Video Cognitive Behavioral Therapy to Prevent Depression in Patients with Inflammatory Bowel Disease

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VIDEO COGNITIVE BEHAVIORAL THERAPY TO PREVENT DEPRESSION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

June 2021

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ABSTRACT

Inflammatory bowel disease patients have higher rates of depression and anxiety compared to other diseases and the general population, which can lead to a lower quality of life. There is a critical need to investigate treatments for mental health in patients with inflammatory bowel disease. Cognitive behavioral therapy is widely studied and has proven effective in improving depression. There are no randomized controlled trials comparing early psychotherapeutic intervention with standard of care for this population. We hypothesize that early initiation of cognitive behavioral therapy will reduce depression and anxiety severity and improve quality of life in newly diagnosed inflammatory bowel disease patients compared to standard care. Participants will be randomized to either video therapy or standard care for 12 weeks. Findings may inform the need for early mental health intervention in the disease management of this population.
CHAPTER 1: INTRODUCTION

1.1 Background

Inflammatory bowel disease (IBD) is a chronic relapsing-remitting illness of the gastrointestinal tract that mainly consists of ulcerative colitis (UC) and Crohn’s disease (CD). The incidence and prevalence of IBD in the United States and worldwide has steadily increased over time.\(^1\)\(^2\) Its course and prognosis can be uncertain and unpredictable; no conclusive cure exists. Disease activity is classified as mild, moderate, severe, or fulminant based on combined clinical and endoscopic assessments.\(^3\) Physical symptoms include diarrhea, bowel spasms, feces containing blood or mucus, pain, and fatigue.\(^4\) Treatment is often life-long and associated with undesired side effects and complications.\(^5\) Relapses can be intense and affect daily functioning.\(^6\) Those with moderate-severe IBD can experience complications including abscesses and fistulas that cause chronic pain and severely impact quality of life.\(^5\) Current treatment for moderate-severe IBD includes biologic therapy; however, there remain appreciable rates of primary non-response, loss of response, or adverse reactions.\(^2\) Overall, IBD symptoms and treatments affect patients’ physical, mental, and social well-being, which encompasses their health-related quality of life (HRQOL).\(^7\) Because this disease typically appears early in life, between ages 15 and 29\(^8\), with no contribution to a shortened life span, treatment early in the disease course is crucial.\(^9\)

Rates of depression and anxiety are higher among those with UC and CD as compared to other diseases and the general population. One systematic review found that depression was as high as 21.2% in patients with IBD vs 13.4% in healthy controls.\(^10\) Other clinical studies have shown the prevalence of anxiety/depression symptoms to be
about 30% in IBD cohorts compared to the general population. Additionally, there are higher rates of anxiety and depression in the early period around IBD diagnosis and in those with active disease compared to those in remission. Lastly, there are higher rates of hospitalization and disease severity in IBD patients with depression/anxiety compared to those without. These higher rates of psychiatric disorders are similar to those with rheumatoid arthritis and diabetes, and may be higher compared to those with heart failure. One controlled study investigated the need for psychological interventions in patients with IBD compared to rheumatoid arthritis (RA), another chronic inflammatory disorder. Stepwise logistic regression analysis showed an independent association between inflammatory bowel disease patients who expressed a need for psychotherapy and short disease duration (≤ 2 years) (p = 0.005). In this study, a significantly higher percentage of patients with IBD (31%) expressed a need for psychological intervention when compared to patients with RA (13%; p < 0.001). This shows the increased need for psychotherapeutic intervention in the IBD population with short disease duration specifically.

A bidirectional relationship exists between depression/anxiety and IBD. The severity of IBD inflammation and its associated symptoms can lead to depression/anxiety, while depression/anxiety can exacerbate inflammation. In four large studies, pooled data showed that adults with active IBD had much higher rates of anxiety, 66.4%, compared to 22% in adults with inactive IBD. Similarly, in five studies, the pooled rate of depressive symptoms during active IBD was 34.7% compared to 19.9% in inactive IBD. Those with untreated and/or unrecognized psychologic disorders are at risk for increased hospitalizations and disease flares, lower compliance with treatment,
and increased healthcare costs. Despite high levels of depression and anxiety in IBD patients, one study showed that many experiencing psychiatric symptoms were undertreated.20

While the impact of depression and anxiety on the course of IBD is known, the research for depression and anxiety treatments is limited by the number of studies and low methodological quality.21,22 Treatment for depression and anxiety in IBD patients is usually pharmacologic therapy or psychotherapy. One systematic review found that the use of antidepressants was effective in improving disease activity, IBD symptoms, and depression, but these findings were limited due to lack of randomized controlled trials and small sample sizes.11 Additionally, antidepressants have potential adverse side effects.11 The same systematic review reported patient satisfaction with psychotherapy.11 Psychotherapeutic interventions may be beneficial in IBD by not only improving quality of life and mental health, but also by reducing inflammation.23 A 2019 systematic review showed that mindfulness interventions had significantly long-term improvements on depression.21 Another systematic review showed that newly diagnosed IBD patients have the greatest need for early psychotherapy intervention.24 Generalizability of results has been limited by past samples excluding those with moderate-severe IBD25-27 and those with moderate-severe depression.28

Cognitive behavioral therapy is a psychotherapeutic intervention that is well-developed and has been found to enhance quality of life while reducing psychological distress.5,29 A previous review concluded that patients with IBD are most likely to benefit from psychological therapy if it is individualized, holistic, targets psychological symptoms and individual stressors, and is CBT-based.30 CBT intervention focuses on
directly targeting symptoms, reducing distress, re-evaluating thinking and promoting helpful behavioral responses. The duration of CBT varies, often ranging between 10 and 20 sessions. CBT has been found to be effective in people with other chronic illnesses such as chronic obstructive pulmonary disease, diabetes, and cancer.

Among adult patients with IBD who report comorbid psychiatric symptoms or low quality of life, research suggests that CBT can be effective for these individuals. One 2013 study shows evidence that CBT improves mental health in patients with IBD both immediately following the interventions and at > 6 months of follow-up. Research has also suggested that CBT is likely more effective for those with higher baseline depression and anxiety severity due to the larger margin for symptoms reduction compared to a relatively low baseline severity. However, limitations of traditional CBT include travel to the therapist’s office, constraints with the therapist’s schedule, and long waiting lists.

Many people that require treatment for depression may not receive it due to poor accessibility or affordability of the available options. Using online interventions to deliver psychotherapy can solve this problem. A 2018 systematic review looked at the efficacy and economic value of online cognitive behavioral therapy (oCBT) for major depressive disorder. The format of oCBT varies, but it mostly entails self-help guidance with the use of written materials, audio, or video files, guided by a therapist via email or phone call engagement. There are clear indications that the presence of a therapist guiding the patients and providing feedback is important for adherence and outcome. There is also evidence that guided oCBT is equally as effective as traditional CBT in improving depressive symptoms. Although this review included only those with
diagnosed major depressive disorder, the results strongly suggest that therapist-guided oCBT can reduce symptom severity.

In addition to studying the effectiveness of CBT, the acceptance of CBT should be considered. Patient experiences with blended video- and internet-based psychotherapy intervention has been studied in adults suffering from major depressive disorder. This intervention consists of four core components: (1) a face-to-face diagnostic interview (2) video-based synchronous therapy sessions (VTS) (3) online self-help treatment modules (OTM) (4) online and smartphone based monitoring of behavior and symptoms (BSM). In a study evaluating the patient’s experience with blended video- and internet-based CBT service in routine care, the treatment was tailored specifically to each patient directed by the therapist. A disadvantage of internet based guided self-help intervention is tailoring it towards individuals, but the addition of video-based synchronous therapy sessions helps overcome this issue. Patients found this blended therapy equal or superior to traditional face-to-face therapy. The many advantages of online CBT are that patients can schedule and receive therapy from any location with Internet access, patients with physical limitations can receive care, social stigma is lessened or eliminated, and introverted patients may be more open and receptive to treatment. The combination of telemedicine with traditional cognitive behavioral therapy is a feasible, affordable, and effective treatment.

During the Covid-19 pandemic, telemedicine consultations (video/audio) proved to be a feasible and acceptable option for care of IBD patients. Patients can undergo a video consultation via a mobile app or video-based digital platform. This allows patients to receive care without travel limitations. One study reported 60.5% percent of IBD
adults met criteria for at least moderate depression, anxiety, and/or stress during the pandemic and more than two-thirds of those with pre-existing diagnoses reported worsening symptoms due to the psychological impact of the pandemic. During this pandemic, people suffering from chronic illnesses have experienced greater distress than the general population which demonstrates the need for mental health treatment in this population.

There is not yet an established first-line treatment for moderate-severe depression and anxiety in adults with moderate-severe inflammatory bowel disease. Newly diagnosed patients demonstrate the greatest need for psychotherapy and early intervention. Yet several barriers exist, such as social stigma, financial burden, lack of mental health professionals trained in working with IBD patients, and lack of timely referrals to a mental health specialists. Additionally, CBT has a greater impact for those with higher scores of anxiety and low mood at baseline. With today’s era largely shifting to telemedicine, video-based, therapist-guided cognitive behavioral therapy is a feasible, cost-effective, and accessible treatment option that has proven to improve depression and anxiety. This form of therapy may be more accessible to our IBD population who suffer from moderate-severe disease symptoms and moderate-severe psychological symptoms at baseline. With proper equipment, video-based, therapist-guided cognitive behavioral therapy may increase adherence and remain a similar experience to traditional face-to-face CBT. Thus, this psychotherapeutic intervention could give more newly diagnosed IBD adults a more accessible option to improve their quality of life.

1.2 Statement of the problem
Depression and anxiety independently decrease the quality of life in patients with IBD. Those with moderate to severe IBD have shown to have higher rates of depression and anxiety compared to those with mild or inactive IBD. Patients are recommended to seek treatment after mental health symptoms arise; however, studies show a low proportion of patients have access to psychiatric consultation and psychotherapy, and studies found a low rate of psychiatric referrals among IBD patients. Adults with moderate-severe depression at baseline have experienced benefits from CBT. Research has shown mixed results on the effectiveness of cognitive behavioral therapy in changing disease activity and mental health/quality of life in adults with IBD.

Multiple gaps of literature have been identified: 1. Newly diagnosed IBD patients present with the greatest need for psychotherapeutic intervention, but there is a lack of efficacy trials of CBT in newly diagnosed IBD adults. 2. Prior research studying CBT in adults with IBD have excluded those with active or moderate-severe IBD disease when this subgroup may benefit the most from a psychotherapeutic intervention. 3. Only traditional face-to-face or self-help computerized CBT RCTs have been conducted in this population; there is a lack of RCTs using video-based CBT as an intervention in adults with IBD.

There is a need for more randomized controlled trials (RCTs) comparing the effectiveness and acceptance of video-based, therapist-guided CBT to traditional face-to-face CBT. Because there are many different forms of online/computerized CBT, this limits generalizability from previous studies to this population. Past RCTs were underpowered due to low adherence and high attrition to traditional and even computerized cognitive behavioral therapy. The literature needs to extend to an RCT
comparing video cognitive behavioral therapy to standard medical care in IBD adults to add an accessible and non-invasive option in improving mental health and quality of life.

