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Utilizing Patient-Reported Outcome Measures in the Management of Inflammatory Bowel Disease

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UTILIZING PATIENT-REPORTED OUTCOME MEASURES IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

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Abstract

Inflammatory bowel disease, a chronic relapsing-remitting disorder, affects three million adults in the United States. One of the main therapeutic goals in patients with inflammatory bowel disease is mucosal healing, measured by endoscopy, an invasive procedure that does not always reflect patient symptomatology. To address these limitations, clinicians have developed patient-reported outcome measures, questionnaires evaluating bowel symptoms and quality of life. However, the clinical utility of these patient-reported outcome measures and their correlation to objective markers of inflammation is unclear. **We will determine the efficacy of using a patient-reported outcome measure to inform treatment for inflammatory bowel disease.** In a randomized clinical trial, we will compare disease metrics of patients receiving treatment guided by a patient-reported outcome measure compared to those of patients receiving standard treatment. This study will confirm the utility of patient-reported outcome measures, revolutionizing inflammatory bowel disease treatment and transitioning the field towards patient-centered care.

Chapter 1: Introduction

1.1 Background

Patients with inflammatory bowel disease face significant detriments in health-related quality of life (HRQL) and experience varied symptoms including depression, anxiety, and fatigue. Existing clinical measures to monitor disease activity often fail to evaluate these significant components of the chronic condition. This study proposes a randomized clinical trial to test the use of a patient-reported outcome measure (versus standard of care) on increasing quality of life for patients with IBD in an outpatient clinic setting over the course of six months.

Inflammatory Bowel Disease and Current Disease Monitoring

Inflammatory bowel disease (IBD) refers to a group of chronic relapsing-remitting diseases including ulcerative colitis (UC) and Crohn's disease (CD). Inducing and maintaining clinical remission is the ultimate goal of therapy. In addition, the therapeutic targets of IBD have now evolved beyond clinical remission to include mucosal healing. Mucosal healing refers to the resolution of ulcerations on endoscopic evaluation. Mucosal healing has been associated with favorable outcomes such as decreased rates of hospitalization, surgery, and perianal complications, as well as improvement in quality of life and increased work productivity.[1-3] Unfortunately, previous studies have demonstrated a lack of association between mucosal healing and symptomatology, like those measured by Crohn's Disease Activity Index (CDAI).[4,5] Therefore, the current gold standard for evaluating mucosal healing is endoscopy or imaging for isolated small bowel disease. Unfortunately, endoscopy is not only invasive to perform on patients on a routine basis, but also costly and time-consuming for patients and providers.[6-8] Therefore, clinicians continue to search for a reliable measure of clinical activity that also predicts mucosal healing.

Due to the invasive nature and cost of endoscopy, practitioners often have to rely on other indirect measures of inflammation such as biomarkers. One non-invasive inflammatory marker is C-reactive protein (CRP), a protein produced by the liver in response to inflammation with a half-life of only 19 hours. Although non-invasive, quick, inexpensive, and commonly ordered by clinicians, CRP levels may be affected by many factors including genetics, smoking, or obesity and may be falsely elevated in trauma, infection, cardiovascular events, neoplasia, or extraintestinal inflammation. Additionally, about one quarter of IBD patients have a genetic single nucleotide polymorphism (SNP) in a CRP gene which results in CRP never being elevated even in the setting of active inflammation.[9] Furthermore, although one meta-analysis found CRP to have a high specificity of 0.92 when correlated with endoscopic measures of disease activity, its sensitivity was only 0.49. Results of CRP must be interpreted with caution given this high proportion of falsely negative results.[10]

Another non-invasive marker of inflammation is fecal calprotectin (FCP). Calprotectin is a calcium binding protein found in the cytosol of neutrophils; thus FCP levels are directly proportional to inflammatory migration of neutrophils to the gastrointestinal tract.[7,9] FCP may be falsely elevated in other gastrointestinal disorders such as infection, malignancies, or medication use such as NSAIDs. FCP measurements are also often not covered by insurance and thus expensive for patients.[9]

Clinicians and researchers use standardized scoring systems to incorporate data findings into more objective and quantitative measures of disease activity. The most commonly used clinical scoring systems are the Mayo Clinic Score for UC (Mayo-UC) and the Crohn's Disease Activity Index (CDAI) for CD.[11] Unfortunately, both instruments have limitations. The Mayo Clinic Score is composed of subjective questions completed by clinicians and does not always

correspond with a patient's own perceptions of their disease activity.[12] The CDAI does not always correlate well with endoscopy scores and may be falsely elevated in the presence of other gastrointestinal diseases.[13-16] Additionally, even in clinical trials, definitions of disease activity vary across studies, making the data difficult to compare and incorporate into practice.[14,15] These composite measures of disease activity are time-consuming to collect, lack correlation with endoscopic findings, and leave out the patient's perception of disease.[17]

Inflammatory Bowel Disease & Health-Related Quality of Life

In addition to the aforementioned shortcomings, current disease activity indices do not take into account comorbidities such as depression, anxiety, fatigue, and quality of life impairment which are downstream effects of initial bowel inflammation. A majority of IBD patients must contend with these symptoms, and they are often of utmost importance to patients.[11] As IBD is often diagnosed at an early age, these extraintestinal manifestations of the disease can be devastating to patients, and can lead to a cyclical process of pathology. For example, sleep disturbances have been linked to worsening pain and fatigue in patients with chronic inflammatory conditions.[18] Finally, the chronic nature and potential complications of IBD and the lack of a definitive cure have been shown to contribute to depression in patients, overall reducing HRQL.[19]

In order to promote patient quality of life, it is essential that providers monitor these symptoms. Current disease monitoring tools do not account for these symptoms, instead focusing on bowel inflammation. In order to promote optimal patient outcomes there is a need for a clinically practical tool to ensure these symptoms are monitored and addressed for all patients with IBD.

Patient-Provider Relationship

With any chronic disease, the foundation of effective disease management is the relationship between patient and provider. This is especially true in the care of IBD, as patients must face significant stigma surrounding their physiological symptoms, contend with the lack of a definitive cure for the disorder, manage treatment side effects, and cope with a myriad of psychological effects of the disease. Unfortunately, the rate of addressing these important concerns is low in IBD care. For example, surveys have shown nearly half of gastroenterologists fail to discuss quality of life with their patients.[20] In a more recent qualitative study, despite 78% of patients endorsing that the disorder negatively impacts their quality of life, only 45% of these patients discussed this fact with their provider, and a further 23% minimized these negative effects.[21] Additionally, providers underrate both patient symptoms and the effect of these symptoms on patients' quality of life.[22] This lack of communication leads to worse outcomes including increased levels of patient anxiety and decreased adherence to disease therapeutics.[23-25] Psychological stress has been shown to correlate with increased symptomatology and relapse in IBD.[26] Furthermore, causative factors in medication nonadherence include patient and physician discordance as well as a lack of trust in providers.[27]

These deficits in communication may persist as providers plan treatment options for patients. Research has shown that providers and their patients have diverging views when it comes to treatment goals. Patients generally aimed for symptomatic remission with significant improvements in the quality of their lives, whereas provider targets tended to be focused on objective disease remission or a reduction in other objective markers of inflammation.[28] There is now a shift in the culture of medicine towards more patient-centered care, and an integral part of this transformation will be empowering patients to be involved in the management of their diseases. In one survey, 98% of IBD patients reported that it was "very important" or "quite

important" to be part of the decision-making process with their providers.[29] Clinicians must create opportunities to discuss health-related quality of life in order to foster a trusting relationship with patients and empower them as goal setters in disease management, which will ultimately improve patient outcomes.

The Promise of Patient-Reported Outcome Measures

In response to the limitations of current disease indices, the FDA called for the production and use of patient-reported outcome measures (PROMs) in both clinical practice and research trials in 2006.[30] PROMs are useful tools since they elicit subjective symptom information, such as pain intensity and relief, and remove the need for interpretation from a third party. PROMs provide the opportunity to improve patient-provider communication, improve accuracy of symptom assessment, and ultimately aid patient education and self-management.[31] Additionally, PROMs introduce the opportunity for a review of symptoms that are secondary to a main diagnosis. A driving force behind utilizing PROMs in IBD therapies is promotion of a "co-production" model of care, where patient needs are integrated into clinical decision-making to ultimately create the best outcome. PROMs create the opportunity for interdisciplinary care by standardizing factors of care either within a specialty or outside of that specialty.[11] In addition, another incentive for the use of PROMs is to maintain control over patient symptoms to ensure they remain in remission.[32] Finally, many PROMs also incorporate questions regarding a patient's mental health and fatigue symptoms which has the promise of improving patient health-related quality of life.

PROMs have been shown to be effective when used in the care of a variety of conditions. One randomized control trial demonstrated the utility and benefit of these measures in an oncology setting where the use of an electronic PROM resulted in improved health related

quality of life and reduced hospitalizations.[33] It is important for these tools to be tailored to specific conditions, such as in the case of the Phenylketonuria impact and treatment Quality of Life Questionnaire (PKU-QOL), which allows providers to monitor important factors specific to individuals with metabolic conditions such as dietary protein restrictions.[34] An analysis of existing PROMs by Greenhalgh et al. found that the completion of PROMs enabled a patient to bring up specific symptoms to their provider, since the process of completing the questionnaire allowed for patients to reflect on their health and ultimately recall minute details about their condition.[35] PROMs have become mandated for patients undergoing certain elective surgical procedures in the United Kingdom. These PROMs collect data about health satisfaction and other metrics in the NHS, allowing for continued quality improvement efforts.[36] Another research study in an oncology clinic incorporated PROMs into routine practice and resulted in increased survival with those with metastatic cancer compared to usual care.[37] The application of PROMs has many evident benefits, many of which would be applicable to IBD once an appropriate measure is found to be valid, efficacious and efficient in routine IBD care.

