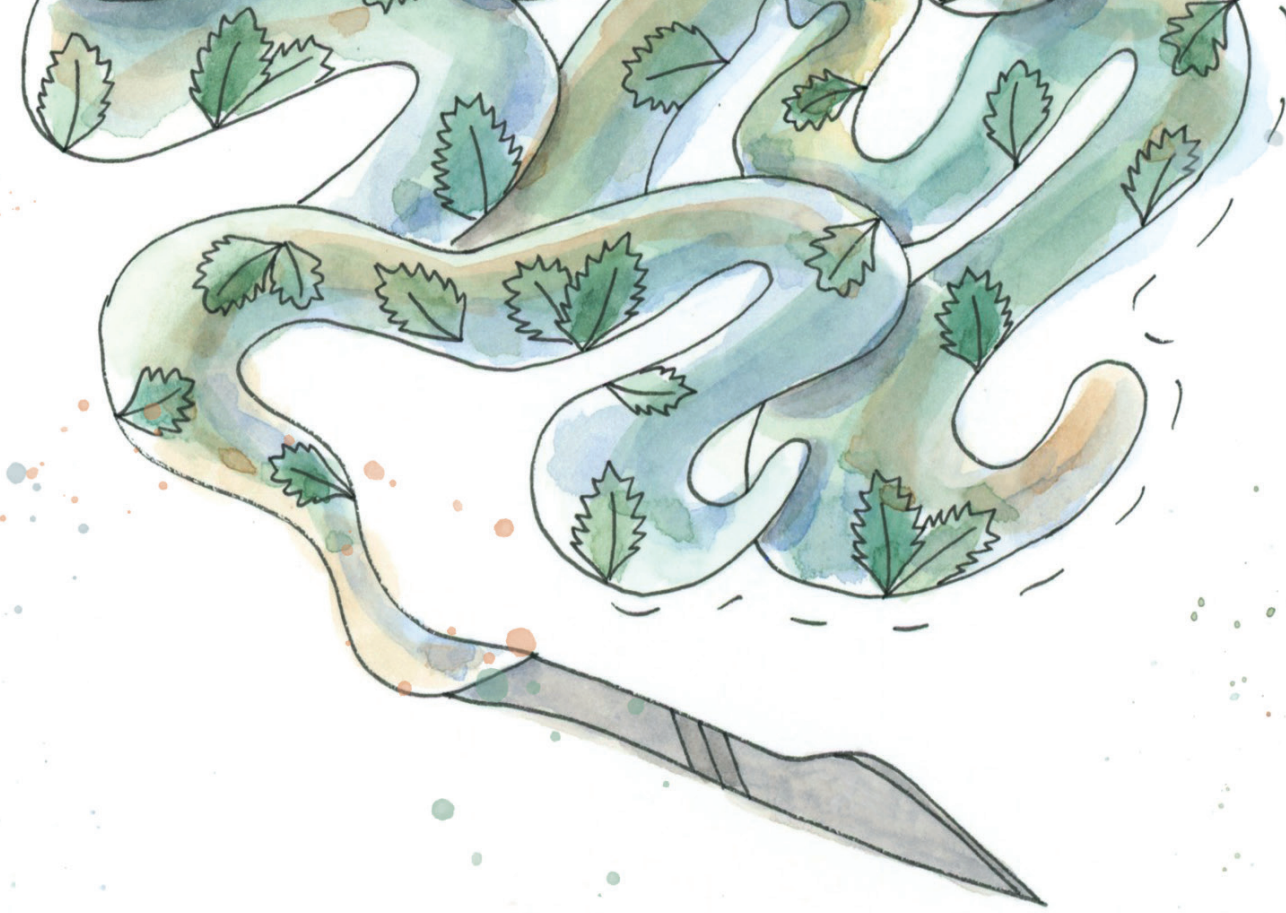

# Chapter 6

## SACRAL NEUROMODULATION IN CHILDREN AND ADOLESCENTS WITH CHRONIC CONSTIPATION REFRACTORY TO CONSERVATIVE TREATMENT

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## ABSTRACT

Purpose

Functional constipation in children and adolescents is a common and invalidating condition. In a minority of patients, symptoms persist despite optimal conservative therapy. The aim of this study was to evaluate whether the short-term effects of sacral neuromodulation (SNM) in children and adolescents with constipation are sustained over prolonged period of time.

Methods

Patients aged 10–20 years, with refractory constipation, fulfilling the Rome III criteria, were included in our study. If SNM test treatment showed >50 % improvement in defecation frequency, a permanent stimulator was implanted. Primary outcome measure was defecation frequency during 3 weeks. Secondary endpoints were abdominal pain and Wexner score. To assess sustainability of treatment effect, a survival analysis was performed. Cross-sectional quality of life was assessed using the EQ-5D VAS score.

Results

Thirty girls, mean age 16 (range 10–20), were included. The mean defecation frequency increased from 5.9 (SD 6.5) in 21 days at baseline to 17.4 (SD 11.6) after 3 weeks of test treatment ($p < 0.001$). During test treatment, abdominal pain and Wexner score decreased from 3.6 to 1.5 and 18.6 to 8.5 ($p < 0.001$), respectively. Improvement of symptoms sustained during a median follow-up of 22.1 months (12.2–36.8) in 42.9 % of patients. On a scale from 0 to 100, quality of life was 7 points lower than the norm score (mean 70 vs. 77).

Conclusion

SNM is a therapeutic option for children with chronic constipation not responding to intensive oral and/or laxative therapy, providing benefits that appear to be sustained over prolonged period of time.

## INTRODUCTION

Constipation is a common problem in childhood and adolescence, with a prevalence ranging between 0.7 and 29.6 % (median 12 %).[1] Functional constipation, as defined by the ROME III criteria[2], has significant impact on quality of life, both for the patient as for his or her family.[3]

Various modalities have been developed in the treatment of functional constipation, including increase of dietary fiber intake, osmotic and stimulant laxatives, retrograde bowel irrigation, and behavioral therapy, including biofeedback training and pelvic floor physiotherapy.[1,4] In the majority of patients, constipation can be effectively treated by these conservative treatments.[5]

A group of patients exists, however, in whom symptoms persist for many years. In these patients, abdominal pain, most likely due to the low defecation frequency, is severely disabled in their daily activities, such as attending school and participation in sports and social events. For these refractory patients, surgical procedures such as antegrade bowel irrigation by means of a Malone stoma, colectomy, or segmental colonic resection may be considered.[6] Such treatments can, however, incur complications such as small bowel obstruction, chronic diarrhea, fecal incontinence, and abdominal pain; moreover, long-term results are highly variable.[7]

Sacral neuromodulation (SNM) was initially developed as a treatment for urinary incontinence and retention in adults.[8] In these series, a subset of patients who suffered from urinary and fecal incontinence experienced improvement in both. In adults, studies of SNM for functional bowel complaints showed a positive effect on idiopathic slow and normal transit constipation resistant to conservative treatment.[9] Our preliminary data suggest that SNM may also be beneficial in young patients aged 10–20 years with refractory constipation.[10] It is unknown, however, whether relief of symptoms is sustained. In this study, we report longer term follow-up results with SNM in children and adolescents with constipation refractory to intensive conservative treatment.

## METHODS

A prospective cohort study was conducted in a tertiary referral hospital to assess the efficacy of SNM in adolescents with refractory constipation. All patients between 10 and 20 years of age, who were referred to our center for chronic (>1 year) constipation refractory to conservative treatment, were eligible to be included in this study. Informed consent was obtained from all patients and their parents.

All patients met the criteria for functional constipation, as defined by the Rome III criteria.[2] Demographic data, disease history, and prior treatments were collected from all patients. Severity of symptoms was determined at baseline by means of a 3-week bowel diary, subjective questionnaires, and Wexner constipation scores.[11] A bowel diary was filled in during a period of optimal conservative treatment, consisting of a combination of different oral and/ or rectal laxatives. Patients were asked to report the frequency of defecation, presence of straining, episodes being unable to evacuate, urge, painful defecation, size of stool, abdominal pain, and absence from school due to constipation-related complaints.

The Wexner score is a composite score ranging from 0 to 30 based on eight domains including frequency, difficulty to evacuate, completeness, painfulness, duration (time in lavatory), successfulness, and need for assistance in defecation, as well as history (duration of symptoms).[11]

Further diagnostic tests included defecography to assess possible outlet obstruction, anal ultrasound, anorectal manometry to exclude Hirschsprung's disease, colonic transit time measurement using radio-opaque markers, and MRI of the lumbar spine.

Operative details

The operative technique for SNM has been described in detail elsewhere.[12] Briefly, patients had a tined lead (Medtronic Interstim model 3889) placed in order to perform a test treatment of sacral neuromodulation. This procedure took place under general anesthesia with antibiotic prophylaxis and was performed by an experienced surgeon. An X-ray was used to determine the location of S3 and to place a needle in the foramen. Correct position of the needle was confirmed by Bellow's contraction. Finally, the electrode was placed in position and connected to the external stimulator. This was followed by a 3–5-week test period to assess treatment benefit and decide on implantation of the permanent stimulator. To qualify for a permanent device, defecation frequency had to be restored to a frequency of minimally three times per week. The permanent implantable stimulator (Medtronic Interstim model 3058) was

implanted under local anesthesia. It was placed in a subcutaneous gluteal pocket under antibiotic prophylaxis. Initial stimulation settings were identical to those during the testing phase. These stimulation settings are identical to those used for adults. Initially, a pulsewidth of 210 μs and a frequency of 16 Hz were used. In the case of unpleasant sensations or suboptimal treatment effect, settings could be changed from 120 to 330 μs and 10 to 21 Hz, respectively.

Assessment and follow-up

Patients were followed up at 1, 3, 6, 12, and 24 months after implantation of the pacemaker. Prior to each follow-up moment, a 3-week bowel diary was completed, and questionnaires and Wexner constipation scores were recorded. Additional use of laxatives, recurrence of symptoms, or technical failure with or without reoperation was recorded. The primary endpoint was the frequency of defecation as recorded in the 3-week bowel diary. Treatment was considered successful when defecation frequency was at least three times per week.



Secondary outcome parameters were change in Wexner constipation score, presence of abdominal pain, pain at defecation, straining, feeling of urge, incomplete evacuation, general comfort, and quality of life. Abdominal pain, pain at defecation, straining, feeling of urge, and incomplete evacuation were assessed using a 5-point scale, ranging from 0 “never,” 1 “rarely,” 2 “sometimes,” 3 “most of the times,” to 4 “always.” Quality of life was assessed by means of the EQ-5D VAS.[13] Recurrence of constipation was defined as a defecation frequency less than three times per week or the need for use of laxatives or bowel lavage to control symptoms.

Statistical analysis

Data are presented as mean (SD) or median (range) for continuous variables, and count (percentage) for categorical variables. Changes over time in severity of symptoms were tested for statistical significance using paired t test and Wilcoxon signed ranks test. A time-to-event analysis was conducted using Kaplan-Meier survival analysis. Event was defined as a remission to a defecation frequency of less than three times per week, with or without lead or pocket revision. Analyses were conducted using SPSS. A p value of 0.05 was considered statistically significant.

## RESULTS

Thirty patients with refractory constipation were referred to our center between February 2009 and December 2011. Table 1 shows the patient characteristics and the progress of abdominal pain and defecation frequency over time. All 30 patients underwent a test stimulation of SNM. In three of these patients, test stimulation was ineffective and the electrode was removed. All remaining 27 patients had a stimulator implanted and were available for follow-up. Median follow-up was 22.1 months (12.2–36.8).

### Baseline characteristics

All patients were female with a mean age of 16 years (range 10–20) at the time of the test stimulation. Mean duration of complaints was 8.1 years (range 1–18). At the time of presentation in our outpatient clinic, all patients had been treated extensively with various conservative treatments for at least 1 year, under supervision of a referral center. All patients used laxatives, including polyethylene glycol, Metamucil, lactulose, bisacodyl, and magnesium oxide, or a combination of these, with or without retrograde bowel irrigation. Duration of laxative use ranged from 1 to 17 years (mean 5.9 years). One patient had a Malone stoma for antegrade bowel irrigation. All patients had been admitted multiple times to hospital for either oral and/or rectal lavage (median 7, range 2–50).

Colonic transit time was assessed in 22 of 30 patients and showed a mean colonic transit time of 92.3 h. Fifteen patients had colonic transit times exceeding 62 h (Table 1). Lumbar spine MRI was performed in 22 of 30 patients and revealed no spinal abnormalities. In 23 of 30 patients, an anorectal manometry was performed, which showed an abnormal result in one patient, in whom the anorectal inhibition reflex could not be elicited (Table 1). In the latter patient, a rectal suction biopsy was performed which showed normal ganglion cells. Results of defecography were available for 21 patients. In five, there was a minimal sign of rectocele (grade 1, smaller than 4 cm), and one patient showed a rectocele, enterocele, and intussusception. Six patients had no evacuation of the contrast at all, and in eight patients, evacuation was incomplete. Twelve patients underwent anal ultrasound. Two of them showed a defect of approximately 30-45° in the internal and the external sphincter, respectively. For one, the defect was possibly the result of sexual abuse. In the remaining 10 patients, no abnormalities were found on anal ultrasound.

### Defecation frequency

At baseline, the mean defecation frequency during a 3-week period was 5.9 (SD 6.5) or 1.96 times per week. During the test phase, the mean defecation frequency increased to 17.4 (SD 11.6) per 3 weeks or 5.8 times per week. During follow-up, the

mean defecation frequency remained stable at this level. At each time at follow-up, the defecation frequency was significantly higher when compared to baseline defecation frequency ($p < 0.001$).

Secondary outcome parameters

The mean Wexner score decreased from 18.6 (SD 8.5) at baseline to 8.2 (SD 8.3) during test phase and remained stable during follow-up (Figure 1). At each follow-up visit, the mean Wexner score was significantly lower as compared to baseline ($p < 0.001$). The abdominal pain score decreased from mean 3.62 at baseline to 1.53 at 1 year follow-up ($p < 0.001$). At baseline, two patients reported to have abdominal pain some of the time, while the other patients reported to have abdominal pain most of the time (9) or always (19). At 1 year follow-up, two patients still had abdominal pain most of the time, nine sometimes, seven rarely, and two never. Accompanying symptoms such as pain at defecation, straining, and incomplete evacuation showed a comparable decrease, while the times of feeling of urge increased. The EQ5D VAS score was 69.90 (SD 17.96) at a median follow-up of 12 months, which is lower than the norm score for healthy Dutch females aged 15–19 (mean 76.73, SD 12.58) (Table 1).[13]



Complications and revisions

A total number of 15 revisions were performed in 12 patients. Reasons for revision were the following: recurrence of symptoms in six patients, a lead revision was performed; pain at the site of the stimulator in five patients, the position of the stimulator was revised; and infection of the electrode in one patient, the electrode was removed and a new test was performed after 4 weeks. No other, more serious adverse events associated with the surgical procedure were observed. At the end of follow-up, 21 of 27 patients were still on SNM therapy.

Fifteen of 27 patients failed on SNM, six of these patients underwent a total colectomy and subsequently had the stimulator removed. The remaining nine patients combined SNM with laxatives and/or bowel irrigation.

Survival analysis

Figure 2 shows the results of the time-to-event analysis, where an event is defined as a decrease of defecation frequency below three times per week, with or without revision. The figure shows that in this population of patients with chronic constipation, refractory to conservative treatment, the 2-year recurrence-free survival was approximately 42.9 %. These events mainly occurred in the first year after treatment, as after 6 and 12 months, the recurrence-free survival was 58 and 50 %, respectively.