1.3 Goals and Objectives

In this RCT, we aim to investigate the multidimensional effects of video-based, therapist-guided cognitive behavioral therapy compared to standard medical care in adults with newly diagnosed moderate-severe inflammatory bowel disease who present with moderate-severe depressive and/or anxiety symptoms at baseline. Our primary aim is to prevent a secondary diagnosis of depression and/or anxiety with early initiation of CBT following new primary diagnosis of IBD in adults. Our secondary aims investigate if it is conducive to perform video CBT and if CBT affects disease activity. Only adults with IBD who meet eligibility criteria will be enrolled in this RCT. Participants will be randomly assigned to one of two groups: video CBT or standard medical care. They will be followed weekly for 12 weeks and at 3-month follow-up. The main objective is to observe differences in mean change from baseline in self-reported depression and anxiety scores as measured by the Hospital Anxiety and Depression Scale (HADS) between groups. Due to the bidirectional relationship between psychological symptoms and disease symptoms, we will also assess disease progression and quality of life. Secondary objectives include: 1. Differences in mean change between groups in quality of life as measured by the Short Form Survey (SF-12), 2. Differences in mean change between groups in disease severity as measured objectively by inflammatory markers, consisting of CBC, ESR, CRP, and fecal calprotectin, and 3. Differences in mean change between groups in disease severity as measured endoscopically by the Simple Endoscopic Score for Crohn’s Disease (SES-CD) and the Mayo Score for ulcerative colitis.
1.4 Hypothesis

Recently diagnosed moderate-severe IBD adults with moderate-severe depression and/or anxiety aged 18–40 who are treated with CBT as adjuvant to standard of care will have a statistically significant decrease in depression and/or anxiety scores as measured by the HADS scale from baseline to 12-week follow-up in comparison to patients receiving standard of care, and results will be maintained 3 months after intervention completion.

1.5 Definitions

*Standard medical care:* Annual visits with gastroenterologists that may include lab draws, medication prescriptions, biologic infusions, colonoscopies, and/or endoscopies.

*Depression:* Feelings of sadness and loss of interest, which stops one from doing normal activities. A score of greater than $> 8$ on the HADS.

*Anxiety:* Feelings of worry, nervousness, or unease, typically about an imminent event or something with an uncertain outcome. A score of greater than $> 8$ on the HADS.

*Moderate-severe IBD:* Measured endoscopically using a Simple Endoscopic Crohn’s Disease score $> 7^{52}$ for those with CD or a Mayo Full Score $> 6$ or Mayo Endoscopic Score $> 2$ for those with UC.$^{53}$

*Online Cognitive Behavioral Therapy (oCBT):* Synonymous with internet cognitive behavioral therapy (iCBT) for the purpose of this paper. Cognitive behavioral therapy administered online. The methodology varies, but it typically consists of one-hour weekly sessions. Sessions differ in the extent to which they provide guidance or support.$^{54}$ Guidance can include informational and supportive automated emails sent to participants, brief weekly phone calls from therapists or research assistants providing encouragement,
support and clarification of lesson content and homework, or text-based communication between clients and clinicians.\textsuperscript{54}

\textit{Computerized Cognitive Behavioral Therapy}: A type of self-help therapy delivered via the internet. It uses the same techniques as a therapist would in face-to-face CBT.

\textit{Video-Based, Therapy-Guided Cognitive Behavioral Therapy}: Formatted as traditional face-to-face CBT but delivered via video-based platform by a therapist.

\textit{Hospital and Anxiety Depression Scale (HADS)}: A self-reported 14-item scale used to determine the levels of anxiety and depression that a person is experiencing. Each item on the questionnaire is scored from 0-3. A person can score between 0-21 for either anxiety or depression.

\textit{Simple Endoscopic Crohn’s Disease (SES-CD)}: A four-component disease activity score measured during endoscopy that assesses the size of mucosal ulcers, the ulcerated surface, the endoscopic extension, and presence of stenosis. The score ranges from 0 to \textgreater15.

\textit{Mayo Score for Ulcerative Colitis}: The most commonly used scoring system for ulcerative colitis disease activity that assesses stool frequency, rectal bleeding, mucosal appearance at endoscopy, and physician rating of disease activity.

\textit{Short Form Survey (SF-12)}: A self-reported 12-item survey assessing the physical and mental health on an individual’s everyday life through eight health domains. It is often used as a quality-of-life measure. It is a shortened version of the SF-36.
1.6 References


CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Introduction

A search of relevant medical literature was conducted between August 2020 and June 2021 using Ovid Medline, EMBASE, PsychINFO, Cochrane, and Scopus. Primary searches were performed using the combination of MeSH terms “inflammatory bowel disease,” “Crohn’s disease,” “ulcerative colitis,” “cognitive behavioral therapy,” “telemedicine,” “psychotherapy,” “depression,” and “anxiety.” Additional search terms included quality of life, health related quality of life, HRQOL, online cognitive behavioral therapy, video cognitive behavioral therapy, videoconferencing, and telemedicine. Articles included in this literature review were written in English with the exception of one randomized controlled trial written in Spanish and translated to English due to the results being pertinent to our study. Articles were analyzed for relevancy to our proposed research study. We analyzed clinical trials, meta-analyses, and systematic reviews, and examined reference lists of primary articles to search for additional relevant references for our study.

The literature search and review demonstrate the prevalence of depression and anxiety in inflammatory bowel disease patients and mixed conclusions about the efficacy of psychotherapy intervention on this population. No randomized controlled trials have been conducted using video-based CBT as an intervention in adults with IBD. The review was expanded to include video-based CBT in other diseases, so we could thoroughly review previous methodology necessary to properly compose our study. Although other modes of CBT have been widely studied in IBD patients, there is much to be learned regarding its efficacy on those recently diagnosed with increased anxiety and depression.
at baseline. Additionally, there is much to be learned regarding the efficacy of video-based CBT in this population.

2.2 Review of Empirical Studies

2.2.1 Depression and Anxiety in Adults with Inflammatory Bowel Disease

Multiple studies have demonstrated the prevalence of depression and anxiety in patients with IBD. An observational study evaluated the prevalence of depression and anxiety in patients with IBD compared to healthy volunteers.\(^1\) Participants took self-assessment tests for depression, using the Patient Health Questionnaire-9 (PHQ-9), and anxiety, using the Symptom Checklist Anxiety Scale (SCL-A20). Results showed a higher prevalence of depression (34.3% vs 5%, \(p < 0.0001\)) and a higher prevalence of anxiety (18.6% vs 2%, \(p = 0.0002\)) in IBD patients compared to controls.\(^1\) Another study determined the prevalence of depression in people with IBD from two nationally representative Canadian self-report surveys.\(^2\) Logistic regression analysis showed that the odds of having depression among those with IBD compared to the general population were highest in those ages 20-49 (ages 20-29: OR 9.14, \(p < 0.001\); ages 30-39: OR 11.79, \(p < 0.001\); ages 40-49: OR 9.70, \(p < 0.001\)), while the odds were lowest among ages 70-79 (OR 1.33, \(p < 0.001\)).\(^2\) Rates of depression from both survey samples were similar (16.3% and 14.7%) and higher than the general Canadian population (5.6%).\(^2\) A population-based cohort study looking at IBD adults compared to matched community samples in the US and New Zealand found that the majority of participants had a psychiatric disorder preceding their diagnoses of IBD (\(p = 0.001\)).\(^3\) Episodes of depression and anxiety are more likely to occur during periods of acute stress; the period around IBD diagnosis can be especially stressful.\(^3\)
A few studies have demonstrated that those with higher IBD disease activity have higher levels of anxiety and depression compared to IBD patients in remission and to the general population. In a retrospective study, researchers used logistic regression analysis to identify risk factors for depression in patients with inflammatory bowel disease. Clinical disease activity was an independent risk factor for depression in CD ($p = 0.001$). 70% of patients with CD in clinical remission had no risk of depression, while 75.6% of patients with active CD had either mild depression or were at risk for major depression. There was no independent risk factor identified for those with UC. Additionally, there was a negative correlation between health-related quality of life, as measured by SF-12 mental sub-scores, and depression, as measured by PHQ-9, in both patients with CD and UC (CD: $p < 0.001$; UC: $p < 0.001$). Another study compared anxiety and depression of CD and UC patients with chronic liver disease patients and the general population, controlling for sociodemographic and medical variables with age- and sex-matched controls. Analysis of variance (ANOVA) showed the frequency of a probable mental disorder was 49.1% in those with moderate/severe disease activity compared to 11.3% in IBD patients in remission ($p < 0.001$).

One study specifically examined if inflammatory bowel disease patients with anxiety/and or depressive symptoms receive the care they need and if clinical and sociodemographic variables are associated with those symptoms. IBD patients scored significantly higher on the anxiety ($p = 0.00$) and depression ($p = 0.00$) subscales of the HADS, with small effect sizes of 0.29 and 0.32 respectively, and significantly lower on the physical health component (PCS) ($p = 0.00$) and the mental health component (MCS) ($p = 0.00$) of the quality of life scale (SF-12), with moderate effect sizes of 0.70 and 0.58.
respectively, compared to the general population. Of the 95 participants (42.6%) who indicated high levels of anxiety and/or depression, only 17 participants (17.9%) received mental help in the preceding four weeks. Only 20 participants (21.1%) who indicated high levels of anxiety/depression were being treated with psychotropic medication. Using multivariate logistic regression analysis, factors associated with high levels of anxiety (HADS anxiety subscale ≥ 8) were active disease (p = 0.024) and Crohn’s disease (p = 0.029). The only factor associated with high levels of depression (HADS depression subscale ≥ 8) was active disease (p = 0.008).

The psychological impact of the Covid-19 pandemic on IBD adults should be considered. There have been few survey studies looking at this impact. One cross-sectional survey investigated the influence of Covid-19 on HRQOL of IBD patients, controlling for disease activity. The study included two samples of 195 IBD patients recruited from an outpatient setting prior to the Covid-19 outbreak and 707 IBD patients recruited through an online survey during the highest pandemic peak (March to May 2020). Results showed large effect sizes; patients with active IBD showed higher psychological distress, as measured by HADS (d = 0.34), and lower disease-specific HRQOL, as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) (d > 0.50). Hierarchical regression analysis determined that the setting (pre-Covid-19 outbreak vs. during lockdown) played a very small factor in IBDQ variance (p < 0.001), demonstrating that psychological distress and quality of life are impaired regardless of the pandemic. This study is limited due to its cross-sectional nature and therefore, inability to make a causal inference. Another study done in Portugal explored the pandemic’s effect on disease and psychological outcomes of people with IBD. Anxiety
and depressive symptoms, measured by HADS, were studied in 124 Portuguese participants ages 18-64 years old. Correlation analyses showed a significant association between IBD symptoms and fear of contracting Covid-19 (p < 0.01).\textsuperscript{10} Regression analyses showed anxiety significantly accounted for IBD symptom perception (p = 0.022), but depression did not.\textsuperscript{10} More frequent symptoms may lead to increased hospital visits for IBD patients, which may prove challenging for those fearful of contracting Covid-19. This study showed that the fear of contracting Covid-19 was the most relevant variable for depressive symptomatology and anxiety severity, which demonstrates the pandemic may have significant contributions to outcomes in this population. Further longitudinal studies are needed to investigate the long-term effects of the Covid-19 pandemic on this population.

2.2.3 Interventions for Depression and Anxiety in People with Inflammatory Bowel Disease

Treatment for depression and anxiety in IBD consists of psychotropic medication and psychotherapy.\textsuperscript{11} Currently, there is no gold standard method for treatment and management of depression and anxiety in IBD. The most widely used pharmacologic agents are tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), such as citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, and a serotonin norepinephrine reuptake inhibitor (SNRI), such as venlafaxine).\textsuperscript{11,12} Antidepressants are recommended for patients with moderate to severe symptom severity with a reduced quality of life.\textsuperscript{12} TCAs are effective in chronic pain syndromes, but adverse effects include sedation, anticholinergic effects, insomnia, nightmares, and agitation.\textsuperscript{12} SSRIs improve symptoms of anxiety and depression, but adverse effects may
be agitation, insomnia, sexual dysfunction, nausea, or diarrhea. SNRIs seem to help reduce pain in pain-related conditions, with less adverse effects than TCAs. IBD patients take more medications than the healthy population, such as antibiotics (OR = 4.01, 95% CI: 3.57-4.51), proton pump inhibitors (OR = 3.90, 95% CI: 3.48-4.36), and nonsteroidal anti-inflammatory analgesics (OR = 1.17, 95% CI: 1.07-1.28). Pharmacologic treatment can be effective but poses adverse effects, concern for tolerance, problems when tapering off medications, cost, fear of becoming dependent, and additional medication burden.

