2007

Identification of symptom domains in ulcerative colitis that occur frequently during flares and are responsive to changes in disease activity

Tahira M. Khan

IDENTIFICATION OF SYMPTOM DOMAINS IN ULCERATIVE COLITIS THAT OCCUR FREQUENTLY DURING FLARES AND ARE RESPONSIVE TO CHANGES IN DISEASE ACTIVITY

by

Tahira M Khan

Thesis

Submitted to the College of Health and Human Services

Eastern Michigan University

In partial fulfillment of the requirements

for the degree of

MASTER OF SCIENCE

in

Clinical Research Administration

Thesis Committee:

Stephen Sonstein, PhD, Chair

Peter D.R. Higgins, MD, PhD, MSc

July 15, 2007

Ypsilanti, Michigan

DEDICATION

This research work is dedicated to all the patients afflicted with Inflammatory Bowel Disease (ulcerative colitis), their physicians, and researchers who are in pursuit of identifying better ways of treating this chronic debilitating illness.

ACKNOWLEDGMENTS

I would like to thank the patients for their participation in this study. Without their cooperation this research would not have been possible. I am grateful to Dr. Stephen Sonstein for his valuable guidance throughout my graduate program, research, and preparation of my thesis. I am highly indebted to Dr. Peter Higgins for mentoring me in applied clinical research and throughout all phases of study design, Institutional Review Board (IRB) approvals, patient selection, data analyses, data presentations, and thesis review.

I would like to thank Joel Joyce and Akbar Waljee in helping me with data analysis and data transfer into Stata and Epi Info. Special thanks are due to my parents, husband, daughter, and son for their understanding my absences during the graduate program. If not for their encouragement and help at home, I would not have been able to complete this program.

This research was supported by National Institutes of Health, National Center for Research Resources (M01-RR000042), and Crohn's and Colitis Foundation of America Senior Research Award.

ABSTRACT

The aim of this study was to determine which symptom domains in ulcerative colitis (UC) are important in the evaluation of disease activity. An important symptom is that which 1) occurs during flares, 2) improves during effective therapy, and 3) resolves during remission. Twenty eight symptom domains were evaluated. Sixty subjects were surveyed, rating each symptom on three criteria with a 100 mm Visual Analog Scale (VAS). Important symptoms were defined *a priori* as those whose median VAS rating for all 3 criteria was significantly greater than 50. Thirteen of the 28 symptom domains proved to be both frequent in UC flares and responsive to changes in disease activity. Seven of these were novel symptoms derived from UC patient focus groups.

In conclusion, development of survey measures of these symptom domains could significantly improve the assessment of disease activity in UC.

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease that affects more than 600,000 Americans (Loftus, 2004). Flares of UC typically result in inflammation of the affected portion of the gastrointestinal tract with symptoms that include frequent diarrhea, urgent bowel movements, and rectal bleeding (Baumgart & Sandborn, 2007; Sands, 2007). Uncontrolled inflammation can result in toxic megacolon and perforation, which has a mortality rate of 40% (Berg et al., 2002). Controlling inflammation and therefore symptoms is the primary goal of treatment, but current therapies are only moderately effective, as 27-45% of patients eventually need total colectomy (Leijonmarck et al., 1990; Turner et al., 2007). Hundreds of potential new therapies are in preclinical testing, including molecules targeting CD3, IL12p40, and IL17, and many are expected to be evaluated in clinical trials in humans.

The efficacy of therapies in UC is assessed with disease activity indices, which typically combine clinical symptoms, physician assessment, and invasive endoscopy to measure severity (Schroeder et al., 1987; Sutherland et al., 1987). Yet there exists no consensus gold standard to evaluate the efficacy of these treatments for UC. There are a number of indices that attempt to measure disease activity in ulcerative colitis, including the Mayo Index (Schroeder et al., 1987), the UCDAI (Sutherland et al., 1987), the Seo Index (Seo et al., 1992), the Ulcerative Colitis Clinical Score (Feagan et al., 2005), the Simple Clinical Colitis Activity Index Walmsley et al., 1998), and the St. Mark's Index (Powell-Tuck et al., 1978). Notably, it has never been established that any of these indices

actually measures all of the important components of ulcerative colitis. Most current indices were developed without patient input, and items were not tested for their responsiveness to change. The lack of a patient-centered index raises the question of whether the indices truly capture all of the symptoms that occur during a flare for patients with UC.

Previously, focus group interviews were conducted with UC patients who discussed their UC experience and how their symptoms related to periods of flare or remission. We recorded and qualitatively analyzed all signs and symptoms discussed during these group interviews and compared our findings with existing index components (Waljee et al., 2007). We concluded that current indices capture only a portion of clinical symptoms and include several symptoms not identified by patients. In addition, patients identified new symptoms not previously assessed in UC disease activity indices. As a result, it is believed that current indices may not completely measure or reflect patients' experience of UC.

The current lack of a patient-centered index and the numerous candidate therapies in developmental stages highlight the need to develop a new disease activity tool for clinical research that is patient-centered and validated and that will provide a rigorous benchmark for determining clinical efficacy of new UC therapies. An ideal index for the measurement of disease activity in UC would include the symptom domains important to patients and would focus on symptoms that occur in most patients and are responsive to changes in disease activity (have a good dynamic range). Symptom domains that are responsive to

changes in disease activity would reproducibly worsen during flares, improve with effective therapy, and be absent during remission. This study chose to evaluate 16 symptom domains from currently existing UC disease activity indices as well as 12 novel symptom domains identified in our previous focus group study (Waljee et al., 2007). All of these 28 symptom domains were identified as important by at least one patient with ulcerative colitis in our focus groups. The aim was to quantitatively determine which symptom domains would be most useful for inclusion in the development of a new patient-centered UC disease activity index by evaluating their frequency and responsiveness to change in patients with ulcerative colitis.

CHAPTER 2: REVIEW OF RELATED LITERATURE

Ulcerative colitis adversely affects the quality of life of many Americans (Loftus, 2004), with symptoms that include frequent diarrhea, urgent bowel movements, rectal bleeding, abdominal pain, and fatigue. Patients' quality of life (Cohen, 2002) and economic productivity (Longobardi et al., 2003) are significantly impaired by chronic ulcerative colitis. This disease often strikes individuals in their teens and twenties, and continues to wax and wane for the remainder of their lives. The severity of the symptoms, as well as the unpredictability of flares of disease, can significantly impair the lives of those affected (Casellas et al., 2002).

Current therapies for ulcerative colitis are only modestly effective, as up to 30% of patients eventually have total surgical removal of the colon. This is a daunting and irreversible choice for young patients to make and is particularly difficult for young females, in whom the scarring of the pelvic organs after total colectomy can result in infertility rates of up to 40% (Gorgun et al., 2004; Johnson et al., 2004). Therefore it is quite important to identify new medical therapies that can control disease activity and maintain remission in patients.

Numerous cytokines and components of the immune system have been therapeutically targeted in animal studies and preliminary human studies of treatment of colitis. These include interleukin-1, interleukin-10, tumor necrosis factor alpha, CD3, and many others. Other approaches have included removal of activated monocytes and granulocytes, infusion of antibodies to important adhesion molecules, enemas with growth factors to promote healing, and

infusion of antisense RNA to adhesion molecules. Many of these therapies are now in development for future human use and need to be rigorously evaluated for their clinical efficacy. This research will develop a new validated tool for clinical research that will provide a rigorous benchmark for clinical efficacy.

There is no gold standard for the evaluation of disease activity in ulcerative colitis. This is illustrated in numerous recent clinical trials, in which investigators measured several different indices of disease activity, since no one index is considered sufficient. Among the many indices for the measurement of ulcerative colitis disease activity, the first was Truelove and Witt's classification of mild, moderate, and severe disease (Truelove & Witts, 1955). This scale did not include the possibility of remission, which likely occurred because corticosteroids had never been used for ulcerative colitis when this classification was created.

This classification was converted into a point scale by Powell-Tuck, the St. Mark's Index, in 1978, when endoscopy was empirically added to the scale (Powell-Tuck et al., 1978). This first index was never tested for validity, reproducibility, or responsiveness. However, its application became common, and the addition of endoscopy remained unquestioned. In practical terms, however, the St. Mark's index was cumbersome, and this led to numerous simplified versions, including the Ulcerative Colitis Disease Activity Index and the Mayo Score (Schroeder et al., 1987; Sutherland et al., 1987). None of these were ever validated, had validated definitions of remission or improvement, nor had even been compared to the St. Mark's Index. Their convenience and simplicity led to their rapid adoption and use. Eventually, regulatory authorities were faced

with this confusing collection of indices when asked to approve new medications.

In response, the FDA asked a panel of experts to create an empiric definition of remission for regulatory purposes, which was defined as a score of 1 or 2 on the Baron endoscopic scale (normal or only mild friability) and the absence of patient-reported blood in the stool. This definition was also not tested or validated, but it has become a standard for the approval of new medications for ulcerative colitis and has driven an increase in endoscopy in clinical trials for ulcerative colitis. Conceptually, mucosal healing as part of a definition of remission in ulcerative colitis is very appealing. Ulcerative colitis is believed to be due in part to abnormal interactions between the gut associated immune system and intestinal bacteria, and damage to the mucosal barrier would seem to be an important intermediate endpoint. However, obtaining data on the colonic mucosa is invasive and costly. Several recent studies have suggested that mucosal healing can be accurately predicted by noninvasive means with survey items and biomarker (Seo et al., 2002; Higgins et al., 2005; Azzolini et al., 2005). Further studies that compared stool biomarkers to endoscopic activity showed that the biomarkers predicted endoscopic findings quite accurately (Kane et al., 2003; Roseth et al., 2004).

