16.1.9 Documentation of statistical methods

The following documents are included:

- Final Statistical Analysis Plan, dated 16 Dec 2015

STATISTICAL ANALYSIS PLAN

A 26-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Tenapanor for the Treatment of Constipation-Predominant Irritable Bowel Syndrome (IBS-C)

Investigational Product:	Tenapanor
Protocol Number:	TEN-01-302
Development Phase:	Phase 3
Sponsor:	Ardelyx, Inc. 34175 Ardenwood Blvd. Fremont, CA 94555

SAP Version V1.1

SAP Date: 16 December 2015

Original Protocol: 2 October 2015

Confidentiality Statement

SIGNATURE PAGE

STUDY TITLE: A 26-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Tenapanor for the Treatment of Constipation-Predominant Irritable Bowel Syndrome (IBS-C)

We, the undersigned, have reviewed and approved this statistical analysis plan.

Signature Date

[redacted]

[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BID	twice per day
BMI	Body mass index
BSFS	Bristol stool form scale
CSBM	Complete spontaneous bowel movement
eCRF	Electronic case report form
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
IBS	Irritable bowel syndrome
IBS-C	Constipation-predominant irritable bowel syndrome
ITT	Intent to treat
IWRS	Interactive web response system
IVRS	Interactive voice response system
n, N	Number of subjects with observations or number of subjects in an analysis set
OC	Observed cases
QoL	Quality of life
QRS	Principal deflection in ECG
QT	ECG interval
QT_c	QT interval which has been corrected by taking into account heart rate
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SBM	Spontaneous bowel movement
TEAE	Treatment-emergent adverse event

1. INTRODUCTION

This document provides a description of the statistical methods and procedures to be implemented for the analyses of data from the Ardelyx, Inc. study with protocol number TEN-01-302. No deviations from this Statistical Analysis Plan (SAP) are anticipated. However, if any deviations occur, they will be documented in the final clinical study report. No deviation from the primary analyses will be considered.

2. STUDY CHARACTERISTICS

2.1 Study Objectives

This SAP will address the primary and secondary objectives for this study. The exploratory objective will be addressed at a later time through a separate analysis plan and/or report.

2.1.1 Primary Objective

The primary objective of this study is:

- To assess the efficacy of tenapanor 50 mg for the treatment of IBS-C when administered twice daily (BID) for 26 consecutive weeks.

2.1.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the safety of tenapanor 50 mg when administered twice daily (BID) for 26 consecutive weeks.
- To assess the tolerability of tenapanor when administered twice daily (BID) for 26 consecutive weeks

2.1.3 Exploratory Objective

The exploratory objective of this study is:

- To collect and store DNA for future exploratory research into plasma biomarkers and genes/genetic variation related to the gastrointestinal disease area or that may influence response (i.e., distribution, safety, tolerability, and efficacy) to tenapanor.

2.2 Study Design and Duration

This is a phase 3, multi-center, randomized, double blind, placebo-controlled study of tenapanor in subjects IBS-C. Subjects who are 18 to 75 years old, meeting the definition of IBS-C as defined by the Rome III Criteria for the Diagnosis of irritable bowel syndrome

(IBS) (see protocol Appendix A) will undergo a battery of screening procedures to determine eligibility for the trial. A 2:1 screen to randomization ratio is expected.

The study will consist of a 2-week screening period, and a 26-week treatment period.

Approximately 2 weeks prior to study randomization, prospective subjects may be assessed with respect to their meeting the eligibility requirements of the study.

At the beginning of the 2-week screening period (Day -14), subjects will be questioned with respect to their eligibility for the study. Those who meet the basic requirements will be asked to provide written informed consent. The basic screening assessments will include: evaluation of the inclusion/exclusion criteria, medical history (including details about co-morbid disorders), physical exam, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory tests, including urinalysis. Subjects must discontinue the use of all prohibited medications at Visit 1 for the duration of the study. During the screening period, subjects will self-report daily information about the status of their IBS symptoms via a touch-tone telephone diary. Each day entries into the interactive voice-response system (IVRS) diary must occur between 6PM and 11:59PM (local time). This will include information about their stool frequency, stool consistency, straining, abdominal pain, abdominal discomfort, abdominal bloating, abdominal fullness, abdominal cramping, and rescue medication usage. IBS severity and constipation severity will be collected weekly through the IVRS diary. Subject compliance with the electronic diary will be monitored actively by the site staff and the electronic diary system.

At the end of the screening period, prior to the subject returning for randomization (Visit 2), a member of the site staff will confirm a subject's eligibility with regard to the information they have reported in their electronic diary during screening. If the information captured in the diary deems them eligible, and they continue to meet the inclusion criteria at Visit 2, a member of the site staff will randomize the subject into a treatment group using an interactive web response system (IWRS).

Subjects will be randomized to receive either tenapanor 50 mg BID or placebo BID according to a computer-generated central randomization schema. At least 600 subjects will be enrolled at approximately 100-120 US clinical centers.

During the 26-week double-blind treatment period, subjects will continue to record daily and weekly assessments via the IVRS as instructed. Subjects will be seen for study assessment visits at weeks 2, 4, 8, 12, 16, 20, and 26 (Days 15, 29, 57, 85, 113, 141, and 183) during the treatment period. Subject compliance with study drug usage will be monitored. Subject compliance with daily diary entries will be monitored on an ongoing basis as described above.

2.2.1 Treatments Administered

Study drug will be dispensed only to eligible subjects under the supervision of the Investigator or identified sub-Investigator(s). Eligible subjects will be randomized 1:1 into one of two treatment groups: tenapanor 50 mg BID or placebo BID. Subjects will take one

tenapanor tablet or one matching placebo tablet twice daily, immediately prior to breakfast or the first meal of the day and immediately prior to dinner.

Subjects will receive one bottle of drug at Visit 2 (Day 1), Visit 4 (Day 29 ± 3), Visit 5 (Day 57 ± 3 days), Visit 6 (Day 85 ± 3 days), and Visit 7 (Day 113 ± 3 days), and two bottles of drug at Visit 8 (Day 141 ± 3 days). At each visit the subject will be asked to return their unused drug and bottles. All unused study drug and bottles should be returned to the study site. Study drug compliance will be monitored closely by the clinical site staff and will be verified by the study monitor during on-site monitoring visits.

2.2.2 Randomization and Blinding

Both randomization and blinding techniques will be used in this study to minimize bias. Randomization will occur at Visit 2 (Day 1). A computer generated randomization schema will be centrally available via an interactive web response system (IWRS) to all clinical centers that meet the requirements for participation in the study. The IWR system can be accessed by a computer by individuals that have been issued a user ID and password.

In order to double blind the study, the study drug is labeled in a manner to ensure that neither investigators nor subjects can distinguish between treatments. The packaging and labeling of the study drug kits will be based on a separate drug packaging randomization schedule. Upon satisfaction of the eligibility criteria, study site personnel will call into the IWRS and obtain permission to randomize the subject. The IWRS will determine which drug package for the site to administer to the subject based on a randomization schedule where each treatment is allocated once using a block size of 4 within each study site. Hence, randomization will be stratified by study site with each study site ending up with whole and/or partial block sizes randomized.

2.2.3 Duration of Study

For each subject, the entire study will last for a total of 28 weeks, including a 2-week screening period and 26 weeks of treatment (tenapanor 50 mg BID or placebo BID). The study flow chart, including all procedures to be performed during the study is presented below.

SCHEDULE OF ASSESSMENTS FOR THE STUDY

The study flow chart, including all procedures to be performed during the study is presented below. Prior to engaging in any study procedure, each subject must sign and date an informed consent form.

Evaluation	**Screen**	**Treatment Period**							
Site Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET[f]**
Study Week	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**26**
Study Day(s)	**-14**	**1**	**15±3**	**29±3**	**57±3**	**85±3**	**113±3**	**141±3**	**183±3**
Informed Consent[a]	X								
Inclusion/Exclusion	X	X							
Demographics	X								
Medical History (including GI history)	X	X[b]							
Prior/Concurrent Medications	X	X	X	X	X	X	X	X	X
Physical Exam	X								X
Vital Signs[c]	X	X	X	X	X	X	X	X	X
Height	X								
Clinical Laboratory Tests	X			X		X			X
Pharmacogenomics sample[g]				X					
Biomarker sample	X			X		X			X
FSH test[d]	X								
Serology	X								
Urine Pregnancy test[d]	X	X		X		X			X
Urinalysis	X			X		X			X
12-lead electronic ECG	X					X			X
IVRS Training/Compliance Check & Reminder	X	X	X	X	X	X	X	X	

Evaluation	**Screen**	**Treatment Period**							
Site Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET[f]**
Study Week	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**26**
Study Day(s)	**-14**	**1**	**15±3**	**29±3**	**57±3**	**85±3**	**113±3**	**141±3**	**183±3**
IBS-QOL PRO		X				X			X
Treatment Satisfaction PRO				X	X	X	X	X	X
Randomization		X							
Daily PROs[e]	X	X	X	X	X	X	X	X	X
Drug Dispensed/returned		D		D/R	D/R	D/R	D/R	D/R	R
Adverse Event Assessments			X	X	X	X	X	X	X

[a]The Informed Consent Form (ICF) must be signed before any study procedures are performed; The ICF may be signed before the Screening Visit.
[b]Medical history for Visit 2; record only changes to Medical history from Visit 1.
[c]Vital signs include systolic and diastolic blood pressure (seated), heart rate, respiratory rate, temperature and body weight.
[d]FSH is performed in post-menopausal women (at screening only); pregnancy tests are performed on all females <60 years of age unless there is a documented method of sterilization, or FSH test confirms post-menopausal status
[e]Daily Patient Reported Outcomes will be collected via a phone diary and will include the following: frequency and time of each Bowel Movement (BM), sensation of complete bowel emptying, stool consistency (BSFS) of each BM, straining, abdominal pain, abdominal discomfort, abdominal bloating, abdominal fullness, abdominal cramping, use of and time of rescue medication, IBS severity (weekly), constipation severity (weekly), adequate relief of IBS symptoms (weekly, after randomization), degree of relief of IBS symptoms (weekly, after randomization)
[f]All end of treatment procedures listed for Visit 9 should be performed in any subject who terminates the study early
[g]The pharmacogenomics sample is optional and requires subject to specify acceptability on the informed consent. If a subject opts in, the blood sample can be taken at any visit after randomization

2.3 Efficacy and Safety Variables

2.3.1 Efficacy Variables

Efficacy variables in this trial will be captured via the IVRS on a daily basis (CSBM frequency, SBM frequency, consistency, straining, and abdominal symptoms of pain, discomfort, bloating, fullness, and cramping) or weekly basis (IBS severity, and constipation severity) during the screening (baseline) period and the 26 week treatment period. Adequate relief of IBS symptoms and degree of relief of IBS symptoms will be collected weekly during the treatment period. The IBS-QOL will be collected at the randomization visit, the week 12 visit, and the week 26 visit. Treatment satisfaction will be recorded at the end of each month during the treatment period through week 20 and again at week 26 Use of rescue medication is also collected daily throughout the screening and treatment periods. Rescue medication usage is incorporated into the derivation of the efficacy variables but is not in itself considered an efficacy variable.

The primary efficacy variable will be the overall responder rate. An overall responder will be defined as a weekly responder for the first 6/12 weeks where both CSBM and abdominal pain response criteria were met for the week. The CSBM and abdominal pain response criteria are defined below. The weekly overall responder rates will be summarized for each week of the treatment period. An endpoint week will be defined as the last valid week during the treatment period with an overall responder criteria assessment.

The CSBM response criteria are defined as an increase of one or more change in average weekly CSBMs from baseline. The definition of a CSBM is as follows: A CSBM is a SBM for which the subject responds “yes” to the following question; “Did you feel like you completely emptied your bowels?” Any SBM which is preceded within 24 hours by the use of rescue medication will not be counted as a SBM and therefore also not counted as a CSBM as defined above. Should a subject not have data reported for a given week (either due to a gap in reporting or due to discontinuation), the subject will be considered to be a non-responder for the week.

A key secondary efficacy variable will be the overall CSBM responder rate. An overall CSBM responder will be defined as a weekly CSBM responder for the first 6/12 weeks where the CSBM response criteria were met for the week. The weekly CSBM responder rates will be summarized for each week of the treatment period. An endpoint week will be defined as the last valid week during the treatment period with a CSBM response criteria assessment.

The average weekly CSBMs will be calculated as the sum of the number of CSBMs reported during each day of the defined weekly period divided by the number of days CSBMs were reported multiplied by 7. A valid week will require at least 4 days of SBM reporting. The average weekly CSBMs and change from baseline (where baseline is the average of the 2-weeks during the screening period) for each week of the treatment period will be summarized. An endpoint week will be defined as the last valid week during the treatment period with an average weekly CSBM.

The abdominal pain response criterion is defined as a decrease of 30% or more of percent change in average weekly worst abdominal pain from baseline. Abdominal pain will be scored daily using the scale 0 = No pain to 10 = very severe pain. The average weekly abdominal pain score will be calculated as the average score for all days during a valid week. A valid week will require at least 4 days of abdominal pain reporting. Should a subject not have data reported for a given week (either due to a gap in reporting or due to discontinuation), the subject will be considered to be a non-responder for the week.

The average weekly abdominal pain score and percent change from baseline (where baseline is the average of the 2-weeks during the screening period) for each week of the treatment period will be summarized. An endpoint week will be defined as the last valid week during the treatment period with an average weekly abdominal pain score.

A key secondary efficacy variable will be the overall abdominal pain responder rate. An overall abdominal pain responder will be defined as a weekly abdominal pain responder for the first 6/12 weeks where the abdominal pain response criteria were met for the week.

Additional key secondary efficacy variables consist of the overall responder rate, overall CSBM responder rate, and overall abdominal pain responder rate calculated using a 13/26 week response criteria. These responder rates encompass the entire 26-week treatment period. Hence, for 13 out of the 26 weeks during the treatment period, the subject met the responder criteria for the 6/12 week responder rates.

Additional key secondary efficacy variables consist of the overall responder rate, overall CSBM responder rate, and overall abdominal pain responder rate calculated using a 9/12 week response criteria. Hence, for 9 out of the first 12 weeks during the treatment period, the subject met the responder criteria for the 6/12 week responder rates. In addition, for the first 9/12 week CSBM responder criteria, it is also required that the average weekly CSBMs for the week are ≥ 3.

