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Use of Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Measures As Clinical Trial Endpoints: Experience From a Multi-Center Pragmatic Trial in Children With Crohn's Disease

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Abstract

Objectives: To evaluate whether PROMIS pediatric patient-reported outcome measures serve as valid endpoints in a clinical trial of a chronic pediatric illness.

Study design: We evaluated the responsiveness of PROMIS Pediatric measures collected through the Clinical Outcomes of Methotrexate Binary Therapy in Practice (COMBINE) trial, a multicenter, randomized, double-blind, placebo-controlled, pragmatic clinical trial in pediatric patients with CD. We examined the relationships between changes in PROMIS pediatric measures and changes in disease activity by evaluating patient-reported outcome (PRO) score changes among patients who did or did not experience improvement in disease activity.

Results: Participants included 266 children and adolescents with CD from a total of 35 institutions. Over the course of follow-up, participants showed improvement in most PRO domains, with the largest effect sizes observed for the clinically improved group. Patients who maintained steroid-free remission showed significantly lower PRO scores for Pain Interference, Fatigue and IBD Symptom and higher Positive Affect scores.

Conclusions: This study demonstrates the responsiveness of the Pediatric PROMIS measures of Fatigue and Pain Interference as study endpoints in a large, multi-center pragmatic trial in

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pediatric CD, extending a growing body of research supporting the use of PROMIS Pediatric measures as reliable PRO endpoints for clinical trials.

Keywords

patient-reported outcomes; inflammatory bowel disease; Crohn's disease; PROMIS; child

Patient reported outcome (PRO) measures reflect physical, mental and social health of patients, and serve as valuable endpoints in clinical monitoring. [1,2] In pediatric chronic disease, PRO measures are particularly important in understanding the relapsing-remitting or progressive nature of a disease and its effect on symptom burden, physiological comorbidities and disruptions in daily life. [3] It is critical to be able to reliably and validly measure the effects of chronic disease on children and adolescents using PROs in order to evaluate diagnostic and therapeutic approaches that affect health-related quality of life.

The Patient-Reported Outcomes Measurement Information System (PROMIS) is a National Institutes of Health (NIH) funded system of PRO measures developed to measure physical, mental, and social health in chronic disease populations. PROMIS Pediatric measures are specifically designed to measure these domains in child respondents and include self-report measures available for children ages 8–17. [4,5] The PROMIS measures have been shown to discriminate between levels of disease activity in a range of pediatric chronic conditions [6–10] and assess health-related quality of life (HRQOL) longitudinally [11]. Specifically, in pediatric Crohn's disease, content validity has been established for the PROMIS measures pertaining to pain interference and fatigue [12]. Additionally, in a direct-to-patient internet cohort, these domains have been shown to be responsive to changes in disease status and HRQOL. [11,13,14] Thus, PROMIS Pediatric measures appear well suited as clinical trial endpoints. Yet, limited studies have used these measures in the clinical setting and/or as clinical trial endpoints. [15,16] It is critical that clinical trials begin to include PRO measures as trial endpoints, as their inclusion promotes a comprehensive evaluation of the clinical effectiveness of an intervention, in the context of a child's physical, emotional, and social health, and based on the child's lived experiences of their disease and treatments. Prior to broad adoption of PROMIS Pediatric measures as trial endpoints, proof-of-concept data are needed to demonstrate responsiveness.

In this study we evaluated the performance of PROMIS Pediatric measures, as well as demonstrate responsiveness of these measures obtained longitudinally in the context of a multi-center pragmatic trial. We hypothesized that the measures would reflect positive and negative changes in clinical status and that the measures would remain stable once the disease was in remission.