The most widely used psychological treatment for depression and anxiety in IBD patients is cognitive behavioral therapy. CBT has shown to be most effective in reducing symptoms and relapse rates out of all psychotherapeutic interventions. CBT is a well-developed intervention proven to improve quality of life and decrease psychological distress. It has shown positive effect in individuals with other chronic somatic illnesses, such as chronic obstructive pulmonary disease, diabetes, and cancer. There has been mixed evidence on the effectiveness of CBT in those with IBD, but research has shown consistent benefits for those with anxiety and depression symptoms. One systematic review found that CBT is indicated for high-risk subgroups, such as those with comorbid psychiatric conditions or elevated stress. CBT as an intervention in IBD patients has been studied in various methods of delivery, such as traditional face-to-face sessions, both face-to-face and computerized, computerized CBT, blended face-to-face and telephone/Skype with a therapist, group sessions, and various types, such as self-help CBT, mindfulness-based, and disease-specific. One study randomized adults with IBD who self-reported fatigue to either an
8-week CBT intervention (one 60-min session and seven 30-min telephone/Skype sessions with a therapist) or a control group. There was an improvement in quality of life (IBDQ) in both groups. The intervention group showed greater change between baseline and 12 months compared to the control group (MD = 8.43 [CI = -1.74, 18.60]), with a between group effect size of 0.98 (CI = -2.10, 0.23). Although this study measured baseline and 3 month follow-up means and standard deviations of anxiety and depression, these outcomes were not included in their statistical analysis. This study was also limited due to a small sample size, lack of generalizability due to recruitment from one tertiary referral center, and self-reporting of disease activity.

In addition to CBT, other non-pharmacologic interventions, such as mindful based stress reduction (MBSR), Breath—Body—Mind Workshop (BBMW), guided imagery and relaxation, solution-focused therapy (SFT), yoga, and gut-directed hypnotherapy have been studied in adults with IBD. A recent meta-analysis of 10 RCTs investigated the effectiveness of non-pharmacological interventions on reducing anxiety, depression, and disease specific quality of life in adults with IBD compared to control groups. It showed the pooled standardized mean differences (SMD) for the effect of non-pharmacological interventions on anxiety was -0.28 (p = 0.004) and the pooled SMD for the effect of non-pharmacological interventions on depression was -0.22 (p = 0.025), suggesting that this intervention significantly reduced anxiety and depression among adults with IBD. Non-pharmacologic interventions prove to be an option for management of anxiety and depression among adults with IBD; all providers should discuss these treatment options with patients in this population.

2.2.4 Benefits of Cognitive Behavioral Therapy
Traditional face-to-face CBT has been widely studied and proven effective in treating depression and anxiety in the general population.\textsuperscript{38} This traditional method requires the individual to work face-to-face with their therapist to identify, challenge, and evaluate the thoughts that maintain the depressive mood.\textsuperscript{13} A review of the benefits of CBT in the primary care setting showed a statistically significant treatment effect (48 studies, 157 effect sizes, \(d = 0.474\), \(p < 0.001\)).\textsuperscript{38} CBT has also demonstrated its use in adults with other chronic, debilitating diseases. A randomized controlled trial study investigated the effectiveness of CBT when applied to patients with relatively early rheumatoid arthritis (disease duration <8 years). Intention-to-treat results demonstrated beneficial effects of CBT in the intervention group compared to the control (standard medical care) group. Univariate test results looking at a time x group interaction effect demonstrated depression significantly decreased in the CBT condition at post-treatment and follow-up (\(t = 3.02, p < 0.01\) and \(t=3.10, p < 0.01\), respectively) compared to the control group (\(t = -0.57, p = 0.58\) and \(t = -1.23, p = 0.23\), respectively).\textsuperscript{39} CBT intervention in early IBD population has yet to be studied; however, rheumatoid arthritis is also a chronic disabling disease which makes the two diseases comparable. A limitation in the methodology remains the same from past CBT studies: 43% of eligible participants refused to participate due to practical concerns, such as traveling distance and scheduling difficulties with participating face-to-face.\textsuperscript{39}

During the Covid-19 pandemic, there has been a shift in CBT delivery from traditional face-to-face to online CBT (oCBT). For the purpose of this literature review, we included studies that utilized videoconferencing psychiatric treatment, digital CBT, internet-delivered, and therapist-supported/guided online CBT to improve depression and
anxiety. Since this intervention has not been widely studied in IBD patients, we studied the efficacy of this intervention in other chronic disease populations. A review of the clinical efficacy and economic evaluation of oCBT vs. face-to-face CBT for major depressive disorder found that oCBT is likely more effective for those with higher baseline severity due to the larger margin for symptom reduction, compared to those with lower baseline severity.\textsuperscript{13} Meta-analysis found oCBT superior and produced a significant improvement in depressive symptoms relative to comparator treatments (p < 0.0001).\textsuperscript{13}

One randomized controlled trial investigated the effectiveness of ten 55 minute sessions of individual CBT delivered online in real time by a therapist compared to usual care for adults aged 18-75 with depression in primary care.\textsuperscript{40} The primary outcome was recovery of depression, measured by a Beck’s Depression Index (BDI) score ≤10 four months after randomization. Results showed participants in the intervention group were more likely to achieve depression recovery at 4 months compared to the control group (p = 0.001).\textsuperscript{40} The benefit from the intervention was also maintained at 8 month follow-up (p = 0.023).\textsuperscript{40} After adjustment for baseline imbalance, the intervention demonstrated improvement in depressive symptoms (p = 0.0002), health status (p = 0.045), and quality of life (p = 0.024) at 8 month follow-up with an effect size of 0.70.\textsuperscript{40} The study reported greater benefit of online, therapist-guided CBT for those with severe symptoms at baseline than those with mild depression; although, the study did not provide the data. It should be noted that participants in the intervention group were more likely to be taking antidepressants at follow-up than those in the control group. However, these differences were small and adjustment for them had no effect on the comparisons for recovery at either follow-up.
The efficacy and feasibility of psychiatric consultations via videoconferencing compared to face-to-face (F2F) for treatment of depression has been studied. In one study, 107 adults with mild depression were randomly allocated into a videoconferencing intervention group or an F2F group consisting of monthly follow-up consultations with a psychiatrist for 5 months.\textsuperscript{41} Outcome measures of depression severity, mental health status, medication course, relapses, satisfaction with treatment, therapeutic relationship, treatment adherence, and medication adherence were assessed at baseline, 6-, and 12-month follow-up. ANOVA revealed both groups showed a significant decrease in severity of depression (videoconferencing: $p < 0.001$, F2F: $p = 0.001$) and significant increase in mental health status (videoconferencing: $p = 0.02$, F2F: $p = 0.01$) over the study period. There were significantly more dropouts in the F2F group than in the videoconferencing group at 6 months ($p = 0.04$).\textsuperscript{41} While there were still more dropouts in the F2F group at 12 months, this difference did not remain significant. This study showed greater improvement in depression severity among videoconferencing compared to face-to-face. However, this study was limited because groups were not balanced with regard to depression severity; the videoconferencing group had a higher mean score (7.92) vs. the F2F group mean score (6.19) at baseline. This limits generalizability because this group had greater potential to decrease in score. While investigators controlled for the same psychiatrists to deliver F2F and videoconferencing consultations, possible bias from personal method preference could have influenced outcomes.\textsuperscript{41} Although this study did not investigate CBT specifically, the efficacy of videoconferencing for psychiatric treatment can be applied to CBT.
In addition to CBT being studied in those with depression, it has also been studied in those with moderate to severe symptoms of generalized anxiety disorder (GAD). One study compared digital CBT to waitlist control in patients with a mean age of 30.9 with moderate to severe symptoms of GAD. Digital CBT was a personalized 6-week CBT program delivered via smartphone that involved a virtual therapist. Results showed a statistically significant reduction in anxiety scores in the digital CBT group compared to the waitlist control group at mid-intervention (p < 0.001), post-intervention (p < 0.001), and follow-up (week 10) (p < 0.001). It should be noted that this virtual therapist was not a live therapist interacting with the patients, making this platform more self-help based. It is difficult to generalize the results of these studies with the various interventions used, but findings show an overall benefit of CBT in improving depression and anxiety symptoms in adults.

2.2.5 Cognitive Behavioral Therapy as an Intervention for Adults with Inflammatory Bowel Disease

Multiple studies have investigated the use of cognitive behavioral therapy as an intervention for depression and/or anxiety in adults with inflammatory bowel disease. Several reviews have investigated the impact of psychotherapy on biopsychosocial outcomes for people with IBD and have found mixed results. However, a Cochrane meta-analysis of RCTs suggested that psychotherapy may benefit IBD adults in either active or quiescent disease, if a certain degree of emotional distress is present. A limitation of this review was that 19 out of 20 studies included IBD adults without distress at baseline, which means there was less potential for treatment effects. Results of past RCTs that found CBT had no effect on mental health were limited due to high
attrition, low adherence, small sample sizes, or low disease burden at baseline. There have been RCTs that investigated the benefits of CBT on those with increased psychological symptoms at baseline; these studies will be discussed here.

First, one 2007 study demonstrated the overall positive effect of CBT on adults with IBD. A randomized controlled trial conducted in Spain investigated the effect of 10-week, 2-hour weekly group sessions of face-to-face CBT on anxiety and depression in IBD adults > age 18. Participants were randomized into the intervention group or the wait-list control group. Exclusion criteria included those in the active phase of the disease at the beginning of the intervention or those who indicated indices of severe psychopathology in baseline questionnaires. Outcomes were measured by the 90 Symptom Questionnaire (SCL-90-R), BDI, and HADS. Friedman’s nonparametric test was used to analyze differences in each of the variables in the different experimental phases. Comparative analysis between groups was determined using the Eta correlation coefficient. There was a statistical improvement in anxiety at 3 months (p = 0.001), 6 months (p = 0.01), and 12 months (p = 0.008) and in depression at 3 months (p = 0.0001), 6 months (p = 0.02), and 12 months (p = 0.01) compared to the control group. This study demonstrated that CBT had significant improvement in all emotional variables that was maintained throughout follow-up. However, limitations of the study include excluding those with active disease and with severe symptoms of anxiety or depression. This limits generalizability to the IBD population who may most benefit.

One pilot study looked at the effect of adding CBT to standard treatment compared to standard therapy alone in prolonging remission in IBD. Adult IBD patients in remission were randomized to a face-to-face/online CBT group or standard care (SC).
Eligible patients were randomized in a 2:1 proportion (experimental vs. control) in anticipation of difficulty recruiting the experimental arm due to large participation burden. The CBT arm was divided into two subgroups, F2F and online but treated as one for the main analysis. Those who could not commit to the time or travel were offered the online therapy option. The F2F group underwent 10 weekly two-hour sessions at the hospital delivered by a psychologist, while the online CBT group received sessions of similar length online that were self-directed. Outcomes included: 1. IBD remission, measured by the Crohn’s Disease Activity Index (CDAI) or the Simple Clinical Colitis Activity Index (SCCAI), 2. mental health status, measured by the Hospital Anxiety and Depression Scale (HADS), and 3. health-related quality of life (HRQOL), measured by the Short Form 36 Health Status Questionnaire (SF-36). The HRQOL questionnaire was broken down into physical and mental component scores. Disease activity was also measured using blood tests: CRP, hemoglobin (HB), platelet, and white cell count (WCC). The primary outcome of this study was IBD remission at 12 months (CDAI score of <15 or the SCCAI score of >3 and confirmed by the treating physician). Two models were constructed to measure the effectiveness of the intervention. Model 1 included time and group variables and a time-group interaction variable and adjusted for the outcome variable at baseline. Model 2 adjusted for sex and age. The p value of less than .05 was considered statistically significant.

