Preferences of Adult Patients With Inflammatory Bowel Disease for Attributes of Clinical Trials: Evidence From a Choice-Based Conjoint Analysis

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Background: Clinical trial recruitment is the rate-limiting step in developing new treatments. To understand inflammatory bowel disease (IBD) patient recruitment, we investigated two questions: Do changes in clinical trial attributes, like monetary compensation, influence recruitment rates, and does this influence differ across subgroups?

Methods: We answered these questions through a conjoint survey of 949 adult IBD patients.

Results: Recruitment rates are influenced by trial attributes: small but significant increases are predicted with lower placebo rates, reduced number of endoscopies, less time commitment, open label extension, and increased involvement of participant's primary GI physician. A much stronger effect was found with increased monetary compensation. Latent class analysis indicated three patient subgroups: some patients quite willing to participate in IBD trials, some quite reluctant, and others who can be persuaded. The persuadable group is quite sensitive to monetary compensation, and payments up to US$2,000 for a 1-year study could significantly increase recruitment rates for IBD clinical trials.

Conclusions: This innovative study provides researchers with a framework for predicting recruitment rates for different IBD clinical trials.

Key Words: inflammatory bowel disease, ulcerative colitis, Crohn's disease, clinical trials, conjoint analysis, patient recruitment

INTRODUCTION

It is estimated that approximately 3.1 million Americans report having an inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis.[1] According to ClinicalTrials.gov, almost 1,500 clinical trials are available to patients with IBD in the United States.[2] However, based on previous research, most of these clinical trials will fail to enroll the required sample size.[3] In fact, more than 50% of clinical research sites fail to achieve enrollment targets in clinical studies.[4] Although patient engagement in study design has grown in recent years, and some researchers have explored the benefits of seeking patient insight into study design and recruitment, such as Anderson et al[5] and Lim et al[6], there is little understanding of why some patients choose to participate in clinical trials while others do not.

A recent study conducted by several coauthors of this paper attempted to answer this question qualitatively. Specifically, Ehrlich et al[2] conducted five focus groups that included a total of 34 patients with IBD to identify barriers to participating in clinical trials. They found that fear of receiving a placebo or ineffective treatment, time constraints, the number of colonoscopies, and potential adverse events were all significant barriers to participating in clinical trials. In addition, they found that offering an open-label extension and (more importantly) obtaining support from their primary gastroenterologist (GI) could be significant motivators for a patient to participate in a trial.

Findings from these focus groups represent a critical first step in understanding why some patients choose to participate in clinical trials and others do not. However, these findings have three major limitations. First, they are qualitative, which means they can tell us whether changing a clinical trial attribute might increase (or decrease) recruitment rates, but they cannot speak to the magnitude of this change. Second, although focus groups can provide information about how changing individual clinical trial attributes can increase (or decrease) recruitment rates, they do not address the willingness to trade a change in one attribute for a change in another.

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Lastly, because these focus group findings are based on a relatively small sample, one must be cautious about generalizing them to all patients with IBD.

The goal of this study was to expand on the findings of Ehrlich et al[2] by addressing all three limitations through an online, choice-based conjoint survey to quantify preferences for different attributes of clinical trials. We used the data from this survey to answer two research questions that address the limitations of the focus group findings: 1) how do changes in clinical trial attributes quantitatively influence recruitment rates among average patients. For example, if the chance of receiving a placebo was lowered from 50% to 20%, how much would recruitment rates increase on average; 2) how do recruitment rates differ across subgroups? For example, do some patients care more about one attribute than other patients? Do these patients differ based on observable characteristics?

METHODS

Data for this study were collected using a web-based survey that was programmed and hosted by SurveyHealthcare (SHC; www.surveyhealthcare.com), a healthcare market research firm. We recruited respondents for this survey through two avenues. First, we recruited followers of the Crohn's & Colitis Foundation (Foundation), an organization that represents the interests of patients with IBD, by directly e-mailing them a link to the survey, by promoting the survey via the Foundation's website, and by promoting the survey through the Foundation's social media channels, including Twitter and Facebook. We refer to this as the Foundation survey even though some participants were on the Foundation email list. Second, we recruited additional respondents by e-mailing a link to the survey to members of the SHC opt-in panel. We refer to this as the SHC panel survey. It is worth noting, as is illustrated in the sample characteristics below, that some members of the SHC panel survey were also involved with the Foundation. Therefore, it is possible that they may have also seen an advertisement for the Foundation survey. However, respondents who participated in the SHC panel survey would not have been allowed to participate in the Foundation survey, as SurveyHealthcare employed numerous measures (such as using an individual's IP address) to prevent the same person from taking the survey multiple times.

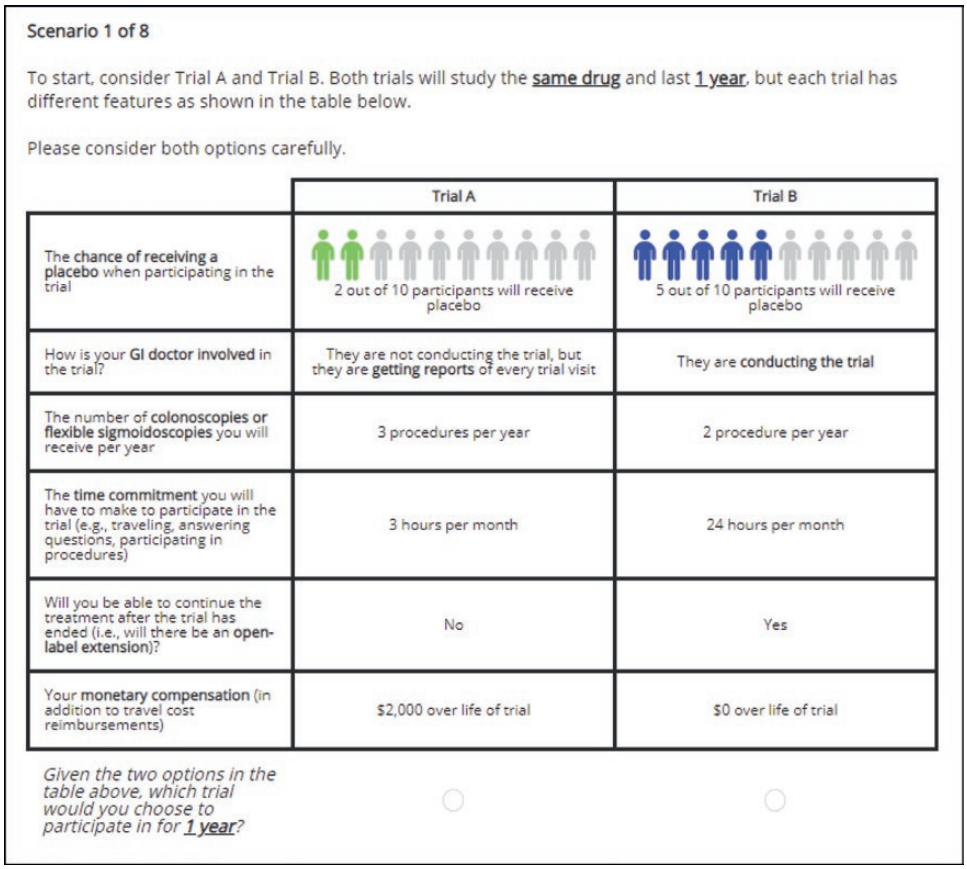
If an individual was interested and clicked on the survey link, they were first asked to complete a brief screening questionnaire. This questionnaire asked for the respondent's age and specific IBD diagnosis. Respondents were eligible to complete the survey if they were adults (18+ yr) and had been diagnosed with Crohn's disease, ulcerative colitis, or indeterminate colitis. If respondents were eligible and completed the survey, they were compensated in one of two ways. First, if a respondent was recruited through the Crohn's & Colitis Foundation's efforts and they provided their name and e-mail address, they were e-mailed a US$5 gift card at the end of data collection (this information was stored separately from the survey data. Respondents could decline to provide their information and subsequently the gift card.). If a respondent was recruited from the SHC panel, they received reward points for completing the survey that could later be redeemed for a variety of reward items.

Survey Development

The primary component of the survey instrument was a set of eight choice questions (see Figure 1 for an example). Each of these choice questions had two parts. First, the respondent was asked to choose between two hypothetical clinical trials (Trial A and Trial B) that differed along six key attributes (described below). Next, after the respondent selected one of the two hypothetical trials, they were asked if they would actually join the trial they selected if they had the opportunity. By combining respondents' answers to these two questions, we were able to frame their choice as one being made between three alternatives: Trial A, Trial B, or Neither Trial. Specifically, a respondent was recorded as choosing Trial A if they selected Trial A over Trial B and said they would join this trial if offered and so on for the other options.

Each hypothetical trial was described as studying the same drug and lasting 1 year but differing across six key attributes. To make the description of these attributes tractable in an experimental setting, we established a set of finite descriptors known as "levels" to describe each attribute. The six attributes we identified and the values these attributes could take are listed in Table 1. These attributes were based on our key findings from the previously mentioned focus groups with 34 adult patients on barriers that may prevent patients from joining clinical trials (results discussed in more detail in Ehrlich et al[2]). We narrowed down the initial list to six attributes that seemed most important to these patients and that researchers designing clinical trials could actually control.