The difficulty and costs of the standard invasive indices led to a desire for less invasive indices of disease activity, and Seo in Japan and Walmsley in the United Kingdom devised non-invasive disease activity indices. The Seo Index used symptoms and laboratory tests to create a score that would parallel Truelove and Witts' categories of disease severity (Seo et al., 1992). Seo found

that his index did predict the Truelove and Witts' indices well and predicted which patients would need colectomy (Seo et al 2002; Seo et al., 1995). Walmsley devised a survey index, the Simple Clinical Colitis Activity Index (SCCAI) for use in clinic encounters, which correlated quite well to the St. Mark's Index and the Seo Index (Walmsley et al., 1998). More recently, Jowett showed that the SCCAI could predict clinician-defined relapse if a SCCAI score of > 5 points occurred (Jowett et al., 2003). This ability to predict important clinical endpoints suggested that the noninvasive indices had some clinical validity, but the necessity of endoscopy for regulatory approval meant that few investigators used these noninvasive indices. The absence of formal validation of any of the indices used to measure disease activity, and the absence of any formal testing of the validity of the criteria for regulatory remission, puts the assessment of any new therapies for ulcerative colitis on very shaky ground. It has never been established that any of these indices actually measures all of the important components of ulcerative colitis, is reproducible, or is responsive to change in disease activity.

The current indices for ulcerative colitis are not validated, and the regulatory definition of remission is a similar empiric non-validated approach. Mucosal healing is only an intermediate endpoint and is not a direct measure of patient health. The goal of disease activity indices in clinical trials is to take the most accurate snapshot of disease activity possible at a given point in time. While biomarkers and mucosal healing are appealing objective surrogate endpoints, they serve us badly if they do not actually predict the health of patients. It is important to be able to determine whether these and other markers

of disease activity do actually correlate with patients' disease status and are not redundant and therefore provide unique additional information in a multivariate model of disease activity. This will be accomplished in the proposed research.

CHAPTER 3: RESEARCH DESIGN AND METHODOLOGY

Subjects

This study was undertaken at the University of Michigan Medical Center. On a weekly basis, the University of Michigan Data Warehouse Team identified all patients with a history of ulcerative colitis (UC) who had a scheduled outpatient appointment to be seen at the University of Michigan. Patients were identified as having a documented history of UC using the ICD-9 code of 556.x. Inpatients with UC were also identified through regular consultation with the inpatient gastroenterology service. Recruitment was performed face to face by a study team member either in the outpatient setting (University of Michigan Gastroenterology Clinic or endoscopy unit) or on the hospital inpatient service.

Inclusion criteria included age between 18 and 75 years, diagnosis of UC as documented in the medical record, and willingness and ability to understand and fill out the questionnaire. Exclusion criteria included a history of colectomy or past participation in this study. The study was approved by the University of Michigan Institutional Review Board and by the Eastern Michigan University Human Subjects Review Board. A written informed consent was obtained from all study participants prior to participation.

Questionnaire

A self-administered questionnaire was used to identify symptom domains in UC that occur frequently during flares and are responsive to changes in disease severity. Symptom domains were defined broadly as a symptom or sign that could be used by the patient to assess his or her disease activity level.

Enrolled study participants were given the symptom domain questionnaire to fill out, and a study team member was present to answer any questions that arose.

The questionnaire consisted of three ratings of 28 symptom domains found in UC. Sixteen of these symptom domains were from standard UC disease activity indices (Schroeder et al., 1987; Sutherland et al., 1987; Seo et al., 1992; Feagan et al., 2005; Walmsley et al., 1998). The remaining 12 symptom domains were novel domains identified from focus group data (Waljee et al., 2007) (Figure 1). For each of the 28 symptom domains, participants were asked to rate the symptom domain on three separate 100 mm visual analogue scales (VAS) for each of the three endpoints: 1) the symptom is present during flares; 2) if present during flares, the symptom improves with effective therapy; and 3) the symptom is absent when in remission (Figure 2). Study participants were instructed to mark the line at whatever point they felt was appropriate for that symptom domain. Study participation was concluded upon successful completion of the survey questionnaire.

Data Management and Statistical Analysis

Two study team members determined each symptom domain's rating for each of the three endpoints by independently measuring the distance in millimeters from the left end of the VAS scale (0 mm) to the point where a mark was made on the VAS scale line. Measurements were made using the same ruler and to the nearest millimeter at the point where the mark crossed the VAS scale line. The study team members independently entered these ratings, along with demographic information, into a Microsoft Access (Microsoft Corporation,

Redmond, WA) database. The Access datasets were imported into Epi Info v. 3.3.2 (Centers for Disease Control and Prevention, Atlanta, GA) to perform error-checking. Any discrepancies in ratings for a given symptom domain endpoint were resolved by having study team members re-examine the original questionnaire and re-measure the VAS scale distance in contention. Consensus was reached for all measurements. The final, corrected Access dataset was imported into Stata 9.2 statistical software (Stata Corporation, College Station, TX) for analysis.

The assumption was made that study participants who assigned a rating of less than 20 mm to the first endpoint ("the symptom is present during flares") for a given symptom domain did not have that particular symptom domain present during an active flare of their UC. Therefore, it was not possible for these study participants to accurately assess the second endpoint ("if present during flares, the symptom improves with effective therapy") since therapy would not have an affect on a symptom that was not originally present during flare. For study participants in this situation, their rating for the second endpoint (improve with therapy) was dropped from the dataset.

As the ratings for each of the three endpoints for the 28 symptom domains were found to have a non-parametric distribution, medians and interquartile ranges were calculated for all symptom domains for each endpoint for accurate comparison. A nonparametric sign test was also performed to determine if the medians for the endpoints were significantly greater than a cutoff of 50 mm on the VAS scale. A two-sided p-value of <0.05 was used to determine statistical

significance for this test. An important symptom domain was defined as one in which ratings for all three VAS endpoints for that symptom domain are significantly (two sided $p < 0.05$) greater than 50 mm (see Figure 1). Symptom domains in which any of the three endpoints were not significantly greater than 50 mm were considered not important.

CHAPTER 4: PRESENTATION AND ANALYSES OF DATA

Patient Characteristics

A total of 60 UC patients were enrolled for participation in the study between 2006 and 2007. The demographic and disease characteristics of the enrolled study participants are presented in Table 1. The enrolled study population had an essentially equal (31 males to 29 females) male/female ratio and represented a broad range of the UC patient population at the investigators' university-based institution. Disease location (proctitis, left-sided, pancolitis, or unknown) was determined by asking the patient if they knew the extent of their disease. Questionable or unknown disease extent was then verified in the medical record from either a recent clinic note or colonoscopy report by the patient's gastroenterologist. Disease severity (quiescent, mild, moderate, severe, or unknown) was determined through consultation with the patient's gastroenterologist at the time of their participation in the study.

Incidence of Symptom Domains that Are Frequent or Responsive

Many (17 of 28) symptom domains were found to be frequently present during a UC flare, as they had a median VAS rating greater 50 mm for our first endpoint (Figure 3). Likewise, a majority of symptoms (27 of 28, or all except for mouth ulcers) were shown to improve with therapy more than half of the time, as they also had a median VAS rating greater than 50 mm for the second endpoint (Figure 4). In addition, all 28 symptom domains were found to be absent in remission the majority of the time in most individuals (median VAS rating greater than 50 mm for the third endpoint) (Figure 5). However, the criteria for defining

an important and responsive symptom domain specifically stated that all three endpoints for a particular symptom domain had to have a median VAS rating that was significantly ($p<0.05$) greater than 50 mm.

Symptoms Domains that are Frequent and Responsive to Change

Thirteen of the 28 symptom domains fulfilled the criteria of an important symptom domain, defined as a median VAS rating for all three endpoints significantly ($p<0.05$) greater than 50 mm. These symptom domains included stool mucus, tenesmus, difficulty telling liquid stool from gas before evacuation, fatigue, rapid post-prandial bowel movements, loud bowel sounds, flatulence, loose stool consistency, stool blood, urgency, frequency, bowel movements during the night, and abdominal pain (Table 2). Approximately half (6/13) of the important symptom domains were derived from standard indices of UC disease activity. However, the remaining important symptom domains (7 of 13, 54%) were novel symptom domains elicited from previously conducted focus groups (Waljee et al., 2007) that were not found in standard UC indices. These seven symptom domains were stool mucus, teems, difficulty telling liquid stool from gas before evacuation, fatigue, rapid post-prandial bowel movements, loud bowel sounds, and flatulence.