For each of the efficacy variables described above (i.e., first 6/12, 13/26, and first 9/12 responders for respective weeks), several sensitivity analyses will be done. Instead of assuming non-response for missing weeks or weeks with less than 4 days of valid diary data, a sensitivity analysis will be carried out imputing response for these weeks. Similarly, instead of assuming a 30% reduction for percent change in abdominal pain, these analyses will be repeated using a 40% reduction and a 50% reduction as response criteria. Note that for these last 2 analyses, the CSBM responder analyses will not repeated, only the overall and abdominal pain responder rates.

Secondary efficacy variables will include the following:

The durable overall responder rate, durable overall CSBM responder rate, and durable overall abdominal pain responder rate will be secondary efficacy variables. The durable responder rates use the same first 9/12 week response criteria and in addition, require the last 3/4 weeks of the first 12 weeks of the treatment period to meet the response criteria.

The proportion of subjects with ≥ 3 CSBMs per week will be summarized for the baseline and treatment periods. An endpoint week will be defined as the last valid week during the treatment period with an average weekly CSBM.

Average weekly SBMs will be calculated as described above for average weekly CSBMs. Change from baseline for each week of the 26-week treatment period will be summarized using the observed data. An endpoint week will be defined as the last valid week during the treatment period with an average weekly SBM.

Subjects will record the consistency of each of their bowel movements on a daily basis through the IVRS utilizing the BSFS scale (Appendix B of the protocol). The average weekly stool consistency will be calculated as the average score for all valid SBMs during the week. For purposes of calculating an average, days with no stools will be scored a 0. Change from baseline for each week of the 26-week treatment period will be summarized using the observed data. Baseline will be calculated as described for the CSBMs and SBMs. An endpoint week will be defined as the last valid week during the treatment period with an average weekly stool consistency.

Straining will be scored for each SBM using the scale 1 = not at all, 2 = a little bit, 3 = a moderate amount, 4 = a great deal, 5 = an extreme amount. The average weekly straining score will be calculated as the average score for all valid SBMs during the week. Change from baseline for each week of the 26-week treatment period will be summarized using the observed data. Baseline will be calculated as described for the CSBMs and SBMs. An endpoint week will be defined as the last valid week during the treatment period with an average weekly straining score.

Abdominal discomfort, abdominal bloating, abdominal fullness, and abdominal cramping will be scored daily using the 0-10 point scale with 0 representing no presence of the symptom and 10 representing very severe presence of the symptom. The average weekly scores will be calculated as the average score for all days during a valid week. Percent change from baseline for each week of the 26-week treatment period will be summarized. In addition, responders at each week (i.e., 30% improvement from baseline) and for the first 6/12 weeks, 9/12 weeks, and 13/26 weeks on treatment will be defined in a similar manner as for abdominal pain responder rates. If no data is present to constitute a valid week, it will be assumed the subject did not respond. Otherwise, observed data will be used to summarize the average weekly abdominal symptom. Baseline will be calculated as described for the CSBMs and SBMs. An endpoint week will be defined as the last valid week during the treatment period with an average weekly abdominal symptom score. Each symptom will be assessed separately so it is possible for different symptoms to have different endpoint weeks.

IBS severity and constipation severity will be scored on a weekly basis using the scale 1 = None, 2 = Mild, 3 = Moderate, 4 = Severe, 5 = Very Severe. IBS severity scores and constipation severity scores for each week of the study will be summarized as categorical and continuous data. Observed data will be used for the summaries. Baseline for these severity ratings will be the average of the two ratings during the screening period. An endpoint week will be defined as the last valid week during the treatment period with an IBS severity or constipation severity rating.

Adequate relief of IBS symptoms (1 = yes, and 2 = no) will be asked on a weekly basis during the treatment period. The percentage of subjects with adequate relief for each week of the study will be summarized using observed data. An endpoint week will be defined as the

last valid week during the treatment period with an adequate relief of IBS symptoms response.

Degree of relief of IBS symptoms will be scored on a weekly basis during the treatment period using 1=completely relieved, 2=considerably relieved, 3=somewhat relieved, 4=unchanged, 5=somewhat worse, 6=considerably worse, 7=as worse as I can imagine. Degree of relief scores for each week of the study will be summarized as categorical and continuous data using observed data. An endpoint week will be defined as the last valid week during the treatment period with a degree of relief of IBS symptoms response.

The IBS-QoL is a validated quality of life tool used for IBS patients (see Appendix D of the protocol). Subjects will be asked to complete this assessment a Visit 2 (randomization visit), Visit 6 (at 12-weeks of treatment), and Visit 9 (at the end of the 26-week treatment period). The IBS-QoL includes 34 individual questions which measure 8 subscales found to be relevant to patients with IBS: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, relationships and overall. Each of the subscale scores is calculated using the criteria described in the IBS-QoL user manual attached as Appendix 1 to this SAP.

All items in the IBS-QoL are negatively framed with the greatest response scale equaling the worst quality of life. When scored, all items are reversed so that the as IBS-QoL scores increase, quality of life increases. i.e., 1changes to 5, 2 changes to 4, 3 stays as 3, 4 changes to 2, and 5 changes to 1. Then the reversed individual responses to the 34 items are summed and averaged for a total score and then transformed to a 0-100 scale for ease of interpretation with higher scores indicating better IBS specific quality of life using the following formula:

$$\text{Subscale Score} = \frac{(\text{the sum of the items - lowest possible score})}{\text{possible raw score range}} \times 100.$$

Actual values and change from baseline values for each of the subscale scores will be calculated and summarized.

Treatment satisfaction will be recorded by the subject at the end of each month during the treatment period (Visits 4, 5, 6, 7, and 8), and at the end of the treatment period (Visit 9). Using the scale: 1= not at all satisfied, 2= a little satisfied, 3= moderately satisfied, 4 =quite satisfied, 5= very satisfied. The treatment satisfaction score will be summarized as a categorical and continuous variable.

The following summarizes the efficacy variables planned for this study:

Table 2-1 Summary of Efficacy Variables and Designation

Variable Designation	Variable name
Primary	6/12 week overall responder rate
Key Secondary	6/12 week overall CSBM responder rate
Key Secondary	6/12 week overall abdominal pain responder rate

Key Secondary	9/12 week overall responder rate
Key Secondary	9/12 week overall CSBM responder rate
Key Secondary	9/12 week overall abdominal pain responder rate
Key Secondary	13/26 week overall responder rate
Key Secondary	13/26 week overall CSBM responder rate
Key Secondary	13/26 week overall abdominal pain responder rate
Sensitivity	6/12 week overall responder rate with imputed responders
Sensitivity	6/12 week overall CSBM responder rate with imputed responders
Sensitivity	6/12 week overall abdominal pain responder rate with imputed responders
Sensitivity	13/26 week overall responder rate with imputed responders
Sensitivity	13/26 week overall CSBM responder rate with imputed responders
Sensitivity	13/26 week overall abdominal pain responder rate with imputed responders
Sensitivity	9/12 week overall responder rate with imputed responders
Sensitivity	9/12 week overall CSBM responder rate with imputed responders
Sensitivity	9/12 week overall abdominal pain responder rate with imputed responders
Sensitivity	6/12 week overall responder rate with 40% change in abdominal pain
Sensitivity	6/12 week overall 40% change in abdominal pain responder rate
Sensitivity	13/26 week overall responder rate with 40% change in abdominal pain
Sensitivity	13/26 week overall 40% change in abdominal pain responder rate
Sensitivity	9/12 week overall responder rate with 40% change in abdominal pain
Sensitivity	9/12 week overall 40% change in abdominal pain responder rate
Sensitivity	6/12 week overall responder rate with 50% change in abdominal pain
Sensitivity	6/12 week overall 50% change in abdominal pain responder rate
Sensitivity	13/26 week overall responder rate with 50% change in abdominal pain
Sensitivity	13/26 week overall 50% change in abdominal pain responder rate
Sensitivity	9/12 week overall responder rate with 50% change in abdominal pain
Sensitivity	9/12 week overall 50% change in abdominal pain responder rate
Secondary	Durable overall responder rate
Secondary	Durable overall CSBM responder rate
Secondary	Durable overall abdominal pain responder rate
Secondary	Weekly overall responder rate
Secondary	Weekly CSBM responder rate
Secondary	Weekly abdominal pain responder rate

Secondary	Weekly proportion of subjects with ≥3 CSBMs per week
Secondary	Average weekly CSBMs
Secondary	Average weekly SBMs
Secondary	Average weekly stool consistency
Secondary	Average weekly straining score
Secondary	6/12, 9/12, and 13/26 Overall abdominal discomfort responder rate
Secondary	6/12, 9/12, and 13/26 Overall abdominal bloating responder rate
Secondary	6/12, 9/12, and 13/26 Overall abdominal cramping responder rate
Secondary	6/12, 9/12, and 13/26 Overall abdominal fullness responder rate
Secondary	Weekly abdominal discomfort responder rate
Secondary	Weekly abdominal bloating responder rate
Secondary	Weekly abdominal cramping responder rate
Secondary	Weekly abdominal fullness responder rate
Secondary	Average weekly abdominal pain score
Secondary	Average weekly abdominal discomfort score
Secondary	Average weekly abdominal bloating score
Secondary	Average weekly abdominal cramping score
Secondary	Average weekly abdominal fullness score
Secondary	Weekly IBS severity score
Secondary	Weekly constipation severity score
Secondary	Weekly adequate relief of IBS symptoms
Secondary	Weekly degree of relief of IBS symptoms score
Secondary	IBS-QOL (9 subscales)
Secondary	Treatment satisfaction

2.3.2 Safety Variables

Safety variables will include adverse event (AE) reporting throughout the trial, clinical laboratory tests (serum chemistry, hematology, and urinalysis), vital signs (including body weight and body mass index [BMI]), 12-lead ECG, and physical examinations.

3. STATISTICAL METHODOLOGY

3.1 Determination of Sample Size

A sample size of 300 in each treatment group would achieve 95% power to detect a difference of 0.15 (15%) between the placebo and tenapanor 50 mg BID first 6/12 week

overall responder rate when the tenapanor 50 mg BID responder rate is at least 45% under the alternative hypothesis and the responder rate in the placebo group is no closer than 15% from tenapanor 50 mg BID. The test statistic used was the two-sided Fisher's exact test with significance level of 0.050 (5%). This sample size also has 80% power to detect an 11.6% difference in responder rates between the treatment groups when the responder rates are in the same range as above.

3.2 Analysis Sets

Safety Analysis Set:

All subjects who receive at least one dose of study drug will be included in all analyses of safety data. Such subjects will be analyzed according to the treatment actually received.

Intent to Treat (ITT) Analysis Set:

All subjects who meet the study entry inclusion/exclusion criteria, are randomized and receive at least one dose of study drug will be included in the ITT analysis set. Subjects will be analyzed according to the treatment group into which they were randomized. The ITT analysis set will be the primary analysis set for efficacy analysis.

Per-Protocol (PP) Analysis Set

All subjects included in the ITT analysis set who complete the study as planned with no major protocol deviations will be included in the PP analysis set. Membership in this analysis set will be determined at a data review meeting prior to unblinding the randomization. This analysis set will be used as a sensitivity analysis relative to the ITT analysis set.

3.3 Procedures for Handling Missing Data

The primary analysis will be based on the observed data where average weekly SBMs and CSBMs will be standardized to 7-day frequencies. This amounts to missing days during the week being imputed with the mean for the non-missing days. A valid week will require at least 4 non-missing diary days. Hence, for the primary analysis, weeks with less than 4 diary days are treated as a non-responder for that week. To further assess the impact of missing weeks on the efficacy analyses, a sensitivity analysis will be carried out by treating weeks with less than 4 diary days as a responder for that week.

The valid week rule will also apply for stool consistency and straining score although it is assumed that if the diary was filled out for frequency of stools, it would also be filled out with respect to these items. However, the average weekly stool consistency and the average weekly straining score will be calculated on the observed number of responses without any standardization. For the purposes of calculating an average, days with no stools reported (i.e., a 0 was recorded for the answer to IVRS question) will be scored as 0 for average weekly stool consistency and average weekly straining score.

An endpoint week will be defined as the last valid week during the first 12-weeks of the treatment period and the last valid week of the 26-week treatment period where each weekly

efficacy variable was obtained. This amounts to creating an endpoint last observation carried forward such that each subject's endpoint value represents the last experience while receiving study drug during the first 12-weeks and the total 26-week treatment period. In the few cases where no efficacy data is collected during the 12-week treatment period, the endpoint week will be considered a non-response or missing if no frequency or stool consistency data are obtained.

Otherwise, all other observed data will be used in the analyses.

3.4 Methods of Pooling Data

For the purpose of adjusting for investigator effects in statistical models, investigator sites will be pooled into groups based on geographic region and number of subjects enrolled with an aim for comparable sample sizes among pooled investigator sites. Initial US geographic regions will consist of north east, east, south east, mid west, mid south, and west, These regions could be further sub-divided based on enrollment but no sites will be classified outside of their logical geographical region.

In terms of achieving comparable sample sizes, the goal of the pooling strategy will be to avoid less than a minimum number of subjects per pooled investigator site. The size of a pooled investigator site would generally not be larger than the total number of subjects enrolled at the highest enrolling individual investigator site. The pooled investigator sites will be used in all applicable analyses where adjustment for investigator effect is desired.

Based on an average of 6 subjects per site to be enrolled, the primary pooled investigator site strategy will target 10 pools of approximately 60 subjects each (approximately 30 per treatment group per pooled investigator site). As a sensitivity analysis, a second pooling will have a target of 20 pools of approximately 30 subjects each (approximately 15 per treatment group per pooled investigator site). The actual designation of membership in a pooled investigator site cannot be made until the final enrollment quantities and final number of sites used is completed. The final pooling strategy will be defined before treatment unblinding, and will be provided as an addendum to the SAP. The goals stated above will be adhered to as closely as possible.

3.5 Visit Windows

Daily IVRS diary data are planned for daily collection starting on the day of the Screening visit and continuing until the planned Week 26 (Visit 9 Day 183).

Weekly IVRS diary data are planned for each week of the 2-week screening period (when applicable), and each week of the 26-week treatment period.

For all IVRS efficacy data, the date collected will be used to calculate a relative study day (Rel Day). The relative study day will be calculated as the number of days from the day of first dose. The day of the first dose date is Day 1. The preceding day is Day -1, the day before that is Day -2, etc. There is no Day 0.