To elicit patient preferences for different attributes of clinical trials, we explored how their choices between hypothetical trials changed as attributes changed. Given the attributes and levels listed in Table 1, 864 ($3 \times 3 \times 3 \times 4 \times 2 \times 4$) different hypothetical clinical trials could be created for adult respondents. However, only a small fraction of these potential trials had to be evaluated by actual respondents if each attribute being considered was assumed to add linearly to a person's "utility" (ie, satisfaction from participating in a trial), a standard assumption in most conjoint analysis studies. When this assumption was made, an optimal subsample of the 864 hypothetical clinical trials was chosen (this subsample is called the "experimental design"), and then statistical analysis could predict how respondents would answer the remaining hypothetical choice tasks.[7] An optimal subsample is a statistically efficient experimental design that possesses several key properties[8,9]:



Scenario 1 of 8

To start, consider Trial A and Trial B. Both trials will study the **same drug** and last **1 year**, but each trial has different features as shown in the table below.

Please consider both options carefully.

	Trial A	Trial B
The **chance of receiving a placebo** when participating in the trial	2 out of 10 participants will receive placebo	5 out of 10 participants will receive placebo
How is your **GI doctor involved** in the trial?	They are not conducting the trial, but they are **getting reports** of every trial visit	They are **conducting the trial**
The number of **colonoscopies or flexible sigmoidoscopies** you will receive per year	3 procedures per year	2 procedure per year
The **time commitment** you will have to make to participate in the trial (e.g., traveling, answering questions, participating in procedures)	3 hours per month	24 hours per month
Will you be able to continue the treatment after the trial has ended (i.e., will there be an **open-label extension**)?	No	Yes
Your **monetary compensation** (in addition to travel cost reimbursements)	$2,000 over life of trial	$0 over life of trial
*Given the two options in the table above, which trial would you choose to participate in for **1 year**?*	○	○

FIG. 1. Example choice task.

- Level balance: The levels of an attribute occur with equal frequency.
- Orthogonality: The occurrences of any two levels of different attributes are uncorrelated.
- Minimal overlap: Cases for which attribute levels do not vary within a choice set should be minimized.

We used Sawtooth Choice-Based Conjoint Software[10] to generate an efficient design incorporating the above attributes.

In addition to the choice questions described above, respondents also answered a variety of other questions about themselves and their experience with IBD. At the start of the survey, we asked respondents whether they were involved with certain patient-advocacy organizations, including the Crohn's & Colitis Foundation, to assess Foundation involvement. We also asked about their experience with IBD (eg, when they were diagnosed, how often they experienced symptoms, and whether they had tried pharmaceutical treatments in the past that were ineffective at controlling their symptoms). In addition, we asked respondents about their experience with clinical trials (eg, whether they had participated in a clinical trial in the past). Lastly, at the end of the survey, we asked respondents a series of standard demographic questions (eg, age, sex, and education).

Before administering the survey, we pretested the survey instrument with three adult patients. This pretest explored two main issues: 1) the patients' ability to understand and accept the clinical trial attributes and levels presented to them in the questionnaire, and 2) the length and wording of the survey instrument. The pretest investigated these issues using in-person cognitive interviewing techniques.[11] Specifically, the respondents first completed the survey under timed conditions. Next, the respondents reviewed their responses to the survey with the interviewer. During this portion of the interview, the respondents were encouraged to "think aloud" and describe the thought process they used to answer each question. RTI International's Committee for the Protection of Human Subjects, which serves as RTI's Institutional Review Board, reviewed and approved the study protocol prior to data collection.

Validity Test

One of the eight choice questions was included in the survey instrument to internally test the validity of each respondent's choices. Specifically, this question asked respondents to choose between two trials where one trial provided more monetary compensation and fewer procedures and all other

TABLE 1. Attributes and Levels for Hypothetical Clinical Trials

Attributes	Levels
The chance of receiving a placebo when participating in the trial	Two out of 10 participants will receive the placebo
	Three out of 10 participants will receive the placebo
	Five out of 10 participants will receive the placebo
Doctor involvement in the trial	They are conducting the trial
	They are not conducting the trial, but they are getting reports of every trial visit
	They are not involved in the trial
Number of colonoscopies and flexible sigmoidoscopies per year	Two procedures per year
	Three procedures per year
	Four procedures per year
Time spent for the study (eg, traveling, answering questions, participating in procedures)	Three h per month
	Six h per month
	Twelve h per month
	Twenty-four h per month
Ability to continue treatment after the trial has ended (ie, the presence of an open-label extension)	Present
	Not present
Monetary compensation (in addition to travel cost reimbursement)	US$0
	US$300 over life of trial
	US$750 over life of trial
	US$2,000 over life of trial

attributes were the same. This "logic test" allowed us to determine whether an individual respondent sufficiently understood the choice questions, so they could indicate a preference for a clearly better trial, a concept known as "dominance" in the conjoint analysis literature.

Statistical Analysis

We used the data collected to answer the two main research questions of this paper. Our first research question was how changes in clinical trial attributes quantitatively influence recruitment rates on average. We answered this research question by first using our data to estimate satisfaction scores for each clinical trial attribute level for the average respondent in our sample. Satisfaction scores quantify how much utility (or satisfaction) the average respondent receives from an attribute level (larger scores indicate more satisfaction). Specifically, we estimated satisfaction scores for all attribute levels listed in Table 1. We also estimated satisfaction scores for a "neither trial" indicator. The "neither trial" indicator tells us how much satisfaction the average respondent derives from not participating in any clinical trial at all. We estimated these satisfaction scores for the average respondent in each sample using a conditional logit model. This means we estimated three sets of satisfaction scores: one for the average SHC panel respondent, one for the average Foundation respondent, and one for the average respondent across both samples. This analysis was conducted using STATA 15.[12]

On their own, satisfaction scores can be difficult to interpret. Therefore, to make our results more easily understood in this context, we used them to estimate how much clinical trial recruitment rates would change on average when different clinical trial attributes were changed. We answered this question by using the following procedure. We started by calculating the recruitment rate for the least preferred hypothetical trial. This trial can serve as a baseline and estimates what the recruitment rate would be if all known clinical trial attributes were set to their least preferred values and nothing else was known about the trial (eg, attributes of the drug being tested, like side effects). The recruitment rate for this hypothetical trial is the probability that a given individual will choose to participate in a hypothetical trial instead of not participating. Next, we improved the level for a single attribute while holding all other attribute levels constant. For example, we might lower the chance of receiving a placebo from 50% (the least preferred level) to 20% (a more preferred level) and leave all other attribute levels unchanged at their least preferred values. We then estimated the recruitment rate for this new hypothetical trial. We repeated this procedure for every attribute level to see how much recruitment rates were improved by changing each attribute. Next, we calculated the absolute difference between recruitment rates to see how much they were increased by improving an attribute level. For example, we might see that reducing the chance of receiving a placebo from 50% to 20% increased the recruitment rate from 5% to 10% (an absolute increase of 5 percentage points). To see whether the increase in recruitment rate was statistically significant, we used the delta method to calculate a 95% confidence interval (CI) around the absolute increase in recruitment rates. If this confidence interval contains 0, then we cannot reject the null hypothesis that there is no increase in recruitment rates at the 5% significant level. It is important to stress that the research question being tested is how recruitment rates change as particular clinical trial attributes are changed and not the recruitment rates on their own. This is because recruitment rates for clinical trials in the real world depend on not only the clinical trial attributes being considered here but also attributes that were not included, which could influence clinical trial recruitment, such as the potential treatment side effects.

Our second research question was how clinical trial recruitment rates differ across subgroups. To answer this question, we used latent class analysis to determine whether respondents could be divided into subgroups or "classes" based on heterogeneity in their preferences. Class membership is unobserved or "latent," so each respondent belongs to each class up to a modeled probability. The probability of respondents belonging

to each class (ie, the population share) is modeled as a multinomial logit, where respondent characteristics (eg, age and gender) can be included as covariates to better predict the likelihood that respondents would be in one of the three classes.[13] Coefficients from this model can be evaluated to determine whether and how each covariate influences latent class membership. Specifically, statistically significant coefficients indicate that the covariate can be used to distinguish between the different classes. For example, if the covariate for Foundation involvement is negatively and significantly associated with a particular class in the membership model, then this is indicative that respondents involved with the Foundation are less likely to belong to that particular class than respondents not involved with the Foundation. However, interpreting raw coefficients beyond their sign can be difficult. Therefore, to make our results more intuitive, we use them to calculate the share of respondents who have each statistically significant characteristic that falls into each class. For example, if we consider respondents who are involved with the Foundation, how many fall into each class?

For this paper, we conducted the latent class analysis using the user-written lclogit command in STATA.[13] First, we conducted a series of specification tests to determine that the pooled sample of 949 adults could be divided into three latent classes. We made this determination by estimating satisfaction scores using a latent class logit model assuming the optimal number of latent classes ranged from two to eight classes. We then compared the models to determine which had the best specification. Specifically, we compared these models based on measures of model fit (eg, Bayesian information criterion, Akaike information criterion, and the consistent Akaike information criterion) and theoretical interpretability (meaning the latent subgroups displayed logical and clinically relevant differences). After making these comparisons, we decided that the optimal number of classes identified in the pooled sample was three.

