Taylor & Francis
Taylor & Francis Group

Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

Menorrhagia Impact Questionnaire: assessing the influence of heavy menstrual bleeding on quality of life

Donald M. Bushnell, Mona L. Martin, Keith A. Moore, Holly E. Richter, Arkady Rubin & Donald L. Patrick

To cite this article: Donald M. Bushnell, Mona L. Martin, Keith A. Moore, Holly E. Richter, Arkady Rubin & Donald L. Patrick (2010) Menorrhagia Impact Questionnaire: assessing the influence of heavy menstrual bleeding on quality of life, Current Medical Research and Opinion, 26:12, 2745-2755, DOI: 10.1185/03007995.2010.532200

To link to this article: https://doi.org/10.1185/03007995.2010.532200

CMRO

Current Medical Research & Opinion Vol. 26, No. 12, 2010, 2745–2755

0300-7995
doi:10.1185/03007995.2010.532200

Article FT-0071.R1/532200

Original article

Menorrhagia Impact Questionnaire: assessing the influence of heavy menstrual bleeding on quality of life

Donald M. Bushnell
Mona L. Martin
Health Research Associates, Inc., Mountlake Terrace, WA, USA

Keith A. Moore
Xanodyne Pharmaceuticals, Inc., Newport, KY, USA

Holly E. Richter
University of Alabama at Birmingham, Birmingham, Alabama, USA

Arkady Rubin
ARSTAT, Flemington, NJ, USA

Donald L. Patrick
University of Washington, Seattle, WA, USA

Address for correspondence:
Don Bushnell, Associate Director, HRA, Inc., 6505 216th St SW, Suite 105, Mountlake Terrace, WA 98043, USA
Tel.: +1 425-775-6565 Ext. 206;
Fax: +1 425-775-6734;
bushnell@hrainc.net

Keywords:
Activity limitation – Heavy menstrual bleeding – Menorrhagia – Patient reported outcome (PRO) – Questionnaire – Quality of life

Accepted: 12 October 2010; published online: 3 November 2010
Citation: Curr Med Res Opin 2010; 26:2745–55

Abstract

Objective:
Menorrhagia, or heavy menstrual bleeding (HMB), has a negative impact on women's quality of life (QOL). The objective was to develop, validate, and assess the performance of a disease-specific patient-reported outcome (PRO) measurement instrument for HMB (the Menorrhagia Impact Questionnaire [MIQ]).

Research design and methods:
The MIQ was designed to measure the effect of HMB on a woman's self-assessment of menstrual blood loss (MBL), limitations in social/leisure activities, physical activities, and ability to work. Meaningfulness of these observed MBL changes were also measured. The development and psychometric validation of the MIQ was performed utilizing data from a long-term safety study of tranexamic acid (Lysteda*), with comparison to an age-matched normal control group recruited from the general population. Performance of the MIQ was also evaluated using data from a six-cycle, randomized, double-blind, clinical study of tranexamic acid for the treatment of HMB. Correlations and sensitivity of each pertinent MIQ item to the treatment-induced changes in MBL were assessed, and the minimally important differences (MID) for the individual MIQ items were determined.

Results:
The psychometric properties of the MIQ were fully validated. Correlations between individual MIQ items and changes in MBL were statistically significant ($p < 0.001$). A clear differentiation between tranexamic acid and placebo groups confirmed sensitivity of the MIQ and its ability to detect treatment-induced changes in MBL. MIDs were estimated for the individual MIQ items, with sensitivities and specificities in the 64–79% and 63–82% ranges using receiver operating characteristic (ROC) curve analyses, respectively. MIDs were found to be equal to or greater than 0.5. Statistically significant treatment differences were also observed for the proportions of subjects achieving at least 1-point improvement in MIQ scores.

Conclusion:
The MIQ contains validated constructs important to women with HMB.

Clinical trial registration: NCT00113568 and NCT00386308 (ClinicalTrials.gov ID)

Introduction

Menorrhagia, or heavy menstrual bleeding (HMB), is diagnosed when menstrual blood loss (MBL) is excessive and accompanied by a negative impact on a woman's quality of life (QOL)[1]. The estimated prevalence of HMB is approximately one-third of women aged 15–49[2]. A prospective study of a general

*Lysteda is a registered trade name of Ferring Pharmaceuticals Inc., Parsippany, NJ, USA.

practice with 10 000 registered patients reported a 25% 12-month cumulative incidence of HMB[3]. A survey of obstetrician/gynecologist respondents reported seeing an average of 18–25 HMB patients per month, with 67% having associated anemia and fatigue. No underlying anatomical cause is found in 40–60% of patients with HMB[4].

In research, an objective definition of MBL is a measured blood loss of 80 mL or more per menstruation (average menstrual blood loss is 30–40 mL with 90% of women having losses less than 80 mL)[5]. However, in one study of 50 patients with HMB, 12 had a monthly menstrual blood loss in excess of 200 mL and five in excess of 450 mL[6]. Unfortunately, objective measurements of MBL are not practical in the clinical setting[7,8]. In addition to an objective absolute blood loss, HMB has a negative impact on QOL in terms of social, physical, and emotional well-being[8,9].

A woman's perception of MBL is subjective. A practical diagnosis of HMB is excessive MBL that is not tolerated by the patient and negatively affects her QOL. The most appropriate methodology and tool for evaluating QOL in patients with HMB continues to be a subject of debate[10]. Certain questions on nonspecific QOL instruments, such as the Short Form 36 (SF-36), lack relatability for patients with HMB, thus making them suboptimal tools for this population[11–13]. Shortcomings in standardized QOL measures have led to a proliferation of questionnaires, although their validity and reliability have not been fully documented[10,12]. Numerous instruments for measuring health outcomes in menorrhagia research have been developed[14–17]. A review of these menorrhagia-specific measures showed: non-specificity to HMB[14], unclear responsiveness statistics[15,17], lack of validity among US patients with menorrhagia[15–17], recall issues[15] and unclear scoring issues[16].