Actual study periods will be defined as follows for the purposes of the efficacy evaluations:

- Screening/Baseline Period (Rel Days -14 through Day -1): For the average weekly CSBMs, average weekly SBMs, average weekly stool consistency, average weekly straining score, and average weekly abdominal symptom score (pain, discomfort, bloating, cramping, and fullness), the most recent 7 days will be used to calculate Week -1 values (i.e., days -1 through -7) and remaining days will be used for Week -2 calculations (i.e., day -8 through -14 or more if applicable). The baseline for these variables will then be based on the average of the week -2 and week -1 values. While the screening period may vary somewhat from 14 days, it will generally be required that subjects provide two weekly ratings of the weekly IVRS diary questions during this period.

- Treatment Period:
    - Week 1 (Rel Day 1-7)
    - Week 2 (Rel Day 8-14),
    - Week 3 (Rel Day 15-21),
    - Week 4 (Rel Day 22-28),
    - Week 5 (Rel Day 29-35),
    - Week 6 (Rel Day 36-42),
    - Week 7 (Rel Day 43-49),
    - Week 8 (Rel Day 50-56),
    - Week 9 (Rel Day 57-63),
    - Week 10 (Rel Day 64-70),
    - Week 11 (Rel Day 70-77),
    - Week 12 (Rel Day 78-84), and
    - Week 13 through Week 26 (Rel Day 85-183 divided by 7 day weeks.

The week during which the day of the last dose occurs will be considered the last valid week during the 26-week treatment period, assuming it contains at least 4 valid daily IVRS diary days. Otherwise, the last valid week will be the preceding week. The last valid week during the treatment period will be used as the endpoint week for weekly efficacy summaries. If the last valid week is before week 12, the week 12 endpoint and week 26 endpoint will use this week. If the last valid week is after week 12, the week 12 endpoint will use week 12 and week 26 endpoint will use the last valid week obtained after week 12.

Only data captured from the first dose until the last dose will be used to derive the weeks during the 26-week treatment period,

All data listings will contain a relative study day, regardless of whether the data was collected via IVRS diary or eCRF.

3.6 Statistical Analyses

Summary tabulations will be presented that will display descriptive statistics for each treatment group. The number of observations, mean, standard deviation, minimum, median, and maximum values will be displayed for continuous variables, and the number and percent of subjects per category will be displayed for categorical data. For subject disposition,

demographic and baseline characteristics, medical history, gastrointestinal disease history, and prior medications, an overall column (i.e., all subjects combined) will be included.

Statistical analyses will be performed at the two-sided significance level of 0.050 according to the testing procedure described below. The testing procedure will preserve the experiment wise Type I error rate at 5%. All secondary p-values will be considered descriptive.

3.6.1 Subject Disposition

Subject disposition information will be summarized by treatment group and overall. The number and percent of subjects who are randomized, who took a dose of study drug, who complete the study, and who withdraw early from the study will be presented. The primary reason for early withdrawal will also be tabulated. The number of subjects randomized will be used as the denominator for the percentage calculation. Subject disposition, inclusion / exclusion criteria, and protocol deviations will be listed.

The number and percent of subjects in each analysis set will also be tabulated.

3.6.2 Demographic and Background Characteristics

The treatment groups will be descriptively assessed for comparability of demographic and baseline characteristics. Variables included in this assessment will be the demographic characteristics of age at informed consent (years), gender, race, ethnicity, body weight (kg), and BMI (kg/m^2). These variables will be summarized for each treatment group and overall. Screening values (week -1, week -2) and baseline values (average of week -1 and week -2) for average weekly CSBMs, average weekly SBMs, average weekly stool consistency, average weekly straining score, and average weekly abdominal symptoms of pain, discomfort, bloating, fullness, and cramping will also be summarized for each treatment group.

Weekly ratings of IBS severity and constipation severity will also be summarized for each of the 2 weeks of the screening period. Both categorical and continuous descriptive statistics will be used for the weekly ratings.

Medical history and gastrointestinal (GI) history will be summarized for the number and percentage of subjects for each body system by treatment group and overall. Medical history includes verbatim terms recorded for the subjects. GI history includes duration (years) since IBS symptoms began before randomization, duration (months) since last colonoscopy before randomization, and whether colonoscopy findings are not significant. A summary table will be presented for each analysis set. Medical and GI history will also be listed.

3.6.3 Prior/Concomitant Medication

All prior and concomitant medications administered during the study will be coded using the latest available version of the World Health Organization (WHO) Drug Reference List. Prior medications include medications that were started and stopped prior to the first dose of study drug. Concomitant medications include medications that started any time and were taken at any time after the first dose of study drug until the end of the treatment period. Medications

missing both start and stop dates or having a start date prior to the start of study drug and missing stop date will be counted as concomitant.

The number and percentage of subjects taking prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class and preferred name by treatment group. Prior medications will also be summarized overall. If a subject took a particular coded medication more than once, the subject will be counted once for that coded medication total. If a subject had more than one coded medication in a therapeutic class, the subject will be counted only once in that therapeutic class total. Summary tables will be presented for each of the analysis sets. Prior medications will be summarized separately from concomitant medications.

A listing of all medications including the reported term, preferred name, ATC class, start and stop dates, and other relevant data will be provided.

3.6.4 Study Drug Exposure and Compliance

Days of exposure to randomized study drug will be summarized with descriptive statistics by treatment group for each of the analysis sets. In addition, a contingency table will be provided to display the number and percentage of subjects in each treatment group with exposure in the following categories: ≤2 weeks, >2 to ≤4 weeks, >4 to ≤8 weeks, >8 to ≤12 weeks, >12 to ≤16 weeks, >16 to ≤20 weeks, and >20 to ≤26 weeks.

Days of possible exposure is defined as:

date of last dose of study drug – date of first dose of study drug + 1.

When the last known dose date is missing, the last known clinic visit date during the treatment period will be used, and the plus 1 will be removed from the calculation.

The percent compliance to study drug will be calculated as the total number of tablets dispensed minus the total number of tablets returned divided by two times the number of days during the treatment period, then multiplied by 100.

Summary statistics will be presented for percent compliance to study drug by treatment group. The count and percentage of subjects with overall compliance <80%, 80%-100%, 100%-120% and >120% will also be tabulated by treatment group.

3.7 Statistical Analyses

Summary tabulations will be presented that will display descriptive statistics for each treatment group. For subject disposition, demographic and baseline characteristics, medical history, gastrointestinal disease history, and prior medications, an overall column (i.e., all subjects combined) will be included. For continuous variables, descriptive statistics will include the number of subjects, mean, standard deviation, minimum, median, and maximum values. For categorical variables, descriptive statistics will include the number and percent of subjects in each category.

3.7.1 Efficacy Analyses

The primary objective of this study will be to demonstrate the superiority of tenapanor over placebo in the proportion of subjects who are weekly overall responders at 6 or more of the first 12 weeks of treatment.

The ITT analysis set will be used for the analysis of the primary, key secondary, secondary, and all sensitivity analyses. The PP analysis set will be used for the analysis of the primary, key secondary, and secondary variables as a separate sensitivity analysis. All efficacy analyses will be carried out based on observed cases (OC) with imputation as described previously in Section 3.3.

All efficacy variables involving responder rates or proportions will be analyzed using a Cochran-Mantel-Haenszel (CMH) test with pooled investigator site as a stratification (adjustment) variable. These analyses include subject based variables and variables summarized weekly. Summary statistics will include the pairwise risk difference with placebo along with the asymptotic 95% confidence interval (CI). The adjusted relative risk (adjusted for pooled investigator site) will be based on the ratio of responder rates for tenapanor 50 mg BID versus placebo. The 95% CI versus placebo will also be presented for the adjusted relative risk.

All change from baseline or percent change from baseline continuous efficacy variables derived from the daily IVRS questions (i.e., average weekly CSBMs, SBMs, stool consistency, straining score, abdominal symptoms of pain, discomfort, bloating, fullness, and cramping), as well as the weekly IBS severity, constipation severity, and IBS QOL will be analyzed using an analysis of covariance (ANCOVA) model with terms for pooled investigator site, treatment, and baseline as the covariate. These analyses include variables summarized weekly or on a visit basis.

Actual values for degree of relief of IBS symptoms and treatment satisfaction will be analyzed using an analysis of variance (ANOVA) model with terms for pooled investigator site and treatment.

When the ANCOVA model is implemented, the least square means (LSmeans) will be presented for the actual values and change/percent change from baseline values for each treatment group with the 95% CI. Statistical testing will only be carried out using the change/percent change from baseline since the p-values are the same between the two analyses. Treatment effects will be evaluated based on a 2-sided significance level of 0.050 for the difference in LSmeans between treatment groups. The 95% CI for difference in LSmeans will also be presented. When the ANOVA model is implemented, all of the above statistics will be presented for the actual values.

The Mantel-Fleiss criterion for the CMH test will not be computed. Because the sample size of the two treatment groups is relatively large, the CMH test will be valid. Other secondary analyses using the ANCOVA model or ANOVA model will also not have assumptions testing (e.g., normality, parallelism, or homogeneity of variances) carried out.

A sequential testing procedure will be utilized to control the experiment wise Type I error rate for the primary efficacy variable. Because of the desire to also pre-specify key secondary efficacy variables, the sequential testing procedure will not inflate the overall 5% level. The primary efficacy variable will be tested at the 5% level of significance. If this test is significant, the first key secondary efficacy variable listed in Table 2-1 will be tested at the 5% level. If this test is significant, then the next key secondary efficacy variable is tested at the 5% level. This procedure continues until one of the key secondary variables in the list (8 total variables) results in a p-value >5%. Key secondary efficacy variables up to this point in the list will be declared statistically significant.

In addition to the summaries of the efficacy variables described, figures will be provided depicting the actual means or the change/percent change from baseline for each treatment group at each assessment time. Figures depicting the means for each treatment group over time will be presented for average weekly CSBMs, SBMs, stool consistency, straining score, abdominal pain, discomfort, bloating, cramping, and fullness scores. Figures depicting the means for each treatment group over time will be presented for weekly IBS severity score, constipation severity score, adequate relief of IBS symptoms, and degree of relief of IBS symptoms.

A secondary analysis will also include graphs depicting the cumulative distribution of the percentage reduction from baseline in abdominal pain.

3.8 Safety Analyses

Safety assessments will be based on the incidence, severity, and type of adverse events, and clinically significant changes in the subject's clinical laboratory tests, vital signs, ECGs, and physical examinations.

3.8.1 Adverse Events

Adverse events will be coded using the MedDRA adverse event coding system for purposes of summarization. All adverse events reported will be listed in the data listings. Treatment emergent adverse events (TEAEs) will be tabulated. A treatment-emergent AE (TEAE) is any AE that starts on or after the first dose of study drug through the end of the treatment period or any event that is considered drug related regardless of the start date, or any event which occurs prior to the first dose of study drug and worsens in severity after the first dose of study drug. An AE is considered drug related if it is possibly related or probably related to study drug.

TEAEs will also be tabulated by whether events are considered related to treatment and by severe severity. Serious adverse events and TEAEs resulting in study discontinuation will be tabulated.

Summarization of AEs will include subject incidence of the following:

- All TEAEs
- Drug-related TEAEs

- Severe TEAEs
- Severe and drug-related TEAEs
- Serious Adverse Events (SAEs)
- Drug-related SAEs
- Death due to AEs
- TEAEs leading to study drug discontinuation
- Drug-related TEAEs leading to study drug discontinuation

An overall summary table will contain the number and percentage of subjects ever having one of the above listed subsets of AEs. All TEAEs will be summarized for each treatment group by MedDRA system organ class (SOC), by SOC and preferred term (PT), and by PT with the number and percentage of subjects. If a subject has more than 1 occurrence of the same TEAE, he/she will be counted only once within that preferred term and system organ class in the summary tables. The most severe occurrence of a repeat TEAE, as well as the most extreme relationship of the TEAE to the study drug will be used for the analyses.

TEAEs related to study drug, severe TEAEs, serious adverse events (SAEs), and TEAEs leading to study drug discontinuation will be summarized in the same manner. That is, summaries will be provided for the numbers and percentages of subjects by SOC, SOC and PT, and PT.

All AEs will be included in by-subject listings. Specific by-subject listings of SAEs and TEAEs leading to study drug discontinuation will be provided. The number of days between first dose and when the event occurred will be presented in listings as well (i.e., relative study day), as will duration of the AE.

3.8.2 Clinical Laboratory Tests

The list of clinical laboratory tests collected for this study are presented in Appendix C of the protocol. Serum chemistry, hematology, and urinalysis results will be summarized with descriptive statistics at Screening (Visit 1/Day -14), Week 4 (Visit 4/Day 29), Week 12 (Visit 6/Day 85), and Week 26 (Visit 9/Day 183) by treatment group. For continuous tests, actual values and change from screening will be summarized. For categorical tests, the number and percentage of subjects in each category will be presented for each visit. Serum chemistry tests included in these summaries will be albumin, alkaline phosphatase, ALT, AST, bicarb/CO_2, total bilirubin, direct bilirubin, indirect bilirubin, calcium, chloride, total cholesterol, creatinine, glucose, inorganic phosphorous, LDH, potassium, total protein, sodium, triglycerides, BUN/urea, and uric acid. Hematology tests included in these summaries will be WBC, RBC, MCV, MCH, MCHC, hemoglobin, hematocrit, and platelet count. Differentials consisting of bands, monophils, neutrophils, eosinophils, lymphocytes, and basophils will be included in the listings only. Urinalysis tests included in these summaries will be appearance, specific gravity, and pH. Protein, glucose, ketones, blood, nitrite, and microscopic results will be presented in listings only.

The frequency of clinically significant abnormal laboratory test values will be tabulated by treatment group.

Shift tables classifying normal range results (low out of normal range, normal, or high out of normal range) between Screening and Week 4 (Visit 4/Day 29), Week 12 (Visit 6/Day 85), and Week 26 (Visit 9/Day 183) values will be tabulated by treatment group. Missing results for each pairwise summary will be tabulated.

Data listings of clinical laboratory tests will include flags for abnormal results.

3.8.3 Vital Signs and 12-lead Electrocardiogram

Vital signs (body weight, BMI, heart rate, respiratory rate, mean sitting systolic blood pressure, mean sitting diastolic blood pressure, and temperature) will be summarized descriptively for actual values and change from baseline values by treatment group and visit. Vital signs are collected at all study visits during the screening period and treatment period. Baseline for the vital signs will be the average of results obtained during the screening period.

Electrocardiogram results (heart rate, PR interval, QRS duration, QT, QTcB and QTcF intervals) will be summarized descriptively for actual values and change from screening values by treatment group and visit (Screening (Visit 1/Day -14), Week 12 (Visit 6/Day 85), and Week 26 (Visit 9/Day 183)). The overall interpretation will be summarized with number of subjects and percentages for the normal and abnormal ECG result categories.