Methods:

The Clinical Outcomes of Methotrexate Binary Therapy in Practice (COMBINE, [NCT02772965](#)) study is a multicenter, randomized, double-blind, placebo-controlled, pragmatic clinical trial to compare the effectiveness of anti-TNF monotherapy versus anti-Tumor Necrosis Factor (TNF) combination therapy with low dose oral methotrexate in the induction and maintenance of steroid free remission in children and young adults with

Crohn's disease. In this study, we evaluated the performance of PROMIS Pediatric measures and are not reporting on the clinical outcomes of the trial. General eligibility criteria include a diagnosis of Crohn's disease, age <21 years, initiation of infliximab or adalimumab at the discretion of the treating physician in the six weeks prior to randomization, and no contraindication to methotrexate. Although enrollment in the COMBINE trial has closed, study follow-up is ongoing.

In this analysis, we defined study baseline (Time 1) as the month of each participant's first PRO completion. Randomization to methotrexate or placebo typically occurred shortly after baseline, but for 22% of participants there was an interval of 1–3 months between baseline and randomization. Over a follow-up period of up to 3 years, standardized clinical information (eg, disease characteristics including the short Pediatric Crohn's Disease Activity Index[17] and Physician Global Assessment [18], laboratory data, adverse events, medication use, etc.) was collected during study visits. In addition, children ages 8–20 years completed PROMIS Pediatric measures at enrollment and at the time of (or close to) follow up visits scheduled approximately 3, 6, 12, 24, and, in some cases, 36 months following randomization. If a patient missed an appointment, they were able to complete the PRO survey at the following visit. Most questionnaires (94% of total) were self-administered using paper and pen. Study staff manually entered responses in two separate spreadsheets to ensure reliability, and discrepancies were resolved by checking the original records. During the COVID-19 pandemic, questionnaires were also self-administered online (4%) and administered by study coordinators by telephone (2%).

PROMIS Measures

We administered PROMIS Pediatric Pain Interference[19] and Fatigue[20] measures as 8-item short forms and Positive Affect [21] as a 4-item short form. We also evaluated IBD symptoms using a 4-item measure. (Schuchard 2021) The PRO questions were the same for all ages, and children were instructed to complete the measures on their own, without assistance from parents. The scores for these measures are predictions of individuals' level of health based on the item properties and the individual's pattern of responses to the items, as opposed to a simple sum or average of the responses. We used Mplus 8 [22] and the published item parameters to produce item response theory (IRT) scores. Scores were converted to the PROMIS T-scale ($T\text{-score} = 10 \times \text{score} + 50$). The measures are scored in the direction of their concept name, such that higher Positive Affect corresponds to better outcomes, whereas higher IBD Symptoms, Pain Interference, or Fatigue correspond to worse outcomes.

Clinical Anchors

We measured disease severity using the short Pediatric Crohn's Disease Activity Index (sPCDAI)[17] and Physician Global Assessment (PGA)[18]. The sPCDAI includes items specific to Crohn's disease, including abdominal pain, diarrheal stools and general well-being. The sPCDAI is scored from 0–90 with items that assess abdominal pain, stools, weight, extra-intestinal manifestations, and well-being. Disease activity was classified as inactive (sPCDAI < 15), mild (15 to <30), or moderate-severe (≥ 30). The Physician Global Assessment (PGA) is a physician rating of disease activity using a Likert scale

of 1 (inactive) to 4 (severe)[18]. Physician assessment of disease severity was performed independently of patient survey.

Additionally, the COMBINE trial protocol identifies a set of outcomes that indicate treatment failure at various points in the three-year follow-up phase of the study. Pre-specified outcomes considered treatment failure included inability to achieve remission by week 26, failure to taper off steroids by week 16, hospitalization or surgery after week 25, sPCDAI ≥ 15 at two or more consecutive visits beyond week 26, use of steroids for a period of over 10 weeks cumulatively beyond week 16, and discontinuation of anti-TNF therapy due to lack of effectiveness or toxicity