To illustrate the results for a representative important symptom domain, the findings for the symptom domain stool mucus are presented in Figure 6. In this symptom domain, 48 of 60 individuals had a VAS rating greater than 50 mm for the first endpoint (“present during flare”), 46 of 53 individuals had a VAS rating greater than 50 mm for the second endpoint (“improved with therapy”), and

56 of 60 had a VAS rating of greater than 50 mm for the third endpoint (“absent in remission”). In the case of the second endpoint for stool mucus, seven individuals were not included because the values for their first endpoint were less than 20 mm (see Methods). As the median VAS ratings for each of the three endpoints of the symptom domain stool mucus were all greater than 50 mm, this is a representative example of a symptom domain that fulfilled our criteria for a symptom that is frequently present and is responsive to change.

Uncommon or Unresponsive Symptom Domains

Fifteen of the 28 symptom domains did not fulfill the criteria of an important symptom domain. These symptom domains are listed in Table 2. Noteworthy among these 15 symptom domains were 10 symptom domains that are commonly found in standard UC disease activity indices but were not found to be important symptom domains in this study.

Anorexia was an example of a symptom domain that did not fulfill the criteria. In the case of the symptom domain anorexia, 34 of 60 individuals had a VAS rating greater than 50 mm for the first endpoint (“present during flare”), 39 of 47 individuals had a VAS rating greater than 50 mm for the second endpoint (“improved with therapy”), and 55 of 60 individuals had a VAS rating of greater than 50 mm for the third endpoint (“absent in remission”) (Figure 7). As in the example with stool mucus, 13 individuals for the second endpoint in anorexia were not included because their VAS ratings for the first endpoint in anorexia were not greater than 20 mm (see Methods). As the medians of the three endpoints for the symptom domain anorexia were not all significantly greater than

50 by the sign test, this is an example of a symptom domain found on commonly used indices that did not meet our criteria for an important symptom domain.

CHAPTER 5: SUMMARY, CONCLUSIONS, INFERENCES, AND RECOMMENDATIONS FOR FURTHER RESEARCH AND ACTION

Conventional assessment of disease activity in ulcerative colitis is done using any one of a number of disease activity indices that measure various symptoms and signs that have been deemed relevant by the designers of these indices. For the most part, the symptoms and signs included in the various indices were determined solely by physician scientists without patient input. Therefore, it is quite possible that the symptoms included in the UC disease activity indices by their designers may not include all of the symptoms that are most important to patients in assessing their disease activity. In previous work by our research group (Waljee et al., 2007), we identified, through ulcerative colitis patient focus groups, a number of symptoms that are important to these patients but that are not currently included in the measure of UC disease activity. Subsequently, as a result of this research study, it was found that a number of those symptoms identified in our focus group study occur frequently during flares of UC and are responsive to changes in disease activity. This qualifies them as important symptom domains according to our criteria. It was also determined that while several symptoms derived from currently used UC disease activity indices qualify by our definition as important symptom domains, many of the symptoms currently measured in UC disease activity indices do not qualify.

The results of this study provide the opportunity to develop a UC disease activity index that better incorporates all of the symptom domains that are frequently present during flares and are responsive to changes in disease

activity. Thirteen symptom domains were identified that met our criteria of an important symptom that is frequently present during flare and responsive to change. Noteworthy is the fact that 7 of these 13 symptoms are not included on currently utilized disease activity indices for UC. In addition, 10 of the 15 symptom domains found not to fit our criteria of an important symptom domain were obtained from currently used disease activity indices (Table 2).

This research study had several limitations. First, the study population had a somewhat homogenous composition of patients seen at a major university-affiliated medical center that may represent individuals with a more severe ulcerative colitis disease course than those seen in the general patient population. However, it would be expected that while there is some diversity of symptoms present during flare for any given individual with ulcerative colitis, the disease occurs in such away that there is bound to be much common overlap of symptomology. In addition, the study sample consisted of 52 individuals from the outpatient setting and only 8 individuals who were admitted as inpatients at the time of their participation. Yet it is believed that this may not be a major limitation as the majority of individuals afflicted with ulcerative colitis are treated on an outpatient basis.

Second, while we sought to assess three endpoints for each symptom domain, namely “present during flare,” “improves with therapy,” and “absent in remission,” if a particular individual did not experience a certain symptom, then it would not be possible to assign a VAS rating to the second endpoint, “improves with therapy.” The study attempted to control for this using the method outlined in

the Analysis section of Methods, but the possibility exists that this biased how a study participant assigned VAS ratings for a given symptom domain. Future investigations should offer an option where a study participant would be given an option to indicate that they have never experienced a particular symptom and therefore would not assign any VAS ratings.

It is possible that several of the symptoms that were identified as important (found to be present during a flare of UC and responsive to change) could in fact be concurrent irritable bowel syndrome (IBS) symptoms, not directly related to inflammatory bowel disease activity (IBD). Post-inflammatory IBS symptoms have been shown to be relatively common in patients with IBD (Minderhoud et al., 2004) and it is possible that these IBS symptoms are in fact what is being reported by participants in this study. Contrary to this view is the recent report that IBS-related symptoms in IBD correlate with increased fecal calprotectin levels, a biomarker of inflammatory activity. This suggests that symptoms frequently attributed to IBS may indicate occult inflammation in UC patients (Keohane et al., 2007).

The findings presented in this study are important because they provide quantitative evidence that the additional symptoms identified in our previous work with UC patient focus groups [13] are in fact reasonable choices for further investigation into their utility as part of a new index to assess UC disease activity. These symptoms identified in focus groups that were also found to be important by our criteria have great value in particular since they were identified with patient input. The importance of patient input in the development and validation

of new disease activity markers cannot be overemphasized because it allows us to capture a better picture of disease activity in patients with ulcerative colitis. In addition, the finding that a number of symptoms used at this time in common UC disease activity indices in fact rarely present in UC flares and/or less responsive to change only furthers the point that at this time we may not be optimally assessing a patient's UC activity.

This quantitative research study is an additional step in the process to develop a patient-centered assessment of disease activity in patients with UC that will be an improvement upon currently available methods. Some of the novel symptoms identified in the focus group interviews have now been shown to occur frequently and be responsive to change. It is now possible to proceed in developing survey questions to better capture all of the symptom domains that relate to a patient's experience of ulcerative colitis. It is expected that the future combination of improved survey questions for UC assessment and biomarkers of UC inflammation will result in better assessment of disease activity and therefore better care for patients.

Overall Study Highlights

What is Current Knowledge?

- Ulcerative colitis disease activity is measured through symptoms and signs selected by researchers without the input of patients.
- We do not know if these symptoms represent all of the important symptoms in the measurement of disease activity in UC.

- We do not know if all of the symptoms we currently measure are helpful in the measurement of disease activity in ulcerative colitis.

What is New Here?

- Several novel symptoms previously obtained from UC patient focus groups were found to be frequent during flares and responsive to changes in disease activity.
- Several of the symptoms we currently measure in UC activity indices were found to be either infrequent or unresponsive to changes in disease activity.
- Careful measurement of these common symptoms that are responsive to changes in disease activity is likely to improve the future assessment of ulcerative colitis disease activity.

REFERENCES

Azzolini, F., Pagnini, C., Camellini, L., Scarcelli, A., Merighi, A., Primerano, A.M., Bertani, A., Antonioli, A., Manenti, F., & Rigo, G.P. (2005). Proposal of a new clinical index predictive of endoscopic severity in ulcerative colitis. *Dig Dis Sci, 50(2)*, 246-251.

Baumgart, D.C., & Sandborn, W.J. (2007). Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet*, *369*, 1641-1657.

Berg, D.F., Bahadursingh, A.M., Kaminski, D.L., & Longo, W.E. (2002). Acute surgical emergencies in inflammatory bowel disease. *Am J Surg, 184*, 45-51.

Casellas, F., Lopez-Vivancos, J., Casado, A., & Malagelada, J.R. (2002). Factors affecting health related quality of life of patients with inflammatory bowel disease. *Qual Life Res, 11(8)*, 775-781.

Cohen, R.D. (2002). The quality of life in patients with Crohn's disease. *Aliment Pharmacol Ther, 16(9)*, 1603-1609.

Feagan, B.G., Greenberg, G.R., Wild, G., Fedorak, R.N., Pare, P., McDonald, J.W., Dube, R., Cohen, A., Steinhart, A.H., Landau, S., Aguzzi, R.A., Fox, I.H., & Vandervoort, M.K. (2005). Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. *N Engl J Med, 352*, 2499-2507.

Gorgun, E., Remzi, F.H., Goldberg, J.M., Thornton, J., Bast, J., Hull, T.L., Loparo, B., & Fazio, V.W. (2004). Fertility is reduced after restorative proctocolectomy with ileal pouch anal anastomosis: A study of 300

patients. *Surgery, 136(4)*, 795-803.

Johnson, P., Richard, C., Ravid, A., Spencer. L., Pinto, E., Hanna, M., Cohen, Z., & McLeod, R. (2004). Female infertility after ileal pouch-anal anastomosis for ulcerative colitis. *Dis Colon Rectum, 47(7)*, 1119-1126.

Jowett, S.L., Seal, C.J., Phillips, E., Gregory, W., Barton, J.R., & Welfare, M.R. (2003). Defining relapse of ulcerative colitis using a symptom-based activity index. *Scand J Gastroenterol, 38(2)*, 164-171.