All vital signs and electrocardiogram results will be listed. Abnormal or clinically significant results will be flagged.

3.8.4 Physical Examination

Physical examinations (general appearance, HEENT, respiratory, cardiovascular, abdomen, skin, lymph nodes, musculoskeletal, extremities, and neurological) are collected at Screening (Visit 1/Day -14), and Week 26 (Visit 9/Day 183). The number and percentage of subjects in each category will be presented for each visit by treatment group.

All physical examination results will be listed. Abnormal physical exam results will be flagged.

4. PROGRAMMING SPECIFICATIONS

The programming specifications, including the mock-up validity listings, list of analysis tables, figures, and data listings, will be prepared in a stand-alone document. The programming specification document will be finalized prior to database lock.

A QUALITY OF LIFE MEASURE FOR PERSONS WITH IRRITABLE BOWEL SYNDROME (IBS-QOL)

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June 1997

User's Manual and Scoring Diskette

U.S. Version

University of Washington
Seattle, Washington
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Emblem...Soul Catcher: a Northwest Coast Indian symbol of physical and mental well-being. Artist: Marvin Oliver

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PURPOSE OF THIS MANUAL

The purpose of this manual is to facilitate instrument administration, scoring, and interpretation of the United States version of the Irritable Bowel Syndrome Quality-of-Life Instrument. This manual is specific to the U.S. version of the IBS-QOL instrument.

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The views expressed in this manual are the authors' own and do not necessarily represent the opinions of the other investigators participating in the project nor the views or policy of the Novartis Corporation.

USER AGREEMENT

The University of Washington, the University of North Carolina, and Novartis Pharmaceuticals jointly hold the copyright to the IBS-QOL and one of these copyright holders must be notified in writing prior to using the instrument. Permission to use the instrument in any pharmaceutical-related project must be requested and granted in writing from Novartis Pharmaceuticals.

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SUMMARY

How irritable bowel syndrome and its treatment affect quality of life is important to patients and their significant others, clinicians, researchers, and administrators of health care systems. The overall objective of this project is to develop a quality-of-life measure specific to irritable bowel syndrome (IBS-QOL) that is grounded in the experience of persons with the syndrome and that meets criteria for use in epidemiologic investigations and clinical trials. To date, the psychometric properties of the instrument have been tested at a point in time only, permitting evaluation of the IBS-QOL to discriminate among known groups and to test the measurement model, internal consistency, reproducibility, construct validity, interpretability and burden. Later studies will permit investigation of the responsiveness of the measure and calculation of effect sizes for clinical trial use

Instruments were sought using a conceptual model of the components of health-related quality of life that includes symptoms, functional status, perceived quality of life, and disability. No measure of perceived quality of life specific to IBS was found and thus instrument development proceeded for the IBS-QOL. Finally, because the measure is intended for international use, cultural adaptation of the IBS-QOL was sought prior to the test of the cross-sectional psychometric properties of the instrument in the United States.

Qualitative interviews were conducted with persons who were diagnosed with irritable bowel syndrome using the Rome criteria. Clinicians in the U.S. and Europe were also interviewed to elicit an item pool consisting of 117 items describing the subjective effects of IBS and its treatment. This item pool was reduced through cognitive debriefing with an additional sample of persons with IBS and investigator review of each potential item. Cultural adaptation for European versions was achieved through interviews with patients in European countries, forward and back translation, and harmonization. These steps produced a 41-item version for testing in the U.S.

Psychometric properties were evaluated with 156 persons with IBS, involving two administrations with 89 persons and comparison with generic health status and psychologic instruments. Persons with IBS were recruited from advertisements in local newspapers and consulters in outpatient clinics in Seattle, Washington and Chapel Hill\Durham, North Carolina.

The final IBS-QOL consists of 34 items that produce an overall score and eight subscale scores including Dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, and relationships.

The IBS-QOL demonstrated high internal consistency (Cronbach's alpha= 0.95) and high reproducibility (ICC=0.86) with average time of 7 days (SD 1). For discriminant validity: number of symptoms ($p<.05$), self-reported severity of symptoms ($p<.001$), and a validated severity measure for IBS, FBDSI ($p<.001$) significantly predicted IBS-QOL scores. Convergent validity analyses confirmed predictions that scores are more closely related to overall well-being (PGWB) than function (SF-36). The IBS-QOL correlated strongly with total well-being (.45), health worry and concern (.45), and behavioral and emotional control (.41), and less strongly

with physical functioning (.36) and vitality (.30). A lower correlation of -.22 was observed between the IBS-QOL and FBDSI.

The original U.S. version of the IBS -QOL has high content validity, meets established psychometric criteria for reliability and cross-sectional validity, and is translated into five languages. Testing of its responsiveness is warranted in future studies.

BACKGROUND AND SIGNIFICANCE

Quality of Life in Persons with Irritable Bowel Syndrome

Irritable Bowel Syndrome (IBS) is a gastrointestinal disorder that manifests itself as chronic or recurrent symptoms of abdominal pain associated with disturbed bowel function, i.e., diarrhea and/or constipation and/or symptoms of bloatedness and distension. Symptoms consistent with the diagnosis of IBS vary from 9-22% in the population and tend to vary in frequency depending on the criteria used [1]. Like many functional disorders, IBS may be influenced by a variety of cultural, social environmental and behavioral factors. Diet, hormonal influences (e.g., menses), psychologic stress and activity level may exacerbate IBS symptoms [2].

Irritable bowel syndrome is a common disorder that can be associated with significant disability and health care costs [3]. Despite its prevalence in the population, understanding of the disorder and management of persons with the disorder has been difficult, in part because of a lack of precise definition and conflicting views of the pathophysiology of the condition. IBS is now believed to result from dysregulation of intestinal motor, sensory, and CNS function. Symptoms arise from both disturbances in intestinal motility and enhanced visceral sensitivity. Psychosocial processes play a role in the disorder, although are not part of the irritable bowel *per se*, since they influence illness recognition, use of services and treatments, and response to treatments, pharmacologic and non-pharmacologic.

To improve the recognition and diagnosis, international working teams of experts, using a consensus approach, have developed a classification system known as the "Rome" criteria for 24 functional gastrointestinal disorders [4]. The irritable bowel syndrome was defined as a "combination of chronic or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities" which is "attributed to the intestines and associated with symptoms of pain and disturbed defecation and/or symptoms of bloatedness and distension". Thus, IBS can present with a constellation of symptoms that can be characterized by the layperson as abdominal pain, diarrhea, constipation, or a mixture of both.

As scientific attention focuses increasingly on the understanding of and care for persons with IBS, concomitant interest arises in exploring how the disorder and its treatment influence health-related quality of life (HRQoL) of patients. Given the lack of clearly-identified structural and biochemical bases for IBS, quality of life concerns are extremely important to the understanding of how biology intermingles with the cultural, social, interpersonal, and psychological aspects.

Reviews of the concepts contained in existing generic and gastrointestinal-specific measures of HRQoL and reports from focus groups with patients with IBS indicated, however, that no measure was currently available that addressed their specific concerns. Furthermore, no measures were organized according to a formal conceptual structure for assessing quality of life for persons with IBS. Because of these concerns, we developed and validated the Irritable Bowel Syndrome Quality of Life (IBS-QOL) instrument [5].

CONCEPTUAL MODEL AND APPROACH TO THE IBS-QOL

Conceptual Model of Quality of Life

The IBS-QOL instrument was constructed using a conceptual model of health-related quality of life proposed by Patrick and Erickson [6] that distinguishes symptoms, functional status, perceived quality of life and social disability as components. In this multidimensional approach, assessment of disease and treatment outcomes may include measures of all these concepts and their relationships. Where possible, existing measures are preferable to the time and other resources necessary to create and validate instruments. Although a number of clinical assessment tools exist for IBS and numerous generic functional status measures are available, no measure specific to IBS was available that included self-reported measures of symptom frequency and bothersomeness as well as perceived quality of life. While construction of symptom frequency and bothersomeness measures involve clinical consensus of items to include, the definition and assessment of perceived quality of life is grounded in the persons with the disorder and instrument development must involve these persons as closely as possible.

Perceived quality of life is defined according to a needs-based model [7] that identifies quality of life as the degree to which most or all human needs are met. This approach is similar to that developed by the World Health Organization in the cross-cultural development of a generic quality-of-life measure [8]. The WHOQOL group defined quality of life as *individuals' perceptions of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns* [9]. The IBS-QOL was conceived to be such a quality-of-life measure specific to persons with the symptom constellations of irritable bowel syndrome and including all the human concerns related to these symptoms.

Cultural Adaptation of the Instrument

Because we wanted the IBS-QOL to be available for eventual use in international clinical trials, we also utilized standardized steps in the development and validation of cross-cultural quality-of-life measures formulated at the University of Washington [10], [11], [12]. Thus, we embarked on a cultural adaptation of the instrument concurrent with its development and validation in the United States. The IBS-QOL has been adapted for use in the following language versions: UK English; Dutch; French; German; and Italian.

Prior to the final generation of items for the first draft of the IBS-QOL, the list of potential items were reviewed by QOL-translation specialists for obvious difficulties that would be encountered in the translation process. The final formulation of selected items was influenced by this early stage, as first step towards cross-cultural adaptation.

The next step involved, primary and secondary consultants in each country. In most cases, the primary consultants were quality-of-life experts and the secondary consultants were linguistic experts, thus combining diverse, yet relevant expertise. Both consultants produced forward translations of the IBS-QOL, the Rome criteria for IBS, and demographic information. The primary and secondary consultants then worked together to reconcile their forward

translations. The primary consultant presented the reconciled version to a group of eight individuals with irritable bowel syndrome selected according to the Rome Criteria. The purpose of this pretest was to ensure that people with IBS in that culture (1) found each question relevant in that culture; (2) identified items or questions that had not been elicited in the U.S., and (3) could understand each item. The adaptation culminated in a harmonization meeting in which all problems in conceptual and linguistic equivalence of items generated in the U.S. were discussed, suggestions for additional items from each culture were presented and discussed, and a final forward translation was prepared for all components of the IBS-QOL, symptom measures, demographic information, and data collection forms. A single back translation was prepared by an independent translator and all discrepancies were reconciled with the primary consultant. Final modifications were made in the U.S. version of the IBS-QOL before proceeding with the U.S. validation study.

Persons interested in the different language versions of the IBS-QOL should contact the following person for information on their availability:

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The IBS-QOL Instrument

The IBS-QOL consists of 34 items (see Appendix B) relating to symptoms of IBS. The IBS-QOL uses a 5-point Likert response scale to assess how much each item describes the respondent's feelings to a particular symptom: not at all, slightly, moderately, quite a bit, and extremely or a great deal. All 34 items are scored through simple, summative scaling to derive an overall total score and eight subscales including Dysphoria, Interference with activity, Body Image, Health worry, Food avoidance, Social Reaction, Sexual, and Relationships. To facilitate interpretation of scores, the summed total score is transformed to a 0-100 scale ranging from 0 (poor quality of life) to 100 (maximum quality of life). The IBS-QOL can be administered with the IBS Symptom Frequency and Bothersomeness Questionnaires contained in Appendix C.

PSYCHOMETRIC PROPERTIES OF THE IBS-QOL

Overview

Five consecutive steps were followed to develop and to conduct psychometric testing on the IBS-QOL: (1) establishment of a framework for assessment that identified components of a self-reported health and outcomes battery to contain measures of the symptoms of IBS, generic functional status and well-being, perceived quality of life specific to IBS, and work disability; (2) elicitation of QOL items specific to IBS in the United States; (3) evaluation of the cross-cultural conceptual and linguistic equivalence of symptoms and QOL items; (4) development and refinement of the draft IBS-QOL questionnaire; and (5) evaluation of the psychometric properties of the IBS-QOL in a formal validation study using other instruments for validation and comparison.

Early Development: Item Generation and Reduction

Items for the IBS-QOL measure were developed from literature review, interviews with clinicians in the United States and Europe, and in-depth interviews of 40 individuals at the Universities of Washington and North Carolina with three symptom constellations of IBS: constipation predominant, diarrhea predominant, and mixed constipation/diarrhea. These patients were identified and classified according to symptom constellation using the Rome Criteria (Appendix A).

Interviews began by asking patients how IBS affected their quality of life and continued with prompts and open-ended responses. Interviews were taped and transcribed to aid identification of statements considered important by respondents. This elicitation process produced 117 potential items describing *in the language of the participants* how IBS affected perceived quality of life, interfered with the attainment of personal goals, or kept persons with the condition from meeting their perceived needs. No items were copied from existing questionnaires. All items were reviewed by investigators for their potential ability to be translated into European languages, their relevance to the needs-based model and all persons with the condition, their potential ability to discriminate among different levels of IBS severity, their importance as rated by patients, and their potential ability to detect change over time.

For the initial item reduction phase, an additional 30 individuals participated in cognitive debriefing interviews to refine the measure. Items that did not apply to all persons with IBS, were not subjective perceptions related to identified needs, were less important to persons with the condition, and were not potentially able to be culturally adapted in European languages were eliminated. In cognitive debriefing, persons with the condition were asked to "think aloud" in responding to items, to address the meaning of their responses, to evaluate the format of the questions and response scales, and to address the relative importance of each item to overall quality of life.

Investigator review of all items, the cognitive debriefing with thirty persons with IBS, and the cultural adaptation process reduced the original 117 items to a 41-item pilot quality-of-life measure for the U.S. validation study.

Validation Study Sites, Recruitment, and Participation

Following a written protocol of standardized procedures, a multi-center, cross-sectional validation study was conducted by a multi-disciplinary team at the University of Washington in Seattle (UW) and the University of North Carolina at Chapel Hill (UNC). The study was approved by the Institutional Review Boards (IRBs) at both universities.

We set out to recruit 145 participants to participate in the study through GI practitioners and newspaper advertisement. We established a sampling quota by type of IBS symptom pattern as follows: 60 with constipation-predominant symptoms, 35 with diarrhea predominant symptoms, and 50 with mixed symptomatology. Enrollment criteria included persons who a) met the Rome Criteria diagnosis for IBS; b) had abdominal symptoms for at least 2 days each week; c) were age 18 to 65 years. We excluded persons unable to clearly understand the study procedures or questions posed to him or her; unable to complete the requirements of the study; and those with another medical condition that could explain bowel symptoms. This assessment was made by chart review or discussion with the referring physician by one of the authors at the University of North Carolina at Chapel Hill and by a gastroenterologist in Seattle, Washington.