*Table 1: Baseline characteristics and follow-up*

| Patient | Age | Duration of symptoms (years) | Admissions | CTT (hours) | Manometry RAIR |
|---|---|---|---|---|---|
| 1 | 18 | 18 | m | 60 | np |
| 2 | 16 | 6 | 2 | np | np |
| 3 | 15 | 9 | 11 | np | RAIR+ |
| 4 | 14 | 9 | 10 | 144 | np |
| 5 | 19 | 18 | 20 | 148 | RAIR+ |
| 6 | 17 | 17 | 50 | 148 | RAIR+ |
| 7 | 17 | 16 | 20 | 92 | RAIR+ |
| 8 | 15 | 14 | 50 | 50 | RAIR+ |
| 9 | 13 | 1 | 10 | 50 | RAIR+ |
| 10 | 10 | 5 | 12 | 80 | RAIR+ |
| 11 | 14 | 4 | m | np | RAIR+ |
| 12 | 19 | 10 | 2 | 96 | RAIR+ |
| 13 | 14 | 14 | 6 | np | RAIR+ |
| 14 | 18 | 16 | 3 | 62 | RAIR+ |
| 15 | 17 | 5 | 3 | 38 | RAIR+ |
| 16 | 14 | 6 | 3 | np | np |
| 17 | 13 | 13 | 30 | 144 | RAIR+ |
| 18 | 18 | 2 | 12 | np | RAIR+ |
| 19 | 16 | 2 | 1 | 48 | RAIR+ |
| 20 | 15 | 3 | 7 | 136 | RAIR+ |
| 21 | 16 | 3 | 4 | 132 | RAIR+ |
| 22 | 16 | 1 | 7 | 67 | RAIR - |
| 23 | 16 | 3 | 9 | 96 | RAIR+ |
| 24 | 16 | 10 | 3 | 74 | RAIR+ |
| 25 | 16 | 1 | 6 | 86 | np |
| 26 | 16 | 8 | 2 | 120 | RAIR+ |
| 27 | 15 | 15 | 25 | 19 | RAIR+ |
| 28 | 15 | 8 | 15 | 139 | RAIR+ |
| 29 | 15 | 1 | 3 | np | np |
| 30 | 16 | 2 | 2 | np | np |

np: not performed
m: missing
x: electrode removed, no follow-up data available
RAIR recto-anal inhibition reflex: + intact, - no RAIR

| Abdominal pain baseline | Abdominal pain test | Abdominal pain 1y | Def bl /3weeks | Def test /3weeks | QoL EQ5D-VAS |
|---|---|---|---|---|---|
| 4 | 3 | 2 | 1 | 6 | m |
| 3 | 2 | 2 | 6 | 6 | 43 |
| 4 | 2 | 3 | 3 | 15 | 93 |
| 4 | 2 | 2 | 1 | 10 | 65 |
| 4 | 2 | 2 | 3 | 12 | 68 |
| 4 | 1 | 1 | 9 | 32 | 54 |
| 4 | 2 | 1 | 1 | 9 | 57 |
| 4 | 1 | 3 | 2 | 3 | m |
| 4 | 2 | 2 | 6 | 17 | 91 |
| 3 | 2 | 0 | 8 | 9 | 22 |
| 3 | 3 | x | 3 | 0 | x |
| 4 | 0 | 2 | 6 | 54 | 91 |
| 4 | 1 | m | 21 | 8 | 69 |
| 4 | 2 | 2 | 1 | 21 | 71 |
| 3 | 1 | 1 | 9 | 20 | 75 |
| 3 | 1 | 1 | 9 | 19 | 70 |
| 4 | 3 | m | 3 | 15 | m |
| 4 | 1 | 2 | 20 | 27 | 60 |
| 4 | 0 | 1 | 1 | 24 | m |
| 2 | 0 | 1 | 8 | 10 | 71 |
| 3 | 0 | m | 3 | 20 | 80 |
| 3 | 2 | x | 1 | 1 | x |
| 4 | 4 | m | 21 | 20 | m |
| 4 | 4 | 1 | 0 | 4 | 91 |
| 4 | 1 | m | 0 | 15 | 79 |
| 3 | 0 | 0 | 0 | 39 | 89 |
| 4 | 0 | m | 3 | 27 | 59 |
| 3 | 3 | x | 0 | 0 | x |
| 4 | 3 | m | 0 | 9 | m |
| 2 | 1 | 2 | 2 | 8 | m |

Abdominal pain: 4 always, 3 most of the tome, 2 sometimes, 1 rarely, 0 never
Def bl: defecation frequency at baseline
Def test: defecation frequency during test phase

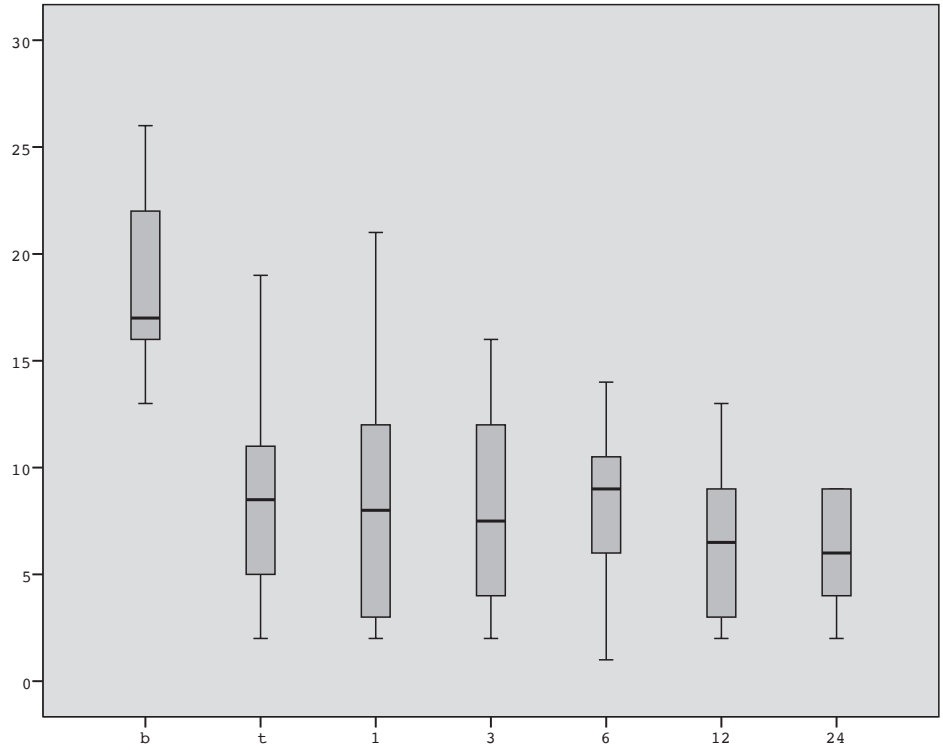


*Figure 1: Box plot of Wexner scores at baseline (b), during test phase (t), and at 1, 3, 6, 12, and 24 months follow-up, respectively. n = 30/30 (baseline), n = 30/30 (test), n = 27/27 (1), n = 24/27 (3), n = 25/27 (6), n = 20/27 (12), and n = 10/25 (24). x-axis: time. y-axis: Wexner score*

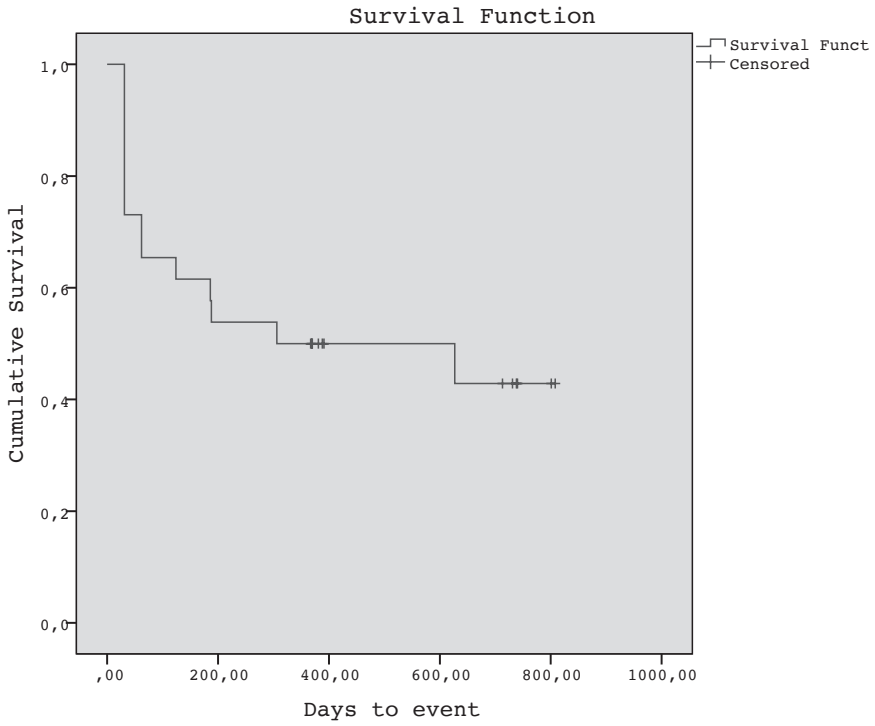


*Figure 2: Kaplan-Meier survival curve, showing recurrence of constipation symptoms over time. Censored observations represent end of follow-up. End-point is recurrence of symptoms, with or without reoperation. x-axis: days to event. y-axis: cumulative survival*

## DISCUSSION

This study shows that in some patients, SNM has a long-lasting beneficial effect on defecation frequency and accompanying symptoms such as abdominal pain and difficulties with evacuation in adolescent patients with severe constipation resistant to conservative treatment.

Sacral nerve modulation in our cohort of children and adolescents with therapy-resistant constipation shows similar efficacy and safety rates as in adults with refractory constipation.[9] Improvement in defecation-related parameters has been reported in adults, in terms of defecation frequency, abdominal pain, and use of laxatives. Many different outcome parameters are used however, which makes adequate comparison difficult, and this probably also results in the wide range of success rates (42–100 %).[14,15] In the prospective study by Kamm *et al.,* the indication to proceed to permanent implantation was an improvement of at least 50 % in defecation frequency or a frequency of three or more per week as well. This resulted in a success rate of 63 % at a median follow-up of 28 months.[9] The higher success rates reported of SNM for constipation in adults compared to the current population is possibly a result from the severity of symptoms these adolescents experience. Moreover, this finding contributes to the suggestion of different etiologies of constipation for children and adults.[1]

A recent study in children with fecal and urinary incontinence and constipation reported that six of 11 patients with a pre-SNM cecostomy tube no longer required an antegrade bowel regimen as they had voluntary bowel movements.[16] Furthermore, ten of 11 patients (91 %) no longer required anticholinergic medications for bladder overactivity after receiving SNM. Since the short-term follow-up in this small heterogeneous group of patients, longer follow-up studies are required to identify longer-term effects of SNM for patients with bowel and bladder dysfunction and potentially identify subgroups of patients that are more likely to respond to sacral neuromodulation. Our study shows that the 2-year recurrence-free survival was approximately 42.9 %, without major complications. Based on these results, we decided not to remove the permanent stimulator in these successfully treated patients. Data are lacking to estimate after which time it is possible to switch off and remove the stimulator.[9,16]

Of the 21 patients who underwent defecography, only 1 did not show some degree of evacuatory dysfunction. Knowles *et al.* suggested that evacuatory dysfunction should not be an exclusion criterion for SNM.[17] It might even lead to sensory improvement in patients suffering from rectal hyposensitivity. Unfortunately, follow-up data of manometry to assess dyssynergia and rectal sensitivity are not available for the cohort of patients in this trial.

In 15 out of 22 patients in whom colonic transit time was assessed at baseline, colonic transit appeared to be delayed. The increase in defecation frequency suggests that colonic transit time improves after SNM. Clarke *et al.* concluded that colonic transit time was significantly shorter after interferential therapy (IFT) compared to sham.[18] IFT, a form of transcutaneous electrical nerve stimulation (TENS)[19,20], is similar to SNM as both techniques aim to modulate neural activity by electrical stimulation. However, IFT is even less invasive as it makes use of surface electrodes and transcutaneous stimulation instead of the percutaneous implantation of an electrode, which is connected to an implantable stimulator. Indeed, children with slow transit constipation, who failed conventional therapy, were effectively treated with TENS.[19,20] More importantly, after daily treatment for 1–6 months, colonic function improved for several years and some children were even able to withdraw medication. Large randomized controlled trials are required to compare both neuromodulation techniques in both children and adults with refractory constipation.



The extensive diagnostic workup prior to the test period was performed in an attempt to identify possible prognostic factors for success regarding SNM. Unfortunately, the number of patients in this study is too small to draw any conclusions in this regard.

The high rate of revisions in this population is the major drawback of this surgical intervention. In accordance with the other pediatric study, in approximately half of the cases, the indication for revision was pain in the area of the implanted stimulator.[16] This is despite the fact that we already implanted the smallest device (Medtronic Interstim2, model 3889). The other revisions were because of recurrence of symptoms. Important to note is that the present population is very young and active, which may partially explain the higher lead revision rate when compared to adults.[21] Another factor that may be of influence is the fact that these young patients are still growing, affecting lead position.[22] The majority of relapses that could not be resolved by revision occurred during the first year after implantation. Possible explanations for such relapses include gradual adjustment of the pelvic floor and colon to the new stimulation or weaning of an initial placebo effect or other psychological phenomenon.

For fecal incontinence, SNM appeared to be cost-effective.[10,23] For constipation, these analyses have not been performed yet. The high costs associated with the technique make funding more problematic, which probably contributes to the fact that this treatment is not commonly used. The direct costs from the electrode and the stimulator are approximately 8000 euros.[24] Childhood constipation is a common problem and brings a great economic burden to the public health system.[25] The study by Liem *et al.* reported that in the USA, the yearly costs of children with constipation were three times

higher than those of children without constipation.[26] So, adequate treatment of this condition potentially leads to a major reduction in costs due to frequent admissions. For a treatment to be cost-effective, the effect on symptoms and quality of life needs to be taken into account. Unfortunately, from the patients in this study, no data on quality of life before treatment are available. However, in general, the quality of life seems to be impaired in children with constipation.[27] Therefore, it is promising to see that after SNM, quality of life was only 6 points lower than in the general population (on a scale from 0 to 100), especially considering the fact that this group at baseline suffered from the worst complaints in the spectrum.

A major limitation of our study is its observational, noncomparative nature. Causally attributing the improvement in symptoms that we observed to the SNM therefore critically hinges on the assumption that, in the absence of treatment, no such recovery would have occurred. In a survey conducted among residents of Olmsted County, MN, aged 30–64 years, Talley *et al.* (1992) studied the onset and disappearance of symptoms consistent with functional gastrointestinal disorders, including constipation. They found that 89 % of the population surveyed had no change in their symptoms during a period of 12–20 months, suggesting a relative stability in this patient population.[28] Similarly, we cannot exclude the possibility that at least part of the observed improvement may result from a nonspecific placebo effect.[29] To explore these issues further, a randomized, double-blind trial is currently prepared in our center, comparing SNM with sham SNM in children and adolescents with chronic constipation refractory to conservative treatment. A debate among healthcare professionals, patients, and commissioning organizations on the question whether such a study would be appropriate and ethically acceptable is necessary. In such a study, attention should be addressed to the fact that studies on SNM with an observational design encounter the problem that patients who do not benefit from the treatment and proceed to other treatments are lost to follow-up and therefore in the long-term selection takes place. A recently performed review of the literature clearly stated that although SNM appears to be an effective treatment for constipation, larger studies with longer follow-up are needed.[15] An important issue would be to explain heterogeneity in treatment response, allowing for better counseling of patients or patient selection. Clearly, this would require numbers of patients usually not enrolled in single-center studies. To allow for pooled analysis of data from multiple studies in the future, standardization in definitions, assessments, and reporting is vitally important.

In conclusion, for this group of adolescent patients with severe complaints of constipation resistant to conservative treatment, SNM is an effective treatment with beneficial effect on defecation frequency and abdominal pain.