Next, we estimated satisfaction scores for each class of respondents using a latent class logit model (an extension of the conditional logit model). This model included covariates characteristic of the patients themselves (ie, involvement in the Foundation, age, gender, education, income, ethnicity, and whether they are a member of the SHC panel) and characteristics of the patients' experience with IBD (ie, when they were diagnosed, the frequency of their symptoms, and whether their symptoms were resistant to IBD medication). To make our results more easily understood in this context, we used the satisfaction scores to estimate how much clinical trial recruitment rates would change across each class when different clinical trial attributes were changed. Specifically, we estimated changes in recruitment rates across each class using the same procedure described above when we were considering average respondents in each sample.

When conducting the analysis described above, one question that must be answered is whether our sample sizes are large enough to reliably estimate the satisfaction scores that underlie this analysis. We made this assessment using the Orme sample size rule.[7] This rule uses characteristics of the conjoint survey design to determine the minimum sample required to reliably estimate satisfaction scores. Given that our survey involved seven choice tasks (excluding the one choice task used for validity testing), two choices per task, and a maximum of four levels of an attribute, the Orme sample size rule implied that the minimum sample size we needed to estimate our satisfaction score models was 143 respondents. As discussed below, our sample sizes were substantially larger than this minimum number. By collecting data from significantly more respondents than the minimum required, we were able to obtain more precise satisfaction score estimates and more easily investigate differences in preferences across demographic groups.

RESULTS

Sample Characteristics

Data were collected over a 5-week period in October and November 2018. A total of 1,419 respondents started the survey described above (1,123 recruited by Foundation efforts and 296 recruited from the SHC panel). Of these, 949 respondents met the eligibility criteria and completed the survey (698 recruited by Foundation efforts and 251 recruited from the SHC panel). The average response time for the survey was about 12 minutes. We discuss the characteristics of these respondents in more detail below.

Descriptive statistics of the samples we collected for adult patients are provided in Table 2. We used a Pearson's Chi-square test to determine whether the distribution of responses for each categorical variable was different for Foundation survey respondents and SHC panel survey respondents. The majority of the 949 respondents were involved in the Crohn's & Colitis Foundation (51.40%), were white (84.60%), were younger than 45 years old (61.20%), were female (71.40%), had some college education (89.90%), and had household incomes below $75,000 (55.40%). However, there were demographic differences between respondents to the Foundation survey and respondents to the SHC panel survey. Specifically, SHC panel respondents were more likely to be white, were more likely to be female, were older, were less likely to have some college education, and earned lower incomes than respondents to the Foundation survey.

Tables 3 and 4 present findings on the patients' experience with IBD. The majority of the 949 respondents were diagnosed with Crohn's disease (66.0%), had been diagnosed with IBD for less than 10 years (50.2%) and experienced IBD symptoms multiple times per week or daily (58.03%), had used pharmaceutical treatments that did not work to treat their symptoms or could not be tolerated (84.40%), and had not participated in a clinical trial to treat their IBD (86.20%). We also see that the most

TABLE 2. Sample Characteristics for All Respondents

	SHC Panel Survey (N = 251)	Foundation Survey (N = 698)	All Respondents (N = 949)
Respondent involvement in Crohn's & Colitis Foundation ($P < 0.001$)			
Involved	20.3%	62.6%	51.4%
Not Involved	79.7%	37.4%	48.6%
Respondent gender ($P < 0.001$)			
Male	23.9%	30.2%	28.6%
Female	76.1%	69.8%	71.4%
Respondent age ($P < 0.001$)			
18–24 yr	3.6%	10.2%	8.4%
25–34 yr	11.6%	32.0%	26.5%
35–44 yr	15.5%	30.2%	26.3%
45–54 yr	25.1%	11.0%	14.8%
55–64 yr	28.3%	11.5%	15.9%
65 yr or older	15.9%	5.2%	8.0%
Respondent education ($P < 0.001$)			
High school diploma or less	19.9%	5.9%	9.6%
Some college	38.7%	27.8%	30.7%
College graduate	41.4%	65.6%	59.2%
Prefer not to answer	0.0%	0.7%	0.5%
Annual household income ($P < 0.001$)			
<US$25,000	16.7%	6.2%	9.0%
US$25,000–US$34,999	13.9%	6.2%	8.2%
US$35,000–US$49,999	13.6%	13.6%	13.6%
US$50,000–US$74,999	23.9%	24.8%	24.6%
US$75,000–US$99,999	13.9%	14.0%	14.0%
US$100,000+	14.7%	22.4%	20.3%
Prefer not to answer	3.2%	12.9%	10.3%
Respondent race ($P < 0.001$)			
White	95.2%	80.8%	84.6%
Nonwhite	4.8%	19.2%	15.4%

Test for differences in responses across subsamples using χ^2test. *P*-values for this test are reported in parentheses.

TABLE 3. Experience With IBD Among All Respondents

	SHC Panel Survey (N = 251)	Foundation Survey (N = 698)	All Respondents (N = 949)
IBD subtype ($P < 0.001$)			
Crohn's Disease	71.1%	51.8%	66.0%
Ulcerative colitis	25.9%	36.3%	28.7%
Indeterminate colitis	3.0%	12.0%	5.4%
Years since Patient's IBD was first diagnosed ($P = 0.041$)			
<1 yr	18.3%	20.8%	20.1%
1–2 yr	12.4%	8.7%	9.7%
3–5 yr	8.4%	11.8%	10.9%
6–10 yr	6.4%	10.6%	9.5%
>10 yr	54.6%	48.1%	49.8%
Frequency of patient's IBD symptoms ($P < 0.001$)			
Daily	22.4%	32.1%	29.5%
Two to 4 times per week	33.2%	26.9%	28.5%
Once per week	14.1%	21.7%	19.7%
Once per month	14.1%	12.0%	12.6%
Three to 4 times per year	14.5%	6.4%	8.5%
Once per year	0.8%	1.0%	1.0%
Less than 1 yr	0.8%	<0.1%	0.2%
Prefer not to answer	4.0%	3.4%	3.6%
Patient used treatment that did not work or could not be tolerated			
Biologics ($P < 0.001$)	42.4%	23.1%	37.3%
Immunomodulators ($P<0.001$)	47.4%	22.3%	40.8%
Corticosteroids ($P = 0.008$)	44.3%	34.67%	41.7%
Aminosalicylates ($P < 0.001$)	46.6%	32.3%	42.8%
Antibiotics ($P = 0.012$)	34.1%	25.5%	31.8%
None of the above ($P < 0.001$)	11.0%	28.3%	15.6%
Participated in clinical trial to treat IBD ($P < 0.001$)			
Yes	4.4%	17.2%	13.8%
No	95.6%	82.8%	86.2%

Test for differences in responses across subsamples using χ^2test. *P*-values for this test are reported in parentheses.

common symptoms suffered by respondents included abdominal cramps and pain (71.9%), diarrhea (66.6%), and fatigue (60.7%). There were differences between respondents to the Foundation survey and respondents to the SHC panel survey. Specifically, SHC panel respondents were less likely to be involved in the Foundation, were more likely to have been diagnosed with IBD for more than 10 years, and were less likely to have participated in a clinical trial than respondents to the Foundation survey.

Satisfaction Scores and Response of Recruitment Rates to Changes in Clinical Trial Attributes on Average

Figure 2 illustrates the satisfaction scores for each attribute level estimated for each sample using a conditional logit model (the satisfaction scores themselves are reported in Supplementary Appendix A, Table A1). These satisfaction scores quantify preferences for the average respondent in each sample. An attribute level having a higher score indicates that the attribute level yields more satisfaction than an attribute level with a lower satisfaction score. For example, the average respondent in the pooled sample preferred trials in which the chance of receiving a placebo was 20% (+0.17 satisfaction

TABLE 4. Experience With IBD Symptoms Among All Respondents

	SHC Panel Survey (N = 251)	Foundation Survey (N = 698)	All Respondents (N = 949)
Diarrhea* (P = 0.001)	63.5%	75.3%	66.6%
Bloody stool	28.7%	34.3%	30.1%
Urgent need to relieve bowels* (P = 0.008)	61.2%	70.5%	63.7%
Abdominal cramps and pain	70.3%	76.1%	71.9%
Rectal pain	39.4%	40.2%	39.6%
Joint pain	43.8%	40.6%	43.0%
Pain other than abdominal, rectal, or joint pain	23.6%	20.7%	22.9%
Sensation of incomplete evacuation* (P = 0.007)	34.0%	43.4%	36.5%
Constipation	39.0%	40.2%	39.3%
Nausea	43.6%	44.6%	43.8%
Vomiting	24.6%	22.3%	24.0%
Fever	19.8%	15.5%	18.7%
Loss of appetite	36.7%	33.1%	35.7%
Weight loss	27.5%	23.5%	26.5%
Fatigue* (P = 0.044)	62.6%	55.4%	60.7%
Night sweats	30.7%	30.3%	30.6%
Rectal bleeding	25.2%	31.5%	26.9%
None	3.4%	4.0%	3.6%

Test for differences in responses across subsamples using χ^2test for all measures.
*P-values for this test are reported in parentheses for those at least <0.05.

score) to trials in which the chance of receiving a placebo was 50%, (-0.24 satisfaction score).

Based on these scores, we found that the average respondent prefers lower chances of receiving a placebo, more doctor involvement, fewer colonoscopies and other procedures, less time spent participating in the trial, an open-label extension, and more monetary compensation. This finding holds when we restrict our analysis to either the respondents to the Foundation survey or the respondents to the SHC panel survey. However, it is worth noting that the average respondent to the SHC panel survey had a stronger preference for the "neither trial" attribute than the average respondent to the Foundation survey. This implies that the average SHC panel member receives more satisfaction from not participating in a trial than the average Foundation survey respondent.