An appropriate conceptual framework incorporated into a patient-reported outcome (PRO) was necessary for HMB study endpoint evaluation. Following the review of current literature, the review of existing assessments, and expert input, a comprehensive qualitative study was done that included concept elicitation interviews ($n = 26$) and cognitive interviews ($n = 20$). This resulted in the identification of appropriate measurement domains, important features of symptom relief, and meaningful degrees of response. The validity, reliability, specificity, sensitivity, and performance of the Menorrhagia Impact Questionnaire (MIQ) are presented in this report.

A major factor that motivates patients to see a physician regarding their HMB is its interference with daily life[18]. The effect of HMB on QOL is a function of its impact on limitations of daily activities, than from actual MBL volume, although reduction in MBL correlates with treatment satisfaction among other factors[5,19,20]. The acceptance of QOL as an integral part of an HMB evaluation is reflected in the National Institute for Health and Clinical Excellence (NICE) definition of HMB as a condition that 'interferes with the woman's physical, social, emotional and/or material QOL'[21]. Therefore, measurement of QOL, in addition to MBL, is an important facet of evaluating therapeutic and satisfaction response. Achievement of the minimally important differences (MIDs) in QOL parameters can be interpreted as meaningful to women with HMB, and could serve as a criterion for evaluation of the effectiveness of therapy across treatment groups and individual patients.

Methods

Overview

The MIQ was designed to measure the effect of MBL on various aspects of the QOL of women with HMB. The questionnaire includes items on subjective assessment of blood loss, limitations in social/leisure and physical activities, and limitations in ability to work. Overall assessment of the meaningfulness of the observed changes in QOL is also provided. A validation study was completed by using data from (1) patients diagnosed with menorrhagia and undergoing treatment with tranexamic acid (TA) (Lysteda*), and (2) an age-matched normal control group recruited from the general population. For sample (1), a diagnosis of HMB was based on the medical judgment of the investigator after review of the subject's medical history, results of screening physical and gynecologic examinations, clinical laboratory results, impact of menstrual bleeding on the ability to engage in normal activities and menstrual period evaluation during screening. Numerous criteria were included to exclude women with underlying pathologies to HMB (including, but not limited to, anovulatory dysfunctional uterine bleeding; metrorrhagia; menometrorrhagia or polymenorrhea; history of clinically significant hepatic or renal disease, endometrial polyps, endometrial hyperplasia, endometrial carcinoma, or cervical carcinoma; clinically significant cardiac arrhythmia, uncontrolled diabetes or uncontrolled hypertension).

Following instrument validation, sensitivity of the MIQ to treatment-induced changes in MBL were assessed, and minimally important differences for the individual MIQ items were determined using data from a six-cycle, randomized, double-blind, placebo-controlled efficacy study of TA at an oral dose of 1.3 g administered three times daily for up to 5 days during each menstrual period. The study evaluated an objective measurement of MBL improvement based on an alkaline hematin assay method while providing MIQ data[22].

*Lysteda is a registered trade name of Ferring Pharmaceuticals Inc., Parsippany, NJ, USA.

Identification and development of the MIQ items

Development of the MIQ followed the recommended steps contained in the US Food and Drug Administration document, 'FDA Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims'[23,24]. Development began with a review of the PRO literature focusing on the methods used to collect qualitative data from HMB patients. Qualitative interviews determined which concepts were most important and could be included in a draft MIQ.

Women ($n = 26$) from five clinical sites involved in a TA HMB safety study were interviewed during the qualitative research phase. Participants' ages ranged from 24–50 years (with a mean age of approximately 42 years). The mean duration of HMB was 9 years with an average duration of treatment at the time of the interview of 6 months. Of the participating women, 85% described their menstrual flow as severe, 15% considered it as moderate. In all, 53% of the patients were married or living as married, 31% were divorced, 4% were separated, 12% were single or never married, and 61% were Caucasians. The highest grade or year of school completed ranged from 6 years to 20 years (mean 15.9 ± 2.6). Concepts important to the patients were grouped into the following categories: (1) restrictions or limitations in activity or daily function; (2) emotional impact; and (3) notable nuisance or aggravation (such as a need for multiple pad changes to prevent possible embarrassment from leakage). The desired relief from HBL was identified as: (1) changing of pads and tampons less often (most important); (2) increased ability to perform daily activities (second most important); (3) increased ability to work (third most important); and (4) the impact of HMB on others (family members or individuals close to the woman), which was considered as the least important.

Wherever possible, the language used by the patients was retained in the final items of the questionnaire. While areas of impact such as anxiety and fatigue were occasionally discussed by patients, the primary expressions tended to be specific activity restrictions or limitations. In addition to the overall perception of the amount of blood loss, the following activities were considered as the crucial components of the QOL assessments: (1) physical activities, (2) leisure and social activities, and (3) work activities. Qualitative self-assessments of the ability to perform these activities were directly translated into the MIQ items.

Cognitive interviews for MIQ items

Cognitive interviews were conducted to evaluate patient understanding of the proposed MIQ items. Patients ($n = 20$) from three TA safety study sites were selected for the appropriate interviews. Results of the cognitive interview process warranted minor changes in some of the instruction lines, but completely endorsed the MIQ items and their response options.

MIQ response option scoring system

The MIQ consists of six individual measures or items (Appendix A). The first 4 items are evaluated by using 4-point (item 1) or 5-point (items 2–4) response scales. No summative scale is derived for item 5 as it serves as a descriptive tool to characterize limitations of specific activities and is viewed as supporting information for items 2–4. Item 6 represents a global assessment (impact, degree, and meaningfulness) of the change in MBL when compared to the previous period. Impact response options included a 0 ('about the same'), 1 ('better'), or 2 ('worse'). If a change is reported, then a 7-point rating scale is used to specify the degree of improvement (item 6a) or worsening (item 6b). Finally, item 6c (meaningfulness of change in MBL) provides an overall assessment of the subjective perception of the change in MBL and may be considered an important component of the MIQ.