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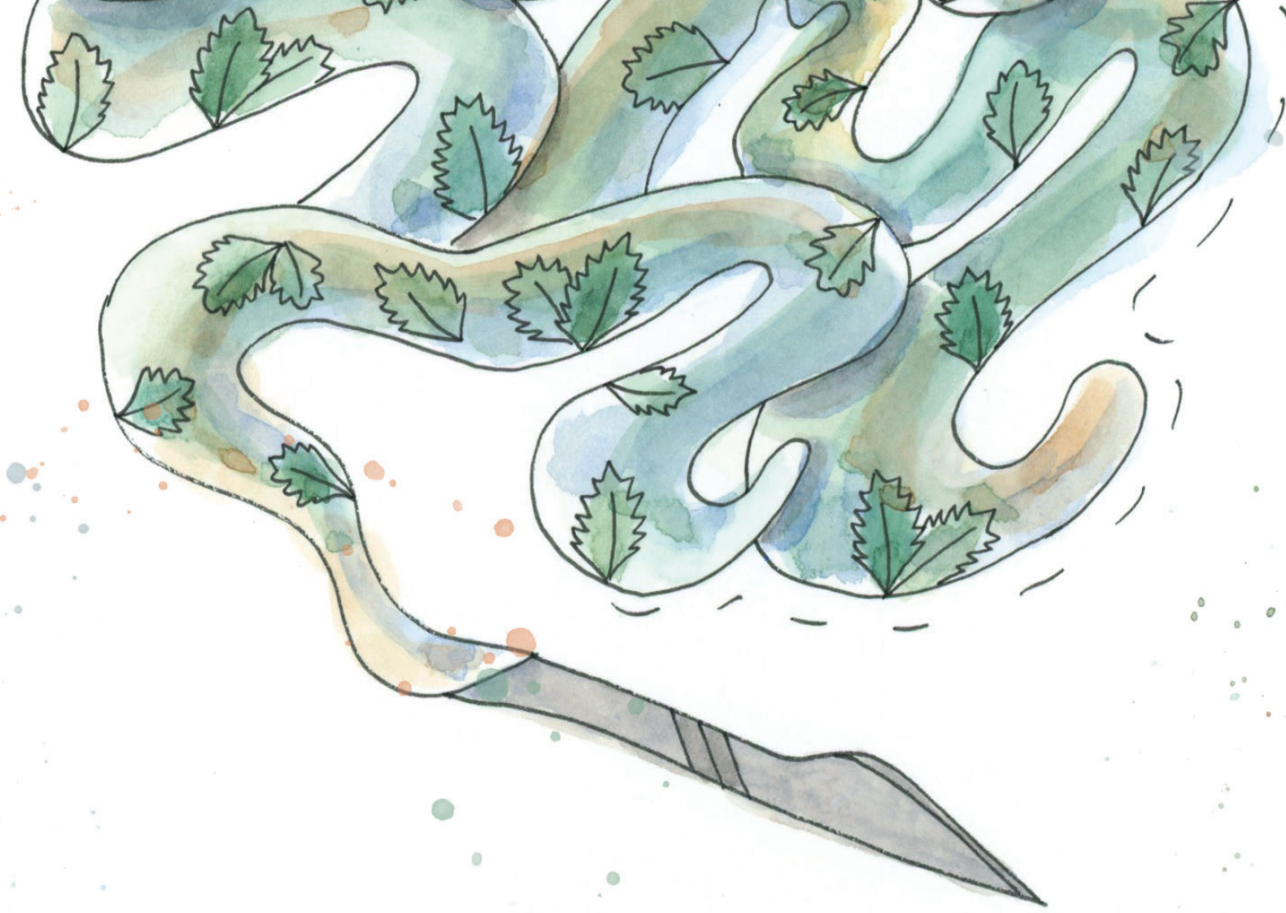

# Chapter 7

## THE ARTIFICIAL BOWEL SPHINCTER IN THE TREATMENT OF FECAL INCONTINENCE, LONG-TERM COMPLICATIONS

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## ABSTRACT

Background
Fecal incontinence is a common and debilitating condition, of which the prevalence increases with age. Several medical and minimally invasive treatment modalities are available. However, for patients with greater sphincter defects, these treatments are often not sufficient. For these patients, the artificial bowel sphincter could be an alternative to colostomy. The artificial bowel sphincter has proven to be effective in the short term. Less is known whether the benefits sustain over time.

Objective
The aim of this study was to assess the long-term outcome of the artificial bowel sphincter in patients with refractory fecal incontinence.

Design
A retrospective record review was conducted in conjunction with questionnaires.

Setting
This study was conducted in a tertiary hospital setting.

Main outcome measures
The primary end point was any complication. The secondary end point was fecal loss.

Patients
The patients included were adults experiencing severe fecal incontinence treated with artificial bowel sphincter, operated on between 1997 and 2014.

Results
Sixty-three patients were included in this study. After a median follow-up of 57 months (range, 1–198), the device had been explanted in 31 patients (49.2%; 95% CI, 36.5–62.0). In total, 101 reoperations were conducted, ranging from 1 to 6 reoperations per patient. The main reasons for revision were device failure and infection. At 5 years follow-up, 80% of the cohort had experienced a complication requiring surgery. Twenty-two (35%) patients had restored continence.

Limitations
This study was limited by its retrospective design and subjective secondary outcome.

Conclusion

Patients with severe end-stage fecal incontinence can benefit from artificial bowel sphincter, but this requires a large number of reoperations, and at least 20% of patients will eventually have a colostomy. Therefore, careful patient selection and the involvement of patients in decision making regarding the potential benefits and limitations of this technique are paramount.

# INTRODUCTION

Fecal incontinence (FI), defined as the involuntary or uncontrolled loss of solid or liquid stool, is a common condition with a reported community prevalence ranging from 2% to 21% (median 7.7%).[1] It usually results from an interaction of multiple mechanisms, including stool consistency, sphincter weakness, loss of sensation, and impaired distension compliance of the rectum. These may be the result of obstetric or surgical injury, inflammation or irradiation, and aggravated by aging.[2] Fecal incontinence strongly impairs quality of life by interfering with daily activities and by causing embarrassment, depression, and social isolation.[3,4] A combination of dietary and medical management and pelvic floor rehabilitation is recommended as first-line therapy for patients with FI.[5]

Nowadays, for patients not responding to either of these treatments, sacral neuromodulation (SNM) is a minimally invasive surgical option. In contrast to the minimally invasive surgical approach, more invasive surgical solutions such as the artificial bowel sphincter and dynamic graciloplasty (DGP) have previously been applied.

The artificial bowel sphincter (ABS) is usually reserved for patients with extensive sphincter destruction, congenital malformations, and neurogenic incontinence from spinal cord injury.[5] The successful use of an ABS was first reported by Christiansen and Lorentzen[6] in 1987. They used an artificial urinary sphincter in a patient with severe anal incontinence and myasthenia gravis who was reluctant to undergo a colostomy. Since then, several studies have been conducted, but with mixed results.[7,8] From our own institute, we previously reported the results with ABS in a cohort of 33 patients with a mean follow-up of 17.4 months.[9] In this study, we report our results with a larger cohort of 63 patients with extended follow-up of a median of 57 months.

## METHODS

Patient Selection

The medical records of a consecutive cohort of patients who underwent an ABS implantation at Maastricht University Medical Center during the period from 1997 to 2014 were reviewed using standard forms. At the time of the treatment, ABS was considered as standard care in our hospital. Therefore, the medical ethics review committee concluded that the Medical Research Involving Human Subjects Act does not apply to this study. Oral informed consent was obtained from all patients after an explanation of the procedure and possible complications.

Preoperative examination consisted of defecography, endoanal ultrasound, and anal manometry. All patients underwent medical treatment and pelvic floor physiotherapy as a first treatment step. In case of sphincter defects of less than one-third of the circumference, the next step in the treatment algorithm was SNM. In case of large sphincter defects, patients were eligible for ABS. However, patients who had undergone SNM and DGP with unsatisfactory results were also eligible for ABS. This illustrates the severity of symptoms in this population with end-stage severe FI. For many, ABS is considered as a last resort to avoid colostomy, at least for a period of time. Patients were not eligible for implantation of ABS in the case of a cloaca-like deformation or insufficient length of the perineum for adequate closing.



Surgical Procedure

An Acticon ABS (American Medical Systems, Minneapolis, MN) was used in all patients. The surgical technique and implantation in our hospital has been described in detail previously.[10] In brief, the ABS implant consists of an inflatable balloon, a cuff, and a pump. Thirty minutes before incision, systemic antibiotic prophylaxis is started and continued until 2 days postoperatively. Perioperatively, local antibiotics are administered in the wounds. The cuff is placed around the anus by using 2 lateral incisions. The size of the cuff is chosen based on circumferential length around the rectum and width. The pump is placed in the labium majus or scrotum, and the pressure-regulating balloon is placed in the cavum Retzii.

Initially, the device is left inactive after the operative procedure to allow the wound to heal. Patients are discharged after 3 to 4 days. After 4 weeks, the device is activated in the outpatient clinic and the patient receives instructions for proper use.

Follow-up

Patients had follow-up at 3, 6, and 12 months after implantation and yearly thereafter. At these visits, clinical evaluation was performed. Any additional treatment including the use of laxatives and bowel irrigation was recorded. Also, data on any reoperations were collected, including reason and type of operation.

The primary end point was any complication, according to Clavien-Dindo classification[11], including the frequency of the revisions of surgery due to device failure or infection. This end point was chosen because previous research and our own experience had already shown that ABS can be a beneficial treatment in some patients, but tends to be accompanied by major morbidity. Definite explantation and reimplantation were recorded as device revisions. When the removal of the device and the implantation of a new device were performed during the same procedure, this was considered as a single revision.

A secondary end point was fecal loss as judged by the patients. All patients were queried about the extent in which fecal continence was restored since implantation of the ABS, about sensation of opening and closing of the cuff, and about the presence of pain in the area of the ABS. In case of persisting symptoms, proper functioning of the device was assessed by digitation.

Statistics

Descriptive statistics were used to characterize the patient population in terms of age, sex, and etiology. Kaplan-Meier survival analyses were used to calculate proportions of patients who remained event-free over time. A separate analysis was conducted with colostomy formation as the end point. Explorative subgroup analyses were conducted for patients with an obstetric etiology of FI. All analyses were conducted using SPSS version 2.1.

## RESULTS

Demographics, Etiology, and Prior Surgical Treatment for FI

Sixty-three patients had an ABS implanted at our center between April 1997 and November 2013 and were included in this study. Fifteen were male (23.8%) and 48 were female (76.2%); mean age at implantation was 54.8 years (range, 23–76). Median follow-up was 57 months (range, 1–198). Nine patients (14.3%) were lost to follow-up (Table 1).

*Table 1: Outcomes after ABS*

| Outcomes | | No of patients |
|---|---|---|
| Restored continence | With ABS alone | 15 |
| | Constipation treated with bowel irrigation | 4 |
| | Constipation treated with laxatives | 2 |
| | After ABS explantation | 1 |
| Persistent incontinence with ABS | With ABS alone | 4 |
| | With bowel irrigation | 7 |
| No ABS in situ with no further treatment | | 8 |
| Dynamic graciloplasty | | 4 |
| Colostomy | | 9 |
| Lost to follow up | | 9 |
| Total | | 63 |

All patients experienced FI resistant to previous treatment. In most patients, FI originated from obstetric trauma (41 patients, 65.1%); in 7 patients the incontinence had a congenital origin, 6 patients had exogenous pelvic floor trauma, and 9 patients had symptoms of an iatrogenic origin (in 7 patients, resulting from surgery; in 2 patients, resulting from a combination of surgery and radiotherapy). Thirty-nine patients (61.9%) had previous surgical treatment: 17 (43.6%) patients had SNM, 10 (25.6%) had anal repair, 3 (7.7%) had DGP. One (2.7%) had anal repair and DGP, 7 (17.9%) had anal repair and SNM, and 1 (2.7%) had DGP and SNM.

Revisions

Figure 1 shows a graphic overview of the number and types of reoperation and the distribution of the patients within the cohort. The flow chart in Figure 2 shows the numbers of patients receiving 1 up to 6 reoperations. From the total cohort of 63 patients, 12 patients (19.0%, with mean follow-up of 43.4 months) had no reoperation.

Of the 51 first reoperations, 31 patients had the device revised, in 17 patients the ABS was removed, and 3 patients had a colostomy. In 3 patients, a new ABS was implanted. A total of 46 patients still had an ABS in situ after the first reoperation (63 – 3 – 17+3). A revision could consist of the proper placement of the cuff or the pressure balloon, reconnection of the tubes, and replacement of one or more parts of the device, for example a leaking cuff.

Most patients had 1 reoperation (25 patients, 39.7%); 14 (20.6%) had 2 reoperations, 6 (9.5%) had 3 reoperations, 2 (3.2%) had 4 reoperations, 2 (3.2%) had 5 reoperations, and 2 (3.2%) had 6 reoperations. In total, 101 reoperations were performed. Indications for reoperation were device failure (51.7%), infection (29.2%), recurrence of symptoms without signs of device failure (9.0%), constipation (2.2%), and pain (6.7%).

Perioperative Surgical Complications

In 1 patient, the rectum was perforated during the placement of the cuff. The procedure was discontinued and the device was not implanted. A temporary ileostomy was created, and, after the perforation had healed, in a second attempt, the ABS was implanted.

Outcomes of ABS

Table 1 shows the functional outcomes of ABS in this cohort. Twenty-two (34.9%) patients had restored continence. However, 2 of these patients used laxatives to treat constipation that developed after the ABS implant, and 1 patient remained continent after ABS explantation. Another 4 patients experienced such severe constipation after ABS implantation that retrograde bowel irrigation was needed. Eleven patients had persistent incontinence after ABS, of which 7 patients used bowel irrigation to treat symptoms.

In 31 patients (49.2%) the device was explanted. In 1 additional patient, the device was explanted because the rectum was perforated perioperatively, and, after a discussion with the patient, a permanent stoma was created. Of these 31 patients, 12 did have a new ABS implanted at some point.

Reasons for removal of the ABS were infection (n = 21), device failure (n = 2), recurrent symptoms of FI (n = 5), pain (n = 2), and constipation (n = 1). After removal of the device, 9 patients had colostomy (apart from the 1 patient mentioned above) and 4 had a DGP (Table 1). Five of these patients with explanted ABS performed retrograde washouts to treat the FI; in 2 patients, symptoms had resolved, and 1 patient was treated conservatively.

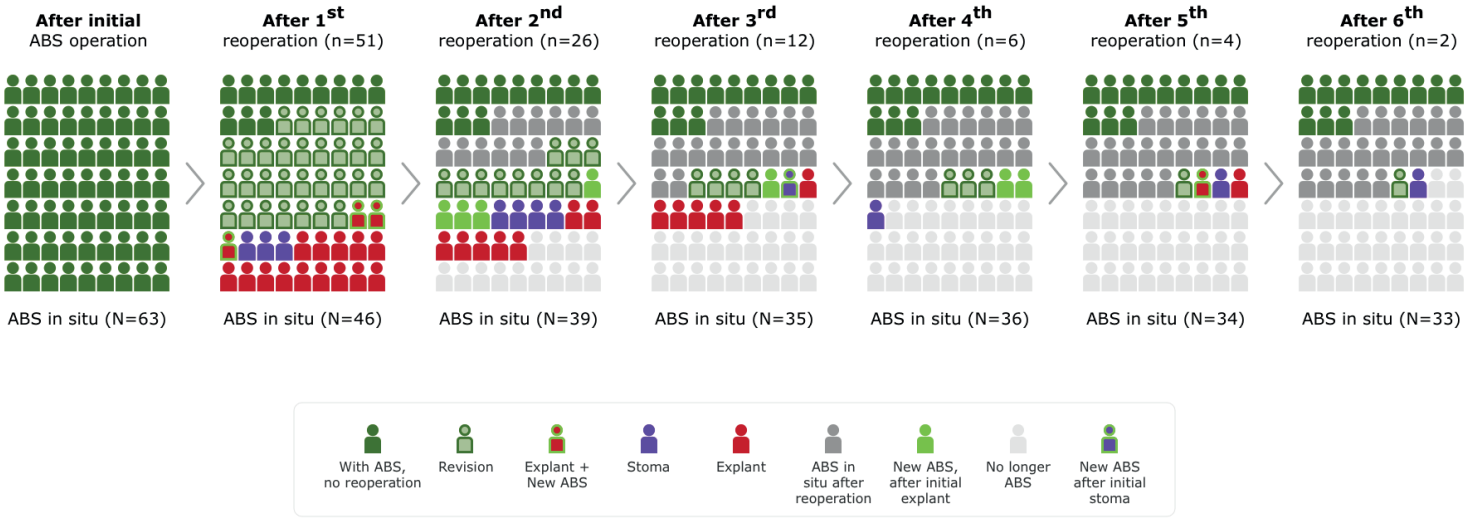


*Figure 1: Overview of the number of reoperations (n), specified by type. Revision is the reoperation on the ABS device in situ, possibly with replacement of some parts. Explant + new ABS is the explantation of ABS and implantation of new ABS in 1 session. Stoma is the explantation of ABS and creation of a permanent stoma. Explant is the explantation of ABS. New ABS, after the initial explantation is the implantation of a new ABS after a previous ABS has been removed. ABS = artificial bowel sphincter; n = number of reoperations performed; N = number of patients who still have active ABS.*