Specific IBD Related Patient-Reported Outcome Measures

There is currently a need for a PROM in IBD that is both feasible for routine clinical use and accurately predicts objective measures of inflammation such as mucosal healing. One potential tool is the 13 item IBD-Control Questionnaire (IBD-CQ). This questionnaire was designed for use in clinical settings to assess four core domains of IBD control: physical symptoms, social impact, emotional impact, and treatment efficacy. Patients with IBD were directly involved in the development of each item of the questionnaire and it takes just over a minute to complete.[38] The questionnaire has demonstrated utility in a variety of clinical settings evidenced by its successful use in recent studies to monitor IBD care in the National Health

System of the UK, determine the prevalence of IBD in Iran, and evaluate the utility of a web-based ulcerative colitis program.[39-41]

The National Institute of Health (NIH) developed another such tool in 2005, the Patient-Reported Outcome Measurement Information System (PROMIS), for use in patients with a variety of chronic disorders. The PROMIS questionnaires are designed to provide standardized information and assess many domains including physical health (function and symptoms), mental health (emotional distress, cognitive function, and positive psychological functioning), and social health (role participation and social support). The PROMIS questionnaires have been used effectively in research studies, clinical practice, and policy development across a variety of diseases.[42]

1.2 Statement of the Problem

Current strategies to monitor patients with IBD are invasive, costly, and do not capture common patient symptomatology such as fatigue and mental health issues. PROMs have the potential to address these gaps; however, there is a significant lack of research evaluating these measurement tools. Currently, few clinical practices utilize standardized PROMs for various reasons from administrative costs and training to the reluctance to move away from conventional patient interviewing methods.[11] Furthermore, some PROMs require specialized technology that is not readily available to all providers. Also, certain PROMs have issues with interpretability, which may make providers reluctant to utilize them. Finally, some providers are hesitant to utilize PROMs since they feel as though the questions may be too intrusive and damage the patient-clinician relationship.[43] A thorough randomized controlled clinical trial is required to

confirm the efficacy and validity of specific IBD patient-reported outcome measures, which would ultimately result in their implementation into clinical practice.

Additionally, a successful study would confirm the validity of the IBD-CQ and PROMIS questionnaires by determining whether these PROM scores correlate to objective measures of inflammation such as mucosal healing as measured by endoscopy. In one review of PROMs currently available for use in the IBD population, only six have been validated using findings from endoscopy. Additionally, the measures showed only moderate accuracy when used to predict disease activity with an area under the curve for correct classification ranging from 0.63 to 0.82. Finally, some PROMs only contain one question about ongoing disease activity, a factor that may be an issue since IBD has a multifactorial disease process.[8]

As a chronic relapsing disease with peak incidence of early thirties, the prevalence of IBD is rising dramatically as the population ages. IBD care is currently estimated to cost anywhere from $14 to $31 billion in the United States. As the population of patients with IBD rises, their care must redirect its aims to become more efficient and patient-centered.[44] PROMs will be instrumental in this transition to value-based care, but require further research to ensure that these measures are effective when used routinely and meet all required validity criteria. Additionally, there are many other factors needed for the effective implementation of these measurement tools. Ease of administration, a short time interval between patient outcome and time of reporting, and good reliability are key items needed for a PROM to be effective in clinical practice.[8] Ideally, PROMs should support decision-making for each individual patient, and also be able to be used in clinical trials in order to seamlessly link research to actual practice.[17] Investigating the efficacy and validity of the IBD-CQ and PROMIS questionnaires in the management of IBD will be a precursor to creating an environment of patient-centered care.

PROMs create the opportunity to evaluate a patient's symptomatology holistically. The inclusion of questions about mental health and fatigue extends evaluation beyond the current guidelines of mucosal healing to include other aspects of a patient's health-related quality of life.

1.3 Goals and Objectives

The proposed study's goal is to determine the efficacy of utilizing a clinically practical PROM, the IBD Control Questionnaire and the PROMIS questionnaires, to individualize disease monitoring and treatment decisions for adult patients with IBD. A secondary aim is to confirm the validity of the aforementioned PROMs by correlating scores to objective measures of inflammation such as mucosal healing as measured by endoscopy over a six-month period. The primary study outcome will be global health-related quality of life as measured by the EuroQol questionnaire (EQ-5D-5L). This questionnaire is both reliable and validated as a measure of patients' quality of life and is commonly used in research.[45] This outcome will speak to the efficacy of using PROMs to individualize treatment of IBD.

Secondary outcomes will include patient disease activity as measured by endoscopic scores (Mayo UC, CDAI), discussion of HRQL in the clinic visit, rate of disease exacerbations, patient and provider satisfaction, cost of treatment, and non-invasive biomarkers of inflammation (fecal calprotectin, erythrocyte sedimentation rate, albumin, c-reactive protein). This information will inform clinical monitoring methods for patients with IBD. Additionally, this information will be used to determine the extent to which the IBD-CQ aligns with traditional measures of disease activity (Mayo UC, CDAI, lab markers) and psychosocial domains (depression, anxiety, fatigue, social functioning). Furthermore, we will determine the IBD-CQ's ability to detect clinically important changes in patient symptomatology after six months of treatment. Both the

primary and secondary outcomes resulting from the proposed study will provide guidelines to promote both patient centered care and holistic disease management.

1.4 Hypothesis

We hypothesize that of 258 adult patients with IBD, those who receive individualized treatment as structured by a PROM will have a statistically significant difference in health-related quality of life as measured by the EuroQoL questionnaire (EQ-5D-5L) as compared to those receiving standard clinical care after a six month period.

Definitions

- *Intervention*: Patients will complete a PROM (IBD-CQ and PROMIS) prior to their initial evaluation appointment. The clinician will receive the results of the PROM and subscores and use this information to discuss treatment during the visit. Six months later, this will be repeated at another clinic visit.
- *Standard of Care*: Designed using evidence-based practice, the standard of care will include a thorough baseline exam, a therapy plan based on current guidelines, clinic and phone call follow-up as needed, as well as information sheets provided about the disease.[46-48] Control participants will complete the same PROM (IBD-CQ and PROMIS) prior to each clinic visit, but results from these measures will not be provided to their treating clinician.

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Chapter Two: Review of the Literature

2.1 Introduction

A detailed review of the literature was performed of references published from January 2000 through April 2020 using a variety of sources, including Ovid (Medline), Pubmed, ScienceDirect, CINAHL, and Cochrane Medical Library. Only English-language articles were included in the review. Selection of articles included within this literature review began with screening study titles and abstracts followed by full text examination of articles to evaluate their relevance to the proposed research study. The following terms were implemented in the search for pertinent literature related to IBD and PROMs in all of the above databases: *patient-reported outcome measure (patient reported outcome measures, patient reported outcome measurement, PROM, patient reported outcome, PRO, patient reported measure, patient reported measures, patient centered outcome measure, patient centered outcome measures, PCOM, routine outcome monitoring, clinical feedback, quality of life, health-related quality of life, HRQL, HRQOL, self-reported outcome, self-reported outcomes),* and *inflammatory bowel disease (inflammatory bowel diseases, ulcerative colitis, Crohn's disease).* To date, no randomized clinical trials have been conducted that directly evaluate the routine use of PROMs in IBD, so the review was expanded to include the use of PROMs in other diseases, as a thorough review of previous methodology in other diseases is necessary to compose a properly investigated study. We also examined the reference lists from all of the eligible studies and literature reviews on the subject to identify additional relevant material. Additional key terms were implemented to search for protocol-specific information: *parallel study design, confounders (confounding variables), statistical analysis,* and *limitations (drawbacks, issues, flaws, defects).*

2.2 Current Burden and Disease Monitoring of Inflammatory Bowel Disease

More than three million adults in North America currently live with inflammatory bowel disease (IBD).[1] This estimate is expected to rise to four million in just the next decade.[2] As IBD is a chronic relapsing-remitting disease, clinicians must regularly monitor disease activity in patients. Clinical remission, which refers to absence of symptoms is one of the main goals of IBD treatment. The therapeutic targets of IBD, however, have evolved beyond clinical remission to include objective evidence and measures of inflammation. One such target is mucosal healing which refers to resolution of ulcerations seen on endoscopy. The gold standard used to assess disease activity is endoscopic evaluation of mucosal inflammation.[3] Unfortunately, endoscopy is not only invasive to perform on patients on a routine basis, but also costly and time-consuming for patients and providers.[3-5] Furthermore, mucosal healing on endoscopy does not always align with clinical remission in patients. Researchers in one study performed endoscopy on 127 patients with IBD who had been in clinical remission for at least one year, and 65% of these patients showed mucosal inflammation indicative of active disease.[6] In a second study of patients with CD, over half of patients continued to show inflammation on endoscopy or biomarkers despite having achieved clinical remission, and about one fifth of patients continued to be symptomatic despite a lack of evidence of inflammation on endoscopy or biomarkers.[7]

Clinicians and researchers use standardized scoring systems to incorporate data findings into a more objective and quantitative measure of disease activity. The most commonly used clinical scoring systems are the Mayo Clinic Score for UC and the Crohn's Disease Activity Index (CDAI) for CD.[8] Despite their widespread use in clinical practice as well as research studies, both metrics are insufficient due to subjective questions, lack of patient perspective, and lack of correlation with endoscopy.[9-13] Additionally, these indices do not measure symptoms that

are often most important to patients: depression, anxiety, fatigue, and quality of life impairment.[8] Finally, even in clinical trials, definitions of disease activity vary across studies, making the data difficult to compare and incorporate into practice.[12-14] These composite measures of disease activity are time-consuming, lack correlation with endoscopic activity, and leave out a patient's perception of disease causing strain in the patient-provider relationship.[15]