MIQ validation study: objectives, design, methods

The validation study was initiated to provide a comprehensive evaluation of the psychometric properties of the MIQ, including construct validation of individual items, test–retest evaluation of the instrument, its ability to reflect changes in the menstrual blood loss, reliability of the individual items, and assessment of the respondent burden. Psychometric properties of MIQ items were validated against the Aberdeen (Ruta) Menorrhagia Clinical Outcome Questionnaire (AMCOQ)[15], the Medical Outcomes Study Short-Form 36 Item Health Status Instrument (SF-36 Version 2; Quality Metrics Inc., Lincoln, RI, USA, and Medical Outcomes Trust, Hanover, NH, USA)[25], and items from a Menstrual Cycle Bleeding Diary. The study objectives and methodology were consistent with FDA guidance parameters[23] and instrument review criteria developed by the Scientific Advisory Committee of the Medical Outcomes Trust[26].

The validation of the MIQ was based on the data from (1) patients diagnosed with menorrhagia and undergoing treatment in a open-label, multicenter, long-term safety study of TA at an oral dose of 1.3 g administered three times daily for up to 5 days during each menstrual period, and (2) an age-matched control group recruited from the general population. The control subjects had to be at least 18 years old, have a normal menstruation pattern (i.e., with a typical menstrual cycle length between 26 and 32

days), and have a duration of menses lasting less than 8 days including less than 4 days that represent their heaviest bleeding for the period. Overall, the menstrual bleeding had to be characterized as 'light' or 'moderate' as opposed to 'heavy' or 'very heavy'.

For the active treatment group, the MIQ, AMCOQ, SF-36, and Menstrual Cycle Bleeding Diary data were evaluated with a baseline cycle and the first treatment cycle. For the control group, the same evaluations were performed for the baseline cycle and the two subsequent menstrual cycles. A subset of women in each cohort returned to the study site 7–10 days after the baseline evaluation to complete the MIQ a second time to evaluate test–retest reliability.

A p-value <0.05 was required to declare statistical significance (two-sided tests). No p-value adjustments were made for the analysis of multiple endpoints. There was also no imputation of missing values. Analyses were performed by SPSS Version 11.5 for Windows (SPSS Inc., Chicago IL, USA). Variability of the MIQ items was assessed via the frequency distributions of the reported option scores by study visit and treatment group. The use of the entire range of the response options was considered as a desirable outcome. Construct-related validity is established when relationships among items, domains, and concepts conform to what was predicted by the conceptual framework for the PRO instrument. This includes convergent, discriminate, and known-groups validity.

Convergent and discriminate validity is present where measures of the same construct are highly related and measures of different constructs are less related. To assess convergent and discriminant validity, correlation coefficients were computed across MIQ items 1-4 and between individual MIQ items (Kendall's tau-b) and scales from SF-36 and AMCOQ as well as metrics derived from the subject's diary cards administered at the same (baseline) visit (Spearman's rank). Known-groups validity determines ability of the MIQ to discriminate between groups of subjects known to be distinct. It was assessed by comparing items 1–4 between the treatment and normal cohorts at baseline using the analysis of variance model.

Test–retest reliability assesses if items produce stable, reliable scores under similar conditions[27]. Reliability was evaluated in a subset of at least 50 subjects from each group 7–10 days after baseline using intra-class correlation coefficient. Coefficients greater than 0.70 indicated stability of the instrument over time. The ability to detect change, or sensitivity, requires that response option values for an item change when the concept the item measures changes. To measure an MIQ item's ability to detect change, longitudinal data were evaluated focusing primarily on changes from baseline to the first menstrual cycle. Differences between groups were assessed using the Stuart–Maxwell test and the Cohen effect size. The pooled standard deviation of the change from baseline was used as the measure of variance[28]. Following the assessment of the MIQ items' ability to detect changes over time, the degree to which changes in MBL were meaningful to patients was examined. The responder was defined as a patient with at least a 1-category change (e.g., from 'Very Heavy' to 'Heavy' or from 'Moderate' to 'Light') from baseline to menstrual cycle 1. The number and percent of responders was calculated.

Further validation and performance of the MIQ in a randomized clinical trial

The MIQ was further validated using data from the placebo-controlled, double-blind efficacy study of TA briefly described earlier. Objective measurements of MBL using an alkaline hematin assay method were used to estimate the correlation between individual MIQ items and the amount of MBL. Comparisons between TA and placebo groups using cumulative frequency distribution curves also confirmed sensitivity of the MIQ and its ability to detect treatment-induced changes in MBL.

In addition, data from this study provided the basis for the determination of the minimally important differences for the individual PRO MIQ items. A receiver operating characteristic (ROC) curve analysis was used to gain estimates of the changes in MIQ items that were meaningful to subjects. The global validated MIQ Question 6c (whether perceived change in blood loss was meaningful or important for the subject or not) was considered the 'gold standard'. Sensitivity and specificity were computed by dichotomizing the MIQ changes from baseline as above/below various thresholds (cut-off points). The maximum of the sum of sensitivity and specificity served as the criterion for the selection of the optimal operating point for the ROC curve. The optimal operating cut-off point was interpreted as the minimally important difference for the particular MIQ item. The percentage of subjects achieving at least 1-point reduction in MIQ items 1–4 was also calculated and compared between treatment groups using chi-square test (2-sided). All analyses for this further validation work were performed using the statistical package SAS Version 9.1 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 262 women were enrolled in the validation study. In all, 131 women had been diagnosed with menorrhagia and were enrolled in the TA HMB safety study, and 131 women were age-matched controls with normal menstrual periods. Data from 80 women with menorrhagia and 51 women with normal periods were used for the evaluation of test–retest reliability.

The mean (SD) age in the treatment group was 38 (6.8) years and the mean (SD) age in the control group was 38 (6.8) years. The mean (SD) duration of HMB for women in the treatment group was 11 (8.6) years. Although significant differences in distribution by race and tobacco and alcohol usage were noted between the treatment and control groups, for the purpose of the validation study these differences were not considered material and both groups were considered to be representative of the respective populations regarding menorrhagia.