Screening for IBS and Classification of IBS Symptom Pattern Types.

We used the symptom-based diagnostic Rome criteria for screening and subclassifying IBS patients into any of three symptom pattern types. Symptom pattern type was assessed by telephone at screening for entry into the study and by self-administration in the first questionnaire. The actual questions and algorithm for classification is contained in Appendix A.

Procedures and Measures

Most participants received the first survey by mail, although five participants self-administered the baseline questionnaire under supervision in the clinic at the University of North Carolina. Of the 156 participants, 89 were randomized to retest 14 days later and received the follow-up questionnaire in a sealed envelope with instructions on the outside for the day it was to be completed and with a postage paid return envelope. Follow-up telephone calls were made two days after the package was mailed and on the day the retest was to be completed.

The following measures, included in the baseline assessment, are described in the order of their appearance in the self-administered survey package:

IBS-QOL. Forty-one IBS-specific quality-of-life items (see Appendix B) were asked as descriptive statements using a recall period of the past month (30 days). A 5-point Likert response scale was used to assess how much the statement described the feelings of the respondent: not at all, slightly, moderately, quite a bit, and extremely or a great deal. All items were sum-scored to calculate total scores. To facilitate analysis and interpretation of scores, the summed scores were transformed to a 0-100 scale ranging from 0 (poor quality of life) to 100 (maximum quality of life). Transformation involved subtracting the lowest possible raw score from the actual raw score, dividing by possible raw score range, and multiplying by 100.

Symptom Frequency and Bothersomeness. A 13-item self-administered IBS symptom questionnaire based on symptoms from the Rome Criteria and others known to be associated with IBS was constructed for use in this study Appendix C. These items were generated by clinicians and researchers familiar with IBS and its treatment in both the United States and Europe. This followed similar methodology used in other HRQoL validation studies using symptom frequency and bothersomeness as a measure of perceived impairment [6], [13]. Symptom frequency was assessed on a 7-point response scale (0=Never, 1=Almost never, 2=Seldom, 3=Sometimes, 4=Often, 5=Almost always, 6=always). Respondents were asked how often they had any of the symptoms in the past month (30 days). Symptom bothersomeness was assessed on a 7-point response scale (0=Not bothersome to 6= Extremely bothersome). Possible scores on both measures range from 0-91. IBS symptom frequency and bothersomeness indexes were calculated by dividing total symptom scores by 13.

Functional Bowel Disorder Severity Index (FBDSI). This measure assesses illness severity in functional bowel disorders and has been used by clinicians to rate and to stratify patients by severity of illness [14]. The three components of this index are pain intensity, (0-100 visual analogue scale), diagnosis of chronic functional abdominal pain, and number of doctor visits in the previous six months. We developed a self-administered version of this clinician rating scale and used this as an assessment of severity in addition to the symptom frequency and bothersomeness measures. Consistent with the severity groupings previously reported [13] subjects having the FBDSI scores in the lowest quartile were considered to have mild severity (mild), those in the middle half, moderate severity (moderate), and those with the highest quartile scores, the greatest severity (severe).

Medical Outcome Study Short Form (SF-36). Generic functional status and well-being was assessed using the SF-36 questionnaire, a measure widely used in clinical practice and research, health care policy evaluations, and general population surveys [15]. This questionnaire produces a profile of eight domain scores, including physical functioning, physical role limitations, emotional role limitations, social functioning, bodily pain, general mental health, vitality, and general health perceptions. Two summary measures can be constructed to assess the physical and mental components. Each domain is scored from 0 (poor health) to 100 (optimal health).

Psychological General Well-Being Scale (PGWB). This 22-item measure of general psychological well-being was developed by [16] and can be scored as a total score or as six subscales of health worry and concern, positive well being, depressed mood, behavioral and emotional control, energy level, and tension and anxiety. Scores range from 0-100; higher scores indicate higher well-being.

The Symptom Check List (SCL90-R). This is a 90-item self-report questionnaire that identifies nine psychological symptom complexes and yields a global score as well as the nine subdomain scores of somatization, obsessive compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Mean scores range from 0-4, with higher scores indicating greater psychological distress [17].

Work-Loss Days. Questions were included to investigate if a participant was not working because of his or her bowel problems and the number of work-loss days in the past year he or she attributed to bowel problems.

Additional questions on the self-administered baseline survey included the following: Rome criteria, a self-rating of the severity of bowel problems on a 3-point response scale of mild, moderate, and severe; and questions on gender, age, education, marital status, race, and income of study participants. The survey completed at retest included the IBS-QOL, a global rating of change in quality of life over the last two weeks on a 15-point rating scale ranging from "a very great deal worse" to "a very great deal better". The retest questionnaire was printed on a different color of paper from the first to avoid any confusion and mistakes in mailing or data handling. Patients were paid $15 for each completed set of questionnaires returned.

Background characteristics of participants were described by frequency, mean, standard deviation, minimum and maximum values, percentages, and missing data. Other characteristics (i.e. gender, race, education level and working status) were described by the frequency and percentage of the response choices. Some of these characteristics were controlled for in further analyses where appropriate. The data from each site were first analyzed separately. Data for both sites were then pooled in analyses after it was found that the samples were statistically similar.

Psychometric Evaluation

The psychometric testing of the IBS-QOL was conducted using standardized procedures [18] and the instrument review criteria developed by the Scientific Advisory Committee of the Medical Outcomes Trust [19]. Because this was a cross-sectional validation study, no data are presented on change over time; this characteristic is being evaluated in the context of a clinical trial and longitudinal epidemiologic investigation.

Item reduction. Poorly performing items in an instrument adversely affect the scale's ability to discriminate between different groups of people (e.g., patients of different disease severity), as well as diminish its chances of detecting important changes that result from treatment. To identify problematic items, the following criteria were used: 1) ceiling effect of an item in which >50% of participants circled *Not at All*, and thus could not improve on the item; 2) an item that had >5% missing data, 3) an item measuring a different construct demonstrated by an item-to-total correlation <0.40, and 4) pairs of items that showed redundancy of measurement by an inter-item correlation >0.70. Items were removed if it was felt that this did not hurt the measure's content validity. Since this is an inherently subjective judgment, we used cognitive debriefing reports, item importance ranking and investigator opinion before eliminating any item.

Factor Analysis and Domain Structure of the IBS-QOL. Confirmatory factor analysis was used to identify a possible subscale structure for representing relationships among sets of many interrelated variables [20]. In this study, principal component factor analysis with orthogonal rotation (using the varimax method) was performed on the 34-item IBS-QOL to explore its domain structure. We expected the items to be grouped into distinct factors representing the different concepts being measured based on the correlation matrix of the items.

Internal Consistency Reliability. Cronbach's alpha was used to assess internal consistency reliability, (i.e. the association among items within domains and the overall measure). A high internal consistency suggests that the scale or subscales are measuring a single construct. A minimum correlation of 0.70 are necessary for group comparisons, but it is preferred to have alpha values above 0.90 for individual comparisons. Cronbach's alphas were computed for the IBS-QOL instrument using baseline data.

Reproducibility, or the extent to which the IBS-QOL yielded stable scores among respondents whose bowel problems did not change, was assessed by comparing the overall IBS-QOL score at baseline and one week later. Sixty percent of the patients within each group were randomly selected to be retested for reproducibility.

We used responses to the global rating of change question at retest (-1 or "about the same/hardly worse at all", 0 or "about the same", and +1 or "about the same/ hardly better at all") to identify respondents with stable bowel symptoms. We used the intraclass correlation coefficient (ICC) to evaluate reproducibility because it accounts for a lack of independence among measurements. We also evaluated reproducibility on respondents who indicated that their bowel symptoms had worsened or improved on the global rating of change (-2 to -7 or +2 to +7). We expected that as the level of change increased, the ICC on the IBS-QOL would go down.

Construct validity. Convergent and discriminant validity, types of construct validity, involve comparing logically related measures to see if they are correlated more strongly (convergent) or more weakly (discriminant) according to *a priori* expectations based on the content and theoretical relationships among constructs and their measures. If expectations are met, then construct validity is supported for the particular population evaluated. The PGWB, SF-36, and SCL90-R were used to assess convergent validity of the IBS-QOL. Strengths of association were tested by calculating Pearson's product moment correlation coefficients on measures collected at baseline. Based on previous correlations among psychologic measures in other HRQoL validation studies, a stronger correlation was considered to be 0.40 or above and a weaker correlation 0.39 or below.

By consensus of the developers, we predicted that the IBS-QOL overall score would show stronger correlations with social functioning, bodily pain, role physical and vitality subscales and a weaker correlation with the general health and mental health subscales of the SF-36. Overall, we expected higher correlations between the overall scores of the IBS-QOL and the PGWB and SCL-90R measures than the correlations with the SF-36 subscales. Furthermore, we hypothesized a stronger association between the positive well-being, depressed mood, tension and anxiety, health and worry concern and energy domains of the PGWB and the overall IBS-QOL score, with the remaining correlations indicating weaker associations. The overall IBS score was anticipated to show lower correlations with all subscales of the SCL-90R.

Known groups validity, another form of discriminant validity, was used to test the ability of the IBS-QOL to discriminate between groups varying on known characteristics independent of or distal to the QOL measure. We examined the distributions of the IBS symptom frequency and bothersomeness indices and used tertiles of the distribution to create three categories (mild, moderate and high) of symptom frequency and bothersomeness. We anticipated that IBS-QOL scores would worsen as symptom frequency and bothersomeness increased. Other severity

measures were also analyzed for known groups validity, including scores on the FBDSI, self-rating of severity, and number of IBS episodes in the past week. We expected inverse associations between the IBS-QOL and FBDSI and number of days in the past week with IBS symptoms. Similar to the symptom indices, we anticipated that IBS-QOL scores would be lower as the perceived rating of severity worsened from mild, moderate to severe. Associations between the IBS-QOL and work loss and number of medical appointments were also explored, although no explicit hypotheses were made. Discriminant validity was assessed using simple factorial analysis of variance (ANOVA). QOL was included as the dependent variable and the main effect separated into tertiles or quartiles if it was a continuous variable to enhance interpretability. Site, age, gender, and marital status were controlled for in these analyses.

Statistical analyses were performed using a commercial software package [20].

RESULTS

Sample Characteristics

Two hundred forty people either responded to advertisements or were approached at Gastroenterology clinics and practices and asked to participate. Of these 240, 169 (70%) were enrolled after fulfilling criteria for IBS and symptom pattern type. Seventy one people who responded to the advertisements were not enrolled for the following reasons: 31 of them did not meet the Rome Criteria for IBS; 13 people qualified for the study but their appropriate IBS-type cells were full; 15 people did not meet the age criteria; 8 people could not be reached by telephone for various reasons; and 4 people decided not to participate. Of the 169 persons recruited, 156 (92%) returned the self-administered questionnaire: 57 in Washington and 99 in North Carolina.

Women comprised 89% of the sample, 53% were married; and the average age was 39 (SD11.8). Eighty-six percent of the sample was white, and 78% had a university education. Median income was between $25,000 to $34,999. Recruitment source was varied with 36% coming from advertisements, 61% from medical centers, and 5% from community medical practice. At baseline, 22% reported symptoms consistent with constipation-predominant IBS, 19% with diarrhea-predominant, and 60% with mixed. Significant differences were observed between participants in North Carolina and Washington for recruitment source (significantly more from advertisements in Washington), age (Washington participants were significantly older), and marital status (significantly more persons had been divorced in Washington). These differences were adjusted for during analysis. No significant difference was seen by IBS type.

Item reduction and Domain Structure of the IBS-QOL

Seven items were eliminated from the 41-item questionnaire to arrive at the 34-item validated questionnaire. One item was eliminated because of its ceiling effect (item 41); 5 items were eliminated because of their redundancy (high inter-item correlation) with other items and 1 item was eliminated because of its low item-scale correlation. Other items were considered for elimination based on their psychometric performance but were kept in the scale because of their relative importance to patients with IBS.

An exploratory principal component factor analysis of this instrument identified a possible substructure of 8 factors, namely Dysphoria, Interference with activity, Body Image, Health worry, Food avoidance, Social Reaction, Sexual, and Relationships (See Appendix B). These were consistent with content of items with a few exceptions, and eigert-subscale structure of the measure was retained [5].

Scores on HRQoL Assessment Instruments

Table 1 shows the scores on the symptoms (Symptom Frequency and Bothersomeness Indices), generic functional status/well-being (SF-36), and IBS-specific quality-of-life (IBS-QOL) measures by age groups and gender (all ages combined). Although females reported more IBS symptoms and greater bothersomeness, no statistical differences were detected with the small number of male participants. No pattern by age or gender was detected for functional status and well-being. There were no significant differences in the IBS-QOL overall score by race, age, gender, education, marital status or income. The subscale results show that quality of life scores were higher in the younger age group than in the older group but these differences were not statistically significant. There was no difference in quality of life scores between male and female participants within subscale scores.