Kane, S.V., Sandborn, W.J., Rufo, P.A., Zholudev, A., Boone, J., Lyerly, D., Camilleri, M., & Hanauer, S.B. (2003). Fecal lactoferrin is a sensitive and specific marker in identifying intestinal inflammation. *Am J Gastroenterol,* Leijonmarck, C.E., Persson, P.G., & Hellers, G. (1990). Factors affecting colectomy rate in ulcerative colitis: An epidemiologic study. *Gut, 31,* 329-333.

Keohane, J., O'Mahony, C., O'Mahony, L., O'Mahony, S., Quigley, E., Shanahan, F. (2007). Co-existence of IBS-Related Symptoms in Patients with Crohn's Disease - A Real Association of a Reflection of Occult Inflammation? *Gastroenterology, 134*, 44(A187).

Loftus, E.V., Jr. (2004). Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology, 126*, 1504-1517.

Longobardi, T., Jacobs, P., & Bernstein, C.N. (2003). Work losses related to inflammatory bowel disease in the United States: Results from the National Health Interview Survey. *Am J Gastroenterol, 98(5)*, 1064-1072.

Minderhoud, I.M., Oldenburg, B., Wismeijer, J.A., van Berge Henegouwen, G.P., & Smout, A.J. (2004). IBS-like symptoms in patients with inflammatory bowel disease in remission; relationships with quality of life and coping behavior. *Dig Dis Sci, 49*, 469-474.

Powell-Tuck, J., Bown, R.L., & Lennard-Jones, J.E. (1978). A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. *Scand J Gastroenterol, 13*, 833-837.

Roseth, A.G., Aadland, E., & Grzyb, K. (2004). Normalization of faecal calprotectin: A predictor of mucosal healing in patients with inflammatory bowel disease. *Scand J Gastroenterol, 39(10)*, 1017-1020.

Sands, B.E. (2007). Inflammatory bowel disease: Past, present, and future. *Gastroenterology, 42*, 16-25.

Schroeder, K.W., Tremaine, W.J., & Ilstrup, D.M. (1987). Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis: A randomized study. *N Engl J Med, 317*, 1625-1629.

Seo, M., Okada, M., Yao, T., Ueki, M., Arima, S., & Okumura, M. (1992). An index of disease activity in patients with ulcerative colitis. *Am J Gastroenterol, 87*, 971-976.

Seo, M., Okada, M., Maeda, K., & Oh, K. (1998). Correlation between endoscopic severity and the clinical activity index in ulcerative colitis. *Am J Gastroenterol, 93(11)*, 2124-2129.

98(6), 1309-1314.

Seo, M., Okada, M., Yao, T., Matake, H., & Maeda, K. (2002). Evaluation of the

clinical course of acute attacks in patients with ulcerative colitis through the use of an activity index. *J Gastroenterol, 37(1)*, 29-34.

Seo, M., Okada, M., Yao, T., Okabe, N., Maeda, K., & Oh, K. (1995). Evaluation of disease activity in patients with moderately active ulcerative colitis: Comparisons between a new activity index and Truelove and Witts' classification. *Am J Gastroenterol, 90(10)*, 1759-1763.

Sutherland, L.R., Martin, F., Greer, S., Robinson, M., Greenberger, N., Saibil, F., Martin, T., Sparr, J., Prokipchuk, E., & Borgen, L. (1987). 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology, 92*, 1894-1898.

Truelove, S.C., & Witts, L.J. (1955). Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J, 4947*, 1041-1048.

Turner, D., Walsh, C.M., Steinhart, A.H., & Griffiths, A.M. (2007). Response to corticosteroids in severe ulcerative colitis: A systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol, 5*, 103-110.

Waljee, A., Joyce, J., Khan, T., Zimmermann, E., Wren, P., & Higgins, P. (2007). Do Currently Available Disease Activity Indices Measure the Symptoms that Ulcerative Colitis Patients Experience During A Flare? *Gastroenterology,132*, 44 (A191).

Walmsley, R.S., Ayres, R.C., Pounder, R.E., & Allan, R.N. (1998). A simple clinical colitis activity index. *Gut, 43*, 29-32.

Table 1

Demographics and disease characteristics of 60 patients with ulcerative colitis who completed questionnaires on ulcerative colitis symptoms.

Characteristics	Participants (n=60)	%
Gender		
Male	31	51.7
Female	29	48.3
NIH Race		
Caucasian	54	90.0
Asian or Pacific Islander	0	0.0
Black	3	5.0
American Indian / Alaskan	1	1.7
Hispanic	1	1.7
Other	1	1.7
Median [range] age (years)	39.4 [18.6-72.8]	
Median [range] disease duration (years)	5.0 [1-37] 1 missing	
Disease location		
Proctitis	4	6.7
Left-sided	26	43.3
Pancolitis	28	46.7
Unknown	2	3.3
Disease Severity		
Quiescent	3	5.0
Mild	24	40.0
Moderate	19	31.7
Severe	13	21.7
Unknown	1	1.7
Medications		
Current rectal therapy	14 of 60	23.3
Current steroids	24 of 60	40.0
Current oral 5-ASA's	51 of 60	85.0
Current thiopurines	15 of 60	25.0
Current infliximab	4 of 60	6.7
Current inpatient		
Yes	8	13.3
No	52	86.7

Table 2

Importance of symptom domains (n=28) based on criteria to determine ulcerative colitis symptom domains that are frequently present during flares and responsive to changes in disease activity.

	Symptoms that are Frequent and Responsive to Change (n=13)	Infrequent or Unresponsive Symptoms (n=15)
Symptom Domains Derived from Common Indices*	Loose stools (consistency) Stool blood Urgency Frequency Nighttime bowel movements Abdominal pain	Anorexia Erythema nodosum Pyoderma gangrenosum Eye redness / pain Fever Use of anti-diarrheals Incontinence Nausea Cramping Joint pain
Symptom Domains Derived from Focus Groups+	Stool mucus Tenesmus Difficulty telling liquid or gas from solid stool before evacuation Rapid post-prandial bowel movements Loud bowel sounds Flatulence Fatigue	Abdominal distention Lightheadedness Mouth ulcers Insomnia Low back pain
*Symptom domains derived from common indices (Truelove and Witts, St. Mark's Index, CAI, SCCAI, UCSS, Mayo, and UCDAI). +Symptom domains identified in focus groups and not found on commonly used indices		

Notes: Symptoms Present and Responsive to Change are those that fit the criteria of an important symptom domain as defined in Figure 1. Uncommon or Unresponsive Symptoms are those that do not fulfill criteria of an important symptom domain.

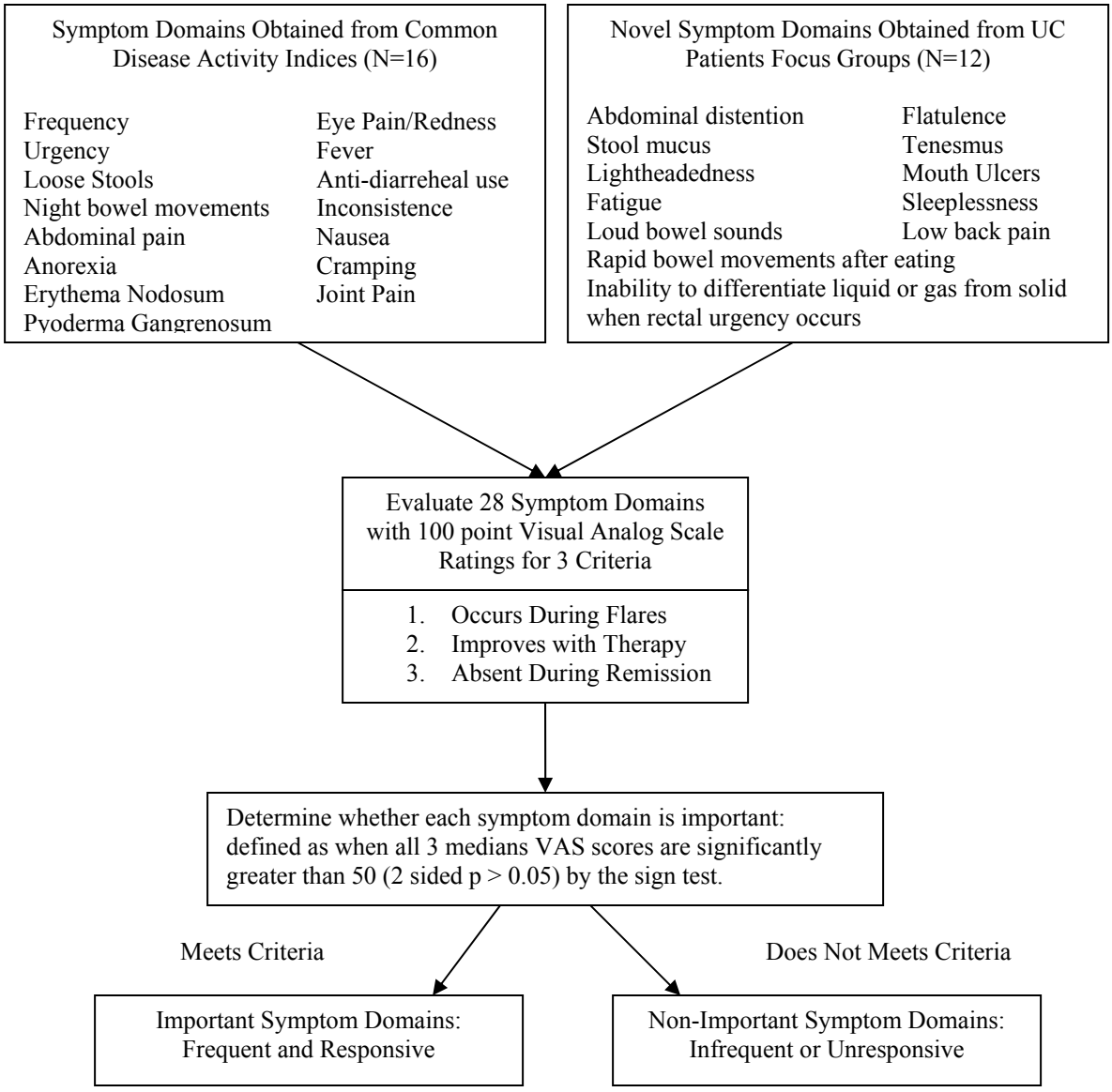


Figure 1. Flow diagram of 28 symptom domains in Q\questionnaire and criteria for determining important symptom domains.