2.3 Clinical Promise of Patient-Reported Outcome Measures in Inflammatory Bowel Disease

In order to combat the drawbacks of current disease monitoring techniques, the FDA began to promote patient-reported outcome measures in 2006 and clinicians have followed suit.[16] These disease monitoring tools are exceptionally useful, as they display subjective symptom information directly from the patient, such as pain intensity and fatigue, without necessitating interpretation by a clinician or others. The utilization of PROMs in the care of IBD will empower patients to become "co-producers" of care and treatment of their disease. Additionally, PROMs standardize outcomes across disciplines in clinical research. This enables both incorporation of clinical research into practice, as well as continuity across various specialties.[8] Additionally, continual use of PROMs facilitates self-monitoring of patients' condition over time, tracking both disease stability and exacerbations.[17]

Despite the demand from practitioners and researchers to use PROMs in IBD, there is a lack of research regarding the efficacy of routine use of these measures in IBD clinical practice. Additionally, few PROMs have demonstrated validity in the IBD patient population. In one review of twenty different measures, only six have been validated using findings from endoscopy.[4] Additionally, the measures showed only moderate accuracy when used to predict

patient mucosal inflammation with an area under the curve for correct classification ranging from 0.63 to 0.82. None of the reviewed PROMs have met the FDA criteria for validity, which recommend evaluating content validity, construct validity, criterion validity, reliability, and responsiveness to change. Finally, some PROMs only contain one question about ongoing disease activity, a factor that may be an issue since IBD has a multifactorial disease process.[4]

A variety of these IBD-specific PROMs have been detailed in Table 1. These six tools differ with regards to reliability, validity, and responsiveness to change, but show some similarity in the outcomes they measure. For example, the IBDQ-32, IBDQ-9, SIBDQ, and EIBDQ all evaluate a patient's quality of life. The best established of these tools is the IBDQ-32.[18] Despite its demonstrated utility in research settings, this PROM has failed to be utilized in clinical practice due to its lengthiness which inconveniences patients, and also its licensing requirement which deters providers.[19] In contrast, the IBD-CQ looks at outcomes of physical, social, emotional, and treatment response, and this tool ranks highest when considering reliability, validity, and responsiveness to change.[19] This thirteen-item metric assesses four core domains of IBD including physical symptoms, social impact, emotional impact, and treatment efficacy. The time of completion is roughly one minute, and the IBD-CQ does not require a license to be utilized.[20] Not only is the IBD-CQ simple to complete, but the results are also easily interpreted, and it has been proven to be effective in clinical settings based on studies set in the UK and Iran.[21,22]

Table 1*. Inflammatory bowel disease specific patient-reported outcome measures*

Measure	Outcomes	Reliability	Internal Consistency	Content Validity	Construct Validity	Responsiveness to Change
Inflammatory Bowel Disease Questionnaire (IBDQ-32)	Quality of life	High	Medium	High	Medium	Medium

Rating Form of IBD Patient Concerns (RFIPC)	IBD or treatment concerns	High	High	High	High	Low
Edinburgh Inflammatory Bowel Disease Questionnaire (EIBDQ)	Physical symptoms and quality of life	Low	Medium	High	Medium	Low
Inflammatory Bowel Disease Questionnaire - Short Form (IBDQ-9)	Quality of life	High	Medium	High	Medium	Low
Short Inflammatory Bowel Disease Questionnaire (SIBDQ)	Quality of life	High	Medium	High	Medium	Low
IBD Control Questionnaire (IBD-CQ)	Physical, social emotional, treatment response	High	High	High	High	High

Chart includes instruments that evaluate patient functioning or quality of life.[19,23]

Non-disease-specific PROMs which show great promise for use in the IBD patient population include the PROMIS system and the EQ-5D-5L. Launched by an initiative from the NIH in 2004, the Patient Reported Outcomes Measurement Information System (PROMIS) is a database of patient-centered tools that can be used to measure the physical and mental health of individuals.[24] These measurement tools are a result of the thrust to incorporate patient experiences into care in order to focus treatment and promote shared decision-making.[25] Additionally, patient experiences are more often being used to evaluate outcomes rather than solely relying on diagnostic information. The items of focus within the database are based on domains of interest, rather than specific disease processes, meaning they look at health factors such as pain, anxiety, or peer relationships.[26] The questionnaires from the PROMIS system have

been implemented in a variety of clinical settings, from gynecologic oncology to total shoulder arthroplasty.[27] Within the setting of IBD, questionnaires from the PROMIS database have been validated and implemented within clinical research for this population.[28-30] The PROMIS system has provided many useful tools for providers around the world to better understand their patients' experiences. A second non-disease specific PROM that has potential for use in the IBD population is the EQ-5D-5L. Developed in the late 1980s, the EQ-5D-5L is an internationally used instrument that has the capability to measure health-related quality of life. By observing the five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, the tool can differentiate between clinically important differences in health-related quality of life between individuals within a specific disease population.[31] The EQ-5D-5L has been successfully used as an outcome measure in other studies evaluating the routine use of PROMs in certain disease populations.[32] Furthermore, within the context of IBD, this tool has shown to be valid, reliable, and responsive.[33,34]

IBD is a chronic disease that often manifests when patients are in their early thirties and has been displaying a dramatic increase in prevalence as the population ages. The financial burden of IBD is considered to be between $14 to $31 billion in the United States each year, and there are significant demands to modify disease management towards effective and economical patient-centered care.[35] PROMs will be of utmost importance to pivot towards this value-based care, yet there is a significant lack of these measurement tools that fully meet the validity criteria. Optimally, PROMs will be integral to the decision-making process for the individualized treatment of each patient.[15] Empowering patients and integrating their perspectives into a treatment process will provide an unparalleled advantage for IBD care as well as the care of

other chronic conditions. Since these tools directly measure patient perspective, they will prove to be invaluable to both the PA practice and the medical field at large.

2.4 Clinical Promise of Patient-Reported Outcome Measures in Other Diseases

The literature on the benefits of using PROMs in routine clinical practice in other diseases is abundant. Their use has been studied in a variety of chronic conditions such as cancer,[36-38] chronic kidney disease,[39] mental health disorders,[40-42] multiple sclerosis,[43] rheumatoid arthritis,[44] among others. There has been significant research and integration of PROMs into routine practice with regards to treatment and management of cancer symptoms, as PROMs ensure patients' experiences and perspectives are involved in health outcome measurement when evaluating clinical research or when assessing quality of care in real world clinical practice.[45] One study researching patients with cirrhosis found 88% of providers found PROMs helpful in commencing patient treatment and counseling for specific symptoms. The same study showed 91% of the sample patient population found PROMs effective in communicating emotional and physical treatment needs to their providers.[46] In qualitative literature on the management of patients with non-malignant pain, providers felt PROMs made important contributions to the clinician-patient interaction, allowing for better goal setting and individualization of treatment.[47-49] Aside from chronic conditions, PROMs have also demonstrated the potential for clinical improvement in surgical subspecialties, exemplified in the United Kingdom with the National Health Service's program to collect PROs for hip and knee replacements, as well as groin hernia and varicose vein surgeries.[27] Additionally, many disease advocacy groups have championed the utilization of PROMs in disease management.[50] In summary, ample evidence suggests that weaving these instruments into routine clinical practice

to glean data on patients' perspectives will positively impact their outcomes via improving patient-provider interaction, communication, and shared decision-making.[51]

Furthermore, some research has gone beyond exploring the use of PROMs in improving the patient-provider relationship to their use in improving overall patient outcomes. One research study examined the use of a PROM during three outpatient clinic visits versus usual care for adolescent patients with Type 1 Diabetes Mellitus. After the three visits, those in the intervention group reported significant improvement in self-esteem and mental health, increased participation in family activities, and fewer behavioral problems as compared to those in the control group.[52] Another study examined the impact of PROMs for patients with advanced solid tumors receiving routine chemotherapy and found that the intervention group had an increase in health related quality of life as compared to the control cohort. Furthermore, patients in the intervention group were less frequently admitted to the emergency room or hospitalized during the study as compared to the control group, as the measurement tool was often able to pick-up on secondary symptoms of advanced cancer that often go undetected.[32] These studies confirm that the improved patient-provider communication found with the use of PROMs leads to a subsequent beneficial impact on patient outcomes.

2.5 Review of Relevant Methodology

Study Design Approaches and Possible Confounders

Most of the published trials evaluating the routine use of PROMs in clinical practice utilized parallel study designs,[32,37,38,40,52-70] but a minority of the trials did use crossover designs.[71,72] Parallel study designs are most commonly used in clinical research as they are both simple and feasible to complete.[73] In this design, patients are randomized to a study arm and will

stay in that assigned treatment arm for the duration of the research study.[74] In contrast, crossover designs, often used when investigating a non-curative and symptomatic treatment for a chronic illness, have many advantages. The chief advantage is the reduction of confounding bias in the study, as each crossover patient is his or her own control.[75] Unfortunately this advantage also leads to the design's major limitation: the effect of the order of intervention.[76] Receiving the intervention initially versus after the control intervention or vice versa may have a significant effect on participant outcomes.[77] Additionally, crossover trials require long periods of study participation.[78] As many of the trials assessed have a limitation of attrition to begin with, this added study time runs the risk of introducing additional selection bias and compromising data of the proposed study.[57,70,79] Finally, due to its relapsing-remitting nature, studying inflammatory bowel disease with the crossover design might not be ideal. Crossover study designs require that participants' disease states will be stable and return to baseline between trial periods, which may not occur in IBD.[80] In conclusion, the use of a parallel study design will be optimal in this clinical investigation as it will avoid the carryover effect of multiple interventions, reduce the length of subject participation, and is most appropriate to evaluate the patient population.