Variability

Across all study visits, the treatment group and the control group participants used the entire range of the possible responses for the evaluated MIQ items. As an example, see the distribution of the responses to MIQ item 1 (Figure 1). An adequate variability of the MIQ assessments was confirmed. For construct-related validity, the correlations across MIQ items 1–4 and between individual MIQ items and scales from SF-36 and AMCOQ as well as metrics derived from the subject's diary cards are shown in Table 1. The MIQ items 1–4 had high correlations with each other; Kendall's tau-b correlation coefficients ranged from 0.624 to 0.787 and were statistically significant. Because MIQ measures closely related domains (self-assessment of the MBL and the MBL-induced limitations of the various activities), this finding confirms internal validity of the developed instrument.

The AMCOQ Global Score was highly correlated (Spearman rank) with each MIQ item (range of correlation coefficients: 0.76–0.81). Much weaker (yet, with very few exceptions, statistically significant) correlations were reported for the MIQ items against the multiple subscales of SF-36. These results provide additional support for MIQ validity and confirm importance of the menorrhagia-specific measures as opposed to the generic QOL instruments for women diagnosed with HMB. The MIQ items displayed strong discriminant properties interpreted as the known-groups validity (see Table 2). For each MIQ item, the mean score for the treatment group was much higher than the mean score in the control group. Between-treatment differences were highly statistically significant ($p < 0.001$).

Reliability

Test–retest reliability was evaluated separately for each group for each MIQ item. The range of intra-class correlation coefficients (ICC) for the treatment group was 0.72–0.77. For the control group, one item's ICC was 0.67 while others ranged from 0.70 to 0.86. Considering ICC = 0.70 as a threshold, MIQ may be characterized as a reliable instrument with adequate stability over time.

Sensitivity

For the treatment group, significant differences were detected for changes in MIQ items 1–4 from baseline to month 1 ($p < 0.001$). The MIQ items were stable over the same period in the control group. Effect size for the MIQ items ranged from 0.94 to 1.23 and from 0.05 to 0.20 in the treatment and control groups, respectively. Figure 1 illustrates changes from baseline in the distribution of responses to MIQ item 1. In the treatment group, a substantial fraction of subjects showed improvement in MBL after 1 month of therapy; no significant changes in the distribution of scores were detected in the control group. Additional analysis indicated that 90% of subjects from the TA group demonstrated at least 1-point improvement

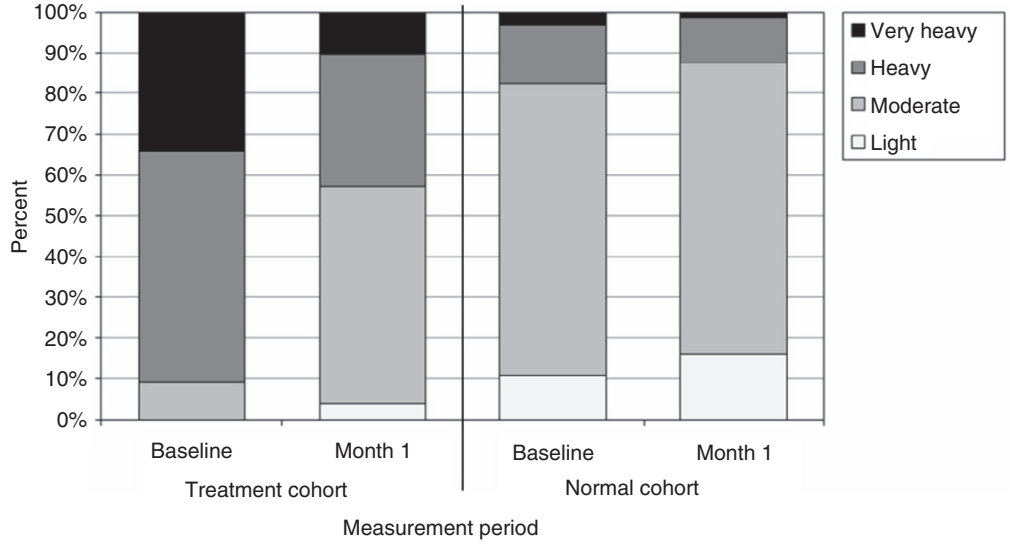

Figure 1. MIQ Item 1, Perceived blood loss: Percentage of patients and controls indicating each response at baseline and month 1.

Table 1. Correlations between MIQ items 1–4 and AMCOQ score, SF-36 subscales, and metrics derived from the diary cards. Treatment and control groups combined ($n = 262$); baseline visit.

	MIQ item 1 Perceived blood loss (PBL) (p-value)	MIQ item 2 Limitations in work outside or inside the home (LWH) (p-value)	MIQ item 3 Limitations in physical activities (LPA) (p-value)	MIQ item 4 Limitations in social/leisure activities (LSLA) (p-value)
MIQ				
Item 1 (PBL)	1.000 (N/A)	0.624 (<0.001)	0.634 (<0.001)	0.631 (<0.001)
Item 2 (LWH)	0.624 (<0.001)	1.000 (N/A)	0.787 (<0.001)	0.770 (<0.001)
Item 3 (LPA)	0.634 (<0.001)	0.787 (<0.001)	1.000 (N/A)	0.784 (<0.001)
Item 4 (LSLA)	0.631 (<0.001)	0.770 (<0.001)	0.784 (<0.001)	1.000 (N/A)
AMCOQ	0.767 (<0.001)	0.785 (<0.001)	0.807 (<0.001)	0.809 (<0.001)
SF-36				
Physical Function	−0.229 (<0.001)	−0.234 (<0.001)	−0.264 (<0.001)	−0.273 (<0.001)
Social Function	−0.118 (0.057)	−0.194 (0.002)	−0.200 (0.001)	−0.261 (<0.001)
Role Physical	−0.200 (0.001)	−0.279 (<0.001)	−0.258 (<0.001)	−0.303 (<0.001)
Vitality	−0.143 (0.021)	−0.193 (0.002)	−0.248 (<0.001)	−0.250 (<0.001)
Bodily Pain	−0.087 (0.163)	−0.168 (0.006)	−0.192 (0.002)	−0.205 (0.001)
PCS	−0.190 (0.002)	−0.271 (<0.001)	−0.285 (<0.001)	−0.275 (<0.001)
Diary card				
Bleeding	0.323 (<0.001)	0.300 (<0.001)	0.353 (<0.001)	0.296 (<0.001)
Small clots	0.209 (0.001)	0.216 (0.001)	0.209 (0.001)	0.174 (0.007)
Large clots	0.350 (<0.001)	0.432 (<0.001)	0.421 (<0.001)	0.385 (<0.001)
Small stains	0.348 (<0.001)	0.291 (<0.001)	0.352 (<0.001)	0.341 (<0.001)
Large stains	0.435 (<0.001)	0.381 (<0.001)	0.380 (<0.001)	0.436 (<0.001)
Sleep	0.368 (<0.001)	0.349 (<0.001)	0.423 (<0.001)	0.410 (<0.001)