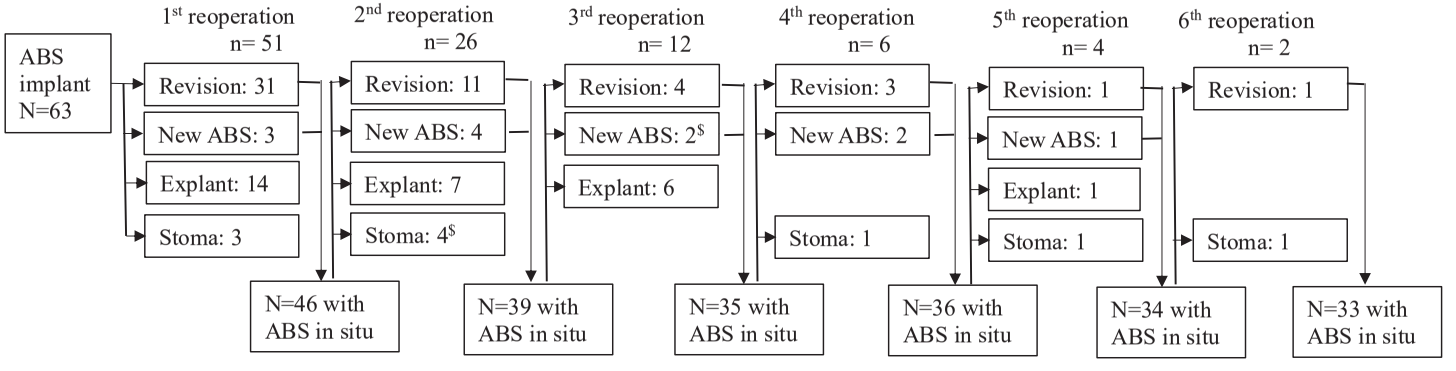


*Figure 2: Flow chart of reoperations and number of patients. New ABS is the implantation of a new ABS after a previous ABS has been removed. Explant is the explantation of ABS.* [a] *One of these patients with a stoma did eventually have a new ABS implanted, registered under 3rd reoperation. ABS = artificial bowel sphincter; n = number of reoperations performed; N = number of patients who still have active ABS.*

Survival Analysis

Figure 3 shows the results of the survival analysis with "complication requiring surgery" as the end point. These included complications requiring revision of the device, explantation of the device, either or not followed by colostomy or implantation of a second device. The results show that, at 5 years follow-up, approximately 80% of the cohort underwent surgery for this indication. In Figure 4, the results of the survival analysis for the end point colostomy are shown. After 5 years of follow-up, 18% of the patients in the cohort underwent a colostomy. Figures 5 and 6 show the results of subgroup analyses for obstetric versus other etiologies. The subgroup of patients with obstetrical etiology fared better than the other patients in terms of complications requiring surgical revision and explantation of the device.

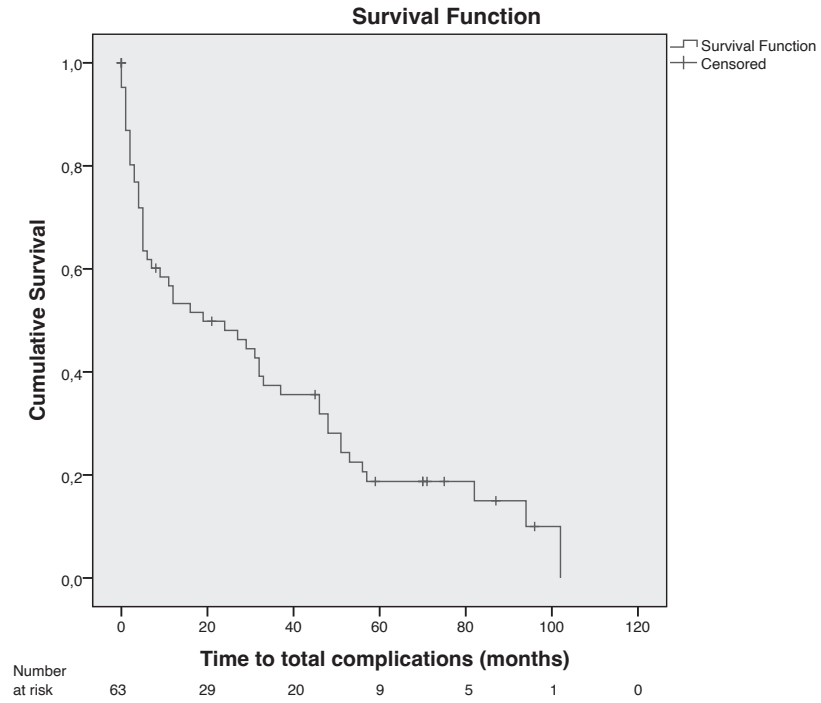


*Figure 3: Kaplan-Meier curve. Time to event; event defined as any complication requiring surgery.*

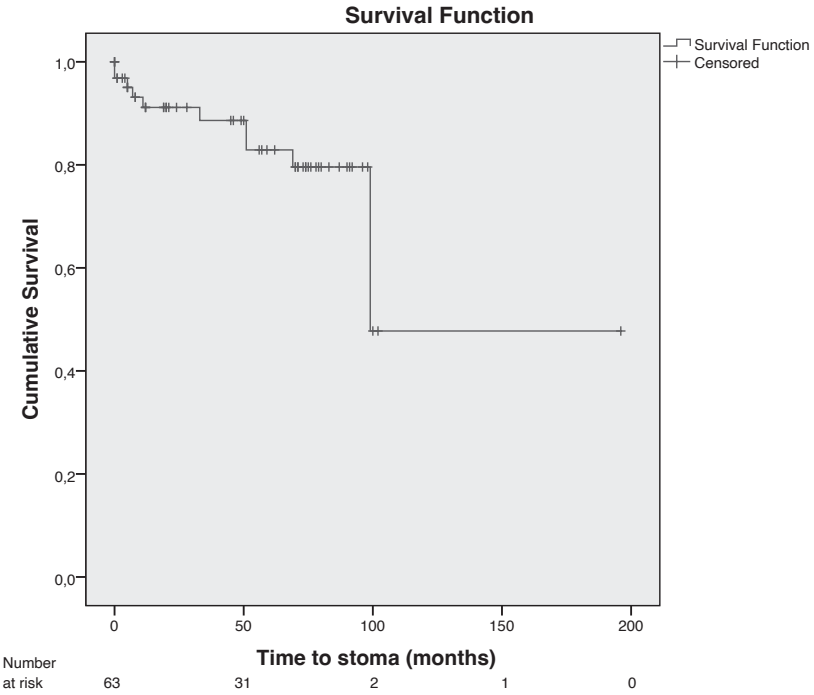


*Figure 4: Kaplan-Meier curve. Time to event; event defined as formation of colostomy.*

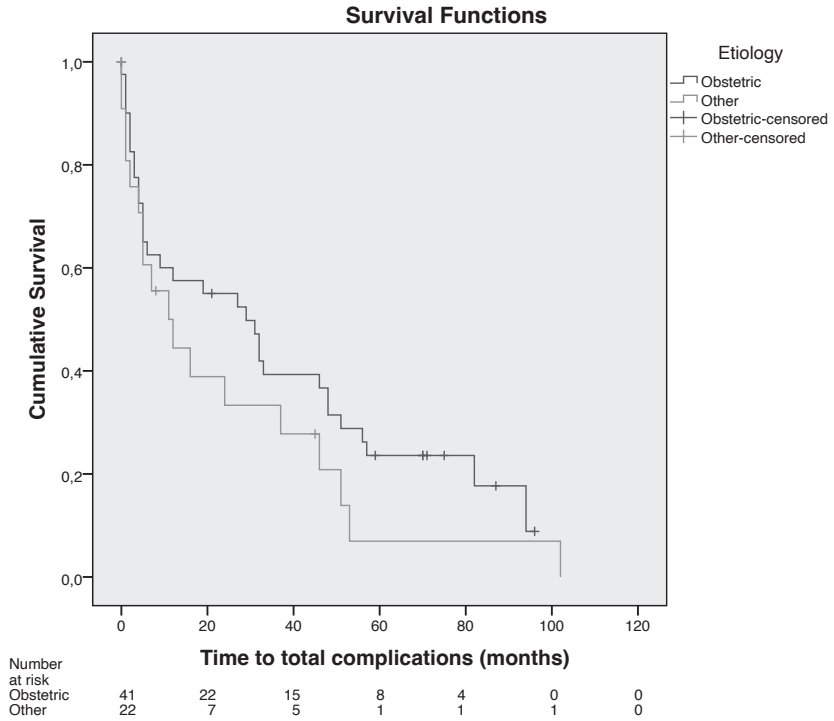


*Figure 5: Kaplan-Meier curve. Time to event; event defined as any complication requiring surgery. Patients divided in 2 groups based on etiology obstetric versus other.*

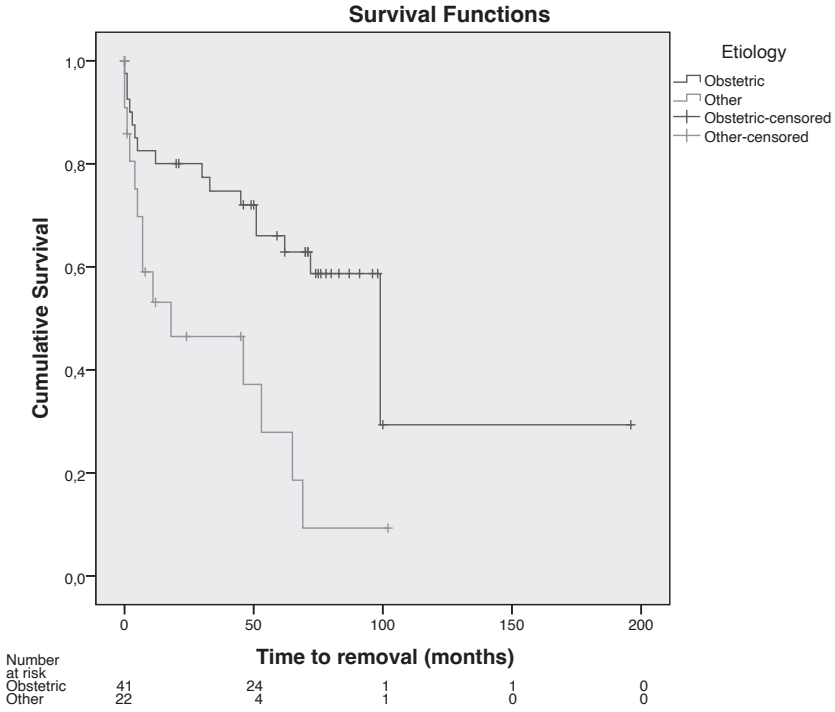


*Figure 6: Kaplan-Meier curve. Time to event; event defined as explantation of the artificial bowel sphincter. Patients divided in 2 groups based on etiology obstetric versus other.*

## DISCUSSION

The key finding of this study is that our long-term results with ABS in the treatment of FI were considerably poorer than initially expected. A drawback of this study is its retrospective design. This also resulted in the fact that no consistent and objective outcome parameter was used to assess secondary outcome, fecal loss.

The outcome parameters as described in Materials and Methods illustrate one of the problems encountered with the technique of the ABS. Being a rather static solution to a dynamic process, the ABS has to be able to close firmly enough to prevent incontinence, but also be able to open properly to facilitate defecation. In case of the recurrence of symptoms, the cause can be a technical problem, such as dislocation of the cuff or leakage of the ABS system. In some cases, this can be confirmed by digital examination or x-ray. When this appears not to be the case, recurrence might be caused by other factors influencing these symptoms, such as stool consistency or pelvic floor function. Being one of the last treatment options for these patients, in many cases, a pragmatic choice is a revision of the ABS system to pursue the improvement of symptoms. This leads to the situation of "recurrence of symptoms without signs of device failure," in which ultimately could be opted to a revision of the ABS anyway. This revision could include implantation of a smaller cuff or just proper positioning of the cuff. From the current cohort, exact data on the extent of each revision (if for example only cuff or balloon was replaced) are unfortunately not available. Although this study focused on the long-term results of ABS, Figure 3 illustrates how revisions occur over the entire period of follow-up. In this light, the study by Wexner *et al*[12] provides interesting additional information, reporting on a group of 51 patients treated with ABS, of which 35.3% became infected in the early stage (<6 weeks after implantation) and 5.9% in the late stage, but late-stage complications continued to increase with time.

The technique of the implantation of the ABS is complex, with many different steps and meticulous maintenance of sterile conditions. Therefore, we have to consider the learning curve associated with this technique. This learning curve could be assessed by comparison of groups from different time periods. However, this goes beyond the scope of this study, and the number of patients in this study would be insufficient for such analysis. Next to technique, patient selection is probably of major impact on success rates as well. In our current cohort, a few oncological patients are included. Some underwent radiotherapy that may cause scarring and may augment surgical complications. Therefore, the risk of infection is probably increased on top of the innate problem of implanting prosthetic material in the anorectal region. Also, the previous treatments for FI, including DGP, illustrate the complexity of this group of patients.

Patients are desperate to control FI, and ABS is often a last resort to avert colostomy. However, the results of this study and others suggest that the long-term outcomes of ABS are disappointing, making it uncertain whether it is truly beneficial to the patient.[8] Moreover, it is questionable whether colostomy worsens patients' quality of life in the way and to the extent it is believed to do. In a Cochrane review, this traditional assumption is challenged because 14 of 35 studies found no significant difference in quality of life between patients with or without a stoma after rectal cancer surgery.[13]

Current Guidance in Need of Revision?

According to the most recent guideline from the National Institute for Health Care and Excellence from 2012, patients with FI, in whom a trial of sacral nerve stimulation has been unsuccessful, can be considered for a neosphincter.[14] Given the accumulating evidence of long-term complications associated with a neosphincter, these guidelines may be in need of revision.[15] Because of our own experience with ABS, we decided that ABS should no longer be offered to patients with FI. On top of that, the production of the device has ceased.

Another question is to what extent do we have to avoid creating a colostomy? According to the National Institute for Health Care and Excellence guideline, a colostomy is still seen as a last resort. It should only be considered if all nonsurgical and surgical options failed or were not indicated. However, the International Consultation on Incontinence guideline states, "Colostomy should not be regarded as a treatment failure but rather a reasonable treatment option for patients whose lives are restricted by fecal incontinence that is not amenable to other therapies or not suitable for more complicated surgical procedures."[16] Data on the effectiveness, perioperative complications, and impact on the quality of life of colostomy for patients with FI are sparse, because colostomy is generally considered as a failure of treatment. The few primary studies available show positive results, and discussing the option of a colostomy with patients with FI is suggested.[17,18] In the field of colorectal oncology, several studies showed that, in terms of quality of life, sphincter-preserving anterior resection is not necessarily superior to colostomy.[13,18] Of course, these results are dependent on population characteristics, pretreatment continence, level of the anastomosis, and use of questionnaires.

Novel Approaches on the Horizon and Evidence Requirements

In addition to lifestyle management, medical therapy, anal plug and anal insert device, physical therapy, SNM, posterior tibial nerve stimulation, and internal anal sphincter support, a number of innovative approaches to the treatment of FI are being developed.[20-22] Novel treatment approaches include anorectal transplantation[23], biomimetic devices with sensory feedback[24], implantation of autologous myoblasts

into the external anal sphincter[25], neurostimulated levator augmentation[26], and novel variants of the artificial anal sphincter[27-29]. In addition, the magnetic anal sphincter is a new development with a mechanism of action similar to ABS. The initial results of the magnetic anal sphincter are promising, and it appears to be as effective as ABS and is associated with fewer complications.[30,31] Unfortunately, it appears that this device is also currently off the market.[32] Some of these new treatments are still of an experimental nature, and a major challenge will be to produce evidence of the safety and clinical- and cost-effectiveness of these innovations. The relevant question is whether such innovations should be preferred over colostomy. The most robust evidence to address this question would be derived from a randomized controlled trial, randomly allocating patients with FI refractory to colostomy or the innovative approach. However, producing evidence of the added value of these surgical innovations by conducting such trials unfortunately would be unethical and probably unfeasible or, at least, quite challenging.