Multivariate analysis showed CBT did not significantly change disease activity at 12 months (CD, p = 0.669; UC, p = 0.549) adjusting for baseline. However, at the univariate level, CBT significantly improved mental quality of life (p = 0.013), depression (p = .018), trait anxiety (p = .042), and maladaptive coping (p = .002) over 12
months. A subgroup of 74 participants, 34 in the +CBT group and 40 in the SC group, classified as ‘in need’ was separately analyzed. Participants ‘in need’ were defined as meeting at least one of the following criteria: aged 18-20, high baseline IBD activity despite considered in IBD remission by the clinician (CDAI > 180; baseline SCCAI > 5), being recently diagnosed (within last 2 years), having poor coping (score of 20-25 on either adaptive or maladaptive coping), and high anxiety or depression (HADS score for either anxiety or depression subscale ≥ 15). Results from this subgroup showed that those who received CBT had significantly improved mental quality of life at 6 months compared to SC (p = .034, d = .56).\(^1\) At 12 months, the difference between groups disappeared, but this subgroup as a whole decreased from 74 (+CBT n = 34 and SC n = 40) to 43 (+CBT n = 11 and SC n = 32). Although the results of this study did not demonstrate that CBT significantly changed disease activity at 12 months, it showed that participants ‘in need,’ such as those with a recent diagnosis or high anxiety or depression, benefitted from CBT in improving mental quality of life. A possible explanation for why this subgroup analysis failed to show improvement in anxiety or depression is the small sample size.

This study had limitations that could potentially explain why CBT as an intervention for all participants did not significantly change anxiety and depression scores at 6 months when controlling for baseline. First, participants had low anxiety and depression scores at baseline [+ CBT 4.3 (SD 3.4) and SC 4.4 (SD 4.1)], which could explain how the intervention had little effect. The subgroup of participants ‘in need’ with higher scores on mental health subscales showed that CBT was effective in improving QoL at 6 months. Therefore, studies should focus on targeting psychotherapeutic
interventions at those ‘in need’ vs the unselected IBD population. A second limitation was high attrition. The attrition in the oCBT group was significantly higher than in the F2F group. The sample size of the F2F group was 22 at baseline, 16 at 6 months, and 15 at 12 months, while the sample size of the oCBT group was 68 at baseline, 35 at 6 months, and 27 at 12 months. At 12 months, the significant difference between +CBT and SC disappeared which can be attributed to this high attrition. Therefore, the analysis became underpowered demonstrating the need for future studies to address high attrition with possibly larger sample sizes. Lastly, offering the intervention group either F2F or oCBT means this study did not classify as an RCT design. Additionally, there is no certainty that the online self-help CBT usage accurately represents complete CBT usage. Future studies should randomly allocate participants to a mode of CBT delivery or choose only one mode with improved monitoring.

Another study was a parallel-group multicenter randomized controlled trial investigating the effect of IBD-specific CBT on QoL, anxiety, and depression in IBD patients with poor mental QoL. IBD patients with a low level of QoL (scores < 23 on the SF-36) were randomized to an experimental group receiving CBT vs. a wait-list control group receiving standard medical care for 3.5 months, followed by CBT. The IBD-specific CBT intervention was eight 1-hour weekly sessions performed by eighteen clinical psychologists specializing in CBT after 16 hours of training and regular group supervision. Standard medical care involved consultation with medical specialists every 3 months for patients receiving immune suppression and once a year for patients not receiving immune suppression. 118 adults (≥ age 18) diagnosed with either CD or UC were eligible and randomized in the study. The average disease duration was 11.9 years.
in the experimental group and 10.4 years in the wait-list control group. Investigators administered self-report questionnaires to measure the outcomes: IBDQ to measure disease-specific quality of life, HADS—Depression Subscale (HADS-D) and Center for Epidemiologic Studies Depression Scale (CES-D) to measure depression, HADS—Anxiety Subscale to measure anxiety, and SF-36 to measure generic QoL. Both groups completed these assessments at baseline and 3.5 months follow-up. Analyses of covariance were used to assess difference between follow-up scores of all continuous outcomes for both groups. Multiple imputation using chained equations (MICE) was used as a sensitivity analyses to handle missing values. Data was then reanalyzed combining results from 10 imputed data sets into pooled estimates. Mean scores on the continuous outcomes were standardized to Cohen’s d using the pooled standard deviation of the baseline scores for both completers group and the MICE group. Cohen’s d of .3, .5, and .8, indicating a small, moderate, and large effect size, respectively, were calculated.

CBT had a statistically significant decrease, with moderate effect size, in HADS total score (d = 0.57, 95% CI -0.88 to -0.01), anxiety (d = 0.47, 95% CI -0.77 to -0.17), and depression (d = 0.58, 95% CI -0.86 to 0.30) subscales at the 3.5-month follow-up. CBT also showed significant effect on disease-specific quality of life (d = 0.55, 95% CI 0.27 to 0.84). When analyses was restricted to patients who attended at least five CBT sessions, the per protocol results were similar to the intention-to-treat results. These results demonstrated that CBT was effective in improving anxiety and depressive symptoms, as well as disease-specific quality of life compared to the wait-list control group.
One strength of this study was the focus on a subgroup of IBD patients with lower mental quality of life at baseline who would be at higher risk for psychiatric disorder and who would benefit more from mental care. Another strength was the use of eighteen clinical psychologists specializing in CBT who performed the intervention after a 16-hour training and group supervision. This helps prevent significant changes in CBT delivery among psychologists. There were also limitations of this study. The study was somewhat underpowered for the primary outcome (n = 96 instead of the planned n = 128). However, statistically significant results for most outcomes were still observed and the MICE calculations showed effect sizes similar to those in the complete case analysis. Secondly, a wait-list control group is not optimal due to information bias of participants knowing they will receive the intervention which may motivate participants to remain depressed until they receive treatment. This may lead to exaggerated effect sizes compared to a no treatment control group. There is a need to reconsider the attrition rate assumption in order to calculate a sample size that will be adequately powered and implement a control group that will provide the most accurate results of the intervention.

While no RCTs have directly studied the effect of CBT on IBD adults with higher anxiety and/or depression at baseline, there is one randomized controlled trial studying the effect of CBT on clinical disease course in adolescents and young adults with IBD and subclinical anxiety and/or depression. Participants who scored above the cutoff of the anxiety and/or depression questionnaire indicating elevated symptoms but not meeting criteria for a psychiatric disorder were eligible for randomization. Participants were randomized to either disease-specific CBT in addition to standard medical care or standard medical care alone. Results found there was no significant difference of time to
first relapse between the groups (p = 0.915). Additionally, clinical disease activity, fecal calprotectin, and CRP did not significantly change over time between or within both groups (p = 0.59, p = 0.158, p = 0.545, respectively). Strengths of this study include focus on the IBD patients with elevated anxiety/depression symptoms, using standard medical care as a control condition, low attrition, and use of objective measures for clinical disease activity (fecal calprotectin and CPR). Limitations of this study are that anxiety and depression symptoms were not investigated as an outcome, the majority of participants were in clinical remission at baseline, and the majority of patients were of Western ethnicity (80.9%), which reduces generalizability of the findings. Based on these limitations, there still remains a need for the active disease population with elevated anxiety/depression symptoms to be studied.

Lastly, a benchmarking study explored whether the benefits of CBT for IBD adults with moderate to severe levels of anxiety or low mood will be superior in reducing levels of anxiety and depression and having greater effect sizes in comparison with past RCTs. Adults aged 18 and over with IBD who indicated moderate to severe levels of anxiety and/or low mood, as scored by ≥10 on the PHQ-9 or the Generalized Anxiety Disorder 7 (GAD-7), were eligible for the nonrandomized uncontrolled trial. Participants underwent weekly 50-minute therapy sessions. The therapist administering CBT was trained in CBT and supervised by a cognitive behavioral psychotherapist familiar with IBD. Primary outcomes were anxiety, as measured by GAD-7, and depression, as measured by PHQ-9. Additional outcomes studied were HRQOL, using the short IBD questionnaire (SIBDQ), and symptomatic disease activity, using the Harvey Bradshaw Index (HBI) for those with CD and the simple clinical colitis activity index (SCCAI) for
those with UC. Paired t-test was used to analyze pre- and post-measures of HRQOL and disease activity. The two sample Wilcoxon rank sum test was used for analysis due to the Shapiro-Wilks test for normality indicating that data may be skewed for post-measures of anxiety (W = 0.053, df = 27, p = 0.01) and low mood (W = 0.758, df = 27, p = 0.001). Additionally, in order to create a benchmark, an RCT with a 1:1 CBT intervention that reported pre and post mean scores and standard deviations for measures of either anxiety, low mood, quality of life, or disease activity, was needed to compare effects. Studies that failed to report outcomes in this format or that used a group intervention were excluded. The only study that remained consisted of two interventions (F2F CBT and online CBT) vs. standard care, but for the purpose of composing a benchmark for this study, only the outcome data from the online CBT group was used. Because this study used different measures for their outcomes, it was not possible to directly compare the differences, so uncontrolled effect sizes were calculated to standardize the treatment effects: 0.2 (small), 0.5 (medium), and 0.8 (large) using a time interval of 6 months.

Results demonstrated a statistically significant decrease in scores for low mood (p < 0.0001) and anxiety (p < 0.001), symptomatic disease activity (CD: p = 0.002, UC: p < 0.001) and significant increases in scores for quality of life (p < 0.001). In the benchmark comparison, large effect sizes in this study (depression: 1.9, anxiety: 2.0, quality of life: -2.09, disease activity: CD: 0.71, UC: 1.1) were seen compared to small-medium effect sizes in the RCT (depression: 0.22, anxiety: 0.21, quality of life: not reported, disease activity: CD: 0.06, UC: 0.13). This study demonstrates the benefits of CBT for IBD patients with moderate-severe depression and anxiety symptoms at baseline. These findings suggest the need for
future RCTs to recruit participants of this subgroup. One limitation of this study was the use of different depression and anxiety measurements in the between study comparisons. It is possible that GAD-7 and PHQ-9 may be more sensitive to change in the IBD population than HADS, used in the comparison RCT. Studies are lacking in which questionnaires are best suited to measure anxiety and depression in IBD. However, the biggest limitations were the small sample size, the design (uncontrolled, nonrandomized), and therefore, lack of control group. Patients received a variable number of sessions compared to the RCT, which may have confounded results. There is a need for a future RCT investigating IBD subgroups in need vs. a control group that will control for confounding variables and enhance generalizability.

2.3 Review of Relevant Methodology

2.3.1 Study Design

The proposed study will be a two-arm, single-blinded RCT investigating the benefits of video-based CBT plus standard medical care compared to standard medical care alone for 12 weeks on depression and anxiety in newly diagnosed IBD adults with moderate-severe disease and moderate-severe depression and anxiety at baseline. The study will recruit from the outpatient Yale Inflammatory Bowel Disease Center locations at Temple Medical Center in New Haven, CT and in North Haven, CT. The study will be conducted in the outpatient clinics and via video-based telemedicine using Zoom.

An RCT design was chosen due to previously conducted studies utilizing the RCT design to compare CBT to a control group with a primary outcome of depression and anxiety in adults with IBD. One study was described as a 2-arm parallel randomized controlled trial, but their trial design offered the experimental group the choice of
completing the CBT intervention face-to-face or online, which does not comply with classic RCT requirements.\textsuperscript{21} Other studies used a wait-list control group vs. a standard of care control group,\textsuperscript{26,30} which as discussed before, is not the ideal control condition. Although it is an ethical alternative to provide treatment to a group in need of treatment, it can alter participants behavior in knowing they will eventually receive the intervention, which can affect study results. However, all participants will receive standard medical care, which includes possible psychiatric referrals and treatment. The only study that directly explored the benefits of CBT in IBD patients with moderate-severe depression and anxiety symptoms was a nonrandomized, uncontrolled trial, limiting validity of the results due to possible bias and confounders.\textsuperscript{48} Another study performed a subgroup analysis of participants ‘in need’ (higher scores on mental health subscales), but the sample size calculation was underpowered for this analysis.\textsuperscript{21} The other studies were relatively underpowered due to small sample sizes\textsuperscript{26,48} or high attrition,\textsuperscript{29} which limits generalizability. A parallel RCT study design to compare CBT vs. standard of care in those with moderate-severe IBD and moderate-severe depression and anxiety symptoms will reduce selection bias and minimizes possible confounders.