MIQ item-to-item correlations are reported by Kendall's tau-b coefficients, otherwise Spearman rank coefficients (p values) are reported. The null hypothesis is that the Spearman rank correlation coefficient equals to 0.
MIQ, Menorrhagia Impact Questionnaire; AMCOQ, Aberdeen Menorrhagia Clinical Outcome Questionnaire; SF-36, Short-Form 36 Item Health Status Instrument Version 2; PCS, physical component summary; N/A, not applicable.

Table 2. Discriminant (known-groups) validity of the MIQ items.

MIQ	Treatment group (baseline)			Control group (baseline)			Between-treatment p-value*
	n	Mean	SD	n	Mean	SD	
Item 1: Perceived blood loss	131	3.25	0.61	131	2.10	0.61	<0.001
Item 2: Limitations in work outside or inside the home	131	3.04	0.99	131	1.34	0.59	<0.001
Item 3: Limitations in physical activities	131	3.28	0.95	131	1.49	0.72	<0.001
Item 4: Limitations in social/leisure activities	131	3.05	1.06	131	1.37	0.72	<0.001

*p-values are estimated from the analysis of variance model.
MIQ, Menorrhagia Impact Questionnaire; SD, standard deviation.

in the MIQ item 1 score and were considered as responders to treatment. For approximately 90% of responders, the improvement was rated as meaningful (MIQ item 6c was used in this evaluation).

Respondent burden

At the first visit, the control group took approximately 10–15 minutes to complete the entire questionnaire packet, including the SF-36, the AMCOQ, and the MIQ items. At subsequent visits, time to complete the questionnaire packet decreased to approximately 7–10 minutes. It took an average of 2 minutes to complete the MIQ items. Respondent burden of MIQ may be considered as minimal and appropriate for the diagnostic and clinical research settings.

Further validation of MIQ in the randomized clinical trial, including determination of MIDs

Statistically significant treatment differences in both MBL and MIQ items were reported in the TA efficacy and safety study[22,29]. These differences suggest a strong relationship between objective and subjective assessments of menstrual blood loss. The correlation between PRO MIQ items 1–4 and changes from baseline in MBL was highly statistically significant ($p < 0.001$) with the Pearson correlation coefficients ranging from 0.3 to 0.4 for both TA and placebo groups combined.

Sensitivity of the MIQ to the changes in the MBL was confirmed during comparative evaluation of the therapy-induced changes in QOL parameters for the TA and placebo groups. Cumulative frequency distributions (Figures 2A–D) clearly display between-treatment

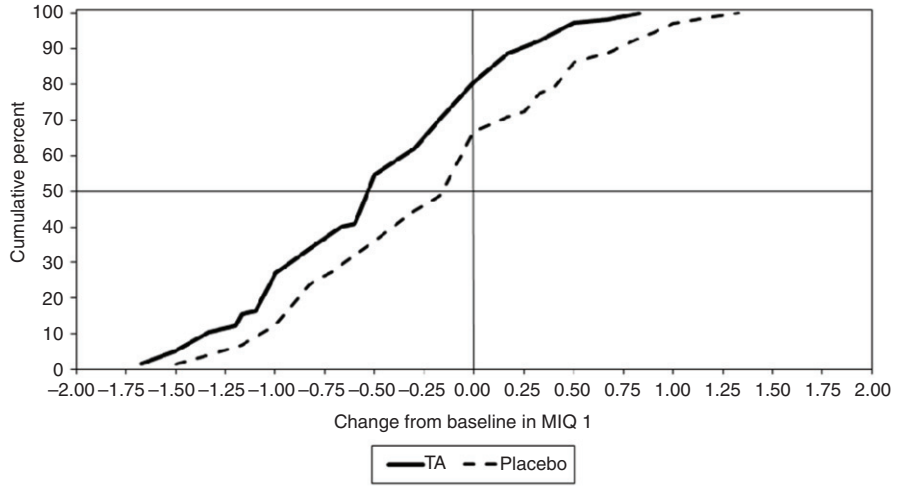

Figure 2A. Cumulative frequency distribution of patients with self-assessed changes in MIQ item 1, Perceived blood loss.

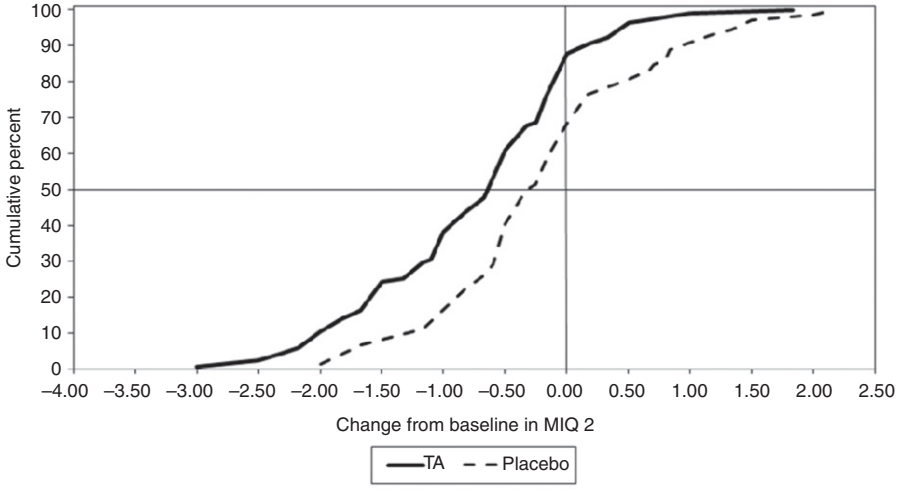

Figure 2B. Cumulative frequency distribution of patients with self-assessed changes in MIQ item 2, Limitations in work outside or inside the home.