## CONCLUSION

The key finding of this study is that our long-term results with ABS in the treatment of FI were considerably poorer than initially expected. About one-third of patients had restored continence with ABS and approximately half of the patients will have a colostomy in the long term. Although some might still consider that this outcome justifies the operation, we need to take into account the very substantial number of complications requiring surgical intervention along the way. Therefore, careful patient selection and the involvement of patients in decision making regarding potential benefits and limitations of this technique are paramount.

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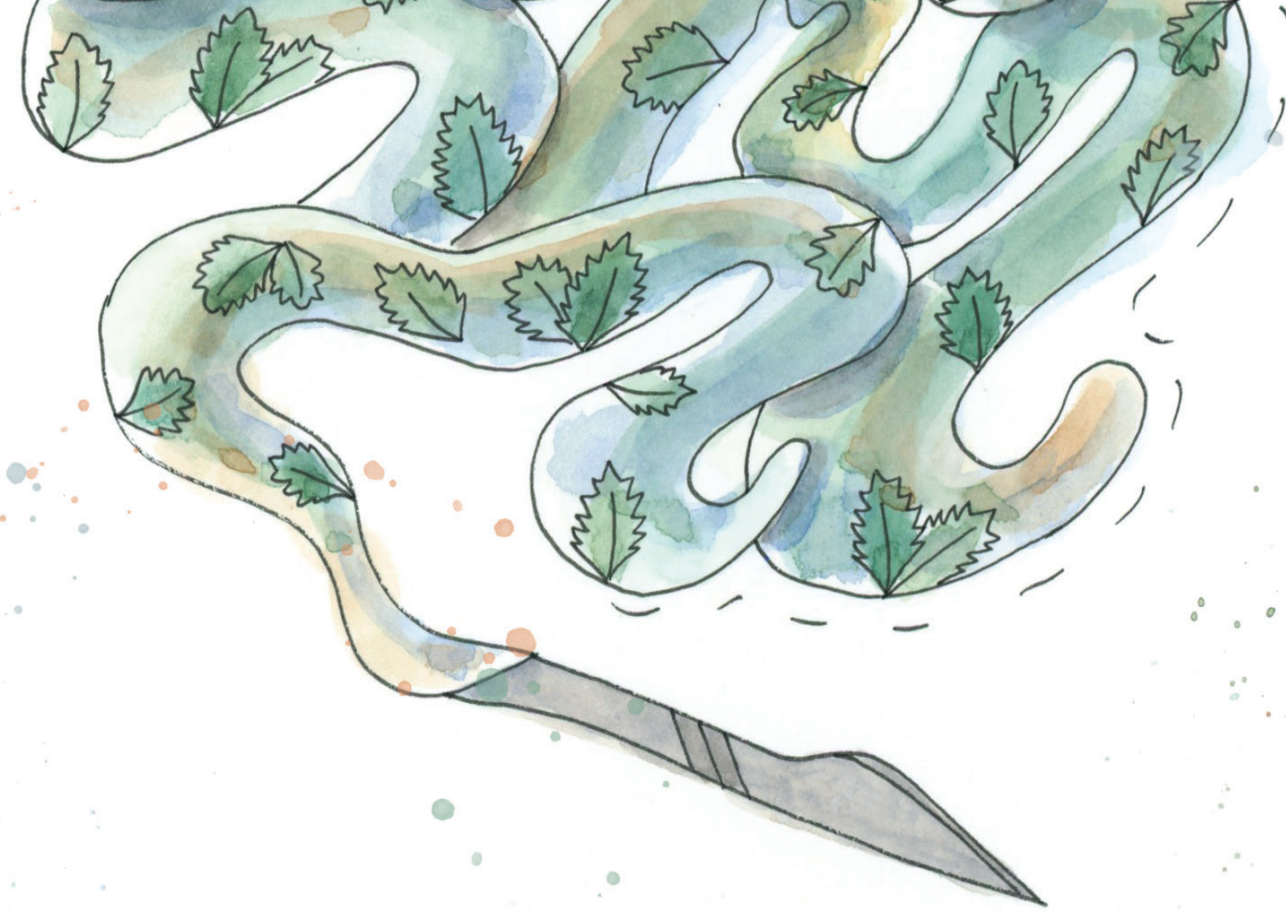
# Part 3

## CONCLUDING REMARKS



# Chapter 8

## GENERAL DISCUSSION

# GENERAL DISCUSSION

In this thesis we investigated different ways of quantifying outcome measures in the field of functional bowel disorders. Patients suffering from DGBIs will frequently consult a gastroenterologist. The therapeutic options for these disorders are characterized by the lack of biomarkers and by the fact that there is no single effective therapy that is suitable for all patients.

Patient Reported Outcome Measures (PROM) are currently used to measure the health status from a patient perspective and thus to provide insight into the burden of a disease. Within the field of IBS, there are different PROMs available to measure the symptoms and severity of the disease. In this thesis, we focused on the EQ-5D-5L which is a questionnaire that measures general health related quality of life (HRQOL) and is used within economic evaluations whereas a condition-specific HRQOL instrument for measuring specific IBS complaints, is the IBS-QoL.[1–3] Symptoms of IBS have a large impact on health-related quality of life and are associated with a considerable use of health care resources. The IBS-QoL is an instrument that contains specific domains that are relevant for IBS patients and these are not represented in the EQ-5D-5L, such as 'food avoidance' and 'social reaction'. These specific domains are particularly relevant for these patients and capture the psychological well-being among IBS patients.[4] In **Chapter 2**, we concluded that these instruments are both responsive in capturing HRQOL changes regarding patient- and disease characteristics. Nonetheless, IBS-QoL contains specific domains for IBS patients, such as 'dysphoria', 'body image', 'food avoidance', 'social reaction' and could therefore be more favorable when different aspects of the disease are required to be addressed during a clinical study. However, to assess the cost-effectiveness of a new treatment, the EQ-5D-5L is necessary for the calculation of the Quality Adjusted Life Year (QALY). Therefore, we developed a mapping algorithm where the IBS-QoL, a condition-specific questionnaire, could be transformed in utility values. This is the first study that enables the estimation of utility values from IBS-specific questionnaire scores. Our algorithm contained the total IBS-QoL score and squared IBS-SSS score, when using the CLAD model. In previous mapping studies, in only 20% a clinical measure was included in the analysis.[5] Including important covariates (e.g., disease characteristics, sociodemographic variables), could lead to more accurate prediction of utility values and is recommended in guidelines.[6]

This mapping algorithm is useful for modeling studies when only studies using the IBS-QoL can be found and in trial-based economic evaluations to estimate QALYs.

During patient consultation, the clinician and patient discuss different treatment options and their pros and cons. Multiple appropriate treatments are available for a patient with a functional bowel disorder. By analyzing and determining which factors are important in the management, treatment efforts can be tailored to individual needs and preferences. Previous studies showed that patients with IBS-D were willing to accept higher risks of serious adverse effects of the therapy, if their symptoms improved.[7,8] Besides, they were willing to pay significant monthly costs.[9] Previous studies in IBS patients have not yet addressed the treatment preferences of patients. Qualitative research is an important step to examine which aspects of treatments are considered important by patients and to reveal the social context and identify patients' perceptions.[10,11] Therefore, we performed qualitative driven research in **Chapter 3** that explored which aspects of treatment are important for patients during decision-making on individual basis. By performing semi-structured interviews with patients, in-depth exploration of the IBS treatment options and previous experiences was achieved. This qualitative method has the advantage, compared to focus groups, that participants are more willing to talk about sensitive subjects involving bowel movements during the one-on-one interviews. In total nine attributes were revealed: effectiveness, time until response, cessation of response, side effects, location, waiting period, treatment burden, frequency of healthcare appointments and willingness to pay. The most important aspects, based on Likert scale scores, were effectiveness, duration of response, side effects and treatment burden, according to patients.

Also, we enlightened differences between patients and physicians by sending questionnaires to physicians specialized in the care of DGBIs. Time to response, location and waiting time were less important for patients compared to physicians. This discrepancy addresses the gap between patient and providers and is crucial for shared-decision making during consultation.

The qualitative research provided important information about what patients considered important and their perceptions. However, to explore treatment preferences and estimate the trade-offs between these relevant attributes in IBS patients, quantitative research such as a DCE is necessary. In **Chapter 4** we reported that dietary interventions were the most preferred treatment among 185 IBS patients from the MIBS cohort. Pharmacotherapy was the second preferred therapy, followed by psychotherapy. The popularity of dietary interventions may be explained by the few risks and side effects of the treatment and the ability for patients to retain greatest control. Moreover, the current ongoing promotion of a healthy lifestyle, could also have contributed to this preference. The discrete choice experiment also revealed that patients preferred a higher effectiveness, shorter time interval to response, longer

time interval until recurrence, no severe side effects and frequent appointments when attending psychotherapy. Moreover, we found specific factors that influenced this preference, such as age of the patient and the potential presence of anxiety. Subgroup analysis showed that younger people (<50 years old) generally preferred dietary intervention and preferred a long duration until recurrence of symptoms, whereas older patients tend to be more willing to choose for pharmacotherapy. Younger patients were more likely to accept psychotherapy than older patients. Analysis between all different IBS subtypes showed no significant preferences. The results from this cohort study provide guidance for which aspects of management could be discussed with your treatment-seeking patient to pursue the optimal personalized management. However, a limitation of our study is that the size of the subgroups were small and therefore the results of the subgroup analysis should be interpreted with caution. Whether treatment preferences differ between the IBS subtypes, could be interesting for future studies to address.

The strengths of a DCE

Measuring benefits of therapeutic options have concentrated on the use of clinical outcomes (PROs) and QALYs. However, benefits of a health care intervention are proven to be multi-factorial, incorporating also process characteristics (e.g., treatment burden, location) and non-health outcomes. Also, costs or the willingness-to-pay can affect the choice of therapy. However, willingness-to-pay is a complex aspect of the health care system, because of the substantial heterogeneity in the healthcare systems worldwide as well as the specificities of the reimbursement rules for certain therapies, and additional non-obvious costs (out-of-pocket costs).



Therefore, the utility (benefit) of an intervention consists not only of health outcomes.[12] Patients are willing to trade changes in health outcome with other characteristics of a therapy that contribute to patient satisfaction.[13] Identifying these process attributes are relevant for examining individuals' preferences.

An appropriate technique to examine treatment preferences and their trade-offs, is the use of a discrete choice experiment.[14] A DCE is the most commonly used method to quantify patients' preferences within health care.[15] This method allows the integration of patients' values on all aspects of care in one measure. Because the respondent can only choose one option each time a choice is offered, patients are required to make a trade-off between the benefits and potential disadvantages. DCEs quantify decision weights indicating relative utility for both treatment attributes, as well as the treatment option as a whole. Moreover, with a DCE the preferences of relevant subgroups can be examined and thus information about specific patient characteristics influencing

a patients' preferences for a treatment can be revealed. The hypothetic scenarios or choices simulate a real-world situation where treatment attributes do not appear in isolation, but are closer to the choice of patients.[16] Previous studies have reported that the external validity of DCEs is satisfactory to predict actual healthcare choices.[17] Considering the fact that patient preferences are essential in patient satisfaction, this significantly affects compliance and ultimately clinical outcomes, DCE-measured preference data are more patient-centered than QALYs.[13] Using this data during shared-decision making with patients suffering from functional bowel disorders are therefore of great significance, where no therapy suits all patients. DCEs may also be valuable for the management of constipation and fecal incontinence.

Surgical interventions

In **Chapter 6** we described the efficacy of sacral neuromodulation in adolescent patients suffering from constipation. Our results showed improvement in symptoms, mostly also sustaining over time. However, the long-term results of the MACE (described in **Chapter 5**) were disappointing due to the high rate of complications, revisions and side effects during treatment. The complication-, explant- and revision rates of the artificial bowel sphincter, described in **Chapter 7** were high, and the number of patients who restored continence was low, resulting that the ABS is no longer prescribed as surgical treatment option in fecal incontinence patients. Other possible surgical management options are a sphincteroplasty and a colostomy for the treatment of fecal incontinence.[18] Colonic resection may be another, more definitive, surgical treatment option for patients suffering from chronic constipation where first line treatment was not deemed sufficient.[19] Potential benefits and limitations should be thoroughly discussed with patients to manage expectations of treatment options. Therefore, it is extremely important to involve patients in decision making regarding their disease management.

Performing a discrete choice experiment for the management of fecal incontinence and constipation would be relevant, not only to reveal preferences for existing therapies but also for the uptake of novel therapies. An example is a previous conjoint analysis that investigated the preferences of IBS patients for the management of acute pain.[20] The results of this study showed that patients prioritize efficient medications and avoidance of nausea and constipation and are also willing to use a rapid-acting subcutaneous treatment. Currently, no specific therapy is available for the treatment of acute pain in IBS. Consequently, DCEs also allow for preference measurement on future interventions including those that may not be currently available. The results from a DCE are not only relevant for health care decision-makers, but also for developers of novel therapies.

Relevance of preference research

The identified patient preferences and treatment aspects, as reported in the studies from **Chapter 3 and 4**, can be used to inform physicians in their daily interaction with patients. This is relevant during shared-decision making with patients suffering from functional bowel disorders. A treatment choice reaches far beyond mere clinical efficacy but should also be informed by other aspects relevant to patients, including side effects and potentially costs. The most appropriate treatment option for functional bowel disorders is not immediately clear, not for clinicals nor for patients, as there are multiple suitable therapies available. Discussing patients' wishes and preferences, forces the way to a better compliance with the prescribed treatments and this is crucial for management success.[21,22] The treatment will be optimized and personalized towards individual needs. A higher management success in patients with functional bowel disorders will eventually lead to a higher HRQOL and less health care costs. Thus, patient preferences play a critical role in patient-centered decision making.[13,23,24]

Implications for clinical practice

An important aspect of decision making is a strong patient-provider relationship. This requires good communications skills, especially in patients with DGBIs.

In the past, the paternalistic approach was widely practiced, meaning the system of doctor-centered care. Nowadays, patients are more involved in decision-making and the patient is considered the source of information. This type of care where patient participation is active and doctors respond to patient cues, is referred to as patient-centered care.[25]

During consultation of a DGBI patient, effective communication and education about the disorder and rationale of the brain-gut axis is necessary, as well as discussing the risks, benefits and expectations of the different available treatments. Approaching a DGBI as a positive diagnosis is essential. Psychoeducation regarding the role of diet, physical activity, sleep and stress will help patients in noticing the role of the gut-brain axis and triggers that may worsen symptoms.[26]

Different (online) educational resources are available to enhance skills to improve the patient-provider relationship in the forms of books, podcasts and training videos.[27,28]

A recent review set up recommendations based on literature review and consensus for optimizing the patient-provider relationship for both patients as physicians.[25] More efficient patient-provider relationships can lead to improved satisfaction, adherence to treatment and clinical outcomes.[29] Evidence showed that this type

of practice improved health status of the patient and increased cost-effectiveness by reducing diagnostic tests and referrals.[23,25]Accurate assessment of patient preferences is important to understand patients' goals in therapy. Our DCE results and other accessible DCEs give insight in patient needs regarding management. This information gives guidance to help decision-makers evaluate such trade-offs during consultation and eventually help in revealing the treatment of choice. Physicians could discuss subthemes of treatment wishes involving the degree of effectiveness, time to response, time until recurrence, side effects and frequency of appointments.

The use of infographics and educational resources for patients can also be relevant.[30]After the consultation, additional information about the different treatments could be given to the patient in writing. This allows the patient to gather more reliable information about the treatment options after consultation. It is also relevant to take into account patients' health literacy and digital skills, when attempting effective transfer of information regarding management strategies and treatment options. An example of an online decision aid tool for patients seeking appropriate IBS management, is the 'PDS keuzehulp', which is a Dutch initiative from the MLDS (Digestive Diseases Foundation) and the NVMDL (Dutch Association of Gastroenterology).[31] This decision aid tool could be discussed during consultation and can be studied afterwards by the patient (see figure 1).

This recently developed tool is in line with preferred delivery of IBS care. A recent study that performed focus group interviews among IBS patients, reported that patients preferred the availability of an (online) information tool by an expert panel where reliable information about IBS could be found.[32] Other whishes regarding IBS care were: open and clear communication, a multidisciplinary dedicated treatment team, expert health care providers, centers of expertise and more scientific research.

These identified wishes of IBS patients regarding global IBS care and treatments and their aspect, are relevant for healthcare providers during daily practice. This will help in directing the choice of treatment during shared-decision making and eventually in more efficient management strategies.