A thorough randomization process will be necessary to mitigate any possible confounding factors when employing a parallel study design. Randomization of study participants will minimize the effect of any confounding from age, sex, diagnosis (UC vs. CD), disease severity or activity, disease location, duration of disease, comorbidities, type of medical therapy, and socioeconomic factors. Previous studies with PROMs and other diseases controlled for covariates such as age, sex, race, and education level.[32,37,43,55,57,59,61,67,79] Trials specific to the population of patients with IBD controlled for gender, age, and disease type.[81,82] Confounding

will be minimized by employing a rigorous randomization protocol in our proposed research study.

Primary and Secondary Outcomes

Literature Review of Outcomes

There are a variety of outcomes measured and reported in the PROM research literature which are often grouped into three main categories.[83-86] The first category relates to delivery of clinical services, including the number of symptoms addressed by providers,[38,57,59,63,69,79] referral to outside resources,[42,72] discussion of health-related quality of life during clinic visit,[53,58,72] and documentation in the patient's medical chart.[58,64] Changes in the delivery of clinical services are cited as the most proximal outcomes, demonstrating changes in patient-provider communication, which will have downstream effects on patient outcomes.[87,88]

The second category of outcomes is change in patient health status, such as patient functioning,[65,68] quality of life,[32,41,52,57,68-70,72,79] number of emergency visits,[32,66] symptom distress,[38,40] and other symptomatology.[37,55,56,61-64,89] These changes in patient health outcomes are more distal to the intervention, downstream from changes to the patient-provider interaction and treatment decisions. The specific outcome of health-related quality of life has demonstrated statistically significant change after intervention in a variety of patient populations.[32,41,52] In most of the studies where this outcome has not been statistically significant, it has still demonstrated a positive trend.[68,70,79] Non-significant results could be due to a number of limitations in the referenced studies including high rates of attrition,[57,70,79] poor adherence to the intervention and missing data,[57,79] lack of education for providers regarding the use of the PROM,[70] poor standardization of the intervention,[69] lack of communication of results to the treating provider,[57,69] priming the treating provider towards discussing quality of care in all treatment

visits,[79] insufficient power,[57,68,69] and finally a short length of intervention and time to follow-up.[68]

The third outcome category was a general assessment of satisfaction with the quality of care, including the perceived utility of the PROM by the provider[53,54,62,70,72,79] or the patient,[32,41,52,54,57,58,61,62,64,67,69-72,79,89] or the cost-effectiveness of the intervention.[65]

A majority of primary outcomes in the literature assessed changes in patients' health status including HRQL[32,41,52,57,68-70,79] and specific patient symptomatology.[37,55,56,61-64,89] Many of the research papers reviewed used patient-physician communication measures as a primary outcome measure, such as discussion of quality of life during the clinic appointment[53,58,72] or the number of symptoms addressed in the appointment or in the medical record.[38,59,79] Still fewer used a primary outcome measure of satisfaction.[54,58,67]

Selected Outcomes for Research Proposal

For the purposes of our proposed intervention, we elected to use the primary outcome of change in patient health-related quality of life (HRQL) as measured by the EQ-5D-5L. With regards to secondary outcomes, we selected patient disease activity as measured by endoscopic scores (Mayo UC, CDAI), discussion of HRQL in the clinic visit, rate of disease exacerbations, patient and provider satisfaction, cost of treatment, and noninvasive biomarkers of disease activity (albumin, fecal calprotectin, CRP, ESR). As discussed earlier in the research proposal, the results of the PROM will also be assessed as to whether or not they correspond to disease activity and to measures of psychosocial domains, as well as the PROM's responsiveness across the six-month interval.

Study Population and Recruitment Approaches

Previous studies have included a variety of sample populations of patients with chronic conditions as these tools give providers information about patient symptomatology, functional capacity, and emotional status that are inaccessible from diagnostic tests alone.[88,90] PROMs assess SPADE (sleep, pain, anxiety, depression, energy) symptoms as well as any other nonspecific symptoms that patients often fail to bring up to their provider.[64] The relative anonymity of completing a PROM allows for the discretion of certain symptoms that carry significant stigma. For example, some clinicians have found that the implementation of PROMs enables frank conversations regarding sexual dysfunction, incontinence, and rectal bleeding in patients with prostate cancer, symptoms that were often downplayed or not discussed at all by patients prior to their use.[91] PROMs are ideal to use in the care of IBD due to the prevalence of anxiety, depression, fatigue, and reduced quality of life, symptoms not commonly addressed by providers, but of utmost importance to patients.[8,92] Furthermore, many of the symptoms involved in the condition carry significant stigma, which has the potential for interfering with patient-provider communication, a factor circumvented by the use of PROMs.[93]

Based on previous research, our recruitment approach will draw participants from a specialized inflammatory bowel disease gastroenterology outpatient clinic. This does have the potential limitation of selection bias, including only patients highly motivated and already connected to care. Since the proposed intervention would most benefit this select group of patients, this limitation is acceptable.

Inclusion and Exclusion Criteria

Most of the research studies reviewed used minimal restrictions on study populations, making each study more generalizable and comparable to real-world clinical practice. Most studies restricted participation to adult patients with a specific disorder.[53,55,56,61,65,66,68,69] Often

studies also required participants to have basic language proficiency,[32,37,54,56,58,61,62,64,72,79,89] and excluded those unable to provide informed consent.[37,56,57] A few studies listed an exclusion criteria of concurrently participating in any other HRQL studies, as there could potentially be a risk of contamination across different study interventions.[32,72,79] In some interventions, the computerized delivery of the PROM necessitated inclusion criteria of basic computer literacy[58,62,66] as well as exclusion criteria if the participant had no access to an email account.[65] Rarely studies excluded patients with other chronic medical issues that may influence the results of the PROM used.[37] Studies that did so suffered from a large loss of external validity as the number of patients with multiple chronic conditions has been estimated to be from 20 to 30 percent of the older population.[94]

Most of the reviewed interventions involving patients with IBD also restricted patient populations to adults with the disease diagnosis.[92,95-98] Some studies used specific exclusion criteria regarding the location of disease or the presence of a stoma due to difficulty with assessing disease activity indices in these patients.[92] Other studies confirmed the disease diagnosis with a central reader evaluating the patients' endoscopic data.[17,99] Some studies excluded patients with comorbidities of autoimmune diseases, infections, malignancies, small bowel obstruction, or ileostomy due to concerns that it could alter some of the laboratory assessments used in the study such as CRP or fecal calprotectin, resulting in limitations to the study's real world applications.[99]

As IBD is a chronic condition with a patient population that has many comorbidities, it will be important to stringently define the inclusion and exclusion criteria in order to maximize both external and internal validity. The inclusion criteria of adults with a diagnosis of IBD with basic literacy are necessary when using a PROM as an intervention in our study population.

Additionally, patients with an inability to provide informed consent or who are participating in other clinical studies will be excluded due to ethical and internal validity reasons, respectively. In order to maximize the study's generalizability and impact on clinical practice, exclusions to other comorbidities will not be used. Importantly, these few restrictions on patient eligibility criteria will enable our proposed study to feasibly recruit an adequate number of participants and make the results of our study generalizable to real world practice.

Intervention

The reviewed literature varied in regard to design and implementation of the PROM intervention. Most researchers provided feedback to clinicians regarding the results of patients' PROMs, but a few of the studies merely provided PROMs to patients without involving clinician feedback.[56,57] Failing to disclose PROM results to clinicians greatly reduces their potential utility to influence patient-physician communication and thus patient outcomes. Physician notification of the results of patients' PROMs is vital to our proposed intervention.

The studies also varied in the amount of education provided to clinicians regarding the intervention, with some interventions providing no provider training at all.[32,53,61,62,89] One recent literature review found no correlation between provider training and the success of a PROM intervention.[83] Contrary to this finding, researchers suggest that clinicians fail to implement these measures into practice due to skepticism regarding the validity of the measures, misconceptions about the time required to administer the measures, and unfamiliarity or lack of knowledge about how to effectively use the data in clinical practice.[49,100,101] Despite the mixed evidence in the literature that clinician education improves the implementation of the PROM in clinical practice, we believe this education will be necessary for the success of the intervention.

Finally, in a majority of the studies reviewed, the participants self-administered the PROM without the involvement of an interviewer, but a few studies involved telephone administration of the questions.[61,70] The self-administration method aligns with the original intent of the PROM to provide patients' perspectives, without the involvement of a clinician or third party, so this method will be used in our proposed intervention.[16] Although most PROMs were paper questionnaires, some did provide electronic modes of completion[32,38,58,70,71] which is more relevant to current practice as healthcare becomes more digitized, so this will be offered as an option in our research protocol.

Sample Size

The PROM studies reviewed had a large range of participants, the smallest being n=43[68] and the largest being n=1134[55]. Although not all studies reviewed reached statistical significance in outcome variables, this could be due to a variety of limitations in study designs as outlined in the "Primary and Secondary Outcomes" section of this chapter. Recruiting a large sample size is realistic given the large number of IBD patients seen annually in the specialized Yale IBD clinic.

2.6 Conclusion

This review of the relevant literature demonstrates the promise of the routine use of PROMs for the care of a variety of chronic conditions based on a wide array of studies which exhibit the tool's ability to improve patient-provider communication, increase recognition of symptoms, and improve patient outcomes and symptomatology. With an increasing prevalence of IBD in the general population, it is vital to evaluate the efficacy of the use of a PROM in this population clinically, as it may be used in lieu of more invasive and expensive disease monitoring procedures such as endoscopy. A majority of studies evaluating PROMs employed a

parallel design, as it reduces the length of participation and concern for participant attrition, as well as eliminates carryover effect implicit to crossover designs. The primary outcome elected for this research proposal was health-related quality of life, which was demonstrated throughout the studies in this literature review as a statistically significant outcome when implementing a PROM and will provide meaningful results, underscoring the utility of routine PROMs in IBD.