Statistical Analyses

We examined the relationships between changes in PROs and changes in the clinical anchors by evaluating PRO score changes among patients who did or did not experience improvement in disease activity. Then we examined the trajectories of PRO scores for patients that did or did not experience treatment failures during the course of the study. Analyses were conducted in R Version 4.0.0.[23] We initially focused on changes that occurred between baseline and the first follow up because this interval most closely followed initiation of therapy and showed the largest changes in patients' clinical outcomes. First follow-up visit PROs included PROs completed 2–5 months post-baseline (n = 235). Participants were divided into three subgroups based on their sPCDAI scores: (1) inactive disease at both baseline and first follow-up, (2) improved between baseline and first follow-up by a decrease of 15 or more on sPCDAI, or (3) active disease at baseline and not improved at first follow-up. For each subgroup, we used dependent-samples t-tests and Cohen *d* effect sizes to examine change on each PRO. These procedures were repeated after dividing participants into three subgroups based on their PGA scores: (1) inactive at Time 1 and Time 2, (2) improved between Time 1 and Time 2 by a decrease on PGA of 1 or more, or (3) active at Time 1 and not improved at Time 2. Only disease activity indices collected the same month as a patient's PRO completion were included in the analyses. A Cohen *d* statistic was used to evaluate effect size (moderate is 0.5 to 0.79, large = 0.8).[24]

To examine post-treatment PRO score trajectories for participants that did and did not experience treatment failure, we used multilevel regression models to regress sPCDAI and PRO scores on time with by-participant random intercepts and slopes using the lmerTest package in R. [25] These models were used to examine post-baseline change on each measure, controlling for the baseline scores on the measure by including them as a covariate. Time was coded as years, with time zero equal to the participant's first follow-up PRO. To test whether post-baseline scores on average differed by treatment outcome, we included a predictor in each model indicating whether patients did or did not experience a treatment failure during the course of the study. Patient sex and mean-centered age at baseline were included as covariates in each model because these variables often show significant associations with PROs.

Results:

Study Sample

The evaluation of response rate included all enrolled participants (n=299). All other analyses included all eligible participants that completed baseline and at least one follow-up PRO measure before March 2021 (n=266), which included children and adolescents with Crohn's disease from a total of 35 institutions. The ages ranged between 8 and 20 years, 64% were male and 82% White. Baseline scores showed that 67% of participants had either mild or moderate-severe disease based on the PGA and 50% of patients had either mild or moderate-severe disease based on the sPCDAI at baseline. Additional demographic and clinical characteristics of study participants are shown in Table 1. Because PROs were collected as part of visits that occurred during routine practice, the number and timing of follow-up PROs varied across patients. The number of follow-up PROs per participant ranged from 1 to 8 (median = 4). The time interval between baseline and the participant's first follow-up PRO ranged from 2 to 25 months (interquartile range = 3–5 months). The time interval between baseline and the participant's last follow-up PRO ranged from 2 to 39 months (interquartile range = 10–25 months).

PRO Response Rate

We evaluated the attainability of administering and collecting PROs during clinic visits and found collection of PRO measures were initially above 90% for the first 3 visits, with only a modest decline over time. Despite data collection ongoing during the beginning of the COVID-19 pandemic, only by visit 10 and beyond did we see rates of PRO completion below 80%. Importantly, very few questionnaires (0.1%) were missing entire PROMIS domains, and 97% of questionnaires were completed with zero missing items. (Table II; available at www.jpeds.com)

Changes in PROs and Disease Activity

We first grouped participants by whether they had active disease at baseline and improved at first follow-up, active disease at baseline and did not improve, or whether they had inactive disease at baseline and remained inactive. Although participants in all 3 groups showed improvement in most PRO domains, as expected, the largest effect sizes were observed for the clinically improved group. Participants in this group showed significant improvement on IBD symptoms, pain interference, and fatigue. The largest effect sizes were seen in the improved group for the Pain Interference domain ($d = -0.93$) and IBD symptoms ($d = -0.85$). (Table 3) Of note, IBD symptoms, Pain Interference, and Fatigue also improved significantly in the group that was initially determined to be inactive and stayed inactive at follow up. The improvement in positive affect was not statistically significant for any group. Although the main analysis group participants by sPCDAI, a second analysis group participants based on PGA and also showed significant improvement on IBD symptoms, Pain interference, and Fatigue but not positive affect. (Table 4; available at www.jpeds.com)