The impact of more invasive (surgical) options should be thoroughly discussed with the patient suffering from a functional bowel disorder. In some cases, more harm is caused due to (long-term) complications. On the other hand, patient and provider could also conclude during consultation that no treatment is initiated at all. Identifying patients' request and wishes during consultation, may take more

investment and time of the physician, but it will finally result in greater patient satisfaction and ultimately in less health care usage and costs.


*Figure 1: Decision aid tool 'PDS keuzehulp'*

Different decision aid tools may be helpful during decision-making. Future research could integrate the existing decision aid tool for IBS patients with the current data on treatment preferences of IBS patients. This clinical digital instrument may be used by patients and physicians during decision making, where in advance patient- and disease characteristics and preferences should be completed. Think of variables such as, predominant symptom, the presence of psychological complaints, severity of symptoms, age, gender, IBS subtype. This instrument will result in multiple appropriate treatment options based on personal characteristics, that will most likely help this individual patient.

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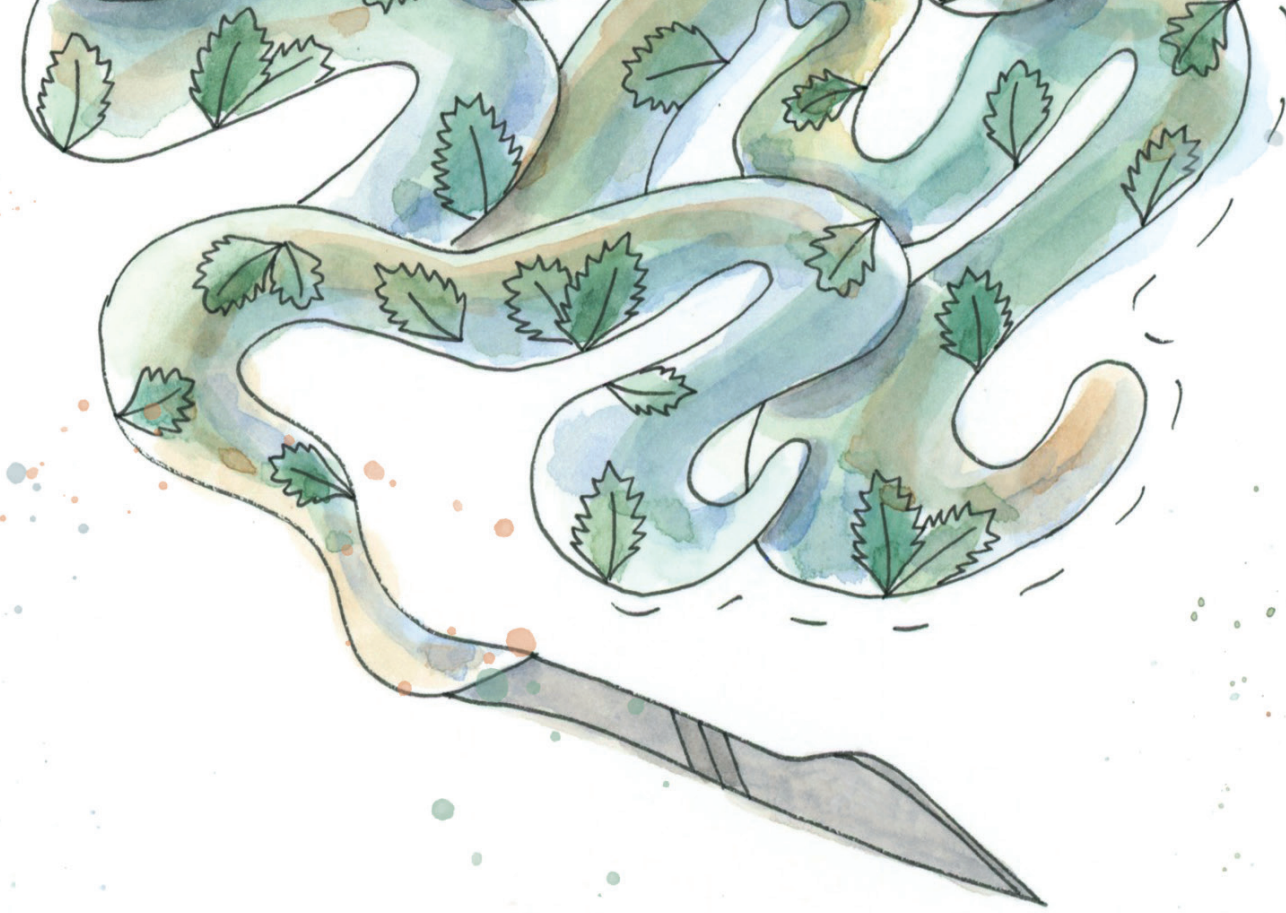


# Chapter 9

## ENGLISH SUMMARY

# ENGLISH SUMMARY

The majority of patients presenting for medical consultation with a gastroenterologist suffer from disorders of the gut-brain interaction, formerly referred to as functional gastrointestinal disorders. These disorders are characterized by recurring and persistent gastrointestinal symptoms and significantly associated with a lower quality of life and very frequent healthcare usage. This dissertation focused on measuring outcomes in irritable bowel syndrome (IBS), functional constipation and fecal incontinence such as quality of life (QoL), treatment preferences and long-term continence scores and complications.

To accomplish symptom control to improve quality of life (QoL), multiple appropriate treatments for these functional bowel disorders are available. The cornerstone of evaluating therapeutic effects in functional disorders (which are characterized by the lack of biomarkers), is the appropriate assessment of subjective symptoms. The US Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) developed guidelines to measure treatment outcomes. This has led to the definition of PROMs, patient reported outcome measures. The PRO measure should capture all of the clinically important signs and symptoms of the target population. In this way, symptoms like the level of abdominal pain, frequency of defecation and symptom severity could be measured using a structured format.



An example of a health-related quality of life (HRQOL) instrument is the EQ-5D which informs cost-utility values for a treatment to determine whether a new therapy delivers value for money. This can be used in economic evaluations to compare benefit between new and established treatments by calculation of standardized quality-adjusted life years (QALYs). This is a generic instrument, because this can measure HRQOL in more conditions. On the other hand, an example of a condition-specific HRQOL instrument is the Irritable Bowel Syndrome Quality of Life questionnaire (IBS-QoL) in IBS patients. This questionnaire is an IBS-specific QoL instrument, but is not preference-based and as such does not allow calculation of QALYs. Condition-specific HRQOL are often preferred in clinical studies, because they capture more disease-specific or relevant aspects of the disease from a clinical and patients' perspective. We explored in **Chapter 2** whether the condition-specific IBS-QoL is more sensitive than the general EQ-5D to capture (mental) health changes in IBS patients. We reported that the overall known-group validity of the IBS-QoL and EQ-5D-5L was quite similar to discriminate between patient and disease characteristics. Moreover, we developed a mapping algorithm where we used data from two multicenter randomized clinical trials as input, to calculate utility values

for use in economic evaluations. The most appropriate mapping model to transform IBS-QoL scores into EQ-5D-5L utility scores, contained the total IBS-QoL score and the squared IBS-SSS (IBS severity scoring system).

In the management of functional bowel disorders, multiple appropriate therapies are available to choose from. Because patients have heterogenous complaints with underlying different (psychological) comorbidities and triggers, it is not possible to design an algorithm that fits all patients. Also, in for example IBS clinical trials, the NNT for IBS treatment is comparable. Therefore, other important treatments aspects should be identified during consultation such as exploring patients' needs, wishes during treatment. The PROs used in clinical trials quantify health outcomes, but these instruments unfortunately do not incorporate patients' preferences and their trade-offs. In **Chapter 3** we determined important factors, next to efficacy, to examine preferences for a specific therapeutic entity of both patients and physicians and compare their perspective. In this study we performed semi-structured interviews with 8 IBS patients and sent out surveys to 15 physicians involved in IBS care. Data revealed nine important treatment aspects: effectiveness, time until response, cessation of response, side effects, location of therapy, waiting period, treatment burden, frequency of healthcare appointments and willingness to pay. We found that effectiveness, duration of response, side effects and treatment burden were all scored as important by patients and physicians. Time to response, location and waiting time were less important for patients compared to physicians.

**In Chapter 4** we used the results of the study described in **Chapter 3** to develop a discrete choice experiment to examine the treatment preferences and trade-offs between different attributes in IBS patients. In this prospective cohort study, a total of 185 patients from the Maastricht IBS cohort completed our survey. Patients were represented with nine different hypothetical choice sets with each three treatment options (medication, diet, psychotherapy) and six attributes. Looking at the varying properties of each treatment, patients were asked which treatment they preferred. This study showed that the most-preferred treatment was dietary intervention, subsequently pharmacotherapy and psychotherapy. IBS patients preferred a higher effectiveness, shorter time interval to response, longer time interval until recurrence, no severe side effects and frequent appointments when attending psychotherapy. Identifying patients' treatment preferences during shared decision-making, will provide more optimal management strategies for these patients.

In some of the patients with functional bowel disorders conservative treatments like pharmacological options, are not effective enough. For this subgroup of patients different surgical options are available. Until now, the long-term effects such as

efficacy, continence scores and complications, were not clear. Therefore, in **Chapter 5** we reported the success rate, QoL- and morbidity scores of the MACE in patients with fecal incontinence or constipation. In this retrospective single-center study 30% developed a postoperative complication. The overall success rate of 37%, determined by using the Malone's continence scale, was disappointing. However, the long-term quality of life scores of these patients did not differ from the general Dutch population.

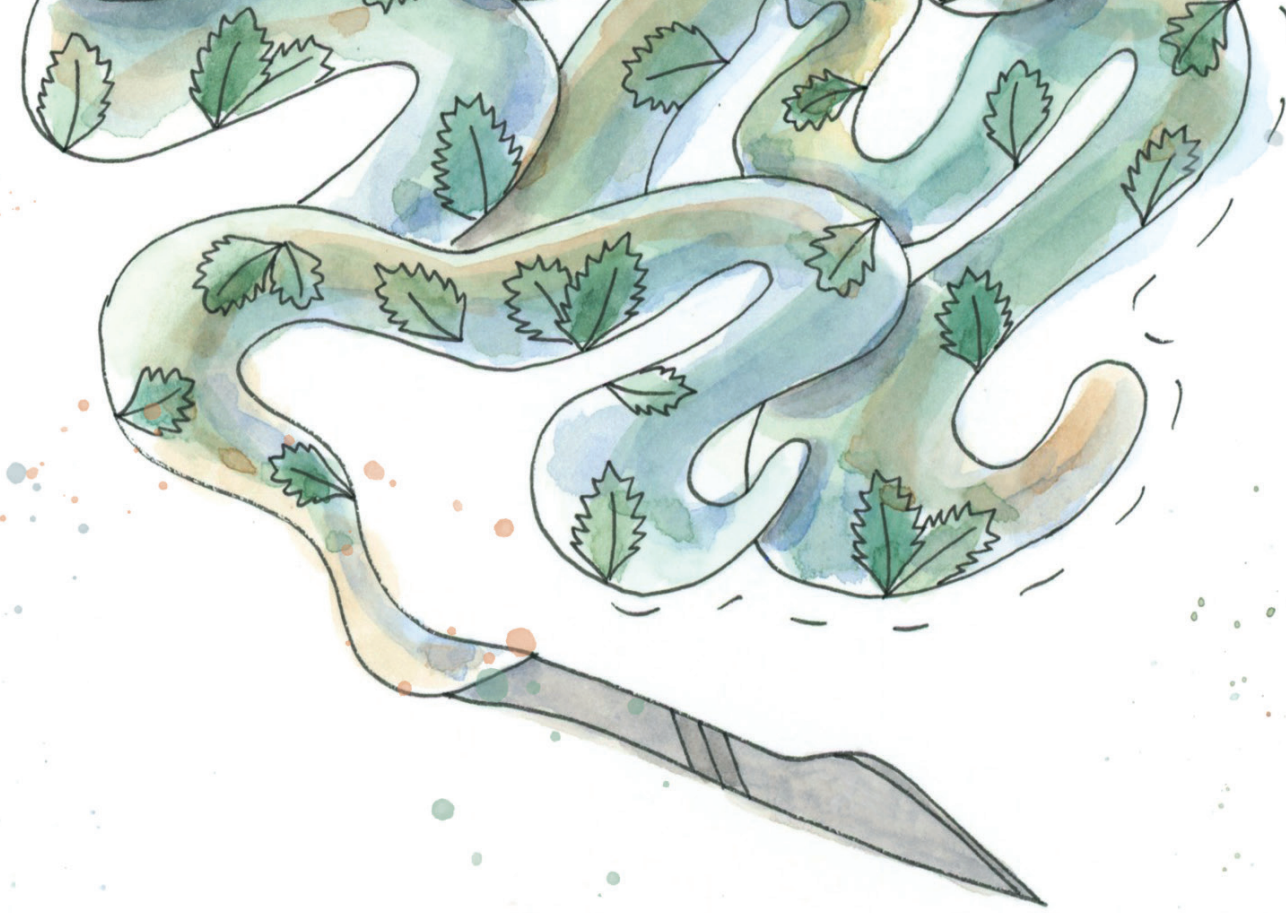
Another possible surgical option to treat functional bowel disorders, is sacral neuromodulation (SNM). Sacral neuromodulation is effective as minimal invasive surgical option to treat fecal incontinence. However, the long-term effects of sacral neuromodulation in patients with constipation were not known. In **Chapter 6** we performed a prospective study where we included thirty adolescents who received sacral neuromodulation. We showed in this study that defecation frequency, abdominal pain and Wexner score significantly improved over time. The 2-year recurrence-free survival was approximately 42.9%. Incorporating this beneficial effect of SNM on defecation frequency and accompanying symptoms, we can conclude that SNM is an effective treatment in adolescent patients with severe complaints of constipation resistant to conservative treatment. In line with our conclusion, current guidelines recommend discussing SNM as a therapeutic option in patient with fecal incontinence.

Patients suffering from fecal incontinence also have several conservative options, including pelvic floor physiotherapy, bulking agents and antidiarrheals. For patients with greater sphincter defects, these treatments are often not sufficient. In **Chapter 7** we reported the long-term outcomes of the artificial bowel sphincter (ABS) in this category of patients. This retrospective record review study included sixty-three patients who were treated with an ABS. We reported that the device was explanted in 49.2% of the patient after a median follow-up of 57 months due to complications. 101 revisions were conducted in total because of device failure or infection. At 5-years follow-up only 35% of the patients had restored continence and 80% had experienced a complication requiring surgery. These limitations of this technique were found to be significant and should be carefully discussed during decision-making. Because of the availability of more effective treatment options, this procedure is generally not offered to patients anymore.

Therefore, shared decision-making is a preferable strategy to pursue where wishes and needs of patients with functional bowel disorders are incorporated.

**Chapter 8** comprises directions for further research and future perspectives in relation to the main findings of our studies.

# Appendices



# Appendix

## NEDERLANDSE SAMENVATTING

# NEDERLANDSE SAMENVATTING

Het merendeel van patiënten die een MDL-arts consulteert, lijdt aan aandoeningen van de zogenoemde hersen-darm as, voorheen functionele gastro-intestinale aandoeningen genoemd. Deze aandoeningen worden gekenmerkt door terugkerende en aanhoudende gastro-intestinale symptomen en zijn geassocieerd met een lagere kwaliteit van leven en een hoge zorgconsumptie. Dit proefschrift concentreerde zich op het meten van uitkomsten bij het prikkelbare darmsyndroom (PDS), functionele obstipatie en fecale incontinentie, zoals kwaliteit van leven (QoL), behandelvoorkeuren en lange termijn continentie scores en complicaties.

Om de symptomen onder controle te krijgen en uiteindelijk de kwaliteit van leven (QoL) te verbeteren, zijn er meerdere behandelingen voor deze functionele darmaandoeningen geschikt.

De hoeksteen van het evalueren van therapeutische effecten bij functionele stoornissen (die worden gekenmerkt door het ontbreken van biomarkers), is de juiste beoordeling van subjectieve symptomen. De Amerikaanse Voedsel en Medicijnen administratie (FDA) en het Europees Geneesmiddelenbureau (EMA) hebben richtlijnen ontwikkeld om behandeluitkomsten te meten. Dit heeft geleid tot de definitie van PROM's, oftewel door patiënten gerapporteerde uitkomstmaten. De PRO (patiënt gerapporteerde uitkomst) maat zou alle klinische belangrijke kenmerken en symptomen van de doelpopulatie moeten vastleggen. Op deze manier kunnen symptomen zoals de mate van buikpijn, de frequentie van ontlasting en de ernst van de symptomen in een gestructureerd format worden gemeten.