Table 1. HRQoL Scores by age and gender

HRQoL Measures	18-44 Yrs (n=110) Mean (SD)	45-65 Yrs (n=45) Mean (SD)	All Ages (n=155) Mean (SD)	Gender*** Male (n=17) Mean (SD)	Female (n=138) Mean SD)
IBS - Specific Quality of Life (IBS-QOL) **					
Overall	64.3 (18.0)	60.6 (19.4)	63.2 (18.5)	64.2 (17.4)	63.1 (18.6)
Dysphoria	64.0 (23.8)	61.0 (24.4)	63.1 (23.9)	60.7 (24.2)	63.4 (23.9)
Interference with Activity	65.5 (21.5)	57.3 (23.4)	63.1 (22.3)	56.1 (22.9)	64.0 (22.2)
Body Image	63.6 (24.1)	59.6 (24.6)	62.5 (24.3)	76.8 (21.5)	60.7 (24.1)
Health Worry	59.2 (24.6)	59.3 (24.9)	59.2 (24.6)	66.2 (20.5)	58.3 (25.0)
Food Avoidance	43.6 (26.9)	43.2 (26.4)	43.4 (26.7)	44.1 (24.1)	43.4 (27.0)
Social Reaction	69.1 (22.1)	70.3 (25.0)	69.4 (22.9)	71.7 (17.7)	69.2 (23.5)
Sexual	76.3 (23.7)	66.7 (34.9)	73.5 (27.6)	83.1 (22.5)	72.3 (28.0)
Relationships	74.2 (21.2)	67.6 (22.4)	72.3 (21.7)	71.1 (20.0)	72.5 (21.9)
Symptoms:					
Symptom Frequency Index*	42.6 (9.0)	41.1 (11.2)	42.2 (9.7)	36.7 (7.3)	42.9 (9.7)
Symptom Bothersomeness Index*	42.5 (11.7)	39.4 (12.9)	41.6 (12.1)	34.4 (10.7)	42.5 (12.0)
Generic functional status/well-being: SF-36**					
Physical Functioning	85.2 (19.2)	73.3 (25.7)	81.7 (21.9)	79.1 (22.0)	82.1 (21.9)
Role Physical	53.6 (39.8)	43.3 (41.8)	50.7 (40.5)	52.9 (44.1)	50.4 (40.2)
Role Emotional	49.4 (41.8)	50.4 (43.6)	49.7 (42.2)	45.1 (45.6)	50.2 (41.9)
Social Functioning	63.0 (21.8)	59.4 (23.1)	61.9 (22.1)	61.0 (22.1)	62.1 (22.2)
Bodily Pain	50.4 (18.2)	46.1 (21.4)	49.2 (19.2)	55.2 (19.0)	48.4 (19.2)
Mental Health	57.6 (19.1)	55.9 (18.8)	57.1 (18.9)	54.4 (22.2)	57.5 (18.6)
Vitality	37.9 (20.0)	36.9 (19.2)	37.6 (19.7)	39.4 (21.4)	37.4 (19.6)
General Health	58.3 (22.6)	52.4 (27.0)	56.6 (24.0)	52.3 (22.9)	57.1 (24.2)
Physical Component Summary	57.9 (17.7)	51.9 (22.0)	56.2 (19.2)	56.7 (20.7)	56.1 (19.1)
Mental Component Summary	53.1 (18.2)	50.5 (19.9)	52.4 (18.7)	50.4 (21.3)	52.6 (18.4)

***Higher values indicate worse HRQoL **Higher values indicate better HRQoL**
*****Includes all ages**

(Numbers for individual measures vary slightly because of missing data)

RELIABILITY

The overall IBS-QOL showed a high internal consistency reliability as indicated by a Cronbach's Alpha value of 0.95, indicating that the 34 items performed well together as a composite measure. Each of the identified subscales had a high alpha value (0.74-0.93) with the exception of Relationships (0.63). The internal reliability of the IBS-QOL (0.95) was comparable to the physical functioning of the SF-36 subscale (0.91) but higher than all the other subscales of the SF-36. The Symptom frequency measure had an alpha of 0.71 and the symptom bothersomeness measure had an alpha value of 0.74.

Reproducibility, as assessed with the intraclass correlation coefficient (ICC), was 0.86 for those participants who reported no change in their bowel problems. As expected, the ICC was lower for persons reporting change in their bowel problems. Within the subscales, ICC ranged from 0.76 (Food Avoidance) to 0.89 (Body Image) with the exception of Relationships (0.69). Similarly, ICC was lower for persons reporting change in the bowel problems within subscales. The average retest period was 7 days (SD 1).

Table 2. IBS-QOL Internal Consistency and Reproducibility Results

IBS-QOL	Cronbach's Alpha Coefficient (Time 1)	Intraclass Correlation Coefficient (ICC)
Overall Scale	0.95	0.86
Subscales:		
Dysphoria	0.92	0.89
Interference with Activity	0.84	0.88
Body Image	0.75	0.85
Health Worry	0.70	0.86
Food Avoidance	0.76	0.76
Social Reaction	0.74	0.84
Sexual	0.83	0.77
Relationships	0.65	0.69

CONSTRUCT VALIDITY

The convergent and discriminant validity results comparing the IBS-QOL overall score and the SF-36 subscales confirmed our predicted hypothesis of stronger or weaker correlations with the exceptions of role-physical, mental health, and vitality (Table 3). The strongest associations were with bodily pain (0.47) and social functioning (0.44). Construct validity predictions for the relationship between overall IBS-QOL and the PGWB were confirmed only for the total score and health worry and concerns, which we thought, would correlate more strongly. Again, energy and vitality correlations were lower than anticipated. No exceptionally strong correlations were observed (Table 3). IBS-QOL convergent and discriminant validity comparisons with the SCL-90R scores confirmed all but three of our predictions. Correlations were particularly stronger than predicted for the global score, somatization, and obsessive-compulsiveness subscales of the SCL-90R.

Table 3. Predicted vs. actual correlations between overall IBS-QOL and SF-36, PGWB, and SCL90-R.

		Predicted	IBS-QOL Actual	Confirmed (y/n)
SF-36	Physical Functioning	Weaker	.36	Yes
	Social Functioning	Stronger	.44	Yes
	Role Physical	Stronger	.40	Yes
	Role Emotional	Weaker	.31	Yes
	Mental Health	Weaker	.41	No
	Vitality	Stronger	.30	No
	Bodily Pain	Stronger	.47	Yes
	General Health	Weaker	.37	Yes
PGWB	Total Score	Stronger	.45	Yes
	Positive Well Being	Stronger	.37	No
	Health Worry Concern	Stronger	.45	Yes
	Depressed Mood	Stronger	.33	No
	Behavioral and Emotional Control	Weaker	.41	No
	Energy and Vitality	Stronger	.31	No
	Tension and Anxiety	Stronger	.37	No
SCL90-R	Global Score	Weaker	-.45	No
	Somatization	Weaker	-.44	No
	Obsessive Compulsiveness	Weaker	-.46	No
	Interpersonal Sensitivity	Weaker	-.35	Yes
	Depression	Weaker	-.37	Yes
	Anxiety	Weaker	-.39	Yes
	Hostility	Weaker	-.27	Yes
	Phobic Anxiety	Weaker	-.36	Yes
	Paranoid Ideation	Weaker	-.31	Yes
	Pyschoticism	Weaker	-.34	Yes

- Weaker Correlation: <.40
- Stronger Correlation: = >.40

KNOWN-GROUPS DISCRIMINANT VALIDITY

Table 4 compares the mean scores on the SF-36 and IBS-QOL for mild, moderate, and high IBS Symptom Frequency and Bothersomeness Index scores. Participants with lower frequency and bothersomeness of IBS symptoms reported higher functional status and well-being and higher quality of life. A similar pattern was seen with the subscales scores of the IBS-QOL.

Table 4. Comparison of high and low symptom frequency and bothersomeness reports and health-related quality of life (HRQoL) measures.

	Symptom Frequency Index			Symptom Bothersomeness Index		
HRQoL Measure*	Mild (n = 56)	Moderate (n = 49)	High (n = 48)	Mild (n = 51)	Moderate (n = 49)	High (n = 53)
IBS-Specific Quality of Life(IBS-QOL):						
Overall	69.7	64.6	55.0[a]	72.2	64.8	53.8[a]
Dysphoria	69.3	63.9	55.9[d]	71.9	63.0	55.5[b]
Interference with Activity	67.5	64.3	58.0[e]	70.7	64.4	55.7[b]
Body Image	72.0	64.3	50.3[a]	73.9	64.3	50.5[a]
Health Worry	68.5	62.4	46.2[a]	70.0	64.1	45.3[b]
Food Avoidance	48.1	42.7	39.6[f]	51.8	42.5	37.0[d]
Social reaction	77.6	68.2	61.5[b]	78.3	72.2	58.6[a]
Sexual	80.4	77.6	62.5[c]	84.1	77.3	60.9[a]
Relationships	77.4	76.5	62.9[b]	80.1	75.0	63.1[b]
General functional status/well-being: SF - 36						
Physical Functioning	85.5	87.8	71.8[a]	86.7	85.4	74.2[b]
Role Physical	54.9	56.6	41.2[f]	59.8	57.7	36.8[d]
Role Emotional	56.6	46.3	43.8[f]	58.2	47.6	42.1[f]
Social Functioning	69.2	64.5	50.8[a]	70.6	65.6	50.2[a]
Bodily Pain	57.0	51.5	39.0[a]	59.3	50.9	39.0[a]
Mental Health	63.1	58.4	49.1[b]	65.0	56.4	50.3[a]
Vitality	42.7	40.4	29.4[c]	44.7	37.0	31.8[c]
General Health	63.3	61.1	43.7[a]	61.8	59.5	48.5[d]
Physical Component Summary (PCS)	62.2	60.3	45.4[a]	63.9	59.3	46.3[a]
Mental Component Summary (MCS)	58.7	54.1	42.9[a]	60.1	52.8	44.2[a]

Values are means, and statistical tests are analysis of variance
*Higher values indicate better HRQoL
[a]p< = 0.0001, [b]p< = 0.001, [c]p< = 0.005, [d]p< = 0.01, [e]p< = 0.05, [f] not significant

As expected, the IBS-QOL total score was significantly different among severity groups (Table 5): among mild, moderate, and severe patients with regard to the FBDSI severity measure (p<.0001) and mild, moderate and severe self-ratings by participants (p<.001). The IBS-QOL did not discriminate, however, between the three symptom pattern types. Persons with

diarrhea-predominant symptoms reported the lowest overall quality of life. IBS-QOL scores were also not significantly different for number of episodes per week. A significant association was found between IBS-QOL and the number of visits to the doctor for IBS problems in the past 6 months ($p<.05$) and the number of missed work days in the past year. The trend was for IBS-QOL to be lower as number of visits increased and more work-loss days were reported.

Table 5. Discriminant Validity of IBS-QOL

Characteristic	(n=155)	IBS-QOL Mean (SD)
FBDSI[a]		
Mild		73.04 (16.44)
Moderate		64.25 (14.70)
Severe		50.86 (20.69)
Subjective Severity[b]		
Mild		79.53 (11.72)
Moderate		65.70 (16.01)
Severe		49.77 (17.66)
Type of IBS at Time 1[d]		
Constipation-predominant		61.20 (19.22)
Mixed		65.17 (18.04)
Diarrhea-predominant		58.68 (18.26)
Number of IBS Episodes per Week[d]		
0 to 2		65.18 (19.55)
3 to 5		65.55 (16.62)
6+		58.09 (19.76)
Medical visits in past 6 months[c]		
0 visits		65.60 (16.17)
1 visit		68.73 (15.79)
2 visits		55.52 (23.23)
3 visits		59.76 (20.17)
4 visits		61.56 (20.64)
5 or more visits		53.03 (20.80)
Missed work days in past year[c]		
0 day		68.86 (17.66)
1-2 days		68.63 (14.44)
3-5 days		67.55 (16.54)
6 or more days		54.62 (13.92)

[a]: $p<.0001$, [b]: $p<.001$, [c]: $p<.05$, [d]: not significant

Reproducibility of Symptom-Pattern Classification

A total of 148 patients (95%) were stable with regard to Rome Criteria for IBS, independent of symptom type between screening and time 1. Similarly, 82 patients (92%) of the 89 retest patients fulfilled Rome Criteria for IBS, unrelated to symptom type. Symptom types within Rome IBS overall category moved around. Of the 156 patients enrolled into the study, 108 (69%) remained stable from screening to baseline while 48 (31%) changed IBS types between screening and baseline. Twenty nine patients of those who changed (60%) switched from constipation-predominant to mixed IBS, 14 patients (29%) changed from diarrhea-predominant to mixed IBS, 4 patients (8%) switched from mixed to diarrhea IBS, and 1 patient (2%) changed from mixed to constipation-predominant IBS. Among the 89 patients randomized to retest, 50 (56%) patients remained stable from screening to retest, 27 patients (30%) who switched pattern at baseline did not change at retest, 9 patients (10%) who were stable at baseline switched IBS pattern at retest, while 3 patients (3%) switched type at baseline and switched back to their initial pattern at retest.

DISCUSSION

Within Gastroenterology, recent interest in the measurement of health related quality of life (HRQoL), and particularly with regard to the development of disease-specific questionnaires has occurred primarily for inflammatory bowel disease [21],[22]. However, there is a compelling need to accurately evaluate quality of life in the functional gastrointestinal (GI) disorders. In addition to being the most common of the GI disorders, recent studies now show that persons with functional GI disorders have major impairments in health status, and this has economic and health policy implications.

For example, a randomized national study of 5,430 householders showed that those with irritable bowel syndrome (9.2% of the sample) had significantly more work absenteeism (13.4 vs. 4.9 days; $p<0.0001$) and physician visits (5.52 vs. 1.86 visits/1 year; $p<0.0001$), than those without bowel symptoms, and the results were similar for those with other functional GI disorder.[23]. In addition, a recent cost analysis showed that community subjects with IBS spent $742 (median)/year for health care when compared to $429 for control subjects without bowel symptoms [24].

The health impact is even greater in clinical populations [25] using the SF-36, a generic measure of HRQoL, found that while persons with IBS had poorer physical and mental health than asymptomatic individuals, those with IBS who consulted physicians had poorer general health, vitality, physical role and social functioning than the non-consulters with IBS. In another recent study evaluating the health status of patients seen at a major medical [23] those with functional GI disorders reported significantly more pain, had poorer daily function (Sickness Impact Profile-SIP), greater psychological distress (SCL-90), made more physician visits and even had more surgeries than patients having structural diagnoses (e.g., inflammatory bowel disease, acid peptic disease, liver disease etc.). These studies support previous observations for IBS, that Psychosocial difficulties are greater in clinical populations [26], [27] and it highlights the value of having reliable and valid psychosocial assessment measures for studying clinical populations.

Clearly, there is a need to evaluate HRQoL for patients with functional GI disorders. However, biologic or physiologic standards to assess the severity of these conditions do not exist, and generic measures of HRQoL, such as the SF-36 or SIP may be insensitive and poorly responsive for use in treatment trials. For these reasons, we sought to develop, assess the psychometric properties and validate an IBS-specific quality of life measure that could be used in clinical trials and health status assessment.

This study demonstrates that the IBS-QOL is a highly reliable and valid self-administered questionnaire to assess the perceived quality-of-life for persons with IBS. The internal consistency of the overall IBS-QOL (0.95) exceeded the recommended cut-off of 0.70 for group comparisons and sufficient for individual comparison. The reproducibility over the two-week study period was excellent. Most of the expectations about how the IBS-QOL would perform in relation to other measures and with known groups were confirmed with a high degree of confidence. Specifically, the IBS-QOL scores were strongly correlated with other health status measures including the SF-36, a generic measure of functional status, the SCL-90, a measure of

psychological distress, a disease severity measure (FBDSI), and subjective ratings of severity, symptom frequency and bothersomeness, and the number of physician visits and days missed from work. The strong associations found attest to the construct validity of the IBS-QOL measure. Furthermore, the final items had face validity and cross-cultural relevance to the multinational panel of gastroenterologists involved in the study. The associations with a disease severity measure and a measure of symptom frequency and bothersomeness indicate that the IBS-QOL can augment this type of measure in clinical trials and epidemiologic investigations.