Post-baseline Trajectories

During the post-baseline period of the study, participants that remained in the study and completed PROs for at least one year post-baseline (n = 187; 70% of total) showed small but statistically significant improvement across time on sPCDAI and Pain Interference (Table 5). There was no significant change on IBD Symptoms, Fatigue, or Positive Affect.

Steroid-Free Remission Versus Treatment Failure

We compared post-baseline PRO data between the 54 patients who met any of the components of the primary study endpoint indicating treatment failure and the 133 participants who were able to maintain steroid-free remission for the duration of the study. When compared with patients who experienced a treatment failure, patients who maintained steroid-free remission showed lower PRO scores in the pain interference, fatigue and IBD symptom domains and higher positive affect scores during the follow-up period (Figure). Treatment failure during follow-up was associated with scoring on average 4 points worse on IBD Symptoms ($P < .001$), 5 points worse on Pain Interference ($p < 0.001$), 4 points worse on Fatigue ($p = 0.01$), and 3 points worse on Positive Affect ($p < 0.01$) (Table 5).

Discussion

The use of reliable PROs can improve a clinician's ability to monitor meaningful changes over the course of a patient's disease and is important in clinical research in order to develop treatment and monitoring plans that consider and optimize a child's health-related quality of life. Additionally, the incorporation of PROs as clinical trial endpoints will help evaluate whether clinical interventions improve symptoms and physical and mental functioning as reported directly by the patient, consistent guidance from the Food and Drug Administration. [26] Although PROMIS measures have been shown to be responsive to changes in disease status in pediatric CD and other chronic pediatric diseases[3,6–11,14], however limited data exists regarding the use of PROMIS measures as clinical trial endpoints. [15,16] This study is the first to use PROMIS measures as endpoints in a clinical effectiveness trial in pediatric IBD, demonstrating both attainability and responsiveness of these measures obtained longitudinally in the context of a multi-center pragmatic trial. This study is further evidence that PROMIS scores are responsive to clinical changes in pediatric CD, track with other markers of clinical improvement, and can be reliably used in a clinical trial setting. Given that only very few studies have used PROMIS Pediatric measures as clinical trial endpoints[15,16], this study adds to a growing body of literature supporting adoption of PROMIS Pediatric measures as trial endpoints measures in pediatric chronic disease research.

Our study also evaluated PROMIS over an extended follow-up period of up to 3 years. Throughout the trial, high rates of completion of the PROs were maintained and only fell below 80% by the tenth follow up visit. The high rates of completion demonstrate the attainability of including PROs in pragmatic trials and prospective observational research. Ultimately, including PROs routinely in clinical trials will enhance our ability to assess a pediatric patient's health status over time.

As expected, patients who showed meaningful clinical improvement on sPCDAI also showed significant improvement on IBD Symptoms, Pain Interference, and Fatigue. Score changes on these three PRO measures constituted medium to large effect sizes, exceeding estimates of a Minimally Clinically Important Difference (MCID) for PRO measures [27–30]. These findings suggest that inclusion of these measures can be useful as clinical trial endpoints. It is important to note that significant improvements on PROs were also observed among patients who did not show improvement on disease activity indices, indicating that children classified as having inactive disease often self-report some degree of IBD-related symptoms, and PROs may detect changes in these symptoms that are not captured by other clinical metrics. There was little or no change on study outcomes after the first follow-up visit, with improvement of < 2 points per year on average for sPCDAI and Pain Interference and < 1 point for the other PROs. The results suggest that clinically meaningful improvements on IBD Symptoms, Pain Interference, and Fatigue are most likely to be observed within the first few months after initiating anti-TNF therapy, and these improvements may be retained over the following 1–2 years.