Een voorbeeld van een gezondheidsgerelateerde kwaliteit van leven (HRQOL) meetinstrument is de EQ-5D, die kosten-utiliteitswaarden voor een behandeling weergeeft om te bepalen of een nieuwe therapie zich waarmaakt voor de gemaakte kosten. Dit kan worden gebruikt in economische evaluaties om het voordeel tussen nieuwe en reeds bestaande behandelingen te vergelijken door berekening van gestandaardiseerde voor kwaliteit van leven gecorrigeerde levensjaren (QALY's).

De EQ-5D is een generiek instrument, omdat dit de HRQOL van verschillende aandoeningen kan meten. Daarentegen, een voorbeeld van een aandoeningspecifieke HRQOL-meetinstrument is de 'Irritable Bowel Syndrome Quality of Life' (IBS-QoL) vragenlijst voor PDS-patiënten.

Deze vragenlijst is een PDS specifieke QoL meetinstrument, maar is niet gebaseerd op voorkeuren en laat als zodanig geen berekening van QALY's toe. Een aandoeningspecifieke HRQOL-meetinstrument heeft vaak de voorkeur in klinische onderzoeken, omdat ze meer ziektespecifieke of relevante aspecten van de ziekte vastlegt vanuit een klinisch en patiënten perspectief. In **Hoofdstuk 2** hebben we onderzocht of de aandoeningspecifieke IBS-QoL gevoeliger is dan de algemene EQ-5D om (mentale) gezondheidsveranderingen bij PDS-patiënten vast te leggen. We rapporteerden dat de validiteit van de IBS-QoL en EQ-5D-5L vrij gelijkwaardig was om te kunnen discrimineren tussen patiënt- en ziektekenmerken. Bovendien hebben we een mapping algoritme ontwikkeld waarbij we data uit twee multicenter gerandomiseerde klinische onderzoeken als input hebben gebruikt om utiliteitswaarden te berekenen voor gebruik in economische evaluaties. Het meest geschikte mapping model om IBS-QoL-scores om te zetten in EQ-5D-5L utiliteitswaarden, bevatte de totale IBS-QoL-score en de gekwadrateerde IBS-SSS (IBS ernst scoring systeem).

Bij de behandeling van functionele darmaandoeningen zijn er meerdere geschikte therapieën beschikbaar om uit te kiezen. Omdat patiënten allemaal heterogene klachten hebben met onderliggende verschillende (psychologische) comorbiditeiten en triggers, is het niet mogelijk om een algoritme te ontwerpen dat voor alle patiënten passend is. In bijvoorbeeld klinische onderzoeken over PDS, is de NNT (maat voor effectiviteit van een behandeling) voor PDS behandelingen vergelijkbaar. Daarom zullen tijdens het consult andere belangrijke behandelaspecten moeten worden geïdentificeerd, zoals het verkennen van de behoeften van de patiënt en zijn/haar wensen tijdens de behandeling. De PRO's die in klinische onderzoeken worden gebruikt, kwantificeren de gezondheidsresultaten, maar deze instrumenten houden helaas geen rekening met de voorkeuren van patiënten. In **Hoofdstuk 3** hebben we de belangrijke factoren van behandeling in kaart gebracht, naast de effectiviteit, om de voorkeuren voor een specifieke therapeutische entiteit van zowel patiënten als artsen te onderzoeken en hun perspectief te vergelijken. In deze studie hebben we semigestructureerde interviews uitgevoerd met 8 PDS-patiënten en enquêtes verstuurd naar 15 artsen die betrokken zijn bij PDS-zorg. Uit de onderzoeksgegevens kwamen negen belangrijke behandelaspecten naar voren: effectiviteit, tijd tot respons, tijd tot terugkeer klachten na staken behandeling, bijwerkingen, locatie van therapie, wachttijd, benodigde tijd, frequentie van zorgafspraken en betalingsbereidheid. We ontdekten dat effectiviteit, tijd tot terugkeer klachten na staken behandeling, bijwerkingen en benodigde tijd door patiënten en artsen allemaal als belangrijk werden gescoord. Tijd tot respons, locatie en wachttijd voor de behandeling waren voor patiënten minder belangrijk in vergelijking tot artsen.

In **Hoofdstuk 4** hebben we de resultaten gebruikt van de studie beschreven in hoofdstuk 3, om een keuze-experiment te ontwikkelen om de behandelvoorkeuren en afwegingen tussen verschillende behandelaspecten bij PDS-patiënten te onderzoeken. In deze prospectieve cohortstudie hebben in totaal 185 patiënten uit het Maastrichtse PDS-cohort onze enquête ingevuld. Patiënten werden negen verschillende hypothetische keuzesets voorgelegd met elk drie behandelingsopties (medicatie, dieet, psychotherapie) en zes behandelaspecten. Kijkend naar de verschillende eigenschappen van elke behandeling, werd patiënten gevraagd welke behandeling zij prefereerden. Uit dit onderzoek bleek dat de voorkeursbehandeling dieetinterventie was, gevolgd door farmacotherapie en psychotherapie. PDS-patiënten gaven de voorkeur aan een hogere effectiviteit, kortere tijdsinterval tot respons, langer tijdsinterval tot recidief klachten, geen ernstige bijwerkingen en frequente afspraken bij het bijwonen van psychotherapie. Het identificeren van de behandelvoorkeuren van patiënten tijdens gezamenlijke besluitvorming, zal de managementstrategie voor deze patiënten verder optimaliseren.

Bij sommige patiënten met functionele darmaandoeningen zijn conservatieve behandelingen, zoals farmacologische opties, niet effectief genoeg. Voor deze subgroep van patiënten zijn er verschillende chirurgische opties beschikbaar. Tot nu toe waren de langetermijneffecten zoals werkzaamheid, continentiescores en complicaties niet duidelijk. Daarom hebben we in **Hoofdstuk 5** het succespercentage, de kwaliteit van leven en de morbiditeitsscores van de MACE (Malone stoma) gerapporteerd bij patiënten met fecale incontinentie of obstipatie. In deze retrospectieve single-center studie ontwikkelde 30% een postoperatieve complicatie. Het totale slagingspercentage was 37%, bepaald met behulp van de continentieschaal van Malone, wat teleurstellend bleek. De lange termijn kwaliteit van leven scores van deze patiënten verschilden echter niet van de algemene Nederlandse bevolking.

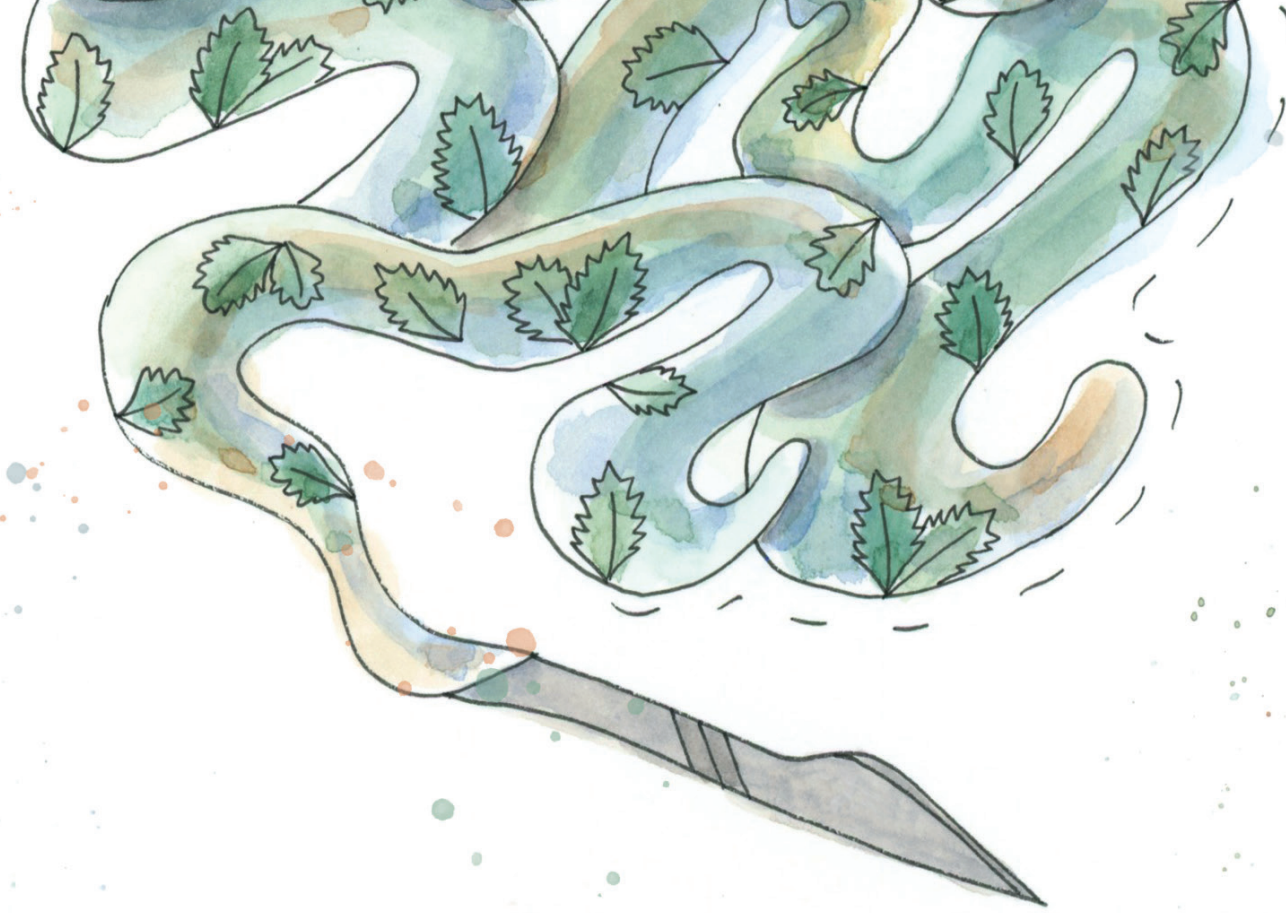
Een andere mogelijke chirurgische optie om functionele darmaandoeningen te behandelen, is sacrale neuromodulatie (SNM). Sacrale neuromodulatie is effectief als minimaal invasieve chirurgische optie om fecale incontinentie te behandelen. De langetermijneffecten van sacrale neuromodulatie bij patiënten met constipatie waren echter nog niet bekend. In **Hoofdstuk 6** hebben we een prospectieve studie uitgevoerd waarin we dertig adolescenten includeerden die sacrale neuromodulatie als behandeling kregen. We lieten in dit onderzoek zien dat de defecatiefrequentie, buikpijn en Wexner score significant verbeterden in de tijd. De twee-jaars recidiefvrije overleving was ongeveer 42,9%. Als we het gunstige effect van SNM op de defecatiefrequentie en bijbehorende symptomen meenemen, kunnen we

concluderen dat SNM een effectieve behandeling is bij adolescente patiënten met ernstige constipatieklachten die resistent zijn voor conservatieve behandeling. In lijn met onze conclusie, bevelen de huidige richtlijnen aan om SNM te bespreken als een therapeutische optie bij patiënten met fecale incontinentie.

Patiënten die last hebben van fecale incontinentie, hebben ook verschillende conservatieve behandelopties, waaronder bekkenbodemfysiotherapie, bulkvormers en diarreeremmers. Voor patiënten met grotere sluitspierdefecten zijn deze behandelingen vaak niet voldoende. In **Hoofdstuk 7** rapporteerden we de langetermijnresultaten van de kunstmatige darmsfincter (ABS) in deze categorie patiënten. Deze retrospectieve recordreview-studie omvatte drieënzestig patiënten die werden behandeld met een ABS. We rapporteerden dat het apparaat bij 49,2% van de patiënt werd verwijderd vanwege complicaties na een mediane follow-up van 57 maanden. Er zijn in totaal 101 revisies uitgevoerd vanwege een defect aan het apparaat of een infectie. Na 5 jaar follow-up had slechts 35% van de patiënten de continentie hersteld en 80% had een complicatie ervaren die een re-operatie vereiste. Deze beperkingen van deze techniek bleken significant van aard te zijn en moeten tijdens de besluitvorming daarom zorgvuldig worden besproken. Vanwege de beschikbaarheid van effectievere behandelingsopties wordt deze procedure over het algemeen niet meer aan patiënten aangeboden.

Daarom is gezamenlijke besluitvorming een strategie van voorkeur, waarin de wensen en behoeften van patiënten met functionele darmaandoeningen kunnen worden nagegaan.

**Hoofdstuk 8** bevat inzichten voor verder onderzoek en toekomstperspectieven met betrekking tot de belangrijkste bevindingen van onze studies.



# Appendix

## IMPACT PARAGRAPH

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The majority of patients presenting for medical consultation with a gastroenterologist suffer from disorders of the gut-brain interaction (DGBIs). These disorders are characterized by persistent and recurring gastrointestinal symptoms. Common illnesses of DGBIs include functional bowel disorders such as irritable bowel syndrome (IBS), functional constipation and fecal incontinence. Many appropriate treatments are available for the treatment of functional bowel disorders. Because of the lack of biomarkers to evaluate the effect of a therapy and a clinical heterogenous population, the management of these disorders remains challenging. Shared-decision making is therefore an important key during consultation.

The main goal of this thesis was to improve the management of functional bowel disorders. Relevant subthemes were insight into treatment preferences that can be used during shared decision-making and examining the long-term outcomes of surgical procedures. A better management of these disorders, can result in improvement of QoL of patients and decreased health care demands and costs.

We developed an algorithm to calculate utility scores for the disease-specific questionnaire, the IBS-QoL, for usage in economic evaluations. Moreover, we explored which treatment aspects are important for patients during decision-making and we revealed their specific treatment preferences and weights regarding IBS therapies. Finally, we examined the long-term outcomes (continence, complications, quality of life) of three surgical procedures for the treatment of constipation and fecal incontinence. All these novel aspects could be discussed and used during consultation of the treatment-seeking patient. These results of the thesis are relevant for clinicals, patients but also for health policy makers.



Scientific relevance

The results are or will be published in international peer-reviewed journals. Moreover, these research findings are presented at (inter)national congresses, such as the Dutch Digestive Disease Days, Lowlands Health Economic Study Group (LolaHESG) conference, European Society of Coloproctology congress, the European NeuroGASTRO meeting and the United European Gastroenterology (UEG) congress.

Different research findings contribute to novel scientific knowledge which are useful for researchers in the field of DGBIs. We were the first to compare the responsiveness of two frequently used PROMs in IBS patients and to develop an algorithm to convert IBS-QoL scores to utility scores for use in trial-based economic evaluations. In clinical

trials where IBS-QoL might be more relevant to use due to disease-specific domains than a general health related questionnaire like the EQ-5D-5L, the IBS scores can now be transformed into utility scores and ultimately QALYs.