The IBS-QOL, specific to this condition, showed a low pattern of scores suggesting some impairment of quality of life. Within the subscales, lower scores were seen especially in interference with activity, food avoidance and health worry concern subscales of the IBS-QOL. This is consistent with clinical observations of patients having IBS. A study of 148 persons with IBS belonging to the IBS Network also found that IBS "affected all aspects of their lives: work, leisure, travel, and relationships" [28]. Another study [29] found that "high proportions of participants were affected in their social, sexual and working lives by IBS symptoms". Our results confirm the findings that IBS has a broad and significant impact on persons' quality of life.

A few other measures of health-related quality of life (HRQoL) have been developed for a variety of GI disorders [30] but do not capture the specific issues that relate to IBS. The IBS-QOL, constructed specifically for persons with IBS using a formal conceptual structure and multi-dimensional assessment, captures the concerns of patients with a high level of specificity and attribution to the bowel symptoms of IBS. It may also prove to be a more responsive measure of HRQoL for persons with IBS, that is one capable of detecting minimally important changes that can be attributed to treatment [18]. This measure is also currently available in four European countries.

Our study did not confirm that there are significant differences in HRQoL among the three symptom patterns of constipation-predominant, diarrhea-predominant, and mixed. In addition, the symptom pattern classification was not highly reproducible in that it changed considerably between screening and baseline. Thus, the concept of symptom pattern in IBS may not be viable, because symptoms shift and this alternating pattern is not stable enough for measuring a predominance of pattern or differences in the impact of different symptoms on HRQoL. We did demonstrate, however, that frequency and bothersomeness of IBS symptoms impacts on HRQoL. Assessment of symptoms and their impact continue to be important areas of investigation.

This study was cross-sectional, and thus cannot investigate responsiveness or identify what is a minimally important difference in the IBS-QOL. The measure is currently being used in a large clinical investigation of IBS and in preliminary clinical trials for drug development. Data from these studies will permit us to investigate this important property of the measure. The validity of the subscale structure will also be better investigated in a study with larger sample size more representative of persons in the population with IBS.

Since no physiologic measure is available for assessing IBS, the rigorous development of subjective, person reports of symptoms and HRQoL are important to the investigation and treatment of this disorder. It is increasingly important to apply these patient report measures in

clinical and community investigations of functional bowel disorders. The IBS-QOL will assist in these applications.

Obtaining Comparative Data

The cross-sectional design of this validation study restricts the generalization of its results. However, this study provides cross-sectional comparison data only on a sample of persons residing in Washington and North Carolina. Tables can be produced by age, gender, level of education, and other characteristics shown in the Demographic Questionnaire contained in Appendix D. upon request to the University of Washington and at the cost of production of these tables. Interpretation of effect sizes awaits longitudinal investigation of the IBS-QOL. The validity of the IBS-QOL was determined for IBS patients without regard to IBS type. We recommend similar usage since the shift in IBS type between pre and post survey was evident. Finally, We have proven the internal consistency of the subscale structure of IBS-QOL. The validity of the subscales will be tested in the longitudinal investigation of the IBS-QOL.

ADMINISTRATION GUIDELINES

The IBS-QOL- is contained in Appendix B.

The IBS-QOL was designed for self-administration, but can be interview-administered if necessary. The 34-item version takes approximately 10 minutes to complete. No specific training is required to complete this instrument since the instructions are self-explanatory. We encountered no problems in respondent completion of the IBS-QOL.

Interview administration requires additional time to complete the IBS-QOL, and is recommended only for persons who cannot self-administer. Because some of the questions are of a personal nature, self-administration is the preferred mode.

Additional factors that should be considered when administering the IBS-QOL include [31].

Participants should be instructed to complete the IBS-QOL in a quiet place away from the influence of others

Educational level should be considered before self-completion. This can be done by asking persons what grade level they have completed or by administering a short reading comprehension test. Persons with low literacy or diverse language skills should always be provided interview assistance.

Interviewers should be trained to not introduce bias. For example, interviewers should encourage respondents to provide one answer (response choice) for each question, and not to persuade participants to answer questions according to how the interviewer feels they should respond.

Interviewer Administration

Interviewers should be trained to minimize bias. For example, interviewers should encourage respondents to provide one answer or response for each questions, to keep a focus on the questions being asked, and to take the time they need to come to an answer. Interviewers can easily introduce bias if they give cues that would persuade participants to answer questions according to how the interviewer feels they should respond. These cues can range from obvious things like language formation to more subtle things like when a smile is given and when it is not.

As with any interviewer administered survey, the following guidelines should be taken into account:

- wear proper attire
- wear visible identification (picture, name, affiliation)
- give explanation of the project
- brief the respondent again on confidentiality
- give approximate time to administer

- **do not** express your own opinions
- maintain eye contact unless reading a long list
- gain the respondent's trust
- make questionnaire accessible to respondent's viewing
- avoid bias in vocal inflection, posture, and facial expression
- **do not** explain questions but respond to inquiries in words of question
- **do not** put words in respondent's mouth
- keep respondent on track
- use probes only when participant needs assistance
- record all comments –yours and the respondent
- record observations
- thank respondents for their time

When sitting down to begin, the interviewer should inform the respondent that there are no right or wrong answers, emphasizing that what is important is how they think and feel. The respondent should be made to feel comfortable enough to ask the interviewer to slow down, repeat a question, speed up, or stop so that he/she can have time to think. If appropriate, the respondent should have a copy of the questionnaire to follow along, regardless of their ability to read.

For long lists, the lead in questions should be repeated sporadically so the respondent does not lose track of the response choices. When about half way through the interview, the respondent should be cued to the time by encouragement that it is half done.

SCORING THE IBS-QOL

The IBS-QOL produces a quality-of-life profile for people with irritable bowel syndrome. It is possible to derive eight subscale scores as well as a single global score. Each item is taken to contribute equally to each subscale with each subscales containing the following items:

Table 6. Subscales

Subscales	IBS-QOL Items
Dysphoria (DY)	IBS01,IBS06,IBS07,IBS09,IBS10,IBS13,IBS16,IBS30
Interference with Activity (IN)	IBS03,IBS18,IBS19,IBS22,IBS27,IBS29,IBS31
Body Image (BI)	IBS05,IBS21,IBS25,IBS26
Health Worry (HW)	IBS04,IBS15,IBS32
Food Avoidance (FA)	IBS11,IBS23,IBS28
Social Reaction (SR)	IBS02,IBS14,IBS17,IBS34
Sexual (SX)	IBS12,IBS20
Relationships (RL)	IBS08,IBS24,IBS33
Overall (OV)	*All Items*

Subscales are scored through simple summative scaling. All items are negatively framed with the greatest response scale equaling the worst quality of life. When scored, all items are reversed so that the as IBS-QOL scores increase, quality of life increases. All final raw scores are transformed to a 0 to 100 scale using the following formula:

$$\text{Scale Score} = \frac{\text{the sum of the items} \; - \; \text{lowest possible score}}{\text{possible raw score range}} * 100$$

This transformation converts the lowest and highest possible scores to zero and 100, respectively. Scores between these values represent the percentage of the total possible score achieved. The IBS-QOL instrument and scoring programs have used this transformation to provide comparative data for interpretation.

Scoring Exercise and Test Dataset for the IBS-QOL

Because of the complexity of scoring the IBS-QOL, a computer diskette with the necessary code for scoring algorithms and a test dataset are included with the manual for use in computing IBS-QOL subscale summary scores and for checking the accuracy of computations.

The following files are included on the diskette:

- **ibsqol.dat** ASCII (fixed format) text file consisting of data from 100 administrations of the IBS-QOL.
- **ibsqoldl.sps** SPSS code to read the data from "ibsqol.dat" into SPSS.
- **ibsqol.sps** SPSS code containing scoring algorithms for obtaining subscale summary scores. A hard copy of this code can be seen in Appendix E.

The purpose of this scoring exercise is to help IBS-QOL users to evaluate results from each step in the process of calculating subscale scores of the instrument. A test dataset and SPSS code for scoring the IBS-QOL has been provided on a computer diskette in this packet. The test dataset, which is called "IBSQOL.DAT" on the diskette, contains data from 100 administrations of the IBS-QOL. The enclosed diskette also provides the user with the SPSS syntax that should be used to:

- import raw data into SPSS format *[IBSQOLDL.SPS*]
- derive the IBS-QOL subscale and overall scores *[IBSQOL.SPS]*

The SPSS code (called "IBSQOL.SPS") on the diskette begins by labeling all items, then recodes all items and checks for out-of-range values. The eight subscales and the overall score are computed, transformed, and labeled. The syntax can be seen in Appendix E).

The following table presents statistics for the transformed scores for the IBS-QOL. After scoring the test dataset, the means, standard deviations, and minimum and maximum observed values should agree with the values seen here.

Table 7. Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
DYSPHORIA SCORE (8 ITEM-TRANSFORMED)	100	.00	93.75	33.8125	22.7238
INTERFERENCE WITH ACTIVITY SCORE (7 ITEM-TRANSFORMED)	100	.00	96.43	34.7143	20.6950
BODY IMAGE SCORE (4 ITEM-TRANSFORMED)	100	.00	87.50	33.5000	22.5350
HEALTH WORRY SCORE (3 ITEM-TRANSFORMED)	100	.00	91.67	38.9167	23.8676
FOOD AVOIDANCE SCORE (3 ITEM-TRANSFORMED)	100	.00	100.00	42.2500	21.8804
SOCIAL REACTION SCORE (4 ITEM-TRANSFORMED)	100	.00	75.00	28.3750	19.8721
SEXUAL SCORE (2 ITEM-TRANSFORMED)	98	.00	87.50	21.3010	22.7895
RELATIONSHIPS SCORE (3 ITEM-TRANSFORMED)	100	.00	83.33	36.0000	20.3739
OVERALL SCORE (34 ITEM-TRANSFORMED)	98	4.41	81.62	33.7785	16.4751
Valid N (listwise)	98				

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APPENDIX A

Screening Questionnaire based on Rome Criteria and Algorithm for Classification of IBS by Type

Screening Questions

Q1. For at least six months, have you had continuous or repeated discomfort or pain in your lower abdomen?

1 YES 2 NO (*if no, skip to Q5)*

Q2. Is this discomfort or pain relieved by a bowel movement?

1 YES 2 NO

Q3. Is this discomfort or pain associated with a change in the frequency of bowel movements, that is, having more or fewer bowel movements?

1 YES 2 NO

Q4. Is this discomfort or pain associated with a change in consistency of the stool, that is, softer or harder?

1 YES 2 NO

Q5. Would you say that at least one fourth (1/4) of the occasions or days in the last three months you have had any of the following? 1YES 2NO

A. Fewer than three bowel movements **a week** (0-2)
B. More than three bowel movements **a day** (4 or more)
C. Hard or lumpy stools
D. Loose or watery stools
E. Straining during a bowel movement
F. Urgency, that is having to rush to the bathroom for a bowel movement
G. Feeling of incomplete bowel movement
H. Passing mucus (white material) during a bowel movement
I. Abdominal fullness, bloating or swelling

Q6. Have you had any of the above symptoms for at least two days out of each week?

1 YES 2 NO

Scoring Algorithm for Diagnosis of IBS

Q1=YES +

Q2=YES or Q3=YES or Q4=YES +
YES to two or more of the following:
Q5=A or B
Q5=C or D
Q5=E or F
Q5=G
Q5=H
Q5=I

Trial Classification of IBS Type

Constipation predominant (Type A): YES to Q5 A, C, and E and NO to Q5 B, D, and F

Diarrhea predominant (Type C): YES to Q5 B, D, and F and NO to Q5 A, C, and E

Mixed Constipation and Diarrhea (Type B): YES to two or more of Q5 A, C, E and two or more of Q% B, D, and F **or** YES to Q5 A or C or E and YES to Q5 B or D or F **or** response patterns that did not fulfill any of these criteria but YES to two or more of Q5 G, H, or I

APPENDIX B

Quality of Life in Persons with Irritable Bowel Syndrome (IBS-QOL)

PARTICIPANT ID:
SITE:

PLEASE WRITE IN
TODAY'S DATE: _____ _____ _____
DAY MONTH YEAR

PLEASE READ THIS CAREFULLY

ON THE FOLLOWING PAGES YOU WILL FIND STATEMENTS CONCERNING BOWEL PROBLEMS (IRRITABLE BOWEL SYNDROME) AND HOW THEY AFFECT YOU.

FOR EACH STATEMENT, PLEASE CHOOSE THE RESPONSE THAT APPLIES BEST TO YOU AND **CIRCLE** THE NUMBER OF YOUR RESPONSE.

IF YOU ARE UNSURE ABOUT HOW TO RESPOND TO A STATEMENT, PLEASE GIVE THE BEST RESPONSE YOU CAN. **THERE ARE NO RIGHT OR WRONG RESPONSES.**

YOUR RESPONSES WILL BE KEPT STRICTLY CONFIDENTIAL.

HOW DID YOU HEAR ABOUT THIS STUDY? *(CIRCLE ONE)*

1 ADVERTISEMENT
2 MEDICAL CENTERS
3 PRIMARY CARE PRACTICE
4 COMMUNITY GI SPECIALIST
5 OTHER (SPECIFY) _____

IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT:

SITE ADDRESS AND PHONE NUMBER TO BE PLACED HERE
(final US version to be used in clinical trials)

About How You Feel

Please think about your life over the **past month (30 days),** and look at the statements below. Each statement has five possible responses. For each statement, please circle the response that best describes your feelings..