Participants will be recruited from clinics at the Yale University Inflammatory Bowel Disease Program, a tertiary care center. Many of these patients may present with moderate-severe disease courses, which is the subgroup of patients that the proposed study is targeting.

2.3.2 Selection Criteria

A complete list of the inclusion and exclusion criteria can be found in Chapter 3. Our selection criteria will be based on Bennebroek Evertsz et al., 2017.\textsuperscript{30} Participants will
be considered for our study if they are aged 18-40, have been diagnosed with either Crohn’s disease or ulcerative colitis in the past 6 months, have been clinically diagnosed with moderate to severe level of disease by a gastroenterologist, and have moderate to severe levels of depression and/or anxiety at baseline assessments. Unlike previous CBT studies who only included IBD adults with current clinical remission or mild symptoms only or excluded those with elevated inflammatory markers, active disease, or severe disease (i.e., recent major surgery and/or complicated disease), we will enroll those who score ≥ 7 on Simple Endoscopic Crohn’s Disease (SES-CD) score for those with CD or ≥ 6 on Mayo Full Score or Mayo Endoscopic Score ≥ 2 for those with UC. These are the cut-off scores between in remission/mild and moderate-severe disease.

Many endoscopic disease scoring systems exist in IBD; one review investigated the most common used scores in clinical trials of CD and UC. The two validated endoscopic activity scores for CD are the SES-CD and Crohn’s disease endoscopic index of severity (CDEIS). While CDEIS is the most commonly used endoscopic tool to assess disease activity in clinical trials, it is limited by its complexity which requires training and experience to utilize. Therefore, the SES-CD is a simplified index proven to be reliable, and it correlates well with the CDEIS (correlation coefficient $r^2 = 0.920$). The most commonly used endoscopic tool to assess disease activity in UC is the Mayo endoscopy sub-score. Strengths of this include ease of use and frequency of use in clinical trials, but limitations include lack of validation. One study defined active UC with a Mayo score of 6-12 points or endoscopic sub-score of at least 2. These cut-off scores have been used in other clinical trials. See Table 1 for disease activity indices scoring ranges and Appendices G and H for complete layout of scores.
Table 1. Inflammatory Bowel Disease Activity Indices

<table>
<thead>
<tr>
<th></th>
<th>SES-CD (Score Range: 0-56)</th>
<th>UC Mayo Score (Score Range: 0-12)</th>
<th>UC Mayo Endoscopic Subscore (Score Range: 0-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive Disease</td>
<td>≤ 2</td>
<td>&lt; 2 and no subscore &gt; 1</td>
<td>0</td>
</tr>
<tr>
<td>Mild Disease</td>
<td>3-6</td>
<td>3-5</td>
<td>1</td>
</tr>
<tr>
<td>Moderate Disease</td>
<td>7-15</td>
<td>6-10</td>
<td>2</td>
</tr>
<tr>
<td>Severe Disease</td>
<td>&gt; 16</td>
<td>11-12</td>
<td>3</td>
</tr>
</tbody>
</table>

Baseline assessments will be administered upon enrollment into the study. Participants with other severe psychiatric disorders, already undergoing treatment for mental health problems (pharmacological and/or psychological), significantly cognitively impaired, undergoing other interventional studies, or having feelings of suicidal ideations will be excluded from our study. This exclusion criteria helps to prevent several factors from potentially interfering with the validity of the results.

2.3.3 Potential Confounding Variables

There are potential confounding variables that can threaten the validity of our proposed study. Similar to previous studies, these variables include gender, age, employment status (full-time or part-time), level of education, diagnosis (UC or CD), disease duration, medications (steroids or biologics), current stoma, or other chronic illnesses. Another confounding variable will be changes in medication, such as the initiation of antidepressant as standard care by a psychiatrist during the study. We will control for these variables with a randomization protocol and account for differences between groups.

2.3.4 Randomization and Blinding Technique

Randomization techniques will be similar to previous studies investigating the effectiveness of CBT on anxiety and depressive symptoms among patients with IBD.
After baseline assessments are completed, eligible participants will be randomized using a computer-generated program into a 1:1 allocation to the intervention and control groups. This controls for baseline characteristics and reduces potential bias from confounding variables between and among both groups.

It is not possible to blind the experimental group to their intervention, but the control group can be blinded to the study’s hypothesis and specific details of the intervention. In accordance with another study, the investigators obtaining assessments and providers assessing disease activity will be blinded; participants in the intervention group will be asked not to discuss their outcome of randomization with their treating providers.29

2.3.5 Intervention

The video-based CBT intervention will be based on the framework of previous studies utilizing traditional CBT22 and video-based CBT in other populations.40 This intervention will model that of traditional face-to-face CBT but delivered by a therapist online via video-based platform. Our CBT program content will follow the 10-week program utilized in the 2017 study by Mikocka-Walus et. al; it focuses on improving coping with IBD.22 Two previous studies added booster sessions following their 10-week CBT program.29,52 These sessions give patients the opportunity to reinforce progress or trouble shoot obstacles, which may improve long-term outcomes.23 A systematic review found that CBT with booster sessions are more effective for mood and anxiety orders than CBT interventions without a booster session.53 Similar to another study that investigated therapist-delivered internet psychotherapy for depression in primary care, every participant will be assigned to one therapist for the duration of the study.40 Length
of CBT sessions have varied in previous studies from 55 minutes to 2 hours.\textsuperscript{20,22,40} Another study considered participants as treatment completers if they attended a minimum of 8 sessions.\textsuperscript{29} The proposed study will be a combination of these studies: a 12-week CBT program consisting of the 10-week content with 2 additional booster sessions. Sessions will be one hour in length and participants need to complete greater than 8 sessions to be considered intervention completers.

Trained psychologists specialized in CBT will conduct the sessions. These psychologists must be experienced in working with and treating depression and anxiety disorders. Following the methodology of one RCT,\textsuperscript{30} CBT sessions will be recorded, and independent raters will conduct integrity checks on at least two treatments per therapist.

The control group will remain standard medical care. Because the patient population will be those with newly diagnosed IBD, all patients will have undergone a colonoscopy and/or endoscopy to establish their baseline disease severity. Standard medical care typically includes follow-up visits with gastroenterologists that can include lab draws, initiation of pharmacologic, steroid, or biologic treatment, or procedures. Standard medical care will also extend to psychiatric referrals made by gastroenterologists and therefore, pharmacologic treatment initiated by psychiatrists.

2.3.6 Primary and Secondary Outcomes

The primary outcome of this study is depression and/or anxiety as measured by the Hospital Anxiety and Depression Scale (HADS). HADS has been widely studied in the past as a reliable screening measure for depression and anxiety disorders.\textsuperscript{54} Patients with IBD can experience both depression and anxiety, so the HADS scale was chosen as the primary outcome measurement. While the Patient Health Questionnaire (PHQ-9)\textsuperscript{25}
and the Beck Depression Inventory (BDI)\textsuperscript{29,52} has been used in past studies to assess depression in patients with inflammatory bowel disease, it is limiting because it does not include anxiety symptoms. However, PHQ-9 does have the advantage of asking about thoughts of death.\textsuperscript{55} Because of this, we will have to include questions asking about suicidal ideations and/or plans prior to screening. The HADS scale is divided into two scores, HADS-A for anxiety and HADS-D for depression.

In a 2002 systematic literature review, researchers found that using a cut-off score of 8 for both HADS-A and HADS-D provided the most optimal sensitivities and specificities around 0.80.\textsuperscript{56} In this review, three studies in primary care populations investigated HADS as a tool to detect DSM-III-defined psychiatric morbidity. Using 8+ as a threshold, the AUCs were analyzed to find the optimal threshold and all three studies showed 0.84-0.96, demonstrating that a score of 8+ on the HADS was reliable in identifying depression and/or anxiety.\textsuperscript{56}

A 2018 study looked into the validity and reliability of screening measures for depression and anxiety disorders in people with IBD. This study had people with IBD complete a Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID), in addition to multiple depression and anxiety screenings: PHQ-9, HADS, Kessler-6 Distress Scale, PROMIS Emotional Distress Depression Short-Form 8a (PROMIS Depression) and Anxiety Short-Form 8a (PROMIS Anxiety), GAD 7-item Scale, and Overall Anxiety and Severity Impairment Scale. For the HADS subscales, this study used a published cut-off point of 8 for possible anxiety and depression and 11 for probable anxiety or depression.\textsuperscript{55} HADS-D had an internal consistency reliability of 0.84 (95\% CI, 0.76-0.92) and test-retest reliability of 0.83 (95\% CI, 0.77-0.87). HADS-A had an
internal consistency reliability of 0.87 (95% CI, 0.79-0.95) and test-retest reliability of 0.83 (95% CI, 0.77-0.87). Researchers found that there were not significant differences in the individual psychometric properties of the different symptom scales. There are advantages and disadvantages to each scale, and there needs to be a balance of both sensitivity and specificity. The advantage of HADS is that it simultaneously evaluates depression and anxiety, two disorders that often co-occur, and is designed specifically for use in medically ill populations. Because of this, we will use HADS to measure our primary outcome. See Appendix E for HADS scoring.

One secondary outcome will be quality of life, as measured by the Short Form-12. This is a self-report questionnaire that is a simplified version of the SF-36. It is a generic quality of life survey that is broken down into two subscales: physical and mental health. Higher scores correspond with better quality of life. An advantage of the SF-12 over the IBDQ, another widely used disease-specific questionnaire that measures HRQOL in patients with IBD, is that it consists of 12 items that assess eight health concepts: (1) physical functioning, (2) role-physical, (3) bodily pain, (4) general health, (5) vitality, (6) social functioning, (7) role-emotional, and (8) mental health, whereas, the IBDQ consists of 32-items that only explore four dimensions: (1) bowel symptoms, (2) systemic symptoms, (3) emotional function, and (4) social function. Another advantage of SF-12 is that scores are norm-based and have been standardized from a national probability sample of 6012 noninstitutionalized adults in the US who participated in a 2009 Internet-based survey. See Appendix F for SF-12 scoring.

Other secondary outcomes include objective measures of disease activity, measured by systemic inflammatory markers: complete blood count (CBC), erythrocyte
sedimentation rate (ESR), C-reactive protein (CRP), and a local inflammatory maker: fecal calprotectin (FCP). As stated before, the severity of IBD inflammation and its associated symptoms can lead to depression/anxiety, while depression/anxiety can exacerbate inflammation. Furthermore, this bi-directional relationship implies an improvement in depression/anxiety symptoms will be accompanied by an improvement in inflammation. Due to the other outcomes being measured by self-reporting, it is important to gather objective data to ascertain whether improvements in disease activity were caused by reduction in inflammation or changes to perception of symptoms. A recent systematic review found that the measuring of both systemic and local inflammatory markers has only been done in three past studies looking at non-pharmacological interventions for anxiety and depression in adults with IBD; none used CBT as their intervention.

2.3.7 Sample Size and Statistical Significance

We will calculate our sample size from a previous study that used CBT as an intervention and the HADS to measure one of their outcomes. This study found a mean difference of 1.04 in total HADS score for the control group and a mean difference of 6.30 in total HADS score for the intervention group. These differences were taken from the total HADS score at baseline and at 3.5-month follow-up in intention to treat analysis. We calculated the standard deviation for difference between means in both the control group and the intervention group. The standard deviation for the control group was 1.46, while the standard deviation for the intervention group was 1.38. We will maintain a power of 80%, alpha of 0.050, and two tails. Previous RCTs studying CBT in unselected IBD have assumed a 10% attrition rate, but their results were still underpowered due
to higher than anticipated dropouts. One study focusing on youth with IBD and subclinical anxiety and/or depressive symptoms at baseline had very low attrition (<3%). Because our proposed study will be selecting similar adult IBD patients, we expect low attrition. However, we will still use an estimated 10% attrition rate, which results in a sample size of 70 participants in each group, or 140 total participants needed for recruitment into our study.