Note: Sixteen symptom domains were included from commonly used indices of ulcerative colitis disease activity (Truelove and Witts, St. Mark's Index, CAI, SCCAI, UCSS, Mayo, and UCDAI), and twelve novel symptom domains were included from previously conducted focus group input (Waljee et al., 2007). The questionnaire required ratings of the three criteria listed on a 100 mm VAS scale for each of the 28 symptom domains. Symptom domains were determined to be either important or non-important for evaluation of disease activity based on significance of the sign test.

(a) Do you have this symptom (loose stools) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometime occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometime improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometime present	Always present

Figure 2. Visual analogue scale used on questionnaire for assessing each of three endpoints for all 28 symptom domains.

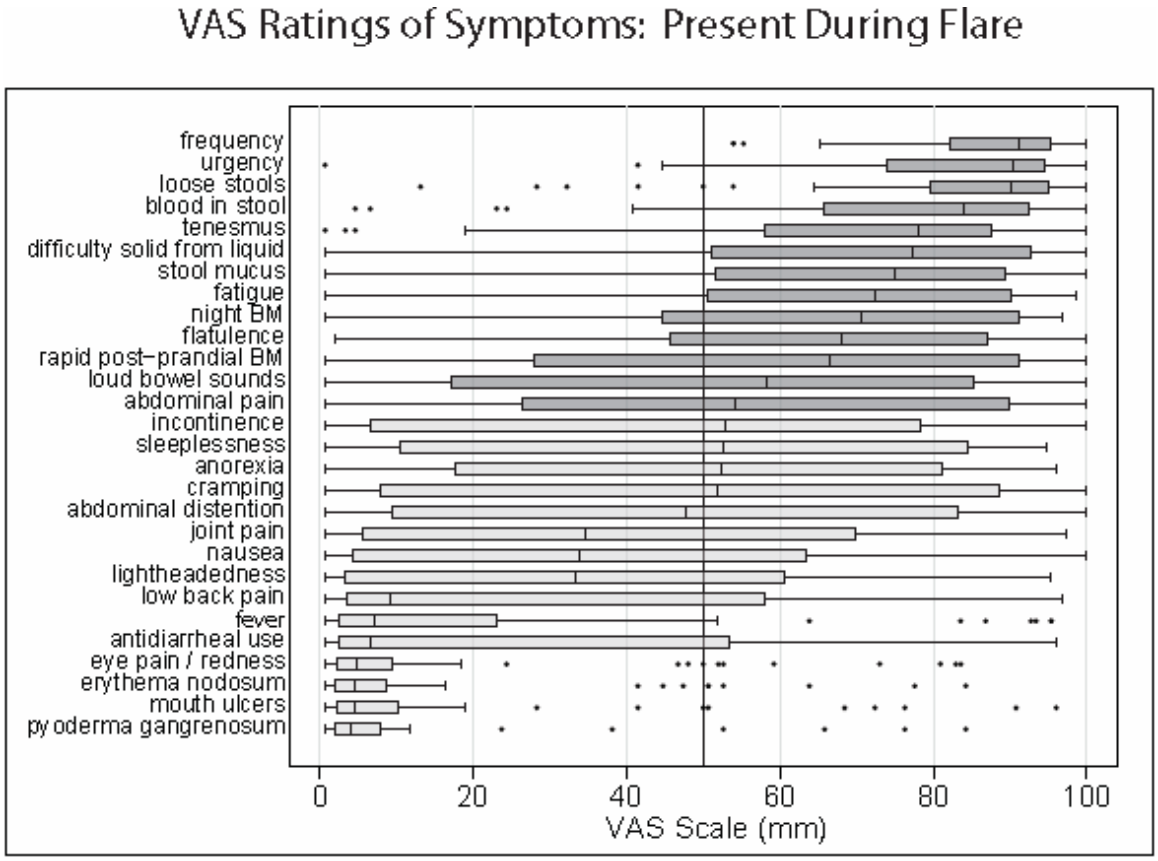


Figure 3. Visual analogue scale ratings of the three criteria.

Figure 3a. A box plot of the VAS ratings of symptoms present during flares for the 28 symptom domains is presented.

Note: Each box bounds the region from the 25th to 75th percentile of responses. The vertical line in each box is the median. Lines connect the boxes to the next observation beyond the box and the dots represent remaining outliers. The vertical line at VAS=50 signifies the *a priori* cutoff value for significantly frequent symptoms during flare. The symptoms presented in dark gray boxes are those that met all 3 criteria for symptom importance.

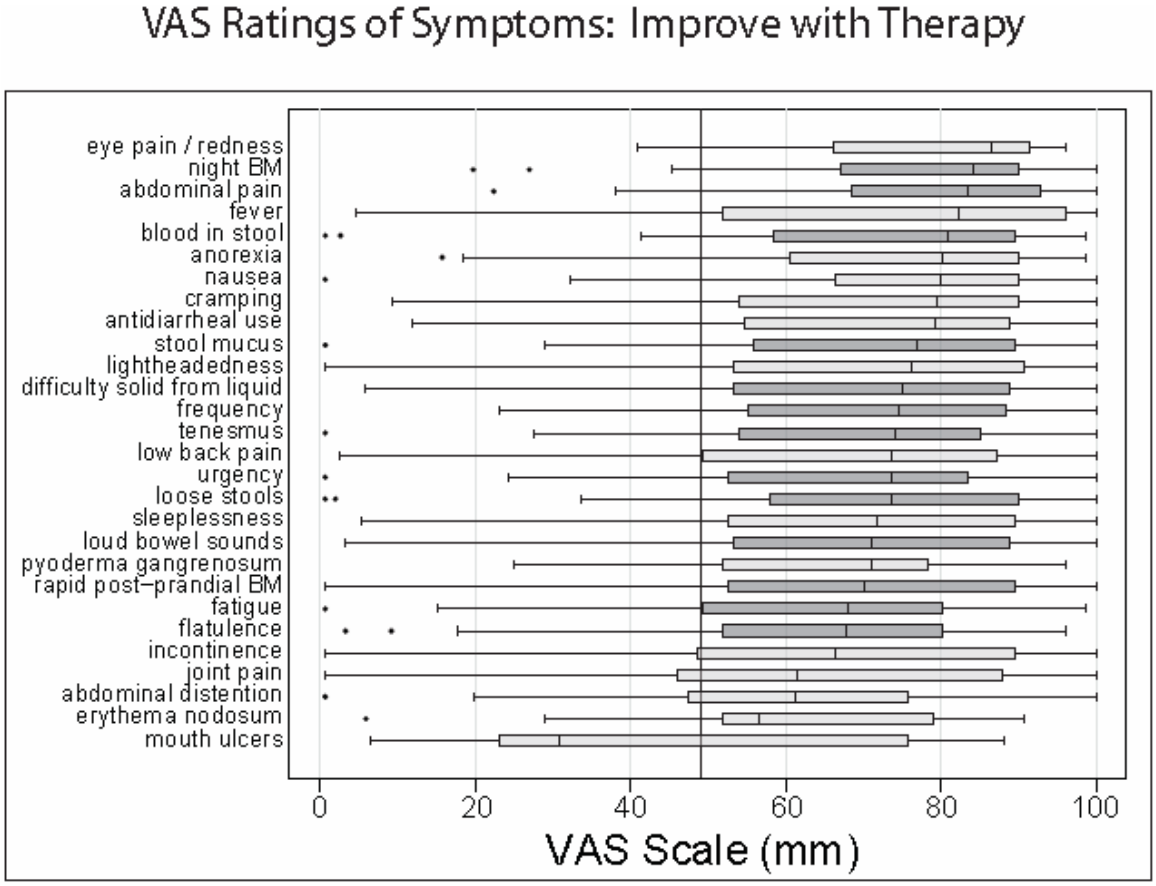


Figure 3b. A similar box plot is presented in the same format for the symptoms that improve during therapy.