To make these results easier to interpret, we used these scores to calculate how much recruitment rates increased when a single attribute was improved and all other attribute levels were held constant. The results of these calculations are illustrated in Figure 3 (numerical results are reported in Supplementary Appendix A, Table A2). Next, as discussed above, we calculated confidence intervals around the absolute difference between recruitment rates when an attribute level was set at its most preferred and least preferred level. This allowed us to determine whether the differences were statistically different from zero. We found the following for the analysis of all respondents:

- *Recruitment rate rises as the chance of receiving a placebo falls:* Lowering the chance of receiving a placebo from 50% to 20% would result in an absolute increase in recruitment rates by an average of 5.10 percentage points (pp) among all respondents (95% CI, 3.92pp–6.28pp).
- *Recruitment rate rises as the patient's GI doctor becomes more involved:* Changing doctor involvement from its least preferred level (not involved in the trial) to its most preferred level (conducting the trial) increases absolute recruitment rates by an average of 6.08pp among all respondents (95% CI, 4.85pp–7.32pp). Similarly, changing doctor involvement from its least preferred level to its second most preferred level (keeping the patient's local gastroenterologist informed with regular reports) increases absolute recruitment rates by 3.63pp among all respondents (95% CI, 1.26pp–3.65pp).
- *Recruitment rate rises as the number of colonoscopies and flexible sigmoidoscopies decreases:* Reducing the number of procedures from four per year to two per year increases absolute recruitment rates by 4.45pp or 36.32% among all respondents (95% CI, 3.31pp–5.59pp).
- *Recruitment rate rises as the time required for the study falls:* Reducing the time required to participate in the study from 24 hours per month to 3 hours per month increases absolute recruitment rates by 7.57pp among all respondents (95% CI, 6.08pp–9.07pp).
- *Recruitment rate rises when an open-label extension is offered:* Adding an open-label extension to the least preferred hypothetical trial, holding all other attribute levels constant, increases absolute recruitment rates by 4.26pp among all respondents (95% CI, 3.37pp–5.15pp).
- *Recruitment rate rises as more monetary compensation is offered:* Increasing monetary compensation for participating in the study from US$0 to US$2,000 over the life of the trial, holding all other attribute levels constant, increases absolute recruitment rates among all respondents by 17.49pp (95% CI, 15.48pp–19.49pp).

Overall, these results tell us that recruitment rates can be increased by lowering the chances of receiving a placebo, increasing doctor involvement, decreasing the number of colonoscopies and other procedures, decreasing the time requirements of the trial, adding an open-label extension, and increasing monetary compensation. Increasing monetary compensation has the biggest impact on patient recruitment (we investigate whether the importance of monetary compensation to recruitment was influenced by household income in Supplementary Appendix B and find no evidence this is the case). We also see that estimated recruitment rates tend to be lower among SHC panel members due to the fact that SHC panel members receive greater satisfaction from not participating in a trial than Foundation survey respondents.

Further, one could significantly increase recruitment rates by improving all attributes at once. We illustrate the magnitude of this increase in Figure 4 by comparing the "least preferred" trial (where all attribute levels are set to their least preferred value) with

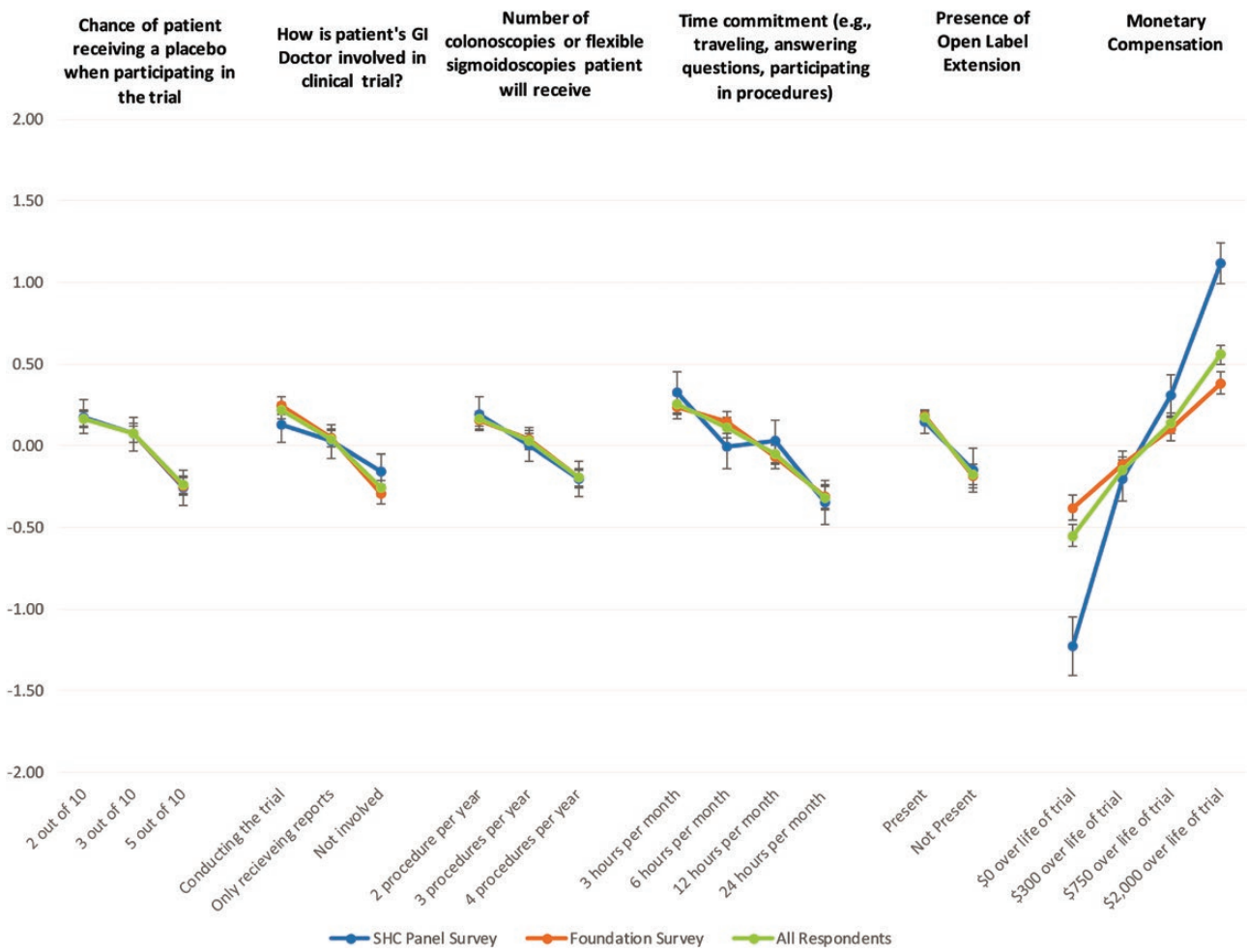


FIG. 2. Satisfaction scores from conditional logit model by sample. Note: Figure reflects estimated satisfaction scores as reported in Supplementary Appendix A, Table A1. Upper and lower bars indicate 95% confidence intervals.

the "most preferred" trial (where all attribute levels are set to their most preferred value). As one can see, changing multiple attribute levels at once has the potential to yield significant gains in respondent recruitment. For example, only 12.2% of all respondents are willing to enroll in the least preferred trial. By contrast, 78.7% of all respondents are willing to enroll in the most preferred trial.

By changing multiple attribute levels at once, we can also see that respondents are willing to trade changes in one attribute for changes in another. For example, if we were to increase the chance of receiving a placebo from 20% to 50%, enrollment would decrease by 5.10pp among all respondents (from 17.38% to 12.28%). By contrast, if we were to increase monetary compensation from US$0 to US$300, enrollment would increase by 5pp among all respondents (12.28% to 17.33%). This implies that if we made both changes at the same time, recruitment rates would not change. In other words, this finding suggests that the average adult patient in our pooled sample is willing to trade an increase in the chance of receiving a placebo (from 20% to 50%) for an increase in monetary compensation (from US$0 to US$300).