2.4 Conclusion

This literature review demonstrates the need to study CBT in newly diagnosed adults with moderate-severe IBD and moderate-severe depression/anxiety at baseline of diagnosis. Due to adherence challenges with traditional CBT, this review demonstrates evidence supporting the use of a video-based, therapist-guided online CBT in the IBD population. Research has shown CBT as an effective treatment for depression and anxiety symptoms in IBD. However, no studies currently exist using video-based CBT as an intervention. Past studies have largely remained underpowered due to high attrition rates. Additionally, past studies have failed to focus on the subgroup in most need of a psychotherapeutic intervention: those with moderate to severe IBD. Our proposed study is a single-blinded RCT studying the effects of video-based CBT compared to standard care in newly diagnosed IBD patients with moderate-severe disease and moderate-severe depression/anxiety at baseline. This addition to the literature will inform providers on additional treatment that can be initiated upon new diagnoses of IBD.
2.5 References


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CHAPTER 3: METHODS

3.1 Study Design

The study design will be a two-arm, single-blinded RCT. The study will comprise of randomization to a 12-week intervention or standard care with a 6-month follow-up from start of intervention of both groups. The research staff will create a Qualtrics survey to measure the primary outcome (change in depression/anxiety measured by HADS) and the secondary outcome (change in quality of life measured by SF-12). Participants will fill out forms at the start of the study, weekly for 12 weeks, and 3 months after completion of intervention. This survey will be sent via email along with weekly reminder emails to complete these questionnaires. Participants will undergo lab testing at either Yale New Haven Hospital or any Quest lab in the surrounding area.

3.2 Study Population and Sampling

Participants will be sampled on a non-random, consecutive basis from the outpatient Yale Inflammatory Bowel Disease Program at Temple Medical Center in New Haven, CT and North Haven, CT. Participants will have a primary diagnosis of IBD confirmed endoscopically by gastroenterologists at these locations. See Table 1 for a complete list of inclusion and exclusion criteria. At baseline, each participant will receive an endoscopic score, Ulcerative Colitis Mayo Score for those with UC and Simple Endoscopic Score for Crohn’s Disease (SES-CD) for those with CD. Only those scoring ≥ 7 on the SES-CD score for those with CD or ≥ 6 on the Mayo Full Score or ≥ 2 on the Mayo Endoscopic Score for those with UC will be included in the study. Patients with appointments at these locations will complete the Hospital Anxiety and Depression Scale (HADS). Those scoring ≥ 8 in depression and/or anxiety on the HADS and diagnosed
with moderate to severe IBD in the past 6 months will be asked to participate in the study. Because HADS does not include suicidal questions, participants will be asked if they have thoughts or plans to commit suicide or harm themselves; these participants will be immediately referred to a psychiatrist and excluded from the study.

Participants will also complete the Short Form-12 (SF-12) that measures HRQOL. Inflammatory markers: complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fecal calprotectin will be measured. Other labs that will be measured at baseline are a comprehensive metabolic panel (liver and renal levels), thyroid-stimulating hormone (TSH), vitamin B12, folate, and iron. Additional baseline variables that will be obtained are stools per day, blood in stool, pain, fever, joint pain, appetite, weight loss or gain, all medications, and pathology results from colonoscopy. Baseline characteristics will be measured following enrollment into the study.

Table 2. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tr>
<td>• Age 18-40</td>
<td>• Diagnosis of selective mutism, bipolar disorder, schizophrenia/psychotic disorder, autism spectrum disorders, post traumatic or acute-stress disorder, or substance use disorder</td>
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<tr>
<td>• Recent clinical diagnosis (≤ 6 months) of IBD (either UC or CD)</td>
<td>• Current or past treatment for mental health problems (pharmacological and/or psychological)</td>
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<td>• Sufficient English to understand, answer questionnaires, and participate in therapy</td>
<td>• Significant cognitive impairment</td>
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<tr>
<td>• Access to computer/Internet/smartphone device that is sufficient for video conferencing/telemedicine</td>
<td>• Participation in another interventional study</td>
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<tr>
<td>• Competence to consent</td>
<td>• Participants with severe levels of depression (i.e., associated with suicidal ideations)</td>
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<tr>
<td>• Willingness to participate in CBT sessions</td>
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<tr>
<td>• Baseline score of ≥ 7 in depression and/or anxiety on the HADS</td>
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<tr>
<td>• Baseline score of ≥ 7 on the SES-CD score for those with CD or ≥ 6</td>
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3.3 Subject Protection and Confidentiality

IRB approval will be obtained following the Yale University IRB Policy 100. All staff interacting with research participants will be required to complete the Yale Human Subject Protection and HIPAA Privacy training prior to the start of the study. Only those who have completed this training can access private health information (PHI) in university-approved secure electronic health records (EHR) on encrypted devices. Encryption of home video devices will align with Yale IRB protocol. Eligible subjects will be required to complete a written, informed consent form that follows Yale’s IRB Policy 200 for Informed Consent for Human Research. This consent form will detail the study’s purpose, procedures, duration, benefits, and statements of confidentiality. Data will be de-identified to ensure confidentiality. The form will also state that participants may discontinue the study at any time, and researchers may remove participants from the study at any time (i.e., if participants indicate suicidal thoughts after being randomized). All participants will be given time to read and ask questions regarding the IRB approved consent forms, attached in Appendices A and B.

3.4 Recruitment

The primary recruitment process will involve informing providers at the Yale IBD Program at Temple Medical Center in New Haven and in North Haven of the study. A list will be generated of eligible subjects (newly diagnosed, moderate-severe IBD). Providers will assist in identifying eligible subjects who were not contacted. Providers at
these clinics will introduce the study to eligible subjects, and research staff will provide detailed information about the risks and benefits for those interested. Research staff will schedule appointments in the clinics for informed consent and to conduct baseline assessments. Subjects will be recruited with ongoing enrollment for 1.5 years.

3.5 Study Variables and Measures

**Video-Based Cognitive Behavioral Therapy Intervention:** The video-based, therapist-guided CBT intervention will consist of twelve, 60-minute individual sessions for 12 weeks. The intervention will model face-to-face traditional CBT but will be administered via video conferencing. There will be 2 qualified CBT psychologists trained in treating depression and anxiety and supervised at a specific location. We will base the weekly sessions on the content from the Mikocka-Walus study\(^1\) (see Appendix C) with the addition of 2 booster sessions. The booster sessions will give participants the opportunity to re-visit activities, techniques, or lessons learned in the first 10 weeks. Participants will have weekly appointments scheduled in their Epic MyChart for 12 weeks. They will connect to a therapist via Zoom for their weekly sessions. At any point during the study, if patients’ depression and/or anxiety symptoms significantly worsen (i.e., suicidal thoughts or plans), they will be offered immediate evaluation/management by a psychiatrist.

**Control Group:** Patients will receive standard medical care. This includes pharmaceutical or surgical interventions by their gastroenterology providers along with the usual follow-up visits. This also includes psychiatry referrals as deemed necessary by the gastroenterologists. Furthermore, if a psychiatrist initiates pharmacologic medication, such as an antidepressant, this will constitute as standard medical care. As with the
intervention group, if symptoms worsen (i.e., suicidal thoughts) of patients in the control group, they will be offered further evaluation/management by a psychiatrist.

**Primary and Secondary Outcomes**: The primary outcome for this study is significant improvement in depression and anxiety, as measured by the Hospital and Anxiety Depression Scale (HADS), with 12 weeks of CBT intervention. Secondary outcomes include significant improvement in quality of life, as measured by the Short Form (SF-12), in patients who receive CBT compared to standard care alone.

**Baseline Variables**: Participants will be asked to complete a survey at baseline to ask their age, gender, income, stools per day, blood in stool, pain, fever, joint pain, appetite, weight loss or gain, biologic use, steroid use (i.e., prednisone), any medications, any surgeries, diagnosis of ulcerative colitis vs Crohn’s disease, and other co-morbid diseases. Additional laboratory tests that will be drawn at baseline are a comprehensive metabolic panel, which includes liver and renal tests, thyroid-stimulating hormone (TSH), vitamin B12, folate, and iron. Participants will undergo colonoscopies at baseline and receive a SES-CD or Mayo score at that time. The pathology results from these procedures will also be recorded at baseline. Participants will complete the HADS and SF-12 at baseline, in addition to, completing the blood tests (CBC, ESR, CRP) and stool test (fecal calprotectin) at baseline. See Appendix D for schedule of assessments.

3.6 Methodology Considerations

**Blinding of Intervention**: Due to the nature of this intervention, it cannot be blinded to participants in the experimental group. Therapists administering CBT cannot be blinded, and therefore, will not participate in data collection or outcome assessments. However, we will blind the control group from the study’s hypothesis and content of the
intervention. Participants in the intervention group will be asked not to discuss their outcome of randomization with their treating gastroenterology providers, other study participants, and members of the research staff performing outcome assessments.

**Blinding of Outcome:** Subjects are unable to be blinded to the outcome due to their participation in completing questionnaires at baseline, throughout 12 weeks, at 12-week completion, and 3-month follow-up. However, investigators and outcome accessors will be blinded to the allocations throughout the study.

**Adherence:** Adherence to the intervention will be ensured by subjects’ participation in sessions with CBT therapists. There will be an independent evaluation of intervention session recordings to ensure protocol and treatment consistency. Consent for these sessions recordings is detailed in Appendix B.

### 3.7 Assignment of Intervention

Following completion of baseline assessments, we will verify subjects’ motivation to undergo the CBT intervention prior to randomization. Subjects will be randomly allocated at a 1:1 ratio using a computerized random number generator. One member of the research team will perform the randomization and allocation concealment. This individual will not be involved in the rest of the study. Investigators and other research staff performing outcome assessments will be blinded to this allocation.

### 3.8 Data Collection

Data will be collected over 12 weeks and there will be a 6-month follow-up from start of intervention. Questionnaires will be administered online following each weekly session. Patients will have laboratory tests drawn and submit a stool test to measure
levels of inflammatory markers at baseline, 12 weeks, and 3 months after completion of the study. Patients will undergo a colonoscopy at completion of the study.

3.9 Sample Size Calculation

This study will utilize a two-sided hypothesis with a statistical significance of alpha of 0.05 and power of 80%. A simple t-test calculator G*Power version 3.1.9.6 was used to look for a difference in means on the HADS. Using a previous study, we first calculated the standard error of the mean (SEM) of the intervention and control groups at both baseline and 3.5-month follow-up. We then calculated the standard deviations for the difference between two sample means. A sample size of 128 participants, with 64 participants in each group, was calculated (Appendix I). Based on prior studies, the sample size will account for an estimated 10% dropout rate. Therefore, the adjusted sample size will be 140 participants, with 70 participants in each group.

3.10 Analysis

Baseline characteristics will be analyzed to describe the study sample and to identify statistically significant differences between randomized groups that could be potential confounders in this study. Age and stools per day are continuous variables that will be reported as means with standard deviations. Student t-tests will be used to compare continuous variables at baseline. Income, blood in stool, pain, fever, joint pain, appetite, weight loss or gain, biologic use, steroid use, other medications, surgeries, family history of IBD, diagnosis of UC vs. CD, pathology from the colonoscopy, and other co-morbid diseases are categorical variables that will be reported as frequencies. Chi-square tests will be used to compare categorical variables at baseline.
Intention-to-treat analysis will be used for primary and secondary outcome data. Baseline scores on the HADS and SF-12 will be compared between groups using a student t-test. Baseline levels from the CBC, ESR, CRP, and fecal calprotectin will also be compared between groups using a student t-test. The primary outcome, mean change in HADS score, will be operationalized as a continuous variable. Paired sample t-tests will be run to examine changes within groups over time. Mixed design analyses of covariance will be run to assess differences between follow-up scores for all continuous outcomes for the groups while controlling for baseline variables. Multivariate regression will be run for multivariate analysis, compensating for any missing data.

3.11 Timeline and Resources

The proposed study will take place within two years, from gathering participants to data collection. See Figure 1 for the study’s timeline. Recruitment of participants will take place over the first 1.5 years. The intervention will be 3 months. Follow-up assessments will take place at the end of intervention and at 3 months after completion of the intervention. Data analysis will be completed within 6 months of study completion.