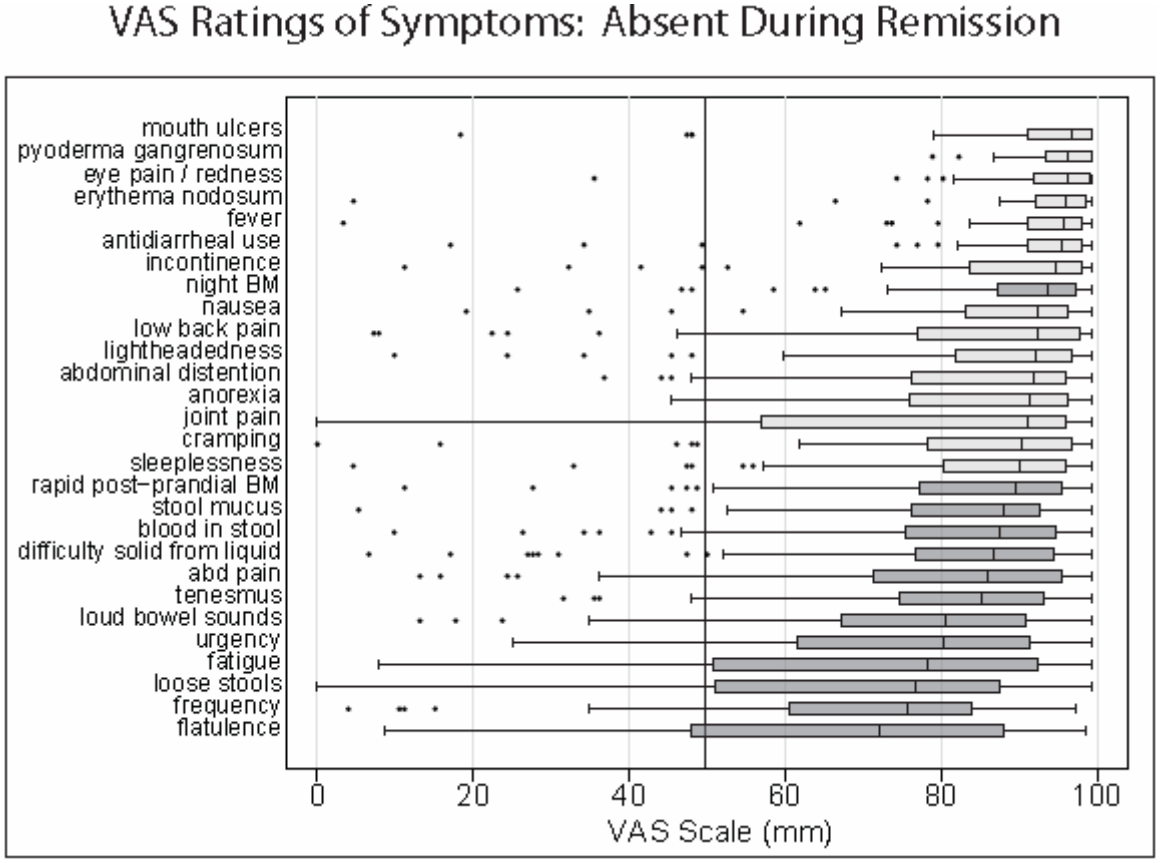


Figure 3c. A similar box plot is presented in the same format for the symptoms that are absent during remission.

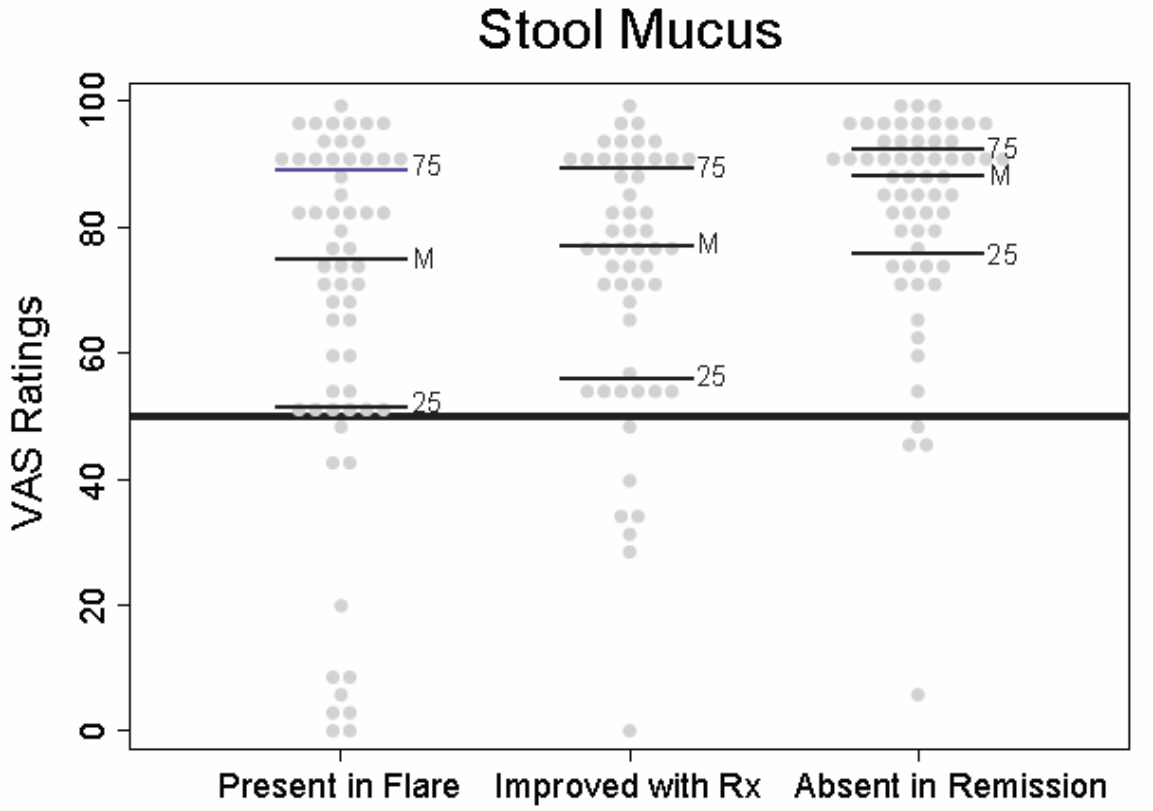


Figure 4. Examples of symptom domains that meet or do not meet criteria for a common symptom with good dynamic range.

Figure 4a. Dotplot of a symptom domain, stool mucus, which meets criteria for an important symptom (one that is frequent with good dynamic range). *Note:* VAS ratings are from the 100 mm scale. Each dot represents one individual's response. The horizontal lines on the graphs are as follows: 25 is the 25th percentile, M is the median, and 75 is the 75th percentile. The horizontal line at VAS=50 signifies the *a priori* cutoff value for important symptoms.

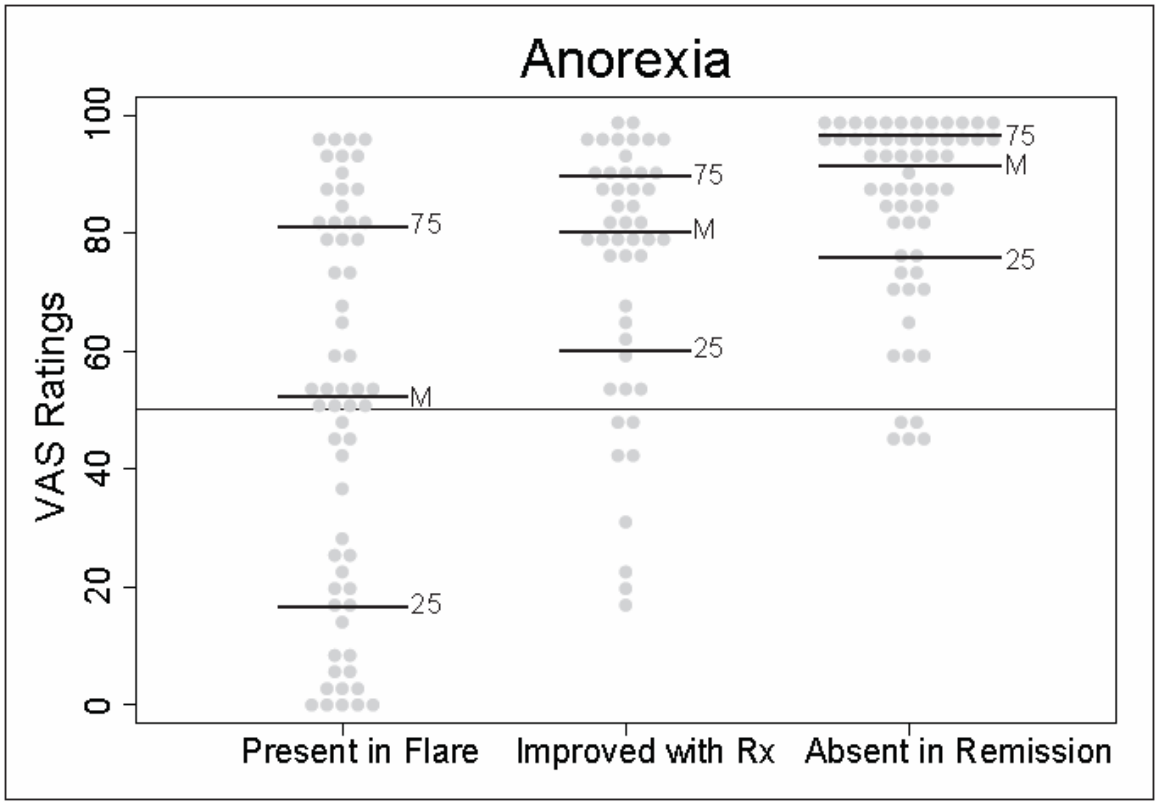


Figure 4b. Dotplot of a symptom domain, anorexia, which did not meet the criteria for an important symptom (one that is frequent with good dynamic range).