In contrast, we did not see significant improvement on Positive Affect between study baseline and the first follow-up visit, making this PRO less useful as a clinical trial endpoint for pediatric IBD than Fatigue and Pain Interference. However, patients who experienced a treatment failure had lower Positive Affect on average than those who did not during the follow-up period of the study, suggesting an association between disease activity and affect over the long term.

An important strength of this study is the methodological rigor of the parent clinical trial, including the robust sample size, double-blind, randomized design, and close attention to data quality and follow-up, as well as the pragmatic nature of the trial without mandated procedures and processes, replicating real life experiences of care. The high rates of PRO completion over an extended follow up period allowed us to evaluate a large cohort of pediatric CD patients during induction of therapy, long-term follow-up and, in some instances, treatment failure. In contrast to many PRO studies, this extended follow up period allowed for monitoring PRO responsiveness with disease evolution.

Limitations in our study include homogeneity of treatment, as the COMBINE study protocol required all patients initiate anti-TNF therapy. Therefore, we were unable to conclude how PROMIS measures may perform overtime in patients not on anti-TNF medications. Additionally, generalizability is somewhat limited, as our cohort was primarily white and had chosen to enroll in the COMBINE study, reflecting high degree of engagement and possibly reflective of high degree of PRO completion. It is critical that future studies of PROs in children prioritize diversity of race/ethnicity, socioeconomic background, and therapy options in order to reflect the broader population of children with CD.

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This study demonstrates the responsiveness of the Pediatric PROMIS measures of Fatigue and Pain Interference in the context of a large, multi-center pragmatic trial in Pediatric Crohn's disease, thus extending a growing body of research supporting the validity of these measures in clinical practice and observational research. Taken together, there is now robust evidence that PROMIS Pediatric measures can serve as reliable PRO endpoints for clinical trials and may complement more traditional endpoints including disease severity indices and mucosal healing.

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Abbreviations:

IBD	Inflammatory bowel disease
CD	Crohn's Disease
HRQOL	Health-related quality of life
PROMIS	Patient-Reported Outcomes Measurement Information System
MCID	Minimal clinically important difference
PROMIS	Patient Reported Outcomes Measurement Information System
sPCDAI	short Pediatric Crohn's Disease Activity Index

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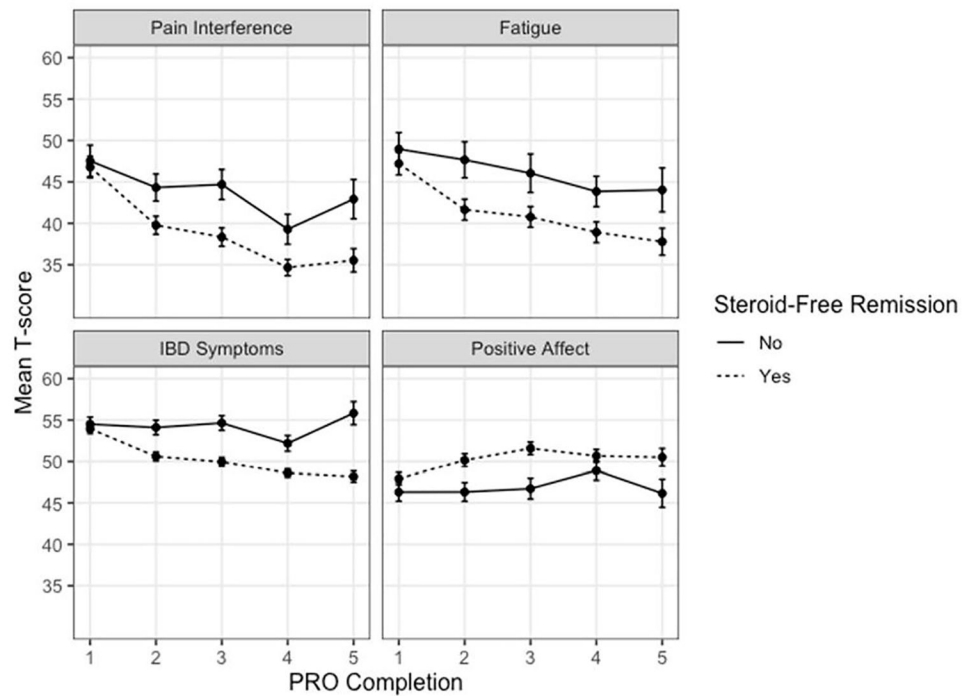