The principal investigator (PI) will be Deborah Proctor, MD, and the co-principal investigator (co-PI) will be Monica Narsolis, PA-SII. Colonoscopies establishing diagnoses will occur at Yale New Haven Hospital. All participants will receive standard medical care at the Yale IBD Center locations at Temple Medical Center in New Haven, CT and in North Haven, CT or at outpatient Yale psychiatric clinics in New Haven, CT. Providers at these clinics will be informed about the proposed study and administer baseline questionnaires (HADS and SF-12) to those documented with newly diagnosed, moderate-severe IBD. Research assistants at Yale University will collect baseline
questionnaires and determine eligible patients for our study. CBT psychologists/therapists will be recruited from the region and compensated for their time.

Figure 1. Timeline of Intervention
3.12 References

CHAPTER 4: CONCLUSION

4.1 Advantages and Disadvantages

This study will be the first RCT comparing video-based CBT to standard medical care in improving depression and anxiety symptoms in newly diagnosed IBD adults with moderate-severe disease and moderate-severe depression and/or anxiety symptoms at baseline. Our proposed study will be novel because we will target those with moderate to severe IBD, unlike previous studies,\(^1\-^4\) and those with greater psychological distress.\(^5,^6\)

Through an RCT design, we hope to gain insight into the effectiveness of CBT by minimizing potential bias from confounding variables. Unlike past studies with high attrition and low adherence to a CBT intervention, we hope to conduct an adequately powered study by utilizing video-based CBT. This will likely increase overall adherence due to its convenience, which will increase generalizability of our results. Finally, the addition of objective measures of disease activity will reveal more insight into the bidirectional relationship between depression/anxiety and IBD.

There are some limitations to our study design that we will consider. First, we were unable to design our study into four categories: 1. mild/in remission IBD and mild depression/anxiety, 2. mild/in remission IBD and moderate/severe depression/anxiety, 3. moderate/severe IBD and mild depression/anxiety, and 4. moderate/severe IBD and moderate/severe depression/anxiety. To create a study with a feasible sample size, we chose to narrow our study to the last category based on previous research showing the 4\(^{th}\) group would likely benefit the most from CBT. However, due to our novel use of video-based CBT compared to standard care in the IBD population, being able to investigate its effectiveness in all four groups could provide more insight into implementing its use in
standard of care. Second, we can only conduct a single-blinded design which presents the potential for participant bias towards their intervention placement. We hope to mitigate adverse effects on results by blinding all participants to the hypothesis of our study. Lastly, participants are required to complete questionnaires weekly for 12 weeks and at 3-month follow-up. To minimize respondent burden and questionnaire fatigue, we chose 2 relatively short, validated measures, HADS and SF-12. This will improve the potential for missing data and information bias that could affect the study’s outcomes.

4.3 Clinical and Public Health Significance

Inflammatory bowel disease is a chronic, relapsing-remitting disease requiring life-long management with medications and invasive procedures, which has the potential to negatively impact one’s quality of life. It is well-known that those with IBD are at increased risk for depression/anxiety, but there is no standard treatment for those who present with moderate to severe depressive and anxiety symptoms at initial IBD diagnosis. It is important that providers recognize these symptoms and have evidence-based guidelines for management. While antidepressants are effective in managing these symptoms, non-pharmacologic treatment should be considered as an additional option in a population with a high medication burden. Preventing a secondary diagnosis of depression and/or anxiety can future prevent hospitalizations and decrease healthcare costs. Also, improving depressive and anxiety symptoms may inadvertently improve disease flares. If the findings of this study improve depression and/or anxiety, providers will have evidence that video-based CBT can be recommended for this group. Overall, this study will highlight modern-day medicine’s transition into video visits while enhancing this chronic disease’s management.
4.4 References


CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE
YALE NEW HAVEN HOSPITAL

Study Title: Video Cognitive Behavioral Therapy to Prevent Depression in Patients with Inflammatory Bowel Disease
Principal Investigator: Deborah Proctor, MD
Co-Investigator: Monica Narsolis, PA-SII
Funding Source: Pending

Invitation to Participate and Description of Project

You are invited to participate in a research study investigating depression and anxiety in inflammatory bowel disease patients using either a video-based psychotherapy intervention (cognitive behavioral therapy) or standard medical care. Standard medical care includes appointments, surgeries, or treatments performed by your gastroenterologists. If your gastroenterologist refers you to a psychiatrist for your symptoms, standard medical care will include appointments or treatments deemed appropriate by them. You have been asked to participate because you have been recently diagnosed with inflammatory bowel disease and are an adult age 18-40. Approximately 140 people will participate in this study.

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

Description of Procedures

If you are interested in this study, you will be asked questions about your health to determine if you are eligible for this study. Information will be collected about your age, current depression and anxiety symptoms, history of depression and anxiety treatments, and current severity of IBD. Before the study begins, you will have completed a colonoscopy and/or endoscopy to diagnose your IBD. At your initial visit with your gastroenterologist following this procedure, you will complete the Hospital Anxiety and Depression Scale, a form used to assess levels of anxiety and depression. Depending on your score, you will be asked to participate in this study.
If you agree to participate in this study, you will be randomly assigned to one of two groups. Both groups will receive standard medical care, but one group will undergo cognitive behavioral therapy in addition to their care. Random assignment is like flipping a coin with a 50/50 chance of one group or the other. Randomization will be done by a computer program and will not be based on any personal baseline information. Your providers will have no influence or knowledge of which group you are randomly assigned to. Those in the cognitive behavioral therapy group will be asked to attend a one-hour session once a week for 12 weeks. During these sessions, participants will interact with a therapist one-on-one online using a videoconferencing platform. Participants will be allowed to undergo these sessions at home or any location that is most convenient for them. You will receive reminder calls or texts for sessions from a research assistant.

Both groups will be asked to undergo laboratory testing and submit a stool sample at the start of the study, 12 weeks following the start of the study, and 6 months following the start of the study. These will be completed either at the lab at Yale New Haven Hospital or any Quest lab in the surrounding New Haven, CT area. Parking will be free of charge. During the course of the study, you will be asked to refrain from any self-help cognitive behavioral therapy at home.

At the start of the study, you will complete 2 questionnaires regarding your depression, anxiety, and quality of life. You will also complete these questionnaires weekly for 12 weeks, and at 6 months following the start of your study. We will create a Qualtrics survey and send the link via text message or email to complete. You will receive reminder calls or texts to complete the questionnaires from a research assistant.

Throughout the study, you will follow up with your gastroenterologists to receive care for your inflammatory bowel disease. These appointments will take place at the Yale IBD Center locations at Temple Medical Center in New Haven, CT and in North Haven, CT. This will be identical to the routine care you would receive regardless of participating in this research study. Your gastroenterologists will have no knowledge of which group you are randomly assigned to. This is done so that a fair evaluation of the results can be made.

**Medical Record Access:**
If you decide to participate in this study, researchers will also access to your medical records for information related to your IBD. They will examine your type of IBD (Crohn’s disease or ulcerative colitis), the location of your disease, when you were diagnosed, pathology results from the colonoscopy, laboratory results related to your IBD (white blood cell count, comprehensive panel (liver and renal tests), thyroid-stimulating hormone, vitamin B12, folate, iron, erythrocyte sedimentation rate, c-reactive protein, and fecal calprotectin), and finally any other disease diagnoses you have. This information will be used to determine whether these factors alter any of the other measurements in the study.
You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate. If research results are published, your name and other personal information will not be given.

**Risks and Inconveniences**

We do not anticipate any major risks in participating in this study. For both groups, your gastroenterologists will provide referrals to appropriate providers if needed to treat your depression and anxiety symptoms. This may include initiation of antidepressant medications, which has the potential risk of side effects. The prescribing providers will discuss these in detail with you prior to starting any medication. For the group receiving cognitive behavioral therapy, you may feel emotionally uncomfortable or more upset at times because it can cause you to explore painful feelings, emotions, and experiences. Your therapist will help you talk through your negative feelings.

Questionnaire contents may include personal information related to physical and psychological symptoms, so there is a risk of breach of confidentiality about your health status and participation in this study. However, this is unlikely to occur. All research staff will be thoroughly trained and certified in the privacy of research studies.

**Benefits**

Benefits of participation in this study may include improvements in managing mental illness, preventing relapse of mental illness symptoms, learning techniques to cope with stressful situations, identifying ways to manage emotions, coping with your new diagnosis of IBD, and managing chronic physical symptoms.

**Economic Consideration**

There is no direct compensation associated with this study. Cognitive behavioral therapy will be delivered by therapists online using Zoom as the video-based platform. This requires access to a computer, iPad, or smartphone device that is sufficient for video conferencing. For those that do not own either of these devices, we will provide you with an iPad for the duration of the study.

Parking will be reimbursed at each clinic or laboratory appointment. You will still be responsible for any co-pays required by your insurance company for standard treatment. If you have any questions regarding your insurance coverage, please contact your insurance company directly. There will be no financial penalty for withdrawing for the study.

**Treatment Alternatives**
The alternative to participating in this study is to decline participation. If you do not wish to participate you will be provided the standard treatment for your mental health at the discretion of your healthcare provider.

**Confidentiality and Privacy**

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or state law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Information will be kept confidential by using only identification numbers on study forms, storing signed forms in locked cabinets, and password protecting data stored on a computer. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific permission for this activity is obtained.

All subjects will be assigned a Yale Central Authorization Service (CAS) ID that ensures secure sessions with therapists and online forms.

Information about your study participation will be entered under a unique identification number in a password-protected software and stored on a secure Yale server until needed for statistical analysis. Health Insurance Portability and Accountability Act (HIPAA) standards will be met and maintained for all devices and personnel. Only approved research personnel will have access to your medical records in order to verify information required for the study. Any information that is not relevant will not be extracted from your medical records. Data auditing will be performed at random points throughout the trial to ensure no inappropriate viewing or disclosure of protected health information has occurred. All records no longer needed for research purposes will be shredded and destroyed in accordance with HIPAA requirements. All data and records used in the study will be kept for 10 years after data analysis has concluded.

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

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose of the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

**Voluntary Participation and Withdrawal**

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health
care, and your health care benefits). You will not be able to enroll in this study and will not receive study procedures as a participant if you do not allow use of your information as part of this study.

If you do become a subject, you are free to withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. Also, the researchers may withdraw you from participating in the research if necessary. Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own providers or with Yale School of Medicine. When you withdraw from the study, no new health information identifying you will be gathered. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

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

**Questions**

We have used some technical terms in this form. Please feel free to ask about anything you do not understand and to consider this research and the consent form carefully—as long as you feel is necessary—before you make a decision.

**Authorization and Permission:**

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

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

Name of Subject: ______________________________________

Signature: ____________________________________________

Date: __________

_______________________________________            ______________

Signature of Principal Investigator                                   Date

Or

_______________________________________            ________________

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

If you have further questions about this project or if you have a research-related problem, you may contact the co-Principal Investigator, Monica Narsolis. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.
Appendix B: Video/Audio Recordings Consent Form

Video Cognitive Behavioral Therapy to Prevent Depression in Patients with Inflammatory Bowel Disease
Consent to Video/Audio Recordings
200 FR 6 (2014-1)

We are requesting your permission to record your video sessions as part of this study. If you agree to the recording, we will use the video or audio recordings for independent raters to conduct integrity checks and on at least two treatments per therapist. In addition, we would like your permission to keep the recordings to ensure protocol is being maintained and treatments are staying consistent. The recording is optional. You may choose to give permission for one or both uses of the recordings, or you may decide not to participate in taping at all. Your decision will not affect your ability to remain in the study.

If you agree to participate, we will keep the tapes on a password-protected software and stored on a secure Yale server. To protect your confidentiality, all recordings will be coded by number, and these codes will be stored on password-protected databases on encrypted computers.

All video/audio recordings used in the study will be kept for 10 years after data analysis has concluded. Recordings will then be destroyed in accordance with HIPAA requirements.