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Chapter Three: Study Methodology

3.1 Study Design

We will perform a prospective, parallel design, randomized clinical trial. Participants will be recruited using a convenience sampling method and enrolled in the study on a rolling basis. They will be randomized to study group using verified computer software and a random number generator. Both study and control groups will complete PROMs during the study period, and only the intervention group will have the data from these measures shared with their clinician to aid in treatment decisions, allowing us to evaluate whether this intervention improves health outcomes. Although the nature of our intervention prevents blinding of participants and treating clinicians, gastroenterologists interpreting colonoscopy reports and radiologists evaluating patient imaging will be blinded to treatment and intervention groups.

3.2 Study Population and Sampling

The study sample will draw from a population of adults with inflammatory bowel diseases including ulcerative colitis, Crohn's disease, either active or in remission. Both English and Spanish speaking subjects will be included, but due to translation constraints patients speaking other languages will be excluded. Patients will be recruited from the Yale Inflammatory Bowel Disease Clinic at Temple Medical Center in New Haven and Devine Center in North Haven. This convenience sampling method has the potential to exclude patients who don't routinely seek medical care, but since the PROM intervention would most benefit a target population of motivated patients who routinely seek medical care this limitation is acceptable.

All patients who meet specific inclusion and exclusion criteria will be eligible to be included in the study. Inclusion criteria include patients 18 years of age and older with a

diagnosis of inflammatory bowel disease who are undergoing a colonoscopy, MR enterography, CT enterography, or capsule endoscopy within 7 days of initial screening and baseline questionnaires. Eligible subjects must also have the ability to provide fully informed written consent for participation in the study and have the literacy skills necessary to complete the questionnaires. Exclusion criteria include concurrent participation in other research studies, cognitive impairment by clinical impression, and non-English or non-Spanish speaking patients.

***Table 2**. Inclusion and Exclusion Criteria*

Inclusion Criteria	**Exclusion Criteria**
18 years or older	Concurrent participation in other research studies
Inflammatory bowel disease diagnosis	Cognitive impairment by clinical impression
Undergoing objective disease assessment within 7 days of initial clinic assessment	Neither Spanish nor English speaking
Language proficiency to complete questionnaires	Inability to provide fully informed written consent

3.3 Subject Protection and Confidentiality

IRB approval has been accomplished per Yale IRB Policy 100 PR.1 Review by a Convened Institutional Review Board, IRB approval number 200026769. All eligible study participants will be required to provide written informed consent. This consent will detail our research study's purpose, procedures, duration, and benefits of participation, as per Yale IRB Policy 200 Informed Consent for Human Research. In addition to any risks of participation, this consent will lay out alternative treatment strategies including other methods of monitoring IBD symptomatology. The consent form will detail patient confidentiality and privacy practices including medical records examined by the research personnel or the IRB. Contact information for all research personnel including the principal investigator, and details regarding participant compensation will also be outlined in the consent form. The form will explain that the

participants may discontinue the study at any time. The participants' disease care will not be influenced by dropping out of the study and participants do not need to provide an explanation for doing so. Additionally, research personnel may also remove participants from the study at their discretion. Any resulting effects from participant discontinuation including changes in compensation will be detailed in the consent form. If any new information emerges that has the potential to change a participant's decision to participate in the research study, that information will be provided to the subjects immediately and they will be re-consented. The consent form is attached in Appendix A.

The research study will comply with the Health Insurance Portability and Accountability Act (HIPAA) regulations including participant recruitment and research protocol. Any personal health information will be encrypted. Confidentiality will be ensured by de-identifying all data and using password protected encrypted computer servers.

3.4 Recruitment

Patients will be recruited from the Yale Inflammatory Bowel Disease Clinic at Temple Medical Center in New Haven, CT and Devine Center in North Haven, CT. In addition, flyers will be posted throughout the New Haven area. A sample flyer is provided in Appendix B. Participants will be compensated with a $100 Visa gift card at each of the two visits which will also aid recruitment.

3.5 Study Variables and Measures: Primary Outcome, Secondary Outcomes

In the study intervention group, patients will complete PROM questionnaires prior to their appointment (IBD-CQ and PROMIS). The PROMIS questionnaires include the short form

measures of Emotional Distress–Depression, Emotional Distress–Anxiety, Fatigue, Sleep Disturbance, Pain Interference, and Satisfaction with Participation in Social Roles. The clinician will receive the results of the PROM and the patient's subscores and use this information to discuss treatment during the visit.

The control group will undergo standard of care which will include a thorough baseline exam, a therapy plan based on current guidelines.[1-3] The control group will complete the same IBD-CQ and PROMIS questionnaires prior to each of their clinical appointments. However, the results of these questionnaires will not be provided to their clinician.

All patients will undergo objective disease assessment within 7 days of completing the initial questionnaires depending on the disease locations with either colonoscopy, video capsule endoscopic, magnetic resonance enterography (MRE). In addition, within 7 days of completing the questionnaires patient will undergo non-invasive inflammatory marker assessment with CRP and fecal calprotectin measurements.

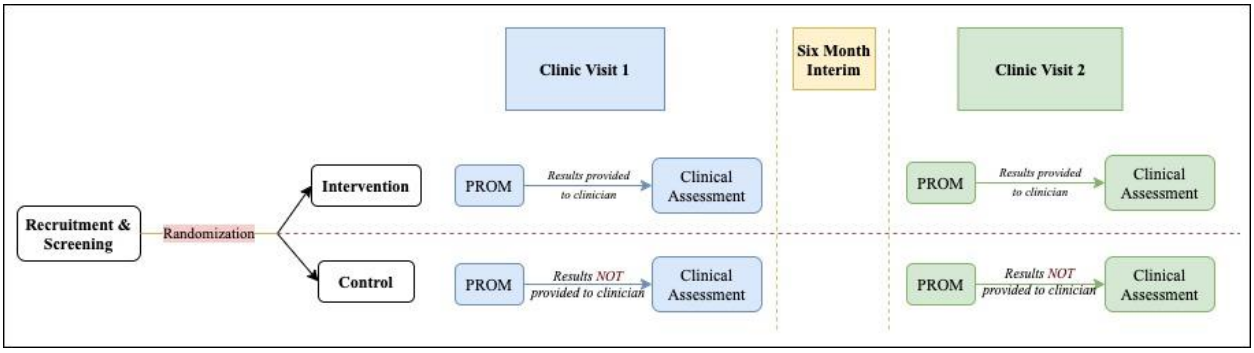
Both intervention and control group patients will have a second clinic visit six months after the initial assessment where the questionnaires and clinical assessment measures will be repeated. Both participants and providers will rate their satisfaction with the clinical interaction after each study visit via a questionnaire. All questionnaires and rating scales used in the research study are detailed in Appendix D.

The primary outcome will be change in the patients' health-related quality of life as measured by a questionnaire (EQ-5D-5L). Secondary outcomes include change in patient disease activity as measured by clinical and endoscopic scoring systems (Mayo UC score for patients with ulcerative colitis and the Crohn's Disease Activity Index (CDAI) for patients with Crohn's disease), discussion of HRQL in the clinic visit, rate of disease exacerbations, patient and

provider satisfaction as measured by questionnaire, cost of treatment, and noninvasive measures of disease activity such as albumin, fecal calprotectin, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

This information will be used to determine the extent to which the IBD-CQ aligns with traditional measures of disease activity and psychosocial domains. Furthermore, we will assess the questionnaires' responsiveness across the six-month interval between study visits. Overall this information will provide guidelines to inform clinical monitoring methods for patients with IBD and promote the practice of patient-centered care.

***Figure 1**. Proposed Research Study Protocol*



3.6 Adherence and Adverse Events

Information about patient adherence will be easily accessible based on whether or not the PROMs are completed. The electronic medical record will be reviewed for evidence of the discussion of health-related quality of life during each clinical visit. Providers and patients will also indicate whether or not patient health related quality of life was discussed during the visit in the short satisfaction questionnaire after each appointment (Appendix D).

Participants will be asked during each study visit detailed questions about any adverse events they have experienced during the study time period. The phone number of both the

research assistant and medical providers will be provided to each participant in case of questions or concerns.

3.7 Data Collection

Disease activity will be measured using standard of care procedures and imaging including colonoscopy, CT enterography, MR enterography, or capsule endoscopy. Mucosal healing will be assessed via review of the colonoscopy reports by a gastroenterologist blinded to the participant's group allocation. Mucosal healing in Crohn's disease will be defined as absence of ulcerations. Mucosal healing in ulcerative colitis will be defined as Mayo-UC score of 0 or 1. Radiologists will be blinded to the patients' study group and questionnaire responses. Non-invasive measures of disease activity will be collected via a blood draw including CRP, albumin, and fecal calprotectin.

Data will be abstracted from the medical record for demographics including age, sex, body mass index, smoking status, type of inflammatory bowel disease and disease location, extent, severity and duration. Previous and current medical and surgical therapy will be noted.

PROM questionnaire data will include the IBD control questionnaire, the PROMIS measures of depression, anxiety, fatigue, sleep, pain, and social functioning, and a health-related quality of life questionnaire (EQ-5D-5L). Participants will receive questionnaires via email and can respond electronically prior to their study visit. In the event that a patient does not have access to the internet, paper copies of the questionnaires will be mailed to their house.