Satisfaction Scores and Response of Recruitment Rates to Changes in Clinical Trial Attributes Across Latent Classes

The satisfaction scores from the latent class logit model are illustrated in Figure 5 (numerical results reported in Supplementary Appendix A, Table A3). These satisfaction scores quantify preferences for the average member of each of the three classes we identified. As one can see, satisfaction scores for each class were qualitatively similar to the average scores we estimated above. Specifically, we found that the average adult patient in each class prefers lower chances of receiving a placebo, more doctor involvement, fewer colonoscopies and other procedures, less time spent participating in the trial, an open-label extension, and more monetary compensation. There are two notable differences in satisfaction scores across subgroups. First, satisfaction received from changes in monetary compensation differs significantly across each group. Specifically, changes in monetary compensation

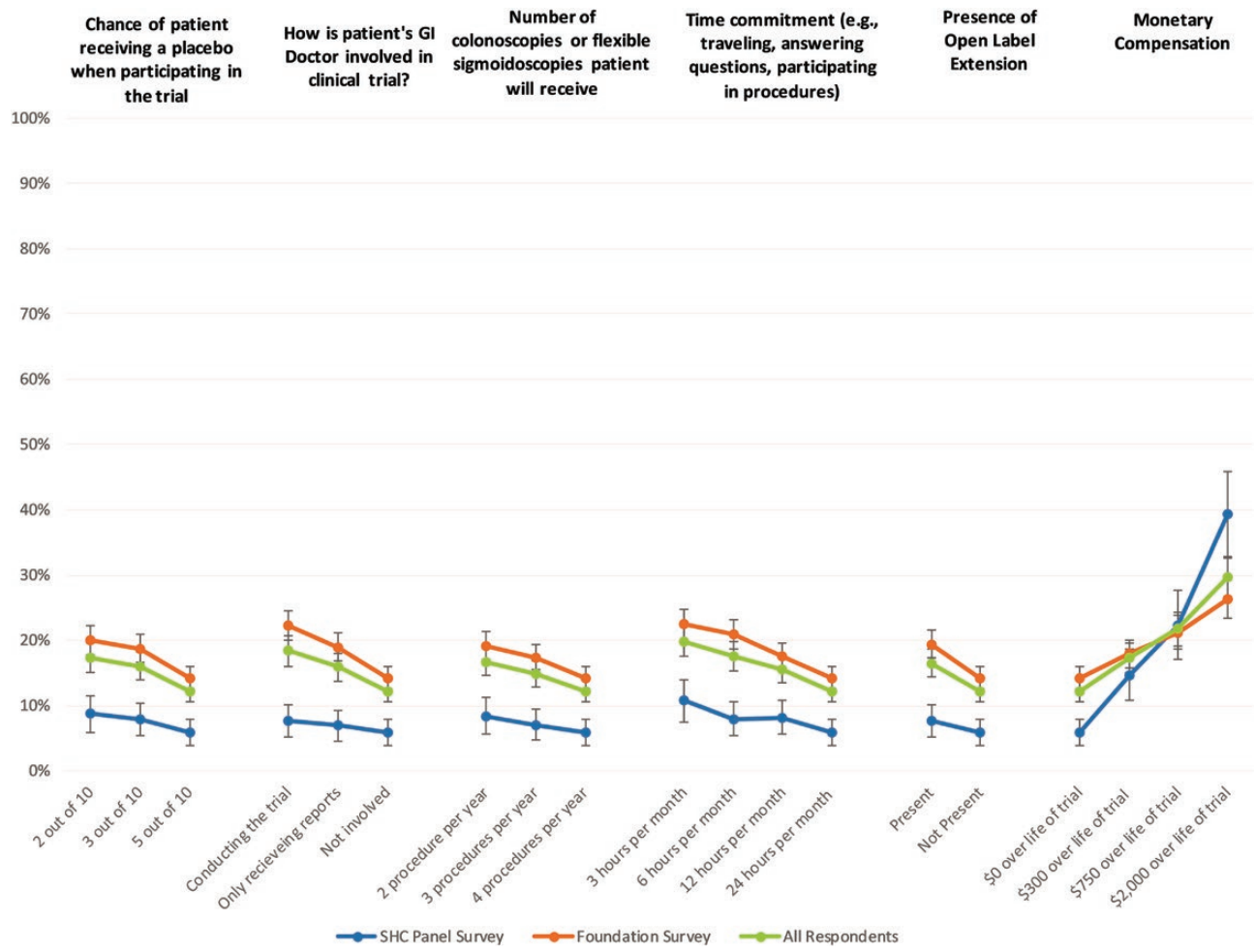


FIG. 3. Response of recruitment rates for adult patients to changes in attribute levels on average. Note: Figure reflects estimated recruitment rates as reported in Supplementary Appendix A, Table A2. Upper and lower bars indicate 95% confidence intervals.

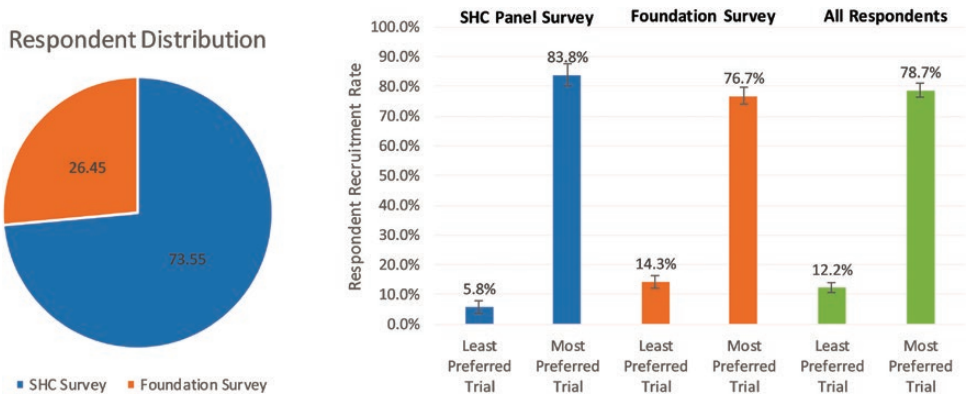


FIG. 4. Comparing recruitment rates for adult patients of least preferred trial and most preferred trial. Note: Figure reflects recruitment for least and most preferred trials estimated using conditional logit. Upper and lower bars indicate 95% confidence intervals.

yield the largest change in satisfaction for Class 2, the least change in Class 3, and a small change in Class 1. Second, members of Class 1 receive substantial satisfaction from not participating in a trial.

Again, to make these results easier to interpret in the context of our research questions, we used these scores to calculate how much recruitment rates for members of each class increase when a single attribute is improved and all other

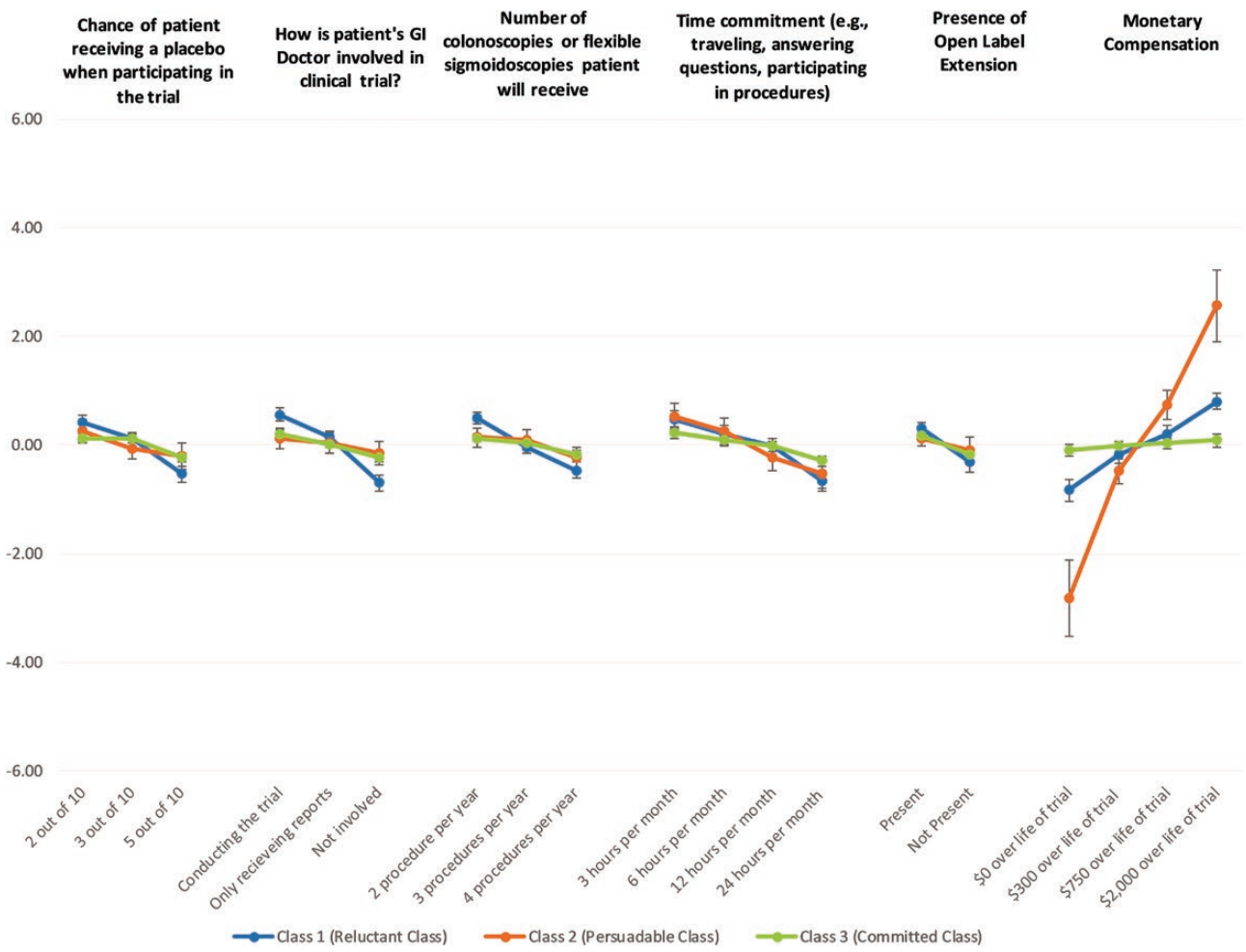


FIG. 5. Satisfaction scores from latent class conditional logit model. Note: Figure reflects estimated satisfaction scores as reported in Supplementary Appendix A, Table A3. Upper and lower bars indicate 95% confidence intervals.

attribute levels are held constant. The results of these calculations are illustrated in Figure 6 (numerical estimates and confidence intervals are reported in Supplementary Appendix A, Table A4). Overall, we see that recruitment rates respond to changes in trial attributes in qualitatively similar ways. For example, recruitment rates in all classes can be increased by increasing monetary compensation. However, we see some important differences across each class. For Class 1 respondents, recruitment rates can be increased significantly by improving most of the attributes. However, since recruitment rates for the least preferred clinical trial are already so low for respondents in this class (only 0.33%), even relatively large increases yield low absolute recruitment rates. For example, increasing monetary compensation for participating in the study from US$0 to US$2,000 over the life of the trial, holding all other attribute levels constant, increases recruitment rates among Class 1 respondents by 409%. However, in absolute terms this means increasing recruitment rates from 0.33% to 1.67%. This is due to the fact that Class 1 respondents gain so much utility from not participating in a trial. Therefore, we refer to this class as the "reluctant" class.