I agree that video/audio recordings may be taken of me as part of the study entitled: Video Cognitive Behavioral Therapy to Prevent Depression in Patients with Inflammatory Bowel Disease

The films may be used for (Check all that apply)
   a. ______ any purpose relevant to research, medical evaluation, training
   b. ______ purposes of the study only

If seeking permission to retain tapes for future use: You have the choice of how long we may keep your tapes.
   a. ______ My tapes may be kept permanently for research, educational or training purposes.
   b. ______ My tapes must be destroyed after completion of study.

I understand that my consent for this part of the study is optional, and I am free to refuse this request and still participate in the study. I understand that I may request at any time during the research that the videotapes or films of me be destroyed and the research staff will honor my request promptly. My signature below indicates my consent for the use of these tapes.
Signature of Subject

Date

Person Obtaining Consent

Date
Appendix C: CBT Content

<table>
<thead>
<tr>
<th>Week</th>
<th>Theme</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Education about IBD and introduction to the program</td>
<td>Video materials about IBD in general and diet in IBD; goal setting</td>
</tr>
<tr>
<td>2</td>
<td>Stress and relaxation</td>
<td>What is stress--its physiology, fight or flight response, symptoms of stress, observe yourself in stressful situations; relaxation training--4 voice recorded sessions of relaxation exercises</td>
</tr>
<tr>
<td>3</td>
<td>Automatic thoughts and cognitive distortions</td>
<td>Thinking, feeling and behavior--introducing CBT basic concepts, observe your thoughts and feelings, identify core beliefs; another 2 recordings to practice relaxation</td>
</tr>
<tr>
<td>4</td>
<td>Cognitive restructuring</td>
<td>Emotional wellbeing, appraisal of mood, automatic thought--identify and challenge them</td>
</tr>
<tr>
<td>5</td>
<td>Exposure and overcoming avoidance</td>
<td>Avoidance and conditioning--how do we learn to be afraid and how do we overcome conditioning; desensitization and another 2 records of relaxation skill building</td>
</tr>
<tr>
<td>6</td>
<td>Coping strategies</td>
<td>What is coping, how do we cope with stress and IBD; worry and sleep; relaxation to help you sleep</td>
</tr>
<tr>
<td>7</td>
<td>Assertiveness training</td>
<td>Taking responsibility; introducing assertiveness in communication with family and health professionals; learning to say no</td>
</tr>
<tr>
<td>8</td>
<td>Relationships and communication</td>
<td>Social support--quality and quantity; maintaining social networks and interests when dealing with IBD; communication strategies</td>
</tr>
<tr>
<td>9</td>
<td>Attention and distraction</td>
<td>Techniques to manage IBD-related pain and discomfort--imagery, focus, distraction</td>
</tr>
<tr>
<td>10</td>
<td>Maintaining good mental health</td>
<td>Keeping up momentum--how not to forget what you have learnt; review old goals and plan new ones</td>
</tr>
</tbody>
</table>

Appendix D: Schedule of Assessments

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Baseline</th>
<th>Week of Intervention</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>HADS</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-12</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fecal Calprotectin</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SES-CD</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC Mayo</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix E: Hospital Anxiety and Depression Scale (HADS)

**Hospital Anxiety and Depression Scale (HADS)**

Tick the box beside the reply that is closest to how you have been feeling in the past week. 

Don’t take too long over your replies; your immediate is best.

<table>
<thead>
<tr>
<th>D</th>
<th>A</th>
<th>D</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel tense or 'wound up':</td>
<td>I feel as if I am slowed down:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Most of the time</td>
<td>3</td>
<td>Nearly all the time</td>
</tr>
<tr>
<td>2</td>
<td>A lot of the time</td>
<td>2</td>
<td>Very often</td>
</tr>
<tr>
<td>1</td>
<td>From time to time, occasionally</td>
<td>1</td>
<td>Sometimes</td>
</tr>
<tr>
<td>0</td>
<td>Not at all</td>
<td>0</td>
<td>Not at all</td>
</tr>
</tbody>
</table>

| I still enjoy the things I used to enjoy: | I get a sort of frightened feeling like 'butterflies' in the stomach: |
| 0 | Definitely as much | 0 | Not at all |
| 1 | Not quite so much | 1 | Occasionally |
| 2 | Only a little | 2 | Quite Often |
| 3 | Hardly at all | 3 | Very Often |

| I get a sort of frightened feeling as if something awful is about to happen: | I have lost interest in my appearance: |
| 3 | Very definitely and quite badly | 3 | Definitely |
| 2 | Yes, but not too badly | 2 | I don’t take as much care as I should |
| 1 | A little, but it doesn’t worry me | 1 | I may not take quite as much care |
| 0 | Not at all | 0 | I take just as much care as ever |

| I can laugh and see the funny side of things: | I feel restless as I have to be on the move: |
| 0 | As much as I always could | 3 | Very much indeed |
| 1 | Not quite so much now | 2 | Quite a lot |
| 2 | Definitely not so much now | 1 | Not very much |
| 3 | Not at all | 0 | Not at all |

| Worrying thoughts go through my mind: | I look forward with enjoyment to things: |
| 3 | A great deal of the time | 0 | As much as I ever did |
| 2 | A lot of the time | 1 | Rather less than I used to |
| 1 | From time to time, but not too often | 2 | Definitely less than I used to |
| 0 | Only occasionally | 3 | Hardly at all |

| I feel cheerful: | I get sudden feelings of panic: |
| 3 | Not at all | 3 | Very often indeed |
| 2 | Not often | 2 | Quite often |
| 1 | Sometimes | 1 | Not very often |
| 0 | Most of the time | 0 | Not at all |

| I can sit at ease and feel relaxed: | I can enjoy a good book or radio or TV program: |
| 0 | Definitely | 0 | Often |
| 1 | Usually | 1 | Sometimes |
| 2 | Not Often | 2 | Not often |
| 3 | Not at all | 3 | Very seldom |

Please check you have answered all the questions.

**Scoring:**

Total score: Depression (D) ___________  Anxiety (A) ___________

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)
Appendix F: 12-Item Short Form Survey (SF-12)

**SF-12 Health Survey**

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. **Answer each question by choosing just one answer.** If you are unsure how to answer a question, please give the best answer you can.

1. In general, would you say your health is:
   - □ Excellent
   - □ Very good
   - □ Good
   - □ Fair
   - □ Poor

The following questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

<table>
<thead>
<tr>
<th>Activity</th>
<th>YES, limited a lot</th>
<th>YES, limited a little</th>
<th>NO, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Moderate activities such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>3. Climbing several flights of stairs.</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
</tbody>
</table>

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

4. Accomplished less than you would like. □ 1 □ 2
5. Were limited in the kind of work or other activities. □ 1 □ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

6. Accomplished less than you would like. □ 1 □ 2
7. Did work or activities less carefully than usual. □ 1 □ 2

8. During the **past 4 weeks**, how much did pain interfere with your normal work (including work outside the home and housework)?
   - □ 1 Not at all
   - □ 2 A little bit
   - □ 3 Moderately
   - □ 4 Quite a bit
   - □ 5 Extremely

These questions are about how you have been feeling during the **past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little bit of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Have you felt calm &amp; peaceful?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>10. Did you have a lot of energy?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>11. Have you felt down-hearted and blue?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
</tbody>
</table>

12. During the **past 4 weeks**, how much of the time have your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives, etc.)?
   - □ 1 All of the time
   - □ 2 Most of the time
   - □ 3 Some of the time
   - □ 4 A little of the time
   - □ 5 None of the time

Patient name: ______________________ Date: ______________________
PCS: _______ MCS: _______

Visit type (circle one)

<table>
<thead>
<tr>
<th>Preop</th>
<th>6 week</th>
<th>3 month</th>
<th>6 month</th>
<th>12 month</th>
<th>24 month</th>
<th>Other: ______</th>
</tr>
</thead>
</table>

72
Appendix G: Simple Endoscopic Score for Crohn’s Disease (SES-CD)

<table>
<thead>
<tr>
<th>SES-CD activity index</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence and size of ulcers</td>
<td>1-5 mm</td>
<td>5-20 mm</td>
<td>&gt;20 mm</td>
<td></td>
</tr>
<tr>
<td>Extent of the ulcerated surface</td>
<td>&lt;10%</td>
<td>&lt;10-30%</td>
<td>&gt;30%</td>
<td></td>
</tr>
<tr>
<td>Extent of the affected surface</td>
<td>&lt;50%</td>
<td>&lt;50-70%</td>
<td>&gt;70%</td>
<td></td>
</tr>
<tr>
<td>Presence and type of stenosis</td>
<td>Single passable</td>
<td>Multiple passable</td>
<td>Impassable</td>
<td></td>
</tr>
<tr>
<td>5 segments</td>
<td>Rectum</td>
<td>Left colon</td>
<td>Transverse colon</td>
<td>Right colon</td>
</tr>
<tr>
<td>SES-CD</td>
<td>&lt;Inactive</td>
<td>3-6 Mild activity</td>
<td>7-15 Moderate activity</td>
<td>&gt;16 Severe activity</td>
</tr>
</tbody>
</table>

Section II.2.1.1. Figure 3. SES-CD activity index.
Appendix H: Mayo Score for Ulcerative Colitis

Table 1. Mayo Scoring System for Assessment of Ulcerative Colitis Activity.*

<table>
<thead>
<tr>
<th>Stool frequency†</th>
<th>Description</th>
<th>Subscore</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal no. of stools for this patient</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1 to 2 stools more than normal</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>3 to 4 stools more than normal</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>5 or more stools more than normal</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rectal bleeding‡</th>
<th>Description</th>
<th>Subscore</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No blood seen</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Streaks of blood with stool less than half the time</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Obvious blood with stool most of the time</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Blood alone passes</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Findings on endoscopy</th>
<th>Description</th>
<th>Subscore</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal or inactive disease</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Mild disease (erythema, decreased vascular pattern, mild friability)</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Severe disease (spontaneous bleeding, ulceration)</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physician’s global assessment§</th>
<th>Description</th>
<th>Subscore</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Mild disease</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Moderate disease</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Severe disease</td>
<td>3</td>
</tr>
</tbody>
</table>

* The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. Data are from Schroeder et al.24
† Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
‡ The daily bleeding score represents the most severe bleeding of the day.
§ The physician’s global assessment acknowledges the three other criteria, the patient’s daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient’s performance status.
Appendix I: Sample Size Calculation

![G*Power Version 3.1.9.6](image)

G*Power Version 3.1.9.6


Bernstein CN, Zhang L, Lix LM, et al. The Validity and Reliability of Screening Measures for Depression and Anxiety Disorders in Inflammatory Bowel Disease. Inflammatory Bowel Diseases. 2018;24(9):1867-1875.


Davis SP, Bolin LP, Crane PB, Crandell J. Non-pharmacological Interventions for Anxiety and Depression in Adults With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. Frontiers in Psychology. 2020;11:538741.


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Hunt MG, Loftus P, Accardo M, Keenan M, Cohen L, Osterman MT. Self-help Cognitive Behavioral Therapy Improves Health-Related Quality of Life for Inflammatory Bowel


Mikocka-Walus A, Bampton P, Hetzel D, Hughes P, Esterman A, Andrews JM. Cognitive-Behavioural Therapy for Inflammatory Bowel Disease: 24-Month Data from a


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van den Brink G, Stapersma L, Bom AS, et al. Effect of Cognitive Behavioral Therapy on Clinical Disease Course in Adolescents and Young Adults With Inflammatory Bowel Disease and Subclinical Anxiety and/or Depression: Results of a Randomized Trial. *Inflammatory Bowel Diseases.* 2019;25(12):1945-1956.


Yarlas A, D’Haens G, Willian MK, Teynor M. Health-Related Quality of Life and Work-Related Outcomes for Patients With Mild-to-Moderate Ulcerative Colitis and Remission Status Following Short-Term and Long-Term Treatment With Multimatrix Mesalamine: A Prospective, Open-Label Study. *Inflammatory Bowel Diseases.* 2018;24(2):450-463.