Figure 1. Mean T-scores for 187 participants that remained in the study and completed PROs for at least one year post-baseline. Means were calculated by the order of PRO completion (1 = baseline, 2 = participants' first follow-up PRO, etc.) up to participants' fourth follow-up PRO. Higher scores indicate worse outcomes on Pain Interference, Fatigue, and IBD symptoms and better outcomes on Positive Affect. Bars represent the standard error of the mean.

Table 1.

Baseline Participant Characteristics

	n (%)
Total study sample	266 (100%)
Age at baseline	
8–12	98 (37%)
13–17	157 (59%)
18–20	11 (4%)
Sex	
Male	170 (64%)
Female	96 (36%)
Race/Ethnicity^a	
Hispanic/Latino	7 (3%)
Black or African American	27 (10%)
White	217 (82%)
Other	13 (5%)
Physician Global Assessment^b	
Inactive	62 (33%)
Mild	83 (44%)
Moderate-Severe	43 (23%)
Short Pediatric Crohn's Disease Activity Index^c	
Inactive (<15)	92 (50%)
Mild (15–<30)	58 (32%)
Moderate-Severe (≥ 30)	33 (18%)
Perianal disease^{*d}	
Yes	22 (22%)
No	79 (78%)
Disease locations^{*e}	
Ileum	150 (82%)
Colon	140 (77%)
Upper tract	114 (62%)
Other Measurements^f	Mean (SD)
Weight (kg)	49 (16)
Height (cm)	156 (15)
Disease duration (years)	0.7 (1.4)
C-reactive protein (mg/L)	3.7 (8.8)
Erythrocyte sedimentation rate (mm/h)	17 (15)
Albumin (g/dL)	4.0 (0.5)
Hematocrit (%)	38 (4)

Note. Missing = not assessed the same calendar month as the baseline PRO questionnaire.

^aMissing n = 2

^bMissing n = 78

^cMissing n = 83

^dMissing n = 165

^eMissing n = 83

^fMissing n = 73–145

* Categories are not mutually exclusive.

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Table 2:

Feasibility/Missing Data Summary

Study Visit	PROs collected, N (%) *		
Baseline	294 (98)		
Visit 3	239 (90)		
Visit 4	206 (85)		
Visit 6	163 (80)		
Visit 10	121 (76)		
Missing Items			
Total number of PRO questionnaires collected: 1090			
Number of questionnaires with 0 missing items: 1061			
Number of missing items per questionnaire (out of 26 items)	Range: 0–14	Mean: 0.1	

* Percentages based on number of PROs collected divided by the total number of outpatient visits that occurred for each time point.

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Table 3.