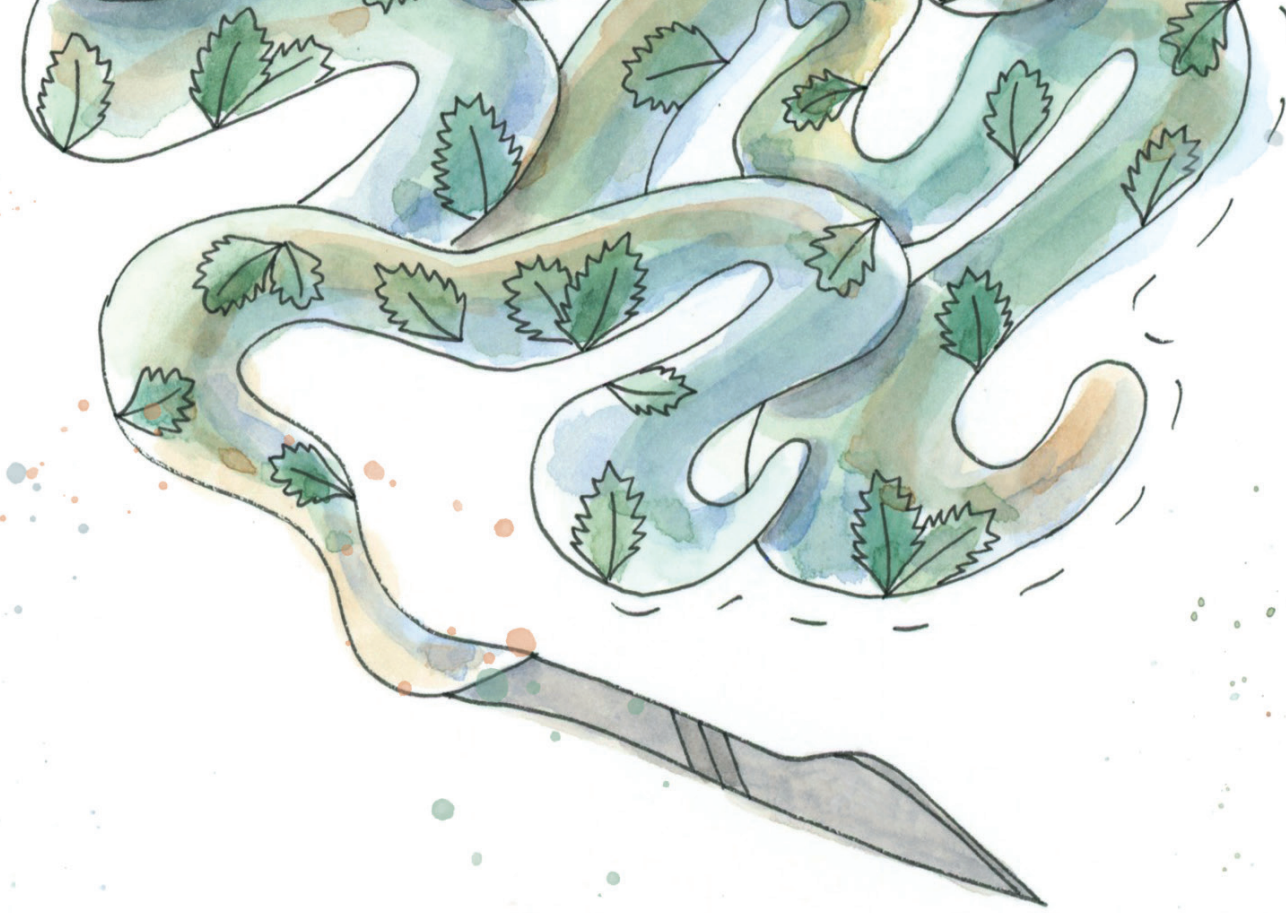
Furthermore, we are the first to identify treatment preferences and estimate their trade-offs in patients with IBS. This could not only be relevant for patients and health care decision makers, but also for developers of novel therapies.

We also examined the long-term outcomes of three surgical procedures: the MACE, SNM and the ABS. These studies reveal novel scientific knowledge regarding the use on long-term, continence rates, complication rates and quality of life scores of patients. This is relevant for the manufactureres of medical technology to adapt their devices according to patients' needs.

Impact on health care providers and patients

These results are not only relevant for patients suffering from DGBIs, but also for different health care providers, such as gastroenterologists, surgeons, general practitioners, dieticians and psychologists. We performed semi-structured interviews with IBS patients to examine their wishes and important aspects of disease management. Moreover, we revealed the strong preference for dietary interventions among IBS patients and different preferences according to a specific subgroup. We encourage health care providers to use shared-decision making as the underlying strategy to discuss treatment options with the treatment-seeking patients. The identification of patients' perspective may help health care providers in understanding patients' wishes. These research findings can also encourage patients to consider what aspects of management are important and which trade-offs apply. A well-considered therapy may lead to better compliance with the prescribed treatment, which is crucial for treatment success. Consequently, patients will experience less disease burden and an improved quality of life. Future research could include the development of a clinical decision tool with the input of the preference data, to help giving an overview of all potential management options personalized on patient- and disease characteristics.

The disappointing results of the surgical procedure, ABS, has reached clinicians and has resulted in the fact that the ABS is no longer prescribed as therapy. This protects patients against possible harm. Patients with a SNM or a MACE may experience a better QoL due to symptom reduction. These studies have revealed potential benefits, limitations and expectations regarding continence and QoL which now could be discussed with patients during consultation.



# Appendix

## LIST OF PUBLICATIONS

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**Sturkenboom R,** Keszthelyi D, Brandts L, Weerts ZZRM, Snijkers JTW, Masclee AAM, Essers BAB. The estimation of a preference-based single index for the IBS-QoL by mapping to the EQ-5D-5L in patients with irritable bowel syndrome. Qual Life Res. 2022 Apr;31(4):1209-1221. doi: 10.1007/s11136-021-02995-y. Epub 2021 Sep 21. PMID: 34546554; PMCID: PMC8960586.

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**Sturkenboom R**, van der Wilt AA, van Kuijk SMJ, Ahmad A, Janssen PT, Stassen LPS, Melenhorst J, Breukink SO. Long-term outcomes of a Malone antegrade continence enema (MACE) for the treatment of fecal incontinence or constipation in adults. Int J Colorectal Dis. 2018 Oct;33(10):1341-1348. doi: 10.1007/s00384-018-3088-5. Epub 2018 Jun 22. PMID: 29934702.

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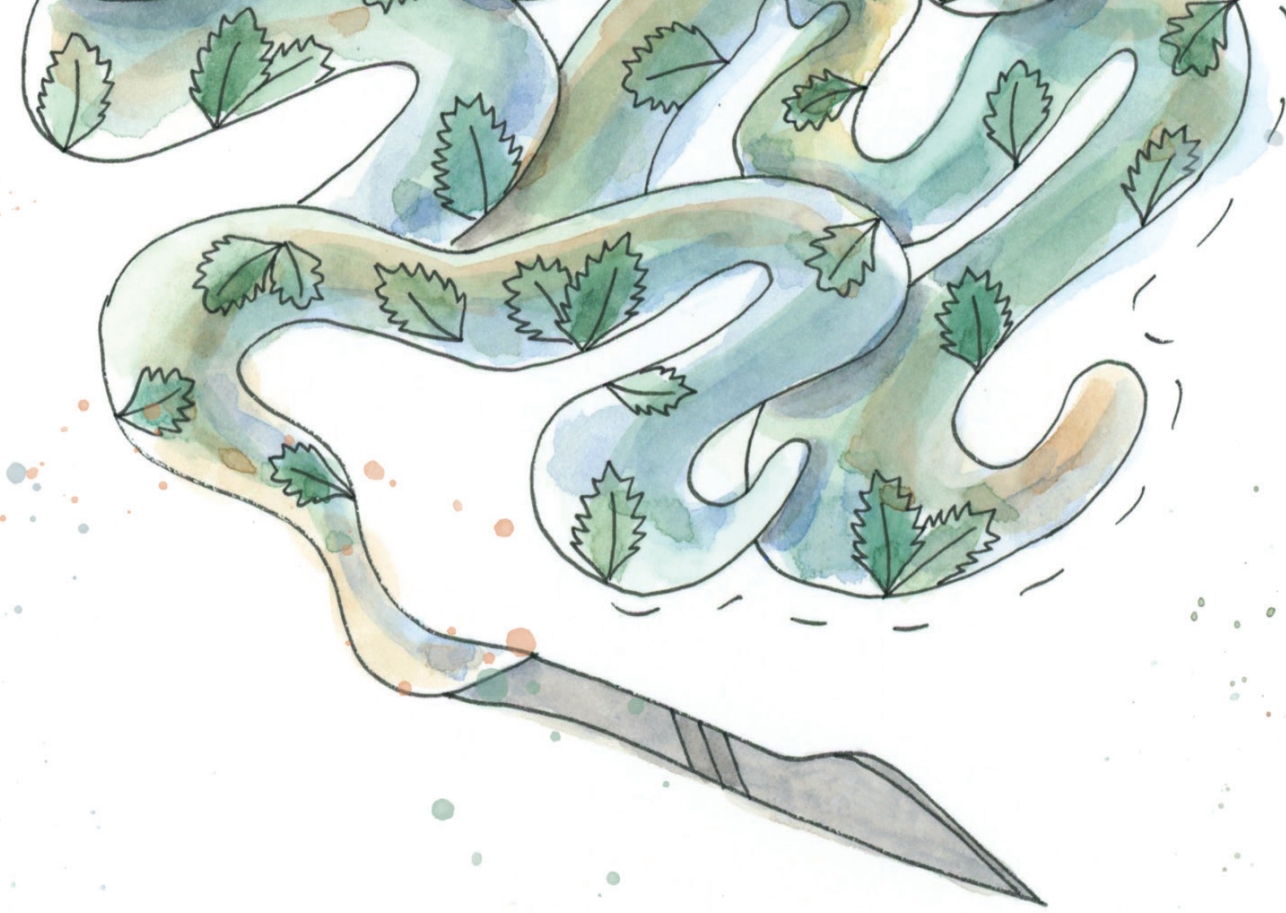
Submitted

**Sturkenboom R,** Essers BAB, Ad A M Masclee AAM, Keszthelyi D. Do patients' and physicians' perspectives differ on preferences for irritable bowel syndrome treatment?

To be submitted

**Sturkenboom R**, Essers BAB, Ad A M Masclee AAM, Keszthelyi D. The treatment preferences of different health care professionals in the management of irritable bowel syndrome patients.



# Appendix

## DANKWOORD

# DANKWOORD

Het is zover, mijn proefschrift is af. Ik kijk met veel plezier terug op de afgelopen jaren.

In 2020, midden in de eerste COVID golf, begon ik aan mijn PhD traject en onderbrak ik mijn MDL-opleiding voor een jaar. Door de pandemie, werkte ik voornamelijk thuis en 1x/week in de lege gang van de KEMTA-afdeling in het Oxfordgebouw. Dit zorgde voor weinig afleiding, zodat ik me volledig kon focussen op de verschillende onderzoeksprojecten. Het afgelopen jaar vervolgde ik mijn opleiding MDL en werkte ik in mijn vrije uren verder aan het onderzoek. Dit vond ik zelf soms een pittige maar ook een fijne afwisseling. Hierdoor kon ik namelijk wel meer mijn creatieve kant kwijt door bezig te zijn met het verkennen van nieuwe software en het vormgeven van verschillende vragenlijsten. Door de combinatie met de opleiding, ging het afronden wat minder snel dan ik zelf voor ogen had, maar daardoor ben ik extra verheugd en trots dat het nu afgerond is! Echter, zonder de inzet van vele anderen had dit proefschrift niet tot stand gekomen. Ik wil dan ook graag iedereen bedanken die hieraan een bijdrage heeft geleverd. In het bijzonder wil ik de volgende personen bedanken:

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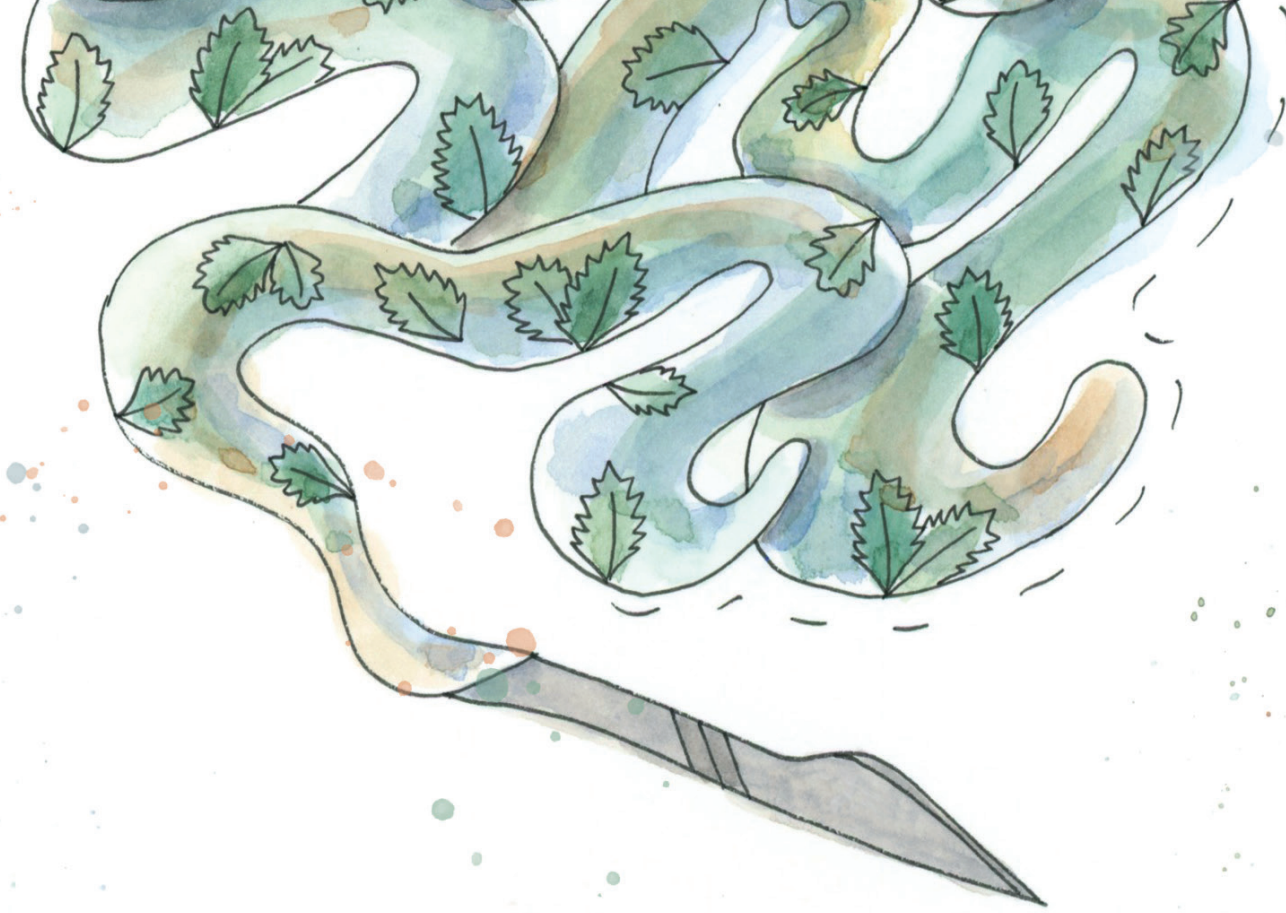

# Appendix

## CURRICULUM VITAE

# CURRICULUM VITAE

Rosel Sturkenboom was born on July 19th 1991 in the hospital of Nieuwegein, the Netherlands. During her childhood, she lived in the village Houten. After graduating from St. Bonifatiuscollege in Utrecht in 2009, she started studying biomedical sciences at the University of Amsterdam. In 2010 she moved to the south, to begin medical school at Maastricht University. During her master, she did several internships abroad, including at Makerere University in Kampala (Uganda) and at Universitas Indonesia, Jakarta (Indonesia). Her research internship involved research on perianal fistulas in Crohn's patients and surgical options for the treatment of constipation and fecal incontinence, which she performed under the supervision of dr. S. Breukink. During an internship of choice at the Gastroenterology department at Diakonessenhuis in Utrecht in the last year of medical school, the love for the specialization of Gastroenterology and Hepatology was grown and she decided that this had to be her residency program.

After graduating in 2016, she started to work as resident Gastroenterology & Hepatology (ANIOS) at St. Elisabeth hospital in Tilburg, which was followed by a residency (ANIOS) at Jeroen Bosch hospital in 's-Hertogenbosch. In 2018 she started her training to become a gastroenterologist (AIOS) in Maastricht. The program started with 1.5 year of residency Internal Medicine in Viecuri in Venlo under the supervision of dr. M. Hermans. Rosel interrupted her residency for eleven months in 2020/2021 to start as a PhD student at the Gastroenterology & Hepatology department and KEMTA at Maastricht University Medical Center under the supervision of Prof. D. Keszthelyi and Dr. B. Essers where she performed research involving both clinical and health technology aspects of patients with functional bowel complaints. In 2021, she started with the Gastroenterology & Hepatology part of her residency program in Maastricht University Medical Center under the supervision of dr. J. Kruimel and dr. J. Haans and simultaneously worked on her PhD research. Recently, she continued her residency program in Catharina Hospital in Eindhoven under the supervision of Prof. E. Schoon and dr. H. Flink.
Rosel currently lives in Eindhoven with her partner Robin.