Q1. I feel helpless because of my bowel problems. (*Please circle one number*)

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q2. I am embarrassed by the smell caused by my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q3. I am bothered by how much time I spend on the toilet. (*Please circle one number*)

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q4. I feel vulnerable to other illnesses because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q5. I feel fat because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q6. I feel like I'm losing control of my life because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q7. I feel my life is less enjoyable because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q8. I feel uncomfortable when I talk about my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q9. I feel depressed about my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q10. I feel isolated from others because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q11. I have to watch the amount of food I eat because of my bowel problems. *(Please circle one number*)

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q12. Because of my bowel problems, sexual activity is difficult for me. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q13. I feel angry that I have bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q14. I feel like I irritate others because of my bowel problems . *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q15. I worry that my bowel problems will get worse. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q16. I feel irritable because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q17. I worry that people think I exaggerate my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q18. I feel I get less done because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q19. I have to avoid stressful situations because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q20. My bowel problems reduce my sexual desire. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q21. My bowel problems limit what I can wear. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q22. I have to avoid strenuous activity because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q23. I have to watch the kind of food I eat because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q24. Because of my bowel problems, I have difficulty being around people I do not know well. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q25. I feel sluggish because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q26. I feel unclean because of my bowel problems. (*Please circle one number*)

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q27. Long trips are difficult for me because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q28. I feel frustrated that I cannot eat when I want because of my bowel problems. (*Please circle one number*)

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q29. It is important to be near a toilet because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q30. My life revolves around my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q31. I worry about losing control of my bowels. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q32. I fear that I won't be able to have a bowel movement. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q33. My bowel problems are affecting my closest relationships. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q34. I feel that no one understands my bowel problems. (*Please circle one number*)

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Items Arranged According to Subscales

Dysphoria

1. I feel helpless because of my bowel problems.
6. I feel like I'm losing control of my life because of my bowel problems.
7. I feel my life is less enjoyable because of my bowel problems.
9. I feel depressed about my bowel problems.
10. I feel isolated from others because of my bowel problems.
13. I feel angry that I have bowel problems.
16. I feel irritable because of my bowel problems.
30. My life revolves around my bowel problems.

Interference with activity:

3. I am bothered by how much time I spend on the toilet.
18. I feel I get less done because of my bowel problems.
19. I have to avoid stressful situations because of my bowel problems.
22. I have to avoid strenuous activity because of my bowel problems.
27. Long trips are difficult for me because of my bowel problems.
29. It is important to be near a toilet because of my bowel problems.
31. I worry about losing control of my bowels.

Body image:

5. I feel fat because of my bowel problems.
21. My bowel problems limit what I can wear.
25. I feel sluggish because of my bowel problems.
26. I feel unclean because of my bowel problems.

Health worry:

4. I feel vulnerable to other illnesses because of my bowel problems.
15. I worry that my bowel problems will get worse.
32. I fear that I won't be able to have a bowel movement.

Food avoidance:

11. I have to watch the amount of food I eat because of my bowel problems.
23. I have to watch the kind of food I eat because of my bowel problems.
28. I feel frustrated that I can not eat when I want because of my bowel problems.

Social reaction:

2. I am embarrassed by the smell caused by my bowel problems.
14. I feel like I irritate others because of my bowel problems.
17. I worry that people think I exaggerate my bowel problems.
34. I feel that no one understands my bowel problems.

Sexual:

12. Because of my bowel problems, sexual activity is difficult for me.
20. My bowel problems reduce my sexual desire.

Relationships:

8. I feel uncomfortable when I talk about my bowel problems.
24. Because of my bowel problems, I have difficulty being around people I do not know well.
33. My bowel problems are affecting my closest relationships.

Items Eliminated in Validation Study

I am worried that my bowel problems hide a more serious illness.
I feel responsible for bringing on my bowel problems.
I feel bad about myself because of my bowel problems.
I worry about not being able to get to the toilet on time.
I worry about my health in general because of my bowel problems.
It is difficult for me to control my weight because of my bowel problems.
I feel rejected because of my bowel problems.

APPENDIX C

IBS Symptom Frequency Questionnaire

How often in the **past month (30 days)** did you have any of the following symptoms? *(Please circle one number for each symptom)*

Symptoms	Never	Almost Never	Seldom	Sometimes	Often	Almost Always	Always
Abdominal discomfort, pain or cramps	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Hard or lumpy stools	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Loose or watery stools	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Straining during a bowel movement	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Urgency- having to rush to the toilet for a bowel movement	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Feeling of incomplete bowel movement	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Passing mucus (white material) during a bowel movement	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Abdominal fullness, bloating or swelling	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Passing gas	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Heartburn or chest pain	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Feeling full soon after starting a meal	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Passing urine more frequently	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Nausea	**0**	**1**	**2**	**3**	**4**	**5**	**6**

IBS Symptom Bothersomeness Questionnaire

On a 0 to 6 point scale, please rate the following symptoms according to how **bothersome** they were in the **past month (30 days)**. *(Please circle one number for each symptom*)

Symptoms	Not Bothersome	→	→	Somewhat Bothersome	→	→	Extremely Bothersome
Abdominal discomfort, pain or cramps	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Hard or lumpy stools	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Loose or watery stools	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Straining during a bowel movement	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Urgency- having to rush to the toilet for a bowel movement	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Feeling of incomplete bowel movement	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Passing mucus (white material) during a bowel movement	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Abdominal fullness, bloating or swelling	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Passing gas	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Heartburn or chest pain	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Feeling full soon after starting a meal	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Passing urine more frequently	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Nausea	**0**	**1**	**2**	**3**	**4**	**5**	**6**

APPENDIX D

Demographic Questions

About You

A1. What is your gender? *(Please circle one number)*

1 MALE
2 FEMALE

A2. When were you born? *(Please write the numbers on the lines provided)*

_____ / _____ / _____
MONTH **DAY** **YEAR**

A3. What is the highest level of education you have completed? *(Please circle one number)*

1 NONE, PRIMARY OR ELEMENTARY SCHOOL
2 SECONDARY OR HIGH SCHOOL
3 APPRENTICESHIP
4 UNIVERSITY OR NON-UNIVERSITY HIGHER EDUCATION
5 POSTGRADUATE DEGREE

A4. What is your current marital status? *(Please circle one number)*

1 MARRIED OR LIVING AS MARRIED
2 WIDOWED
3 SEPARATED
4 DIVORCED
5 NEVER MARRIED

A5. Please indicate the group that describes you best. *(Please circle one number)*

1 WHITE (NON-HISPANIC)
2 BLACK / AFRICAN-AMERICAN
3 AMERICAN INDIAN / ALASKAN NATIVE
4 ASIAN / PACIFIC ISLANDER
5 HISPANIC / LATINO
6 PLEASE SPECIFY _____

A6. Which of these income categories comes closest to the total yearly income for your household, from all sources? *(Please circle one number)*

1 UNDER $5,000
2 $5,000 TO $9,999
3 $10,000 TO $14,999
4 $15,000 TO $24,999
5 $25,000 TO $34,999
6 $35,000 TO $49,999
7 $50,000 TO $74,999
8 $75,000 AND OVER

(If all you know is your monthly income, please write it here) _____

APPENDIX E

SPSS Scoring Syntax from Diskette Labeled: IBS-QOL Instruments SPSS Scoring Diskette

IBS-QOL

FILENAME IN 'A:\IBSQOLDL.SPS';

```
DATA LIST
        FILE='a:\ibsqol.dat' FIXED RECORDS=1 Table /1 id 1-4 ibs01 5
        -5 ibs02 6-6 ibs03 7-7 ibs04 8-8 ibs05 9-9 ibs06 10-10 ibs07 11-11 ibs08 12-12
        ibs09 13-13 ibs10 14-14 ibs11 15-15 ibs12 16-16 ibs13 17-17 ibs14 18-18
        ibs15 19-19 ibs16 20-20 ibs17 21-21 ibs18 22-22 ibs19 23-23 ibs20 24-24
        ibs21 25-25 ibs22 26-26 ibs23 27-27 ibs24 28-28 ibs25 29-29 ibs26 30-30
        ibs27 31-31 ibs28 32-32 ibs29 33-33 ibs30 34-34 ibs31 35-35 ibs32 36-36
        ibs33 37-37 ibs34 38-38 .
EXECUTE.
```

FILENAME IN 'A:\IBSQOL.SPS';

```
* SYNTAX FILE USED TO SCORE THE IBS-QOL
* Filename="ibsqol.sps"
* Written in SPSS for Windows
* Last edited: 3/31/97
* Irritable Bowel Syndrome Quality Of Life Group, Seattle, Washington, USA
* This file creates 9 variables:
*     9 total 100-point scale transformed scores:
*        IBS_DY = DYSPHORIA SCORE (8 ITEM)
*        IBS_IN = INTERFERENCE WITH ACTIVITY SCORE (7 ITEM)
*        IBS_BI = BODY IMAGE SCORE (4 ITEM)
*        IBS_HW = HEALTH WORRY SCORE (3 ITEM)
*        IBS_FA = FOOD AVOIDANCE SCORE (3 ITEM)
*        IBS_SR = SOCIAL REACTION SCORE (4 ITEM)
*        IBS_SX = SEXUAL SCORE (2 ITEM)
*        IBS_RL = RELATIONSHIPS SCORE (3 ITEM)
*        IBS_OV = OVERALL SCORE (34 ITEM)
* Labeling all variables
VARIABLE LABELS
        IBS01 "I feel helpless"
        IBS02 "I am embarrassed by the smell"
        IBS03 "I am bothered by how much time I spend on the toilet"
        IBS04 "I feel vulnerable to other illnesses"
        IBS05 "I feel fat"
        IBS06 "I feel like I'm losing control of my life"
        IBS07 "I feel my life is less enjoyable"
        IBS08 "I feel uncomfortable when I talk about my bowel problems"
        IBS09 "I feel depressed about my bowel problems"
        IBS10 "I feel isolated from others"
        IBS11 "I have to watch the amount of food I eat"
        IBS12 "Sexual activity is difficult for me"
        IBS13 "I feel angry that I have bowel problems"
        IBS14 "I feel like I irritate others"
        IBS15 "I worry that my bowel problems will get worse"
        IBS16 "I feel irritable"
        IBS17 "I worry that people think I exaggerate about my bowel problems"
        IBS18 "I feel I get less done"
```

```
        IBS19 "I have to avoid stressful situations"
        IBS20 "My bowel problems reduce my sexual desire"
        IBS21 "My bowel problems limit what I can wear"
        IBS22 "I have to avoid strenuous activity"
        IBS23 "I have to watch the kind of food I eat"
        IBS24 "I have difficulty being around people I do not know well"
        IBS25 "I feel sluggish because of my bowel problems"
        IBS26 "I feel unclean because of my bowel problems"
        IBS27 "Long trips are difficult for me"
        IBS28 "I feel frustrated that I cannot eat when I want"
        IBS29 "It is important to be near a toilet"
        IBS30 "My life revolves around my bowel problems"
        IBS31 "I worry about losing control of my bowels"
        IBS32 "I fear that I won't be able to have a bowel movement"
        IBS33 "My bowel problems are affecting my closest relationships"
        IBS34 "I feel no one understands my bowel problems" .
EXECUTE .
* Re-coding all variables so low score equals worse quality of life
* Change out-of-range values to missing values
RECODE IBS01 IBS02 IBS03 IBS04 IBS05 IBS06 IBS07 IBS08 IBS09 IBS10 IBS11
    IBS12 IBS13 IBS14 IBS15 IBS16 IBS17 IBS18 IBS19 IBS20 IBS21 IBS22
    IBS23 IBS24 IBS25 IBS26 IBS27 IBS28 IBS29 IBS30 IBS31 IBS32 IBS33
    IBS34 (1=5) (2=4) (3=3) (4=2) (5=1) (ELSE=SYSMIS) .
EXECUTE .
* Labeling values of each item
VALUE LABEL
  IBS01 TO IBS34
    5 'NOT AT ALL'
    4 'SLIGHTLY'
    3 'MODERATELY'
    2 'QUITE A BIT'
    1 'EXTREMELY'.
EXECUTE .
* Adding up item totals for each subscale
                COMPUTE TOT_DY = IBS01 + IBS06 + IBS07 + IBS09 + IBS10 + IBS13 + IBS16 + IBS30 .
                COMPUTE TOT_IN = IBS03 + IBS18 + IBS19 + IBS22 + IBS27 + IBS29 + IBS31 .
                COMPUTE TOT_BI = IBS05 + IBS21 + IBS25 + IBS26 .
                COMPUTE TOT_HW = IBS04 + IBS15 + IBS32 .
                COMPUTE TOT_FA = IBS11 + IBS23 + IBS28 .
                COMPUTE TOT_SR = IBS02 + IBS14 + IBS17 + IBS34 .
                COMPUTE TOT_SX = IBS12 + IBS20 .
                COMPUTE TOT_RL = IBS08 + IBS24 + IBS33 .
                COMPUTE TOT_OV = IBS01 + IBS02 + IBS03 + IBS04 + IBS05 + IBS06 + IBS07 + IBS08 +
                        IBS09 +  IBS10 + IBS11 + IBS12 + IBS13 + IBS14 + IBS15 + IBS16 + IBS17 + IBS18
                        +  IBS19 + IBS20 + IBS21 + IBS22 + IBS23 + IBS24 + IBS25 + IBS26 + IBS27 +
                        IBS28 + IBS29 + IBS30 + IBS31 + IBS32 + IBS33 + IBS34 .
* Computing all subscales scores (transformed 0 to 100 scale)
        COMPUTE IBS_DY=((tot_dy - 8)/(32))*100
        COMPUTE IBS_IN=((tot_in - 7)/(28))*100
        COMPUTE IBS_BI=((tot_bi - 4)/(16))*100
        COMPUTE IBS_HW=((tot_hw - 3)/(12))*100
        COMPUTE IBS_FA=((tot_fa - 3)/(12))*100
        COMPUTE IBS_SR=((tot_sr - 4)/(16))*100
        COMPUTE IBS_SX=((tot_sx - 2)/(8))*100
        COMPUTE IBS_RL=((tot_rl - 3)/(12))*100
```

```
        COMPUTE IBS_OV=((tot_ov -34)/(136))*100
EXECUTE .
* Labeling all scored subscales
VARIABLE LABELS
        IBS_DY 'DYSPHORIA SCORE (8 ITEM-TRANSFORMED)'/
                IBS_IN 'INTERFERENCE WITH ACTIVITY SCORE (7 ITEM-TRANSFORMED)'/
        IBS_BI 'BODY IMAGE SCORE (4 ITEM-TRANSFORMED)'/
        IBS_HW 'HEALTH WORRY SCORE (3 ITEM-TRANSFORMED)'/
        IBS_FA 'FOOD AVOIDANCE SCORE (3 ITEM-TRANSFORMED)'/
        IBS_SR 'SOCIAL REACTION SCORE (4 ITEM-TRANSFORMED)'/
        IBS_SX 'SEXUAL SCORE (2 ITEM-TRANSFORMED)'/
        IBS_RL 'RELATIONSHIPS SCORE (3 ITEM-TRANSFORMED)'/
        IBS_OV 'OVERALL SCORE (34 ITEM-TRANSFORMED)' .
EXECUTE .
```