PROs by Clinical Groups Defined by sPCDAI Change

	Active - Improved	Active - Not Improved	Inactive - Inactive
n	39	32	60
IBD Symptoms			
Baseline mean (SD)	57 (\pm 7)	56 (\pm 5)	53 (\pm 7)
First follow-up mean (SD)	51 (\pm 6)	55 (\pm 6)	50 (\pm 6)
Effect size (Cohen's d)	-0.85	-0.10	-0.55
p-value	<0.001	0.59	<0.001
Pain Interference			
Baseline mean (SD)	53 (\pm 14)	56 (\pm 11)	41 (\pm 13)
First follow-up mean (SD)	40 (\pm 12)	49 (\pm 11)	36 (\pm 11)
Effect size (Cohen's d)	-0.93	-0.61	-0.37
p-value	<0.001	<0.01	<0.01
Fatigue			
Baseline mean (SD)	50 (\pm 17)	55 (\pm 13)	44 (\pm 14)
First follow-up mean (SD)	41 (\pm 16)	50 (\pm 15)	38 (\pm 13)
Effect size (Cohen's d)	-0.58	-0.51	-0.35
p-value	<0.001	<0.01	<0.01
Positive Affect			
Baseline mean (SD)	47 (\pm 10)	45 (\pm 7)	50 (\pm 9)
First follow-up mean (SD)	49 (\pm 10)	45 (\pm 8)	52 (\pm 8)
Effect size (Cohen's d)	0.27	0.00	0.18
p-value	0.10	0.98	0.17

Table 4:

PROs by Clinical Groups Defined by PGA Change

	Active - Improved	Active - Not Improved	Inactive - Inactive
n	88	13	40
IBD Symptoms			
Time 1 mean (SD)	56 (7)	56 (7)	52 (6)
Time 2 mean (SD)	51 (6)	57 (7)	49 (5)
Effect size (Cohen's d)	-0.65	0.10	-0.29
p-value	<0.001	0.73	0.08
Pain Interference			
Time 1 mean (SD)	49 (14)	53 (14)	40 (13)
Time 2 mean (SD)	41 (12)	51 (12)	37 (11)
Effect size (Cohen's d)	-0.64	-0.21	-0.26
p-value	<0.001	0.46	0.11
Fatigue			
Time 1 mean (SD)	49 (17)	54 (14)	42 (13)
Time 2 mean (SD)	42 (15)	50 (22)	38 (13)
Effect size (Cohen's d)	-0.45	-0.32	-0.28
p-value	<0.001	0.30	0.08
Positive Affect			
Time 1 mean (SD)	47 (8)	45 (10)	51 (9)
Time 2 mean (SD)	49 (9)	43 (6)	53 (8)
Effect size (Cohen's d)	0.17	-0.32	0.15
p-value	0.11	0.30	0.35

Table 5.

Post-baseline PRO Score Trajectories

	Model Estimate	Standard Error	p-value
sPCDAI			
Time (annual change in score)	-1.8	0.4	<0.001
Treatment failure (yes vs. no)	4.7	1.2	<0.001
Sex (female vs. male)	1.9	1.2	0.10
Baseline age (years)	0.2	0.2	0.31
IBD Symptoms			
Time (annual change in score)	-0.4	0.3	0.14
Treatment failure (yes vs. no)	3.9	0.7	<0.001
Sex (female vs. male)	1.2	0.7	0.09
Baseline age (years)	0.2	0.1	0.18
Pain Interference			
Time (annual change in score)	-1.7	0.5	<0.01
Treatment failure (yes vs. no)	5.1	1.4	<0.001
Sex (female vs. male)	1.2	1.3	0.37
Baseline age (years)	0.0	0.2	0.95
Fatigue			
Time (annual change in score)	-0.9	0.6	0.11
Treatment failure (yes vs. no)	4.1	1.6	<0.01
Sex (female vs. male)	3.1	1.6	0.048
Baseline age (years)	0.3	0.3	0.25
Positive Affect			
Time (annual change in score)	0.0	0.4	0.97
Treatment failure (yes vs. no)	-2.7	1.0	<0.01
Sex (female vs. male)	-1.7	0.9	0.06
Baseline age (years)	-0.3	0.2	0.07

Note. Each model controlled for baseline scores by including them as a covariate. Model estimates may be interpreted as the difference in sPCDAI score or PRO T-score associated with each of the following: an increase in time of one year; experiencing a treatment failure at any point in the study versus no treatment failure; female versus male; one year older in age at baseline. The models for sPCDAI and Fatigue included by-subject random intercepts but not random slopes because the full models with random slopes did not converge.