3.8 Sample Size Calculation

Our sample size calculation was based on data from a 2016 research study by Basch et al. These researchers compared using a PROM prior to clinic appointments for routine cancer treatment versus usual care, with a primary outcome measure of proportion of patients with a significantly improved health-related quality of life at six months measured by the EuroQol EQ-5D Index. This trial was subject to significant patient attrition given the population studied, and so gives a conservative estimate of the sample size needed for our proposed intervention. Our sample size estimation assumes the proportion of patients with improved quality of life scores after six months will be 34% and 18% in the intervention and control arms respectively, with an absolute difference between groups of 16%. With an alpha of 0.05 and 80% power we calculate a sample size of 234 when assuming a 2-tailed hypothesis. Our anticipated attrition rate is 10%, so subsequently to compensate for this loss of data, we will recruit a goal of 258 participants. Appendix C details the calculations resulting in the required sample size figures.

3.9 Analysis

Baseline characteristics that could be potential confounders including disease type, disease activity or severity, age, sex, disease duration, previous surgery, medication, and location of disease will be operationalized as proportions and so will be compared using Chi-Square tests. Continuous variables including mean change in health-related quality of life score (primary), mean change in clinical disease activity score as measured by CDAI or Mayo-UC Score, and mean change in PROM subscores will be represented as means in standard deviation and analyzed with student's t-test. The data will be adjusted for confounders using multiple logistic regression analysis. Analysis will be performed under the intention-to-treat model. The significance level will be present at $P < 0.05$.

We will assess the underlying structure of the IBD-CQ using principal components analysis. We will consider a factor to be relevant if its eigenvalue is greater than 1.1 and has face validity. Questions that have a loading factor of less than 0.4 will be considered for removal. Additionally, we will assess the internal consistency of the IBD-CQ using item-by-item correlations and Cronbach's alpha. Correlations less than 0.20 and greater than 0.80 will be considered for rejection. Questions where participants answered the same (greater than 80%) will also be considered for rejection as they will not be sensitive enough to discriminate severity. We will also aim for a Cronbach's alpha to be greater than 0.70. We will assess for the agreement between the IBD-CQ and clinical disease activity indices using correlations and Bland-Altman plots. We will assess the correlations between the IBD-CQ and PROMIS questionnaires using Pearson and Spearman's correlations as appropriate. We will assess the responsiveness of the IBD-CQ by repeating the questionnaire six months later and calculating the responsiveness ratio.

We will assess the IBD-CQ ability in predicting mucosal healing by calculating the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio for a positive result (LR+), and likelihood ratio for a negative test result (LR-).

3.10 Timeline and Resources

In total, the study will span two years, from gathering participants to data collection. Participants will be recruited on a rolling basis during the first fifteen months of the study and scheduled for an initial visit at their earliest convenience. A six-month follow-up visit will also be scheduled for each participant. Data analysis will be performed for an additional two to three months after the completion of the study.

The protocol for the initial visit will take place at the Yale IBD Center locations at Temple Medical Center in New Haven, CT and in North Haven, CT. Each participant will complete baseline assessments prior to their visit and within 7 days of objective disease assessment. The baseline assessments include the EuroQol questionnaire (EQ-5D-5L), the IBD-Control Questionnaire, and PROMIS questionnaires of depression, anxiety, fatigue, sleep, pain, and social functioning. In the intervention arm, results of these questionnaires will be provided to the clinician to inform subsequent treatment. In the control group, the results from the questionnaires will not be provided to their treating clinicians.

The baseline assessment will include a history and physical exam conducted by a gastroenterology clinician as well as a colonoscopy, MR enterography, CT enterography, or capsule endoscopy depending on what is appropriate for the individual patient. After their initial study visit, participants will complete a brief satisfaction questionnaire. Patients will be scheduled for a follow-up visit in six months where all assessments will be repeated.

In order for the proposed study to take place, the required staff will include three providers, six nurses, a radiologist, and a research assistant to record and track patient-reported data. All study personnel will attend a three-hour training session led by the research assistant about the use of PROMs in general, and the specific measures used in the study. The PROM will be sent out to participants via email but if necessary, paper copies will be mailed to the participants' homes. Patient parking will either be validated within respective garages or reimbursed if appropriate. Compensation for each participant will consist of $100 per visit, paid in the form of a VISA gift card.

***Figure 2**. Proposed Study Protocol Timeline*

3.11 References

1. D'Haens GR, Panaccione R, Higgins PD, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? *Am J Gastroenterol.* 2011;106(2):199-212; quiz 213.
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Chapter Four: Discussion and Conclusions

4.1 Overview

IBD is a chronic relapsing-remitting disorder with an ever-increasing prevalence that requires frequent monitoring. This monitoring process includes invasive and expensive procedures such as endoscopy. Unfortunately, endoscopic remission often does not correlate with symptomatic remission.[1,2] Additionally, even with frequent monitoring, symptoms such as fatigue and mental health issues are often not considered in patient treatment regimens or do not respond to the IBD medical regimen, despite both the prevalence and severity of these symptoms and their paramount importance to patients.[3] Gastroenterologists currently seek an improved method of disease monitoring that is less invasive, less costly, and more patient-centered. Many in the field look towards PROMs to fill this gap.[4,5] The use of PROMs has been studied in other chronic diseases and they have been shown to be a cost-effective method to improve both provider-patient communication and to improve patient symptomatology. Despite their proven efficacy in other chronic conditions, researchers have not yet studied the efficacy PROM utilization in the population of patients with IBD with a randomized clinical trial. The proposed study aims to fill that gap in knowledge by performing a randomized controlled trial to evaluate the efficacy of utilizing routine PROMs in clinical practice. Results from this trial will inform clinical practice guidelines for monitoring IBD. If successful, this proposed study will provide invaluable insight into the care of chronic conditions across a wide spectrum of disorders.

4.2 Advantages and Disadvantages

This proposal builds on the exhaustive literature exhibiting the utility of PROMs to improve patient-provider communication and patient outcomes in a variety of chronic disorders.

Our research design furthers this information by evaluating the efficacy of routine use of PROMs in the IBD population. The study connects clinical research and real life by evaluating a potential tool that will promote a discussion of IBD symptoms that are prevalent and important to the population, but often overlooked by healthcare professionals. PROMs are often found to foster discussions of quality of life and other symptomatology that is rarely brought up in a clinical encounter, but greatly affects our patients' day-to-day living. In addition, the inclusion of our secondary variables will further inform the functionality of the PROM tool for patients with IBD. This research is a feasible option to confirm the efficacy of PROM monitoring of IBD, creating a more patient-centered approach to managing this chronic condition.

There are a few limitations to our study design that are necessary to evaluate our hypothesis, and we will take various steps to mitigate each of these disadvantages. The first main limitation of the study is its inclusion of a heterogenous study population of patients with both ulcerative colitis and Crohn's disease of varying severities. Although this may introduce confounding, including this diverse set of patients is a necessity to allow for generalizability. We will also control for disease activity and severity. Randomization and the large sample size utilized in the study will minimize potential negative effects from the varied study population. Secondly, our intensive regimen of questionnaires introduces the possibility of questionnaire fatigue which could result in missing data and information bias affecting the study outcomes. Our team chose to employ a relatively short questionnaire, and will send out regular reminders to study participants about questionnaire completion which research has shown improves compliance.[6] Although we considered including serial completion of PROMs every two weeks over the six month interval between clinic visits, this was ultimately rejected to minimize the risk of questionnaire fatigue. Additionally we will thoroughly explain both patient confidentiality and

participation during the consenting process, as misinformation about use of questionnaire data has been shown to decrease patient survey completion.[7] Furthermore, the nature of our intervention renders the blinding of participants and providers to study group impossible, which introduces risk of performance bias. Although this limitation is difficult to avoid, our intervention will blind participants and personnel to the study hypothesis, reducing this bias. Additionally, we will blind outcome assessors when possible, such as reviewers of endoscopy and radiology images. Finally, the research study suffers from the assumption that providing the results of the PROM to the clinician will result in changes in both the clinician treatment and also the subsequent patient outcomes. It remains challenging to measure the direct action taken by each clinician. To mitigate this limitation, the medical record for each visit will be reviewed to determine whether quality of life was discussed during the visit, which we will use as a proxy for the clinician's actions.

4.3 Feasibility

Our proposed research study's timeline spans 24 months, including recruitment, data collection, and data analysis. We have allotted fifteen months for rolling participant recruitment, an additional six months for the patient follow-up visit, and finally three months of data analysis after study completion. This proposed timeline makes our study feasible from a scheduling perspective.

A majority of our intervention involves routine clinical management and tasks that would be performed regardless of whether or not we were engaging in this study. The additional resources required include various flyers, potential postage fees in the event a patient does not have access to the internet, and a research coordinator to ensure recruitment, data collection, and

analysis run smoothly. Intervention training of personnel will include a three-hour session prepared by the research assistant. The personnel that will need to be trained are nurse practitioners, medical doctors, physician assistants, and nurses, ideally all of whom can attend the same training session. The research coordinator along with the principal investigator will consult with a statistician at Yale School of Medicine for data management and analysis. Overall, our proposed research is feasible due to the minimal amount of required resources.

With regards to study subjects, the layout of the proposal maximizes patient safety and ensures they will be able to complete the intervention seamlessly. The questionnaires used in the study are relatively short and completed online at the participant's convenience prior to the visit. Participants will be recruited from current gastroenterology clinics that see a large number of patients each year, making recruitment a feasible task. The intervention in our study adds one additional clinic appointment to each participant's normal IBD monitoring. To maximize compliance of the intervention, subjects will be compensated a $100 Visa gift card at each visit. With these provisions our research protocol is feasible within the allotted 24 months, requiring minimal funding and resources.

4.4 Clinical Implications and Future Directions

Current disease monitoring for IBD is costly and invasive, and also lacks information about certain patient symptomatology and the patient perspective. This gap in diagnostic monitoring could potentially be filled by utilizing PROMs. A myriad of research has been conducted to explore the use of PROMs in multiple different disease cohorts. Despite the depth of this research, the efficacy of PROMs in the IBD population has not yet been explored.