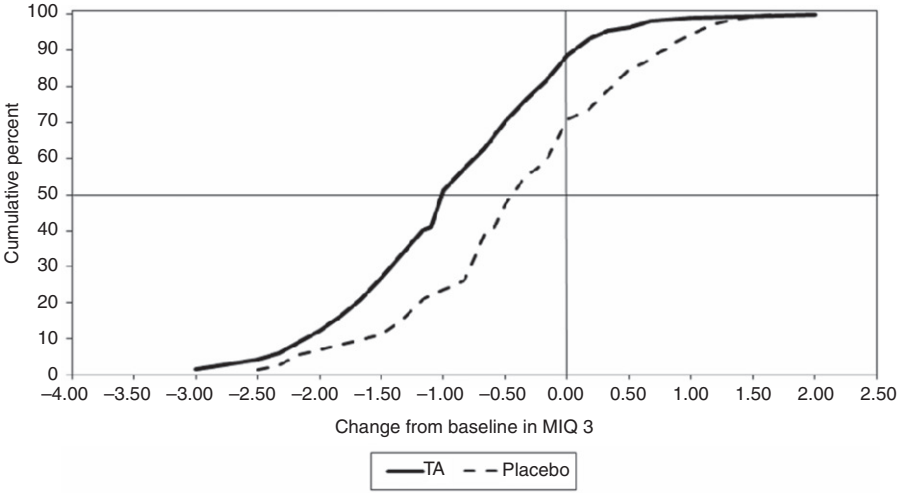

Figure 2C. Cumulative frequency distribution of patients with self-assessed changes in MIQ item 3, Limitations in physical activities.

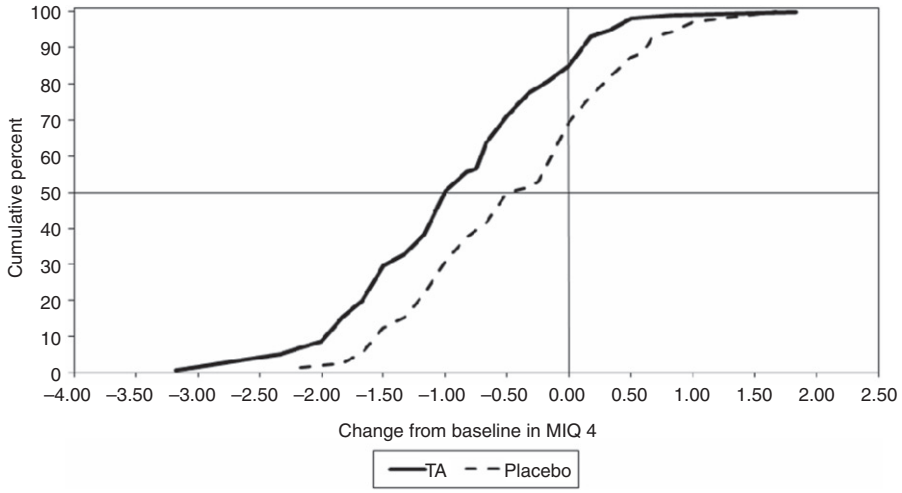

Figure 2D. Cumulative frequency distribution of patients with self-assessed changes in MIQ item 4, Limitations in social/leisure activities.

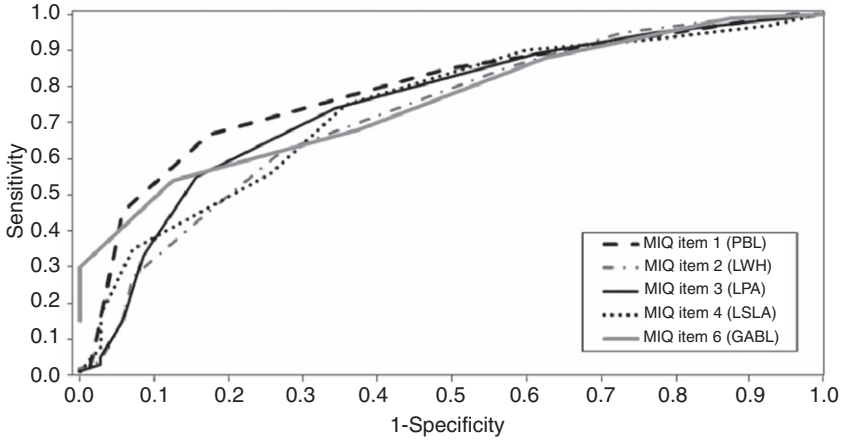

Figure 3. Receiver operating characteristics (ROC) for MIQ items versus meaningfulness of the overall change in MBL. PBL, perceived blood loss; LWH, limitations in work outside or inside the home; LPA, limitations in physical activities; LSLA, limitations in social/leisure activities; GABL, global assessment of change in blood loss.

differences for MIQ items 1–4. For MIQ items 1–4 and 6a, the ROC curves were constructed and the sensitivity and specificity at various cut-off points were calculated. The maximum sum of sensitivity and specificity served as the criterion for the selection of the optimal operating point for the ROC curve. The ROC curves for MIQ items 1–4 and 6a are displayed in Figure 3.