Appendix A: Sample Survey Form

Ulcerative Colitis Symptom Domains Survey

This questionnaire is designed to help us find out what symptoms change when people with UC start a treatment that is effective.

This will help us determine the best way to measure whether new treatments are effective.

Each page will present 3 questions about one symptom.

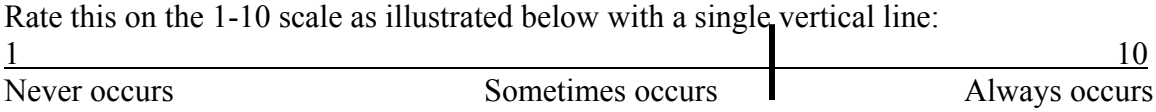
Each symptom has been suggested as a marker of ulcerative colitis disease activity by patients in focus groups.

You may have similar symptoms of ulcerative colitis, or you may not have these symptoms at all. We are interested in finding out more about your experience of ulcerative colitis.

Please answer each question on a 1-10 scale by marking a single vertical line through the scale as illustrated below:

(a) Do you have this symptom when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:



Please do NOT skip questions – if a question seems odd or confusing, please ask the person who gave you this questionnaire for an explanation.

Subject ID# _____

Initials _____

Date _____

(1) When some people with ulcerative colitis have a flare of disease, their stools often become loose or watery. When they start a treatment for ulcerative colitis that works, they often notice that their stools become more solid.

(a) Do you have this symptom (loose stools) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about loose stools in UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line.

(2) When some people with ulcerative colitis have a flare of disease, their stools often contain blood. When they start a treatment for ulcerative colitis that works, they often notice that the blood goes away.

(a) Do you have this symptom (bloody stools) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about bloody stools in UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(3) When some people with ulcerative colitis have a flare of disease, their stools often contain mucus. When they start a treatment for ulcerative colitis that works, they often notice that the mucus goes away.

(a) Do you have this symptom (mucus in stools) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about mucus in stools in UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(4) When some people with ulcerative colitis have a flare of disease, they have very frequent stools. When they start a treatment for ulcerative colitis that works, they often notice that the frequency of stools goes down.

(a) Do you have this symptom (frequent stools) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about frequent stools in UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(5) When some people with ulcerative colitis have a flare of disease, they often become very tired. When they start a treatment for ulcerative colitis that works, they often notice that the tiredness improves.

(a) Do you have this symptom (tiredness) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about tiredness with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single number.

(6) When some people with ulcerative colitis have a flare of disease, they often have to rush to the toilet (urgency). When they start a treatment for ulcerative colitis that works, they often notice that the urgency goes away.

(a) Do you have this symptom (urgency) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about urgency with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(7) When some people with ulcerative colitis have a flare of disease, they often go to the bathroom, then have to go again rapidly in seconds to minutes (tenesmus). When they start a treatment for ulcerative colitis that works, they often notice that they can go once and not have to go again.

(a) Do you have this symptom (tenesmus) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about tenesmus with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(8) When some people with ulcerative colitis have a flare of disease, they notice that they have a lot more gas (flatulence). When they start a treatment for ulcerative colitis that works, they often notice that they have less gas.

(a) Do you have this symptom (flatulence) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about flatulence with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(9) When some people with ulcerative colitis have a flare of disease, they notice that they have trouble telling whether they are going to pass just gas or something liquid or solid, so they have to go to the toilet every time to be safe. When they start a treatment for ulcerative colitis that works, they often notice that they can tell the difference, and don't have to go to the toilet all the time.

(a) Do you have this symptom (difficulty telling if you have gas or stool) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about this symptom with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single number.

(10) When some people with ulcerative colitis have a flare of disease, they notice that they get painful cramps in their rectum with bowel movements. When they start a treatment for ulcerative colitis that works, they often notice that they can have bowel movements without this cramping pain in the rectum.

(a) Do you have this symptom (rectal cramps) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about rectal cramps with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single number.

(11) When some people with ulcerative colitis have a flare of disease, they notice that their abdomen gets more distended and sticks out. When they start a treatment for ulcerative colitis that works, they often notice that this improves.

(a) Do you have this symptom (distention) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about distention with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single number.

(12) When some people with ulcerative colitis have a flare of disease, they notice that they get pain in the lower back. When they start a treatment for ulcerative colitis that works, they often notice that this improves.

(a) Do you have this symptom (low back pain) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about low back pain with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single number.

(13) When some people with ulcerative colitis have a flare of disease, they notice that they get loud digestive sounds from the abdomen. When they start a treatment for ulcerative colitis that works, they often notice that these sounds decrease.

(a) Do you have this symptom (loud abdominal sounds) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about loud abdominal sounds with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(14) When some people with ulcerative colitis have a flare of disease, they notice that they have a lot of nausea and feel like they need to vomit. When they start a treatment for ulcerative colitis that works, they often notice that the nausea gets better.

(a) Do you have this symptom (nausea) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about nausea with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(15) When some people with ulcerative colitis have a flare of disease, they notice that they lose their appetite. When they start a treatment for ulcerative colitis that works, they often notice that their appetite gets better.

(a) Do you have this symptom (loss of appetite) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about loss of appetite with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(16) When some people with ulcerative colitis have a flare of disease, they notice that they have a lot of pain in the abdomen. When they start a treatment for ulcerative colitis that works, they often notice that the pain in the abdomen gets better.

(a) Do you have this symptom (abdominal pain) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about abdominal pain with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(17) When some people with ulcerative colitis have a flare of disease, they notice that their joints hurt. When they start a treatment for ulcerative colitis that works, they often notice that the joint pain gets better.

(a) Do you have this symptom (joint pain) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about joint pain with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(18) When some people with ulcerative colitis have a flare of disease, they notice that they get ulcers in their mouth. When they start a treatment for ulcerative colitis that works, they often notice that the mouth ulcers get better.

(a) Do you have this symptom (mouth ulcers) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about mouth ulcers with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(19) When some people with ulcerative colitis have a flare of disease, they notice that they get redness and pain in the eyes. When they start a treatment for ulcerative colitis that works, they often notice that their eyes get better.

(a) Do you have this symptom (eye pain and redness) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about eye pain and redness with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(20) When some people with ulcerative colitis have a flare of disease, they notice that they get have a lot of bowel movements during the night that can interfere with sleep. When they start a treatment for ulcerative colitis that works, they often notice that they have fewer bowel movements at night.

(a) Do you have this symptom (night BMs) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about night BMs with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(21) When some people with ulcerative colitis have a flare of disease, they notice that they have fever. When they start a treatment for ulcerative colitis that works, they often notice that the fever gets better.

(a) Do you have this symptom (fever) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about fever with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(22) When some people with ulcerative colitis have a flare of disease, they notice that they have accidents and lose control of their stool (incontinence). When they start a treatment for ulcerative colitis that works, they often notice that the incontinence gets better.

(a) Do you have this symptom (incontinence) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about incontinence with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(23) When some people with ulcerative colitis have a flare of disease, they notice that they need to use anti-diarrheal medicines. When they start a treatment for ulcerative colitis that works, they often notice that they need a lot less or no anti-diarrheal medicines.

(a) Do you increase your use of anti-diarrheal medications when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Do you decrease your use of anti-diarrheal medications after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Do you use anti-diarrheal medications when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about anti-diarrheal medication use with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(24) When some people with ulcerative colitis have a flare of disease, they notice that eating even a small amount stimulates almost immediate bowl movements. When they start a treatment for ulcerative colitis that works, they often notice that they can eat and not immediately have a bowel movement.

(a) Do you have this symptom (rapid BMs after eating) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about rapid bowel movements after eating with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(25) When some people with ulcerative colitis have a flare of disease, they notice that they feel lightheaded. When they start a treatment for ulcerative colitis that works, they often notice that the lightheadedness gets better.

(a) Do you have this symptom (lightheadedness) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about lightheadedness with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(26) When some people with ulcerative colitis have a flare of disease, they notice that they sleep less. When they start a treatment for ulcerative colitis that works, they often notice that they get more sleep.

(a) Do you have this symptom (loss of sleep) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about loss of sleep with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(27) When some people with ulcerative colitis have a flare of disease, they notice that they have raised, red, tender bumps on their skin, usually on the shins (erythema nodosum). When they start a treatment for ulcerative colitis that works, they often notice that these bumps go away.

(a) Do you have this symptom (red tender bumps on the skin) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about loss of red tender bumps on the skin with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Please answer each question on a 1-10 scale with a single vertical line:

(28) When some people with ulcerative colitis have a flare of disease, they notice that they get red pimple-like areas on the skin that break down and turn into skin ulcers (pyoderma gangrenosum). When they start a treatment for ulcerative colitis that works, they often notice that these ulcers get better.