For Class 2 respondents, we see that changing some attributes does not yield statistically significant changes in recruitment rates (chance of getting a placebo, GI doctor involvement, number of procedures, and open-label extension). However, recruitment rates among this class are responsive to changes in time involved with the study and monetary compensation. Increasing monetary compensation yields the biggest increase in recruitment rates for respondents in this class. For example, increasing monetary compensation for participating in the study from US$0 to US$2,000 over the life of the trial, holding all other attribute levels constant, increases recruitment rates among Class 2 respondents by 1,519% (from 5.75% to 93.01%). We describe this class as being open to participating in a clinical trial with the proper compensation (ie, the "persuadable" class).

For Class 3 respondents, we see that recruitment rates are much less responsive to changes in any of the attributes. For example, increasing monetary compensation for participating

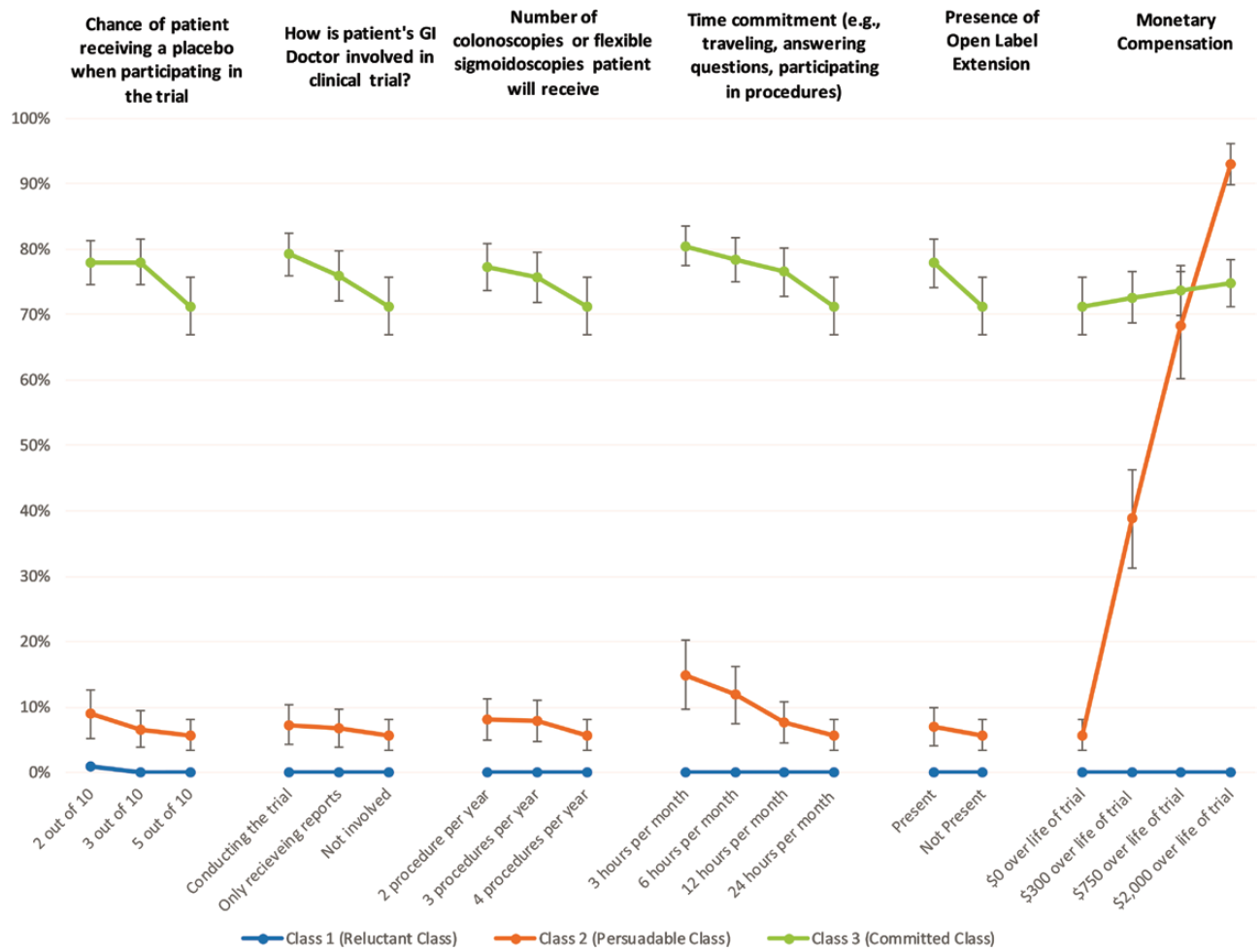


FIG. 6. Response of recruitment rates for adult patients to changes in attribute levels by latent class. Note: Figure reflects estimated recruitment rates as reported in Supplementary Appendix A, Table A4. Upper and lower bars indicate 95% confidence intervals.

in the study from US$0 to US$2,000 over the life of the trial, holding all other attribute levels constant, increases recruitment rates among Class 3 respondents by 5% (from 71.30% to 74.84%). However, recruitment rates for this class are already very high and this increase is not statistically significant. This is due to the fact that respondents in this class prefer to participate in a clinical trial. We describe this class as being committed to participating in clinical trials (ie, the "committed" class).

It is important to reiterate that attributes do not need to be changed one at a time, and one could significantly increase recruitment rates by improving all attributes at once. We illustrate the magnitude of this increase in Figure 7 by comparing the "least preferred" trial (where all attribute levels are set to their least preferred value) with the "most preferred" trial (where all attribute levels are set to their most preferred value) for each class. As one can see, changing multiple attribute levels at once has the potential to yield significant gains in respondent recruitment. This is even true for members of the reluctant class, where the recruitment rate for the least preferred trial is only 0.3%, whereas the recruitment rate for the most preferred trial is 70.7.

The average probability that survey respondents would be in each class was 43% for the reluctant class, 20% for the persuadable class, and 37% for the committed class (it is worth noting again that we did not use a representative sample of IBD patients for this study, so caution should be taken in generalizing these results). In order to shed light on the influence of patient characteristics on latent class membership, we analyzed how different patient characteristics determined the likelihood of belonging to different latent classes (details on the analysis are presented in Supplementary Appendix C).

We found that demographic characteristics, such as age and household income, had a statistically significant impact on class membership. For age, we found that younger respondents are more likely to belong to the persuadable class than the committed class. However, age did not significantly influence the relative likelihood of belonging to the reluctant class (Figure 8A). For income, we found that the likelihood of belonging to the reluctant class (relative to the committed class) increased as household income increased. For example, we estimate that 36.3% of patients with household incomes

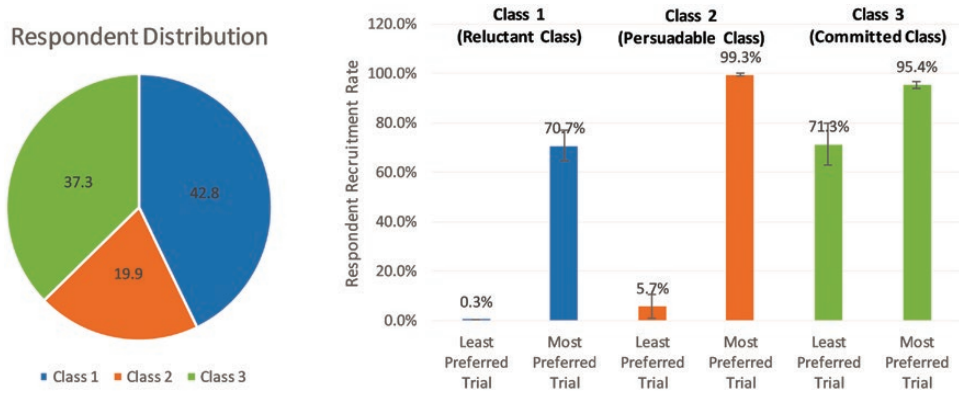


FIG. 7. Comparing recruitment rates for adult patients of least preferred trial and most preferred trial. Note: Figure reflects recruitment for least and most preferred trials estimated using latent class conditional logit. Upper and lower bars indicate 95% confidence intervals.

below US$25,000 belong to the reluctant class, whereas 50.4% belong to the committed class. In contrast, we estimate that 53.8% of patients with household incomes above US$100,000 belong to the reluctant class, whereas 31.9% belong to committed class. In contrast, income did not significantly influence the relative likelihood of belonging to the persuadable class (Figure 8B).