Table 3 presents results of the ROC analyses (sensitivity, specificity, ROC areas under the curve [AUCs]) and optimal operating points interpreted as MIDs. The sensitivities and specificities of the ROC curves were in the 64–79% and 63–82% ranges, respectively; AUCs ranged from 0.76 to 0.8. For the MIQ items measured in 4–5-point scales (MIQ items 1–4), the MID was equal to 0.5. While MIDs provide important benchmarks for the assessment of changes in MIQ items, their usefulness in real clinical practice may be limited. To accurately evaluate the patient's progress, physicians must be able to calculate both pretreatment and post-treatment average scores for the MIQ items. With the difference on MIQ scales equal to 1 point, MID equal to 0.5 may not be used for the direct comparison between the two (one pretreatment and one post-treatment) individual cycles. When the observation period is limited, a 1-point positive change in the MIQ scores may be considered a desirable and easily interpretable outcome.

The proportions of subjects achieving at least 1-point improvement in MIQ items 1–4 were calculated and compared between the treatment groups. The rates were much higher for TA-treated patients when compared to those who received placebo (27 vs. 13%, 38 vs. 17%, 51 vs. 24%, and 50 vs. 31% for MIQ items 1, 2, 3, and 4,

Table 3. Receiver operating characteristic (ROC) curves: MIQ items versus meaningfulness of the overall change in MBL.

MIQ*	Optimal operating points (cut-offs)	ROC curves		
		Sensitivity (%)	Specificity (%)	Area under the ROC curve
MIQ item 1: Perception of blood loss	−0.5	69.0	82.4	0.801
MIQ item 2†: Limitations in work outside or inside the home	−0.5	70.8	77.1	0.772
MIQ item 3: Limitations in physical activities	−0.5	79.2	62.9	0.773
MIQ item 4: Limitations in social/leisure activities	−0.5	79.2	65.7	0.771
MIQ item 6a‡: Global assessment of change in blood loss	+3	63.9	75.0	0.762

*For MIQ items 1–4, the cut-off points represent mean change from baseline; for MIQ item 6a, the cut-off point represents self-assessment difference between the last cycle of baseline and the first cycle on treatment.
†The maximum sum of sensitivity and specificity was marginally higher for the cut-off point = −1 (142.5 vs. 142.1%). The sensitivity and specificity levels for that cut-off were 62.5% and 80.0%, respectively. A cut-off = −0.5 with much greater sensitivity is elected as the most meaningful optimal operating point.
‡Only patients with positive global self-assessment of blood loss (answer to MIQ item 6 = 'Better') are included in this evaluation.
MIQ, Menorrhagia Impact Questionnaire; MBL, menstrual blood loss.

respectively). All differences were statistically significant ($p < 0.05$). This finding further confirms sensitivity of the MIQ.

Discussion

Patient-reported outcome instruments often produce results or response options that physicians are not able to interpret or evaluate concerning their clinical importance, such as they would with a clinical marker like a 10% increase in blood pressure[30]. Alternative means are therefore needed to interpret these valuable responses of patient's well-being, functioning, and QOL.

Supporting our hypothesis about validity, MIQ item 1 ('Perceived Blood Loss') was more highly correlated with the AMCOQ score than with the SF-36. Second, MIQ items showed a stronger correlation with the Menstrual Cycle Bleeding Diary than they did with the non-specific health status SF-36. This is as expected since the SF-36 is not a disease-specific measure, but rather a more general health status measure unable to detect differences between a population of patients with HMB and a control population. Our hypothesis was also confirmed in MIQ item 3 ('Limitations in Physical Activities'), which showed a moderate correlation with the SF-36 Physical Functioning domain. MIQ item 4 ('Limitations in Social/Leisure Activities') also showed a moderate correlation with the SF-36 Social Functioning domain.

The construct-related validation of the MIQ items determined specificity for known groups. This analysis showed a large response in patients undergoing treatment and little to no response in patients who received no treatment. This instrument is capable of identifying the perceived improvement in MBL. Another by-product of the MIQ was a stronger justification of the clinically important changes in QOL metrics. A change of at least 1-point in MIQ item 1 ('Perceived Blood Loss') scores lead to a meaningful/important change (item 6c) in more than 90% of patients; thus, it is more about the patient's perception of the changes (as evidenced by the MIQ items) than real changes in MBL.

The MIQ items are suitable for measuring and sensitive to the concepts for which it was designed to measure. Question 6c from the MIQ (whether or not perceived change in blood loss was meaningful or important for the patient) should be considered the new standard for treatment satisfaction. The meaningfulness and importance of the observed change in MBL most closely relate to the patient's perception of the treatment's impact on the variety of QOL metrics. These changes in the MIQ item scores are closely related to and driven by the changes in MBL. The sensitivity rates shown here may assist physicians in interpreting what amount of MBL is crucial and meaningful for their patients, as this is the amount that is shown to increase QOL. The treatment differences for all MIQ items not only are statistically significant but also clinically important. The analysis results for MIQ item 3 (Limitations in Physical Activities) and MIQ item 4 (Limitations in Social/Leisure Activities) in the final ROC models confirms the importance and validity of these items as prespecified key secondary efficacy endpoints. Importance of MIQ items as predictors of the overall satisfaction is further supported by these analyses. The goal was to determine the percentage of patients with meaningful improvement among those who reported at least a 1-point change from baseline in the first treatment cycles. It may be interpreted as a 'sensitivity analysis' with a 1-point change in MIQ items as a predictor. The results also indicate desirable robustness of the observed treatment effect on the QOL parameters across the domains studied. The test–retest evaluation of the MIQ items provided evidence for their reliability and there was sufficient variability in MIQ item response options.

For all MIQ items, determinations of MIDs at an individual level were identified using a ROC approach. The cut-off points may be interpreted as the MID (as perceived

by individual patients) for the QOL domains. The practical importance of the estimated MIDs is not limited to another proof of robustness of the QOL assessments achieved by different analytical tools. As indicated by Guyatt *et al.*[31], the usefulness of MID is that it ties the magnitude of change to treatment decisions in clinical practice. It also emphasizes the importance of the patient perspective and implicitly links that perspective to the physician. Following well-documented methodology[32], changes in the MIQ items were regressed on the changes in MBL, irrespective of the treatment assigned. The most important outcome of this analysis is an estimate of the MID between treatments in MIQ items. Additionally, evaluation of the ROC curve and associated sensitivity and specificity levels indicated that the 0.5 was perceived as meaningful by patients. This consideration can play a major role when evaluating treatment options and treatment effectiveness for women with HMB.