The use of PROMs has been shown to improve patient-provider communication, refocus disease treatment towards patient goals, and improve patient outcomes. Using our particular study design, results will be generalizable to patients with varying severities and types of IBD. These research results may be incorporated into standard disease management because our pragmatic study design closely aligns with real-world clinical practice. Performing the proposed research study will have lasting implications for gastroenterology clinic practices, and potentially those of other chronic disease specialties.

Following the completion of this proposed research study, there are a variety of subsequent steps that may be taken to further investigate the utility of PROMs in IBD management. For example, a major next step could entail using a PROM to identify each patient's personal priority symptom, and focus disease management to target this specific issue, as has been done with patients with rheumatoid arthritis.[8] In addition, it may be beneficial to build on existing research by studying the use of PROMs within cohorts of patients with treatment-resistant symptoms to best optimize coordination of care for those that utilize a majority of resources.[9] Alternatively, PROMs could be used to identify patients whose disease is quiescent and do not require frequent follow-up appointments. Finally, there is a potential to investigate the combination of weekly patient PROM completion and telemedicine appointments, which could allow the provider to adjust treatment with increased frequency. While there are many different paths that may be taken after the conclusion of this research, our proposed study provides a necessary basis of knowledge for these future investigations.

In conclusion, we will determine the efficacy of using a patient-reported outcome measure to inform treatment for inflammatory bowel disease. This study will confirm the utility of these measures, revolutionizing inflammatory bowel disease treatment, reducing costs and

risks associated with disease management, and transitioning the field toward patient-centered care, providing implications for other chronic disease management.

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Appendices

Appendix A. Participant Consent Form

PERMISSION FOR PARTICIPATION IN A RESEARCH PROJECT
310 FR. 2 (2016-1)

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: Utilizing a patient-reported outcome measure in the management of inflammatory bowel disease
Principal Investigator: Badr Al Bawardy, MD
Co-Principal Investigator: Jennifer Farren, PA-SII
Funding Source: Pending

Invitation to Participate and Description of Project

We are inviting you to participate in a research study designed to look at the routine use of a patient-reported outcome measure in the care of adults with inflammatory bowel disease. Patient-reported outcome measures are questionnaires designed by patients to evaluate important subjective symptoms of disease like pain or fatigue. Information from these questionnaires helps providers gain valuable insight into patient perspectives. You have been asked to participate because you have a diagnosis of inflammatory bowel disease and are 18 years or older. Approximately 250 people will participate in this study.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This permission form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to participating in this study, you will have two clinic appointments at Temple Street Medical Center Digestive Diseases department. Much of what is included in each study visit is identical to your standard clinical care. In addition to this routine IBD care, you will be asked to complete multiple questionnaires. The second variation from your standard appointments is that these two visits will be separated by just six months, so you will be seen by your clinician more frequently than usual.

Clinic Appointment One:

During your first clinic appointment, a member of our research team will complete the consenting process with you. Following the consenting procedure, you will be randomized to one of two groups: the intervention group or the control group.

Randomization means that subjects will be assigned to these groups by chance, without the input of a participant or their provider. A computer, not a clinician will decide which of the two groups you will be in. The decision will be random and due to chance alone, and not based on the patient's or doctor's decision.

Researchers will use a computerized random number generator to put you in either group. In the intervention group, participants will complete questionnaires prior to their clinic appointment, and results of the questionnaires will be given to their treating provider. In the control group, participants will complete the questionnaires prior to their clinic appointment, and their clinician will not receive the results of the questionnaires. The questionnaires you will be asked to complete are detailed below.

During the first clinic visit you will also have an appointment with your provider. Your provider will ask you details about any recent symptoms you have had and more details about your medical history. The provider will also perform a physical exam. Finally, your clinician will use the appropriate imaging tool to evaluate your bowels for inflammation. This tool could be a colonoscopy, MR enterography, CT enterography, or capsule endoscopy. A trained radiologist will evaluate the images from this procedure.

Clinic Appointment Two:

Six months later, you will attend your second clinic appointment. The schedule for this appointment will be very similar to the first. You will again complete many of the same questionnaires and have a similar discussion and physical exam with a provider. Your provider will decide whether or not the imaging tools will be necessary for treatment decisions at this appointment. Based on this decision you may receive a colonoscopy, MR enterography, CT enterography, or capsule endoscopy, and these images will be evaluated by a radiologist.

Questionnaires*:*

All questionnaires will be completed prior to your study visits. The questionnaires will be sent to your email address and completed online. If necessary, paper forms of your questionnaires will be mailed to your home.

For the first study visit, you will be asked to fill out a demographics questionnaire. This will ask you to answer questions about your age, gender, occupation, education, household income, ethnicity, and marital status. It will take approximately two minutes to complete.

For both your first and second study visit, you will be asked to complete the IBD-Control Questionnaire (IBD-CQ), the Patient-Reported Outcome Measure Information System (PROMIS) questionnaires, and the European Quality of Life-Five Dimension (EQ-5D) questionnaire. The IBD-CQ will ask you about your satisfaction with your current IBD treatment, and questions about your IBD symptoms in the past two weeks. It will take about two minutes to complete. The PROMIS questionnaires will ask you questions about your social functioning, anxiety, depression, pain, and fatigue. Completing these will take approximately ten minutes. The EQ-5D will include questions about your quality of life and will take about five minutes to complete.

First Clinic Appointment		**Second Clinic Appointment**	
Questionnaires	**Time**	**Questionnaires**	**Time**
Demographics	2 minutes	IBD-CQ	2 minutes
IBD-CQ	2 minutes	PROMIS	10 minutes
PROMIS	10 minutes	EQ-5D	5 minutes
EQ-5D	5 minutes	***Total***	***17 minutes***
Total	***19 minutes***		

***Medical Record Access*:**

If you decide to participate in this study, researchers will also access your medical records for information related to your IBD. They will examine your type of IBD (ulcerative colitis or Crohn's disease), the location of your disease, when you were diagnosed, what medications or surgeries you have tried for your disease management, any hospitalizations or emergency room visits you have had related to your IBD, laboratory results related to your IBD (fecal calprotectin, erythrocyte sedimentation rate, c-reactive protein, albumin), and finally any other disease diagnoses you have. This information will be used to determine whether these factors alter any of the other measurements in the study.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

Risks and Inconveniences

- Questionnaire contents may include personal information related to physical and psychological symptoms such as fatigue, anxiety, depression, and sexual dysfunction and there is the possible risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.
- The intervention section of this research trial includes provider discussion of questionnaire information. As questionnaires do obtain personal information this may cause psychological stress.
- As listed above, the questionnaires will take at most twenty minutes to complete at each appointment. This time commitment will be streamlined as much as possible by the research coordinator as well as compensated with a $100 Visa gift card.
- One potential inconvenience is the relatively rapid follow-up appointment which occurs six months after the first study visit, which is sooner than the normal standard of care for IBD. This inconvenience ideally will be mitigated by the validation of parking and the compensation of a $100 Visa gift card.

Benefits

- This clinical trial may modify the standard of care of IBD by integrating patient-reported outcome measures (PROMs) into routine clinical monitoring.
- The results from this study may benefit the population of IBD patients and patients with chronic conditions via contributions to scientific literature.
- This study will not directly benefit you.

Economic Considerations

- Participants will be compensated $100 in the form of a Visa gift card at each study visit. Participants that complete only one study visit will receive one $100 Visa gift card. Participants that complete both study visits will receive two $100 Visa gift cards.
- Parking will be reimbursed at each clinic appointment. Transportation costs such as gas, tolls, or bus fare will not be compensated for, and each participant is responsible for these additional costs.
- According to the rules of the Internal Revenue Service (IRS), payments that are made to you as a result of your participation in a study may be considered taxable income.
- You will still be responsible for any co-pays required by your insurance company for standard treatment.

Treatment Alternatives

Alternative IBD disease monitoring does not include completion of the questionnaires detailed above. This is different from our study, as all participants will complete these questionnaires.

Confidentiality

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases.

All data on study participants will be de-identified, removing names, addresses, phone numbers, health insurance information, and all other personal health information. Data will be coded by number, and these codes will be stored on password-protected databases on encrypted computers. Only the principal investigator and the research assistant will have access to these codes. All de-identified data will be stored in locked cabinets. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific permission for this activity is obtained.

Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g. health insurance company, disability provider).

You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

You are free to choose not to participate and if you do decide to become a subject you are free to withdraw from this study at any time during its course. Refusing to participate or withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). If you decide not to participate or if you withdraw, it will not harm you or your relationship with your own doctors or with Yale Digestive Diseases Department or Yale-New Haven Hospital. We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment. Once data for this research has been collected, it will be unable to be withdrawn, as it has been anonymized.

The researchers may withdraw you from participating in the research if necessary. Conditions under which subjects might be withdrawn from the research include noncompliance with study questionnaires or an indeterminate IBD diagnosis.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the permission form carefully – as long as you feel is necessary – before you make a decision.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this permission form.

By signing this form, I give permission to the researchers to use and give out information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Participant: _____

Participant Signature: _____

Date: _____

_____ _____

Signature of Person Obtaining Permission Date

or

_____ _____

Signature of Principal Investigator Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Dr. Badr Al Bawardy, (555) 555-5555.

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at (203) 432-5919.

If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

Appendix B: Study Flyer

Volunteers Needed for Research Study

What is the study?

Researchers at Yale New Haven Health System are running a study to evaluate the routine use of a patient-reported outcome measure in the care of adults with inflammatory bowel disease. Patient-reported outcome measures are questionnaires designed by patients to evaluate important symptoms of disease like pain or fatigue. Information from these questionnaires helps providers gain valuable insight into patient perspectives.

Who is eligible?

You are eligible for the study if you are **18 years or older** and have a medical diagnosis of **inflammatory bowel disease**.