Regarding patient experiences with IBD, we found that the patient's IBD subtype, when the patient was diagnosed, how frequently the patient suffered symptoms, and whether the patient had symptoms resistant to treatment all significantly influenced class membership. For IBD subtype, we found that patients with Crohn's disease were more likely to belong to the committed class than patients with ulcerative colitis or indeterminate colitis. For example, we estimate 38% of patients with Crohn's disease belong to the committed or persuadable classes, whereas 27% of those with ulcerative colitis or indeterminate colitis were members of either class (Figure 9).

For time of diagnosis, we find that patients diagnosed in the past year are significantly more likely to belong to the persuadable class (37.5%) than the committed class (19.3%). In contrast, we estimate that only 16.4% of patients diagnosed more than a year ago belong to the persuadable class and 36.5% belong to the committed class (Figure 10). Time of diagnosis did not influence the relative likelihood of belonging to the reluctant class. This suggests that patients who have been recently diagnosed would consider enrolling in a clinical trial if the compensation were appropriate.

Furthermore, we found that frequency of symptoms and resistance of symptoms to treatment also influenced latent class membership. For symptom frequency, we found that patients with more frequent symptoms were less likely to belong to the reluctant class than the committed class. For example, close to 60% of patients with frequent symptoms (at least once per week) were in the committed or persuadable classes, whereas only 48% of those with infrequent symptoms (once per month or less) were in those classes (Figure 11A). For resistance of symptoms to treatment, we found that patients who had symptoms that were resistant to pharmaceutical treatment were less likely to belong to the reluctant class. For example, we estimate 45% of patients with symptoms resistant to treatment belong to the reluctant class compared with 57% of patients without symptoms resistant to treatment (Figure 11B).

Validity Test Results

As described above, we assessed the validity of our analytical results using the logic test. We found that 13% of all respondents failed the logic test. However, failure rates differ across subsamples. Specifically, we found that 17% of Foundation survey respondents and 4% of SHC panel survey respondents failed the logic test. The difference in failure rates between the two subsamples is likely due to the fact that SHC panel members regularly take surveys like the one we administered. It is difficult to determine whether this failure rate is excessively high, since this is the first study to use a conjoint survey to evaluate patient preferences for clinical trial enrollment. However, these results are within the same range as those found in a conjoint study that investigated the preferences of patients for different IBD patients: Johnson et al[14] found that 13% of their respondents failed an analogous logic test.

To determine whether including respondents who failed these validity tests significantly influenced our results, we excluded these respondents from our sample and re-estimated recruitment rates reported above. Overall, we found these results to be broadly similar regardless of whether we included respondents who failed the validity tests. Specifically, we found that even when excluding individuals who failed the logic test, respondents prefer lower chances of receiving a placebo, more doctor involvement, fewer colonoscopies and other procedures, less time spent participating in the trial, an open-label extension, and more monetary compensation. Similarly, excluding respondents who failed the validity test does not influence which attributes had the biggest impact of recruitment rates (eg,

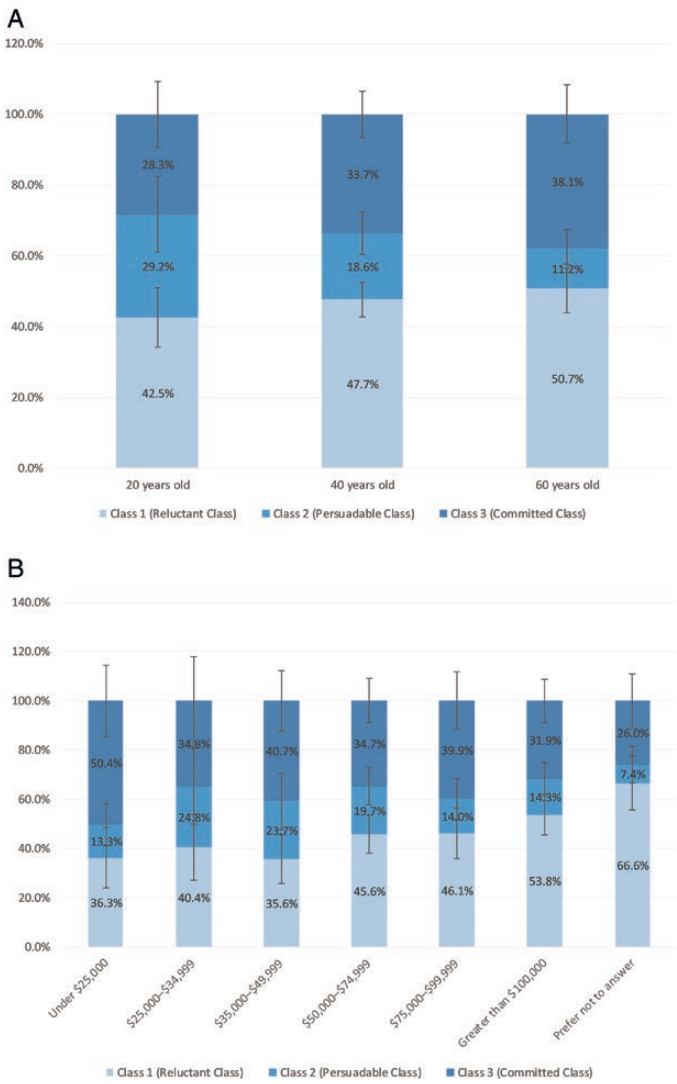


FIG. 8. Influence of demographic characteristics on latent class membership. (A) Patient age. (B) Patient household income. Note: Figure reflects the share of respondents who fall into each latent class by self-reported annual household income (assuming all other characteristics hold at sample averages). For example, we estimate that among that respondents who report earning less than US$25,000 per year, 36.3% fall into Class 1, 13.3% fall into Class 2, and 50.4% fall into Class 3. These shares are based on estimates in Supplementary Appendix C, Table C1. Upper and lower bars indicate 95% confidence intervals, which were estimated using the delta method. These patient characteristics were found to have a statistically significant impact on latent class membership, as discussed in Supplementary Appendix C.

monetary compensation for the average respondent). However, it is important to note that we did find some quantitative differences in our results after we excluded respondents who failed the logic test from our sample. For example, estimated recruitment rates for respondents in Class 3 are lower and more sensitive to changes in attribute levels. We report these results in Supplementary Appendix D.

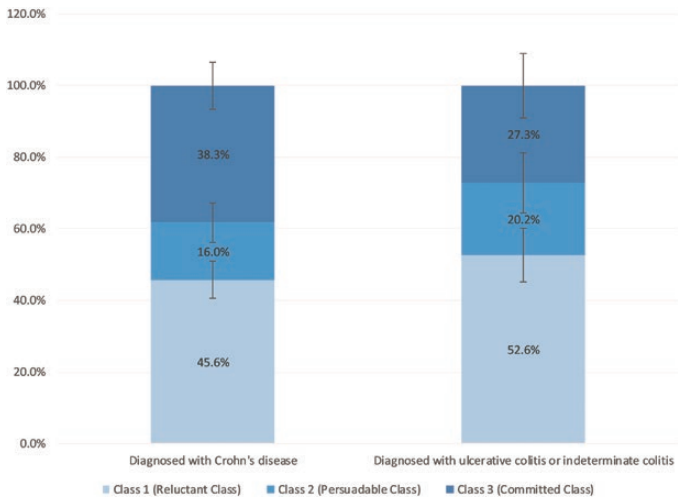


FIG. 9. Influence of IBD subtype on latent class membership. Note: Figure reflects the share of respondents who fall into each latent class by IBD subtype (assuming all other characteristics hold at sample averages). For example, we estimate that among respondents diagnosed with Crohn's disease,45.6% fall into Class 1, 16.0% fall into Class 2, and 38.3% fall into Class 3. These shares are based on estimates in Supplementary Appendix C, Table C1. Upper and lower bars indicate 95% confidence intervals, which were estimated using the delta method. These patient characteristics were found to have a statistically significant impact on latent class membership, as discussed in Supplementary Appendix C.

DISCUSSION

Helping clinical trial researchers improve the design of clinical trials is critical to developing new therapies for IBD patients. As previously mentioned, more than 50% of clinical research sites fail to achieve enrollment targets in clinical studies.[4] A critical prerequisite to improving recruitment rates is to better understand patient preferences for clinical trial design attributes. To the best of our knowledge, this is the first study to elicit these preferences using a choice-based conjoint survey. Data were collected for this survey from 949 adult patients (698 recruited by Foundation efforts and 251 recruited from the SHC panel).