(a) Do you have this symptom (skin ulcers) when you have flares of ulcerative colitis?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never occurs	Sometimes occurs	Always occurs

(b) Does this symptom improve after you start an effective therapy?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never improves	Sometimes improves	Always improves

(c) Is this symptom present when your disease is under good control (in remission)?

Rate this on the 1-10 scale as illustrated below with a single vertical line:

1		10
Never present	Sometimes present	Always present

Free response area: Tell us anything we should know about skin ulcers with UC.
Does it only occur with severe flares? Only in mild flares?
Does it come on early in flares, or only later on?
Does effective treatment clear this up early, or only after a while?
How should we measure this? Number, amount, percentage, or frequency?
Please tell us about your experience with this symptom. Feel free to continue on the back.

Appendix B: Sample Informed Consent

University of Michigan - Consent To Be Part of a Research Study

Information About This Form

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

1. General Information About This Study AND the RESEARCHERS

1.1 Study title:

ValidUC2 Phase 1A: Domains

1.2 Company or agency sponsoring the study:

Crohns and Colitis Foundation of America

Names, degrees, and affiliations of the researchers conducting the study:

Peter Higgins, M.D., Ph.D.- Assistant Professor in Gastroenterology, Internal Medicine, Division of Gastroenterology, University of Michigan.
Tahira Khan, MBBS, Division of Gastroenterology, University of Michigan.
Akbar Waljee, MD, Department of Internal Medicine, University of Michigan
Joel Joyce, Division of Gastroenterology, University of Michigan

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

To identify disease activity symptom domains in ulcerative colitis that:
are related to patients' experience of ulcerative colitis
change when their disease is active vs. when inactive
occur reproducibly when they have a flare of disease

3. Information About STUDY participants (SUBJECTS)

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

Inclusion criteria:
Patients have to have ulcerative colitis and have not had their colon removed by surgery.
Patients who are between 18-75 years of age who are willing and able to fill out a survey form.
Patients primary GI physician must agree that they are appropriate for this study.
Exclusion Criteria:
Students, employees, or family members of the investigators.
Prisoners.
Subjects not competent to consent for themselves.
Subjects who have previously participated in this phase of the study.

3.2 How many people (subjects) are expected to take part in this study?

100

4. information about study procedures

4.1 What exactly will be done to me in this study? What kinds of research procedures will I receive if I agree to take part in this study?

If you are interested in participating, you will be interviewed either in your room (inpatients) or in a consultation room. You will be evaluated to confirm that you meet all of the eligibility criteria. This consent form will be reviewed with you, and any domains (A group of interrelated symptoms within a given category) will be answered by the study staff member. Three copies of the signed consent form will be required.

You will then be provided with a survey form with detailed instructions. You will be asked to review the domains(A group of interrelated symptoms within a given category), and evaluate each domain according to three criteria on a 1-10 visual analog scale. We will also encourage you to write comments, suggestions or edits on the domains themselves. We expect this evaluation of domains to take approximately 25-45 minutes.

4.2 How much of my time will be needed to take part in this study? When will my participation in the study be over?

The time needed for consent process (5-10 minutes) and filling out survey- approximately 25-45 minutes. Your participation will be over as soon as you fill out the survey. Total time is expected to be 30-55 minutes. This survey will be conducted once only.

5. Information about RISKS and benefits

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

The known or expected risks are:

The potential risks to you from being in this study are minimal. Confidentiality Risks: are rare (i.e., approximate incidence < 1%)

All of the patients whose responses are used for the study will be assigned a confidential identification number. All responses will be coded by this number, and not the patient's name or hospital registration number. Identifying information will be placed in a database along with the unique confidential ID number. The data table containing the unique identifier and the clinical information are kept in a separate password- protected secure file.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?

The researchers have taken steps to minimize the known or expected risks. However, you may still experience problems or side effects, even when the researchers are careful to avoid them. If you believe that you have been harmed, notify the researchers listed in Section 10 of this form. The University of Michigan will provide first aid or emergency care. The cost of this first aid or emergency care may be billed to your insurance company, but if it is not covered by your insurance, the University of Michigan will pay for it. Additional medical care will be provided if the University determines that it is responsible to provide such treatment. If you sign this form, you do not give up your right to seek additional compensation if you are harmed as a result of being in this study.

Please note: It is important that you tell the researchers about any injuries, side effects, or other problems that you experience during this study. You may also need to tell your regular doctors.

5.3 If I take part in this study, can I also participate in other studies?

Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?

You may not receive any personal benefits from being in the study. However, the information we gain from you may lead to a better way of measuring ulcerative colitis. This may contribute to the development of new treatments that will improve the symptoms that matter most to patients

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

No, this is a one-time survey study and participation in the study will be completed on the day the survey is filled out.

6. Other options

6.1 If I decide not to take part in this study, what other options do I have?

Whether or not you choose to participate in this study, you will continue your current care as directed by your primary gastroenterologist.
Your care by your doctor will NOT be affected by whether or not you join the study.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?
You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you may otherwise be entitled. Your participation in the study will be completed on the day that the questionnaire will be administered. If there are questions that you do not wish to answer, they may be left blank. If you choose to inform the investigator why you have omitted your answer, please feel free to do so.

7.2 Could there be any harm to me if I decide to leave the study before it is finished?
No

7.3 Could the researchers take me out of the study even if I want to continue to participate?

The researcher will not ask you to enroll in the study if it is not in your best interest. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

The researcher believes that it is not in your best interest to stay in the study.
You become ineligible to participate.
Your condition changes and you need treatment that is not allowed while you are taking part in the study.
You do not follow instructions from the researchers.
The study is suspended or canceled.

8. Financial Information

8.1 Will taking part in this study cost me anything? Will I or my insurance company be billed for any costs of the study? If so, which costs? What happens if my insurance does not cover these costs?

You or your insurance company will NOT be billed for any costs related to the study.

8.2 Will I be paid or given anything for taking part in this study?

Yes, you will be paid $5.00 to cover any parking related costs.

8.3 Who could profit or financially benefit from the study results?

No One

9. confidentiality of subject records and authorization to release your protected health information

University of Michigan policies require that private information about you be protected. This is especially true for your personal health information.

On the other hand, sometimes the law allows or requires others to see your information. The information given below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?

All the patients whose responses are used for the study will be assigned a unique identification number. Identifying information will be placed in a database along with the unique identifier. The data table containing the unique identifier and the clinical information are kept in a password- protected secure file. No one will have access to this information except the research staff listed under section 1.3 of this document.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care.

Information about you may include information about your health and your medical care before, during, and after the study, even if that information wasn't collected as part of this research study. For example:

All records relating to your condition, the treatment you have received, and your response to the treatment to confirm that you truly have ulcerative colitis.

There are many reasons why information about you may be used or seen by the researchers or others during this study. Examples include:

The researchers may need the information to make sure you can take part in the study.

University, Food and Drug Administration [FDA], and other government officials may need the information to make sure that the study is done properly.

Organizations that are funding the study may need the information to make sure that the study is done properly.

Safety monitors or committees may need the information to make sure that the study is safe.

If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over. Examples of reasons for this include:

To avoid losing study results that have already included your information

To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan Notice of Privacy Practices. This information is also available on the web at http://www.med.umich.edu/hipaa/npp.htm. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

10. Contact Information

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

Obtain more information about the study
Ask a question about the study procedures or treatments
Report an illness, injury, or other problem (you may also need to tell your regular doctors)
Leave the study before it is finished
Express a concern about the study

Principal Investigator: Peter D Higgins, M.D. Ph.D.
Mailing Address: 6520 MSRB I, Ann Arbor, MI, 48109
Telephone: 734-763-7278

Study Investigator: Tahira Khan, M.B.B.S.
Mailing Address: 6520 MSRB I, Ann Arbor, MI, 48109
Telephone: 734-615-2457

You may also express a concern about a study by contacting the Institutional Review Board listed below, or by calling the University of Michigan Compliance Help Line at 1-888-296-2481.

University of Michigan Medical School Institutional Review Board (IRBMED)
Argus I
517 W. William
Ann Arbor, MI 48103-4943

Telephone: 734-763-4768
Fax: 734-615-1622
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy, contact the University of Michigan Health System Privacy Officer at 1-888-296-2481.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.
11. record of Information provided

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

□ This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*
□ Other (specify):_____

12. SIGNATURES

Research Subject:
I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____.
My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Signature of Subject: _____ *Date:* _____

Name (Print legal name): _____

Patient ID: _____ *Date of Birth:* _____

Principal Investigator (or Designee):
I have given this research subject (or his/her legally authorized representative, if applicable) information about this study that I believe is accurate and complete. The subject has indicated that he or she understands the nature of the study and the risks and benefits of participating.

Name: _____ *Title:* _____

Signature: _____ *Date of Signature:* _____

Signature: _____ *Date of Signature:* _____

Demographic Information Case Report Form for Domains Survey

Subject Name:_____

Subject Initials: _____

CPI # : _____

Subject Study ID #: _____

Check only one box:

	Male	Female
American Indian or Alaskan Native:		
Asian or Pacific Islander		
Black, not of Hispanic origin:		
Hispanic:		
White, not of Hispanic origin:		
Other		