What will you be asked to do?

Study participants will be asked to attend two clinic visits with a YNHH gastroenterologist within six months. At these visits, they will receive standard clinical care and also fill out questionnaires.

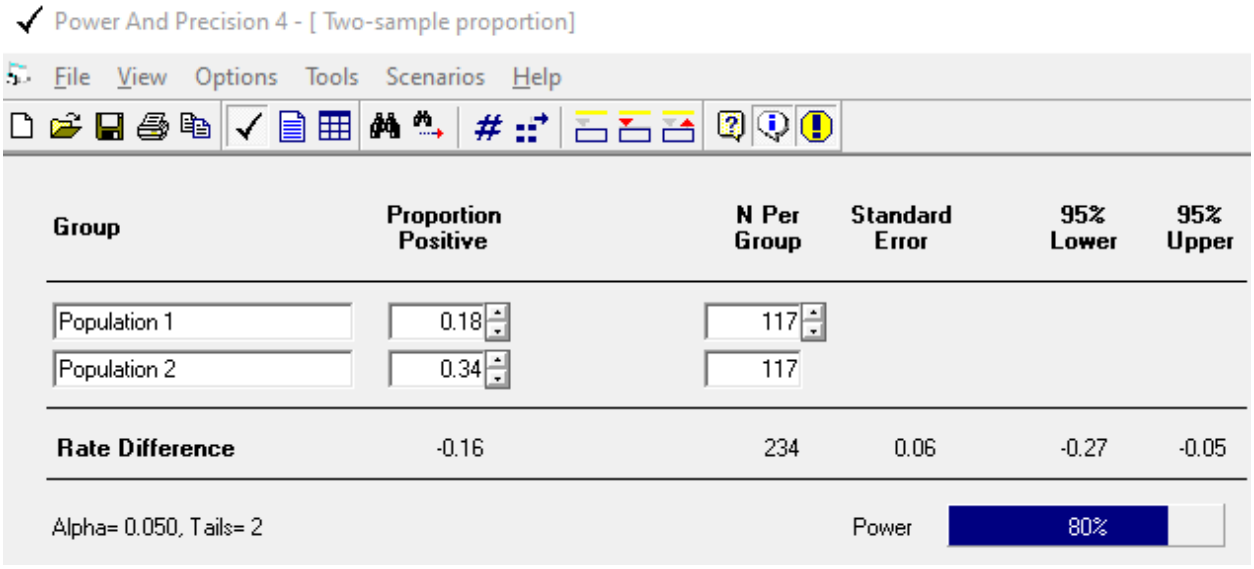
Is there compensation for participation?

Participants will be compensated up to $100 in the form of a Visa gift card and receive parking reimbursement each study visit.

If you are interested in participating or have any questions, please contact our research coordinator at (555)-555-5555 or promresearchcoordinator@ynhh.com.

Appendix C: Sample Size Calculation

Figure 3. Power and Precision Sample Size Calculation



N Per Group above represents the number of participants needed in the intervention and control arms of the study. Factoring in an expected ten percent attrition rate, the total sample size required in the study is n=258.

Calculated using: Power and Precision. Version 4.0. Biostat, Inc. Englewood, New Jersey.

Appendix D: Questionnaires

D.1 Inflammatory Bowel Disease Control Questionnaire (IBD-CQ)

IBD Control

Inflammatory Bowel Disease Control Questionnaire

1 Do you believe that:

	Yes	No	Not sure
a. Your IBD has been well controlled in the past *two weeks* ?	☐	☐	☐
b. Your *current treatment* is useful in controlling your IBD?	☐	☐	☐

(If you are not taking any treatment, please tick this box ☐)

2 Over the past 2 weeks, have your bowel symptoms been getting worse, getting better or not changed?	Better	No change	Worse
	☐	☐	☐

3 In the past 2 weeks, did you:

	Yes	No	Not sure
a. Miss any planned activities because of IBD? (e.g. attending school/college, going to work or a social event)	☐	☐	☐
b. Wake up at night because of symptoms of IBD?	☐	☐	☐
c. Suffer from significant pain or discomfort?	☐	☐	☐
d. Often feel lacking in energy (fatigued) (by 'often' we mean more than half of the the time)	☐	☐	☐
e. Feel anxious or depressed because of your IBD?	☐	☐	☐
f. Think you needed a change to your treatment?	☐	☐	☐

4 At your next clinic visit, would you like to discuss:

	Yes	No	Not sure
a. Alternative types of drug for controlling IBD	☐	☐	☐
b. Ways to adjust your own treatment	☐	☐	☐
c. Side effects or difficulties with using your medicines	☐	☐	☐
d. New symptoms that have developed since your last visit	☐	☐	☐

5 How would you rate the OVERALL control of your IBD in the past *two weeks*?

Please draw a vertical line (|) on the scale below

D.2 Patient Reported Outcomes Measurement Information System (PROMIS)

D.2.1 PROMIS – Depression

Emotional Distress-Depression – Short Form 4a

Please respond to each question or statement by marking one box per row.

	In the past 7 days...	Never	Rarely	Sometimes	Often	Always
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP08	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

D.2.2 PROMIS – Anxiety

Emotional Distress-Anxiety – Short Form 4a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

D.2.3 PROMIS – Fatigue

Fatigue – Short Form 4a

Please respond to each question or statement by marking one box per row.

	During the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…					
FATEXP41	How run-down did you feel on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

D.2.4 PROMIS – Sleep

Sleep Disturbance – Short Form 4a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

D.2.5 PROMIS – Pain

Pain Interference – Short Form 4a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9	How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

D.2.6 PROMIS – Social Functioning

Satisfaction with Participation in Social Roles – Short Form 4a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
SRPSAT07	I am satisfied with how much work I can do (include work at home).....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT24	I am satisfied with my ability to work (include work at home)……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT47	I am satisfied with my ability to do regular personal and household responsibilities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT49	I am satisfied with my ability to perform my daily routines.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

D.3 EuroQoL 5D 5L (EQ-5D-5L)

EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

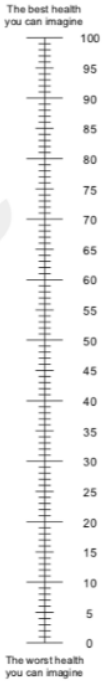
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



D.4 Satisfaction Survey – Patient

Please check one box:	**Yes**		**No**	
Did you discuss your quality of life with your provider at your appointment today?	☐		☐	
Please rate each of the following:	**Excellent**	**Good**	**Fair**	**Poor**
The communication with your physician	☐	☐	☐	☐
The quality of the care you received	☐	☐	☐	☐
Overall, how would you rate your experience?	☐	☐	☐	☐
Do you have any comments?	_____ _____ _____ _____ _____			

D.5 Satisfaction Survey – Provider

Please check one box:	**Yes**		**No**	
Did you discuss your patient's quality of life with your patient at the appointment today?	☐		☐	
Please rate each of the following:	**Excellent**	**Good**	**Fair**	**Poor**
The communication with your patient	☐	☐	☐	☐
The quality of the care you provided	☐	☐	☐	☐
Overall, how would you rate your experience?	☐	☐	☐	☐
Do you have any comments?	_____ _____ _____ _____ _____			

D.6 Mayo UC Score

Parameter	Score
A. Stool Frequency	0 = Normal 1 = 1-2 stools/day more than normal 2 = 3-4 stools/day more than normal 3 = 5 or more stools/day than normal
B. Rectal bleeding	0 = None 1 = Visible blood with stool less than half the time 2 = Visible blood with stool half of the time or more 3 = Passing blood alone
C. Mucosal appearance at endoscopy	0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)
D. Physician rating of disease activity	0 = Normal 1 = Mild 2 = Moderate 3 = Severe
Full Mayo Index Score = A + B + C + D **Partial Mayo Index Score** = A + B + D	

Interpretation of Mayo Index Scores	
Full Mayo Index Score	*Score*
Higher = more severe	0-12
Partial Mayo Index Score	
Remission	0-1
Mild	2-4
Moderate	5-6
Severe	7-9

D.7 Crohn's Disease Activity Index (CDAI)

Parameter	Score	Weight
P1. Number of liquid or soft stools (evaluated within a week)	0, 1, or 2	2
P2. Daily abdominal pain (evaluated within a week)	0 = none 1 = mild 2 = moderate 3 = severe	5
P3. Patient wellbeing (evaluated within a week)	0 = very well 1 = slightly below par 2 = poor 3 = very poor 4 = terrible	7
P4. Complications	0 = No 1-6 = Yes (drop-down menu with multiple selections, each complication is counted as one point) Arthralgia or arthritis Iritis or uveitis Erythema nodosum, pyoderma gangrenosum, or aphthous ulcer Fissures, anal abscesses, or fistulas Other fistulas Fever during the previous week	20
P5. Use of diphenoxylate or opiates as anti-diarrheal	0 = No 1 = Yes	30
P6. Abdominal mass	0 = No 0.4 = Dubious 1 = Yes	10
P7. Hematocrit	0-100% = difference between standard value and current value (# = Standard – Current) *Standard Value: 47 for males, 42 for females*	6
P8. Body weight	-10-100% = the percent change in weight compared to the standard weight (# = 100 x ((Standard-Current)/Standard)) *Standard Value: (height in m)^2 x 22.1 for males, (height in m)^2 x 20.8 for females* *In case of excessive negative change, the maximum score is -10 points*	
Summary Score (CDAI) = (P1 x 2) + (P2 x 5) + (P3 x 7) + (P4 x 20) + (P5 x 30) + (P6 x 10) + (P7 x 6) + P8		

Interpretation of CDAI Summary Scores	
Severity	**Score**
Remission	≤150
Mild activity	151-219
Moderate activity	220-450
Severe or very severe activity	>450

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