The purpose of this study was to answer two research questions. First, we investigated how changes in clinical trial attributes influenced clinical trial recruitment rates. We found that recruitment rates could be increased by lowering the chances of receiving a placebo, increasing GI doctor involvement, performing fewer colonoscopies and other procedures, lowering time requirements for participating in the study, offering an open-label extension, and offering more monetary compensation. These findings are consistent with qualitative findings from studies that also investigated this question, such as Ehrlich et al,[2] Walsh and Sheridan[15], and Costenbader et al.[16]

In particular, we found that changes in monetary compensation have the biggest potential impact on recruitment rates over any other single attribute. For example, increasing

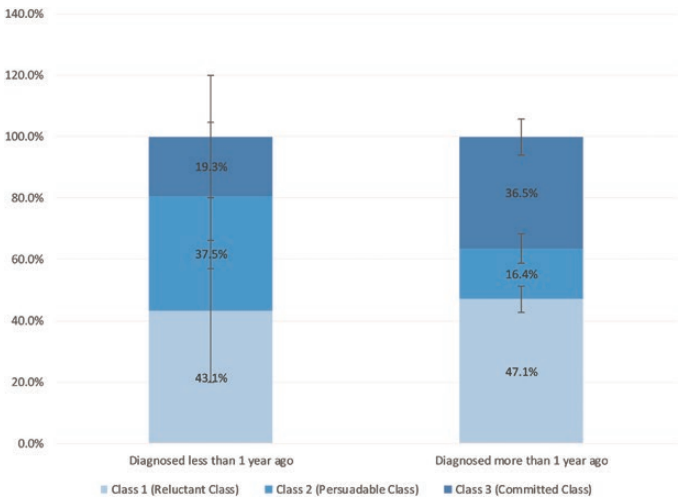


FIG. 10. Influence of year of patient IBD diagnosis on latent class membership. Note: Figure reflects the share of respondents who fall into each latent class by year of diagnosis (assuming all other characteristics hold at sample averages). For example, we estimate that among that respondents who were diagnosed less than 1 year ago, 43.1% fall into Class 1, 37.5% fall into Class 2, and 19.3% fall into Class 3. These shares are based on estimates in Supplementary Appendix C, Table C1. Upper and lower bars indicate 95% confidence intervals, which were estimated using the delta method. These patient characteristics were found to have a statistically significant impact on latent class membership, as discussed in Supplementary Appendix C.

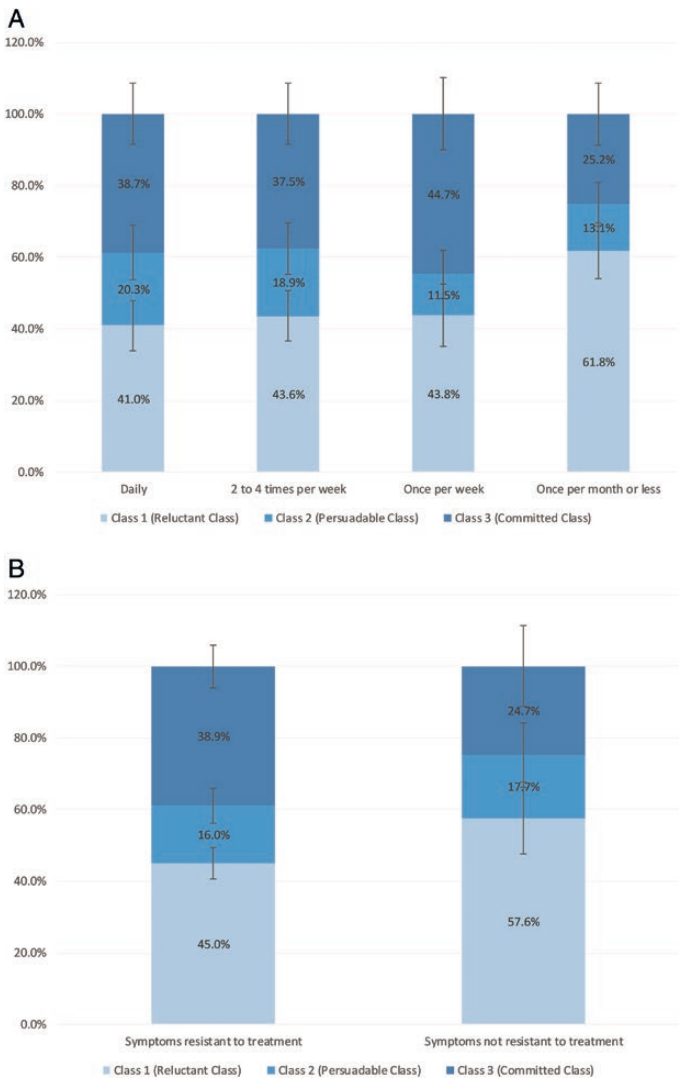


FIG. 11. Influence of symptom frequency and resistance to treatment on latent class membership. (A) Symptom frequency. (B) Symptom resistance to treatment. Note: Figure reflects the share of respondents who fall into each latent class by frequency of IBD symptoms and resistance to treatment (assuming all other characteristics hold at sample averages). For example, we estimate that among respondents with symptoms that are resistant to treatment, 45.0% fall into Class 1, 16.0% fall into Class 2, and 38.9% fall into Class 3. These shares are based on estimates in Supplementary Appendix C, Table C1. Upper and lower bars indicate 95% confidence intervals, which were estimated using the delta method. These patient characteristics were found to have a statistically significant impact on latent membership, as discussed in Supplementary Appendix C.

monetary compensation for participating in the study from US$0 to US$2,000 over the life of the trial, holding all other attribute levels constant, increases average recruitment rates among all respondents by approximately 143% (from 12.25% to 29.74%). This finding is broadly similar to other research. For example, in a review of published literature on factors pertaining to patient participation in clinical trials, Walsh and Sheridan[15] found that financial incentives or rewards were identified as one of the leading factors influencing the decision to participate in a clinical trial. The only factors that were more important than financial rewards and incentives were personal gains to the patient (eg, perceived increase in quality of care and attention when partaking in clinical trials). In theory, these factors can be influenced by the trial setting (IBD Center versus community) and frequency of visits. However, we did not consider these factors in this study.

Because we found that offering a relatively large amount of compensation (eg, US$2,000 over the life of the trial) results in substantial increases in patient recruitment, we must also ask whether this is an "excessive" amount of compensation that exerts an "undue influence" on patients and leads them to act against their own best interests. We do not believe this is an issue in this context for two reasons. First, we do not believe that US$2,000 per year is excessive given the time costs that patients already incur from IBD. According to Park et al,[17] patients with IBD lose approximately US$3,000 per year from time spent on health care (eg, office-related visits, outpatient visits, and hospitalization). This estimate likely underestimates the true cost of IBD, as it does not include individual lost earnings, productivity, or leisure time. Participating in a clinical trial would only add to this significant time burden that patients with IBD already endure. Second, a number of authors have raised concerns about the concept of "undue influence" as it

is typically employed.[18, 19] For example, Largen and Lynch[18] note that 1) "undue influence" is not clearly defined in U.S. regulations or guidance, 2) IRB approval is conditioned on a threshold determination that a study have a favorable risk–benefit ratio that would mitigate the risks from undue inducement, and 3) offering excessively low monetary payments raises the risk of exploiting patients by not properly compensating them for their burden.

The second research question we investigated in this paper was how recruitment rates differ across subgroups. We found that our sample of 949 adults could be divided into three latent subgroups or classes based on their preferences: one class that was reluctant to participate in any trial, another class that could be more easily persuaded to participate in a trial (especially with monetary compensation), and a final class that was committed to participating in almost any clinical trial. These classes composed 43%, 19%, and 38% of the sample, respectively. We found that respondents were more likely to belong to the persuadable or committed class when they were younger, reported lower incomes, had Crohn's disease, reported more frequent symptoms, and reported having symptoms that were resistant to treatment.

Because we found that members of the persuadable class were especially sensitive to monetary compensation, this further raises the question of whether large payments had an undue influence on their decision to join a clinical trial. Is it possible these respondents were poorer and this compensation was leading them to make decisions against their own interest? This fear is alleviated by the fact that the share of respondents that belongs to the persuadable class is approximately the same across income levels. This is consistent with the respondents' decisions reflecting their personal preferences, rather than desperate economic conditions.

These results are important because they can help researchers conducting clinical trials design their clinical trials to be more attractive to enrolling patients. Specifically, our results can be used to simulate how recruitment rates might change as different clinical trial attributes are changed. The Crohn's & Colitis Foundation and RTI International have created a web tool that automates the calculations required to conduct these simulations to assist researchers in designing clinical trials (www.crohnscolitisfoundation.org/research/clinical-trials-community/featured-research/resources-for-professionals). This calculator uses results from the conditional logit analysis. These results are likely useful to researchers conducting clinical trials.

Although we believe that this study makes a major contribution to the literature, our analysis has some limitations. First, the data we collected are from a convenience sample of adult IBD patients. As a result, our estimates may not necessarily reflect the preferences of the entire population. Second, it is possible that the willingness of a patient to participate in a clinical trial will depend on the severity of their disease. Although we collected data on the types of symptoms each patient experienced and their overall frequency, we did not collect data that would allow us to compute a validated disease severity index for each patient. As a result, the influence of disease severity is not considered in this study. Second, conjoint analysis, like all stated preference methods, has been critiqued for potentially being susceptible to hypothetical bias.[20] This bias is created because conjoint analysis collects data by asking participants to complete a series of hypothetical choice tasks, which they may not consider as carefully as they would actual choices. Third, there are a number of other clinical trial attributes we did not ask respondents to consider that may also be influential for trial enrollment. For example, fear of side effects has been found to be a potential deterrent to joining clinical trials. As a result, there are questions our analysis cannot address. We hope future research efforts can work to overcome these limitations in subsequent studies.

CONCLUSION

This innovative study provides researchers designing IBD clinical trials with a framework for conducting simulations to predict recruitment rates for different hypothetical trials. According to this study, researchers can explore lowering the chances of receiving of a placebo, increasing GI doctor involvement, performing fewer colonoscopies and other procedures, lowering time requirements for participating in the study, offering an open-label extension, and offering more monetary compensation in order to increase their study recruitment.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *Crohn's & Colitis 360* online.

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