Conclusion

The MIQ may be considered a validated measure of the QOL in women diagnosed with HMB, and this instrument may be used to track progress in the pharmacological treatment of menorrhagia. The MID is often described as the 'smallest difference' in response score in the domain of interest which patients perceive as beneficial and which would mandate a change in the patient's management[27]. Analysis of the MID is a means by which changes in a PRO measurement score can be translated into terms that are clinically meaningful. The MIQ instrument was able to differentiate the degree of change for each MIQ item that women with HMB perceived as clinically meaningful.

Transparency

Declaration of funding

Financial support for this study was provided by Xanodyne Pharmaceuticals, Inc. and Ferring Pharmaceuticals Inc.

Declaration of financial/other relationships

D.M.B. has disclosed that he has received funding from Xanodyne Pharmaceuticals, Inc. for planning and performing statistical analyses and study report preparation. K.A.M. is an employee of Xanodyne Pharmaceuticals, Inc. A.R. is a statistical consultant for Xanodyne Pharmaceuticals, Inc. M.L.M. has disclosed that she has received funding from Xanodyne Pharmaceuticals, Inc. for performing statistical analyses and study report preparation. H.E.R. receives or has received research support or has acted as a consultant for Pfizer, Astellas Pharmaceuticals, Xanodyne, Uromedica, IDEO as well as receiving Pfizer and Warner Chilcott Education grants. D.L.P. is a consultant for Amgen, Meritage, Amylin, Pfizer, and Merck.

Excerpts from this manuscript were presented at the 2009 American College of Obstetricians and Gynecologists (ACOG) 57th Annual Clinical Meeting, Chicago, Illinois, May 5, 2009.

References

1. NHS Centre for Reviews and Dissemination. Management of menorrhagia. Effective Health Care 1995;1:1-15
2. Lethaby A, Farquhar C. Treatments for heavy menstrual bleeding. BMJ 2003;327:1243-44
3. Shapley M, Jordan K, Croft, PR. An epidemiological survey of symptoms of menstrual loss in the community. Br J Gen Pract 2004;54:359-63
4. Hickey M, Higham JM, Fraser I. Progestogens versus oestrogens and progestogens for irregular uterine bleeding associated with anovulation. Cochrane Database Syst Rev 2007;4:CD001895
5. Apgar BS, Kaufman AH, George-Nwogu U, et al. Treatment of menorrhagia. Am Fam Physician 2007;75:1813-19
6. Haynes PJ, Hodgson H, Anderson AB, et al. Measurement of menstrual blood loss in patients complaining of menorrhagia. Br J Obstet Gynaecol 1977;84:763-8
7. Warner PE, Critchley HOD, Lumsden HA, et al. Menorrhagia II: is the 80 mL blood loss criterion useful in management of complaint of menorrhagia? Am J Obstet Gynecol 2004;190:1224-9
8. National Collaborating Centre for Women's and Children's Health: Heavy menstrual bleeding. National Institute for Health and Clinical Excellence. London, England, 2007. Available at: http://www.nice.org.uk/guidance/CG44/guidance/pdf/English [Last accessed on July 15, 2010]
9. Duckitt K, Collins S. BMJ Clinical Evidence. Menorrhagia. BMJ Publishing Group Ltd., London, England, 2006. Available at: http://clinicalevidence.bmj.com/ceweb/conditions/woh/0805/0805.jsp [Last accessed on July 15, 2010]
10. Shankar M, Chi C, Kadir RA. Review of quality of life: menorrhagia in women with or without inherited bleeding disorders. Haemophilia 2008;14:15-20
11. Habiba M, Julian S, Taub N, et al. Limited role of multi-attribute utility scale and SF-36 in predicting management outcome of heavy menstrual bleeding. Eur J Obstet Gynecol Reprod Biol 2010;148:81-5
12. Matteson KA, Clark MA. Questioning our questions: do frequently asked questions adequately cover the aspects of women's lives most affected by abnormal uterine bleeding? Opinions of women with abnormal uterine bleeding participating in focus group discussions. Women Health 2010; 50:195-211
13. Jenkinson C, Peto V, Coulter A. Making sense of ambiguity: evaluation in internal reliability and face validity of the SF 36 questionnaire in women presenting with menorrhagia. Qual Health Care 1996;5:9-12
14. Moos RH. The Development of a Menstrual Distress Questionnaire. Psych Med 1968;30:853-867
15. Ruta DA, Garratt AM, Chadha YC, et al. Assessment of patients with menorrhagia: how valid is a structured clinical history as a measure of health status? Qual Life Res 1995;4:33-40
16. Shaw RW, Brickley MR, Evans L, et al. Perceptions of women on the impact of menorrhagia on their health using multi-attribute utility assessment. Br J Obstet Gynaecol 1998;105:1155-9
17. Lamping DL, Rowe P, Clarke A, et al. Development and validation of the menorrhagia outcomes questionnaire. Br J Obstet Gynaecol 1998; 105:766-79
18. Shapley M, Jordan K, Croft PR. Abnormal bleeding patterns associated with menorrhagia in women in the community and in women presenting to primary care. Fam Pract 2007;24:532-7
19. Santer M, Wyke S, Warner P. What aspects of periods are most bothersome for women reporting heavy menstrual bleeding? Community survey and qualitative study. BMC Womens Health 2007;7:8
20. Winkler UH. The effect of tranexamic acid on the quality of life of women with heavy menstrual bleeding. Eur J Obstet Gynecol Reprod Biol 2001;99:238-43
21. National Institute for Health and Clinical Excellence. Heavy menstrual bleeding. London, England: NICE Clinical Guideline CG44; 2007. Available at: www.nice.org.uk/CG044 [Last accessed on July 15, 2010]

22. Lukes AS, Moore KA, Muse KN, et al. Tranexamic acid treatment for heavy menstrual bleeding: a randomized trial. Obstet Gynecol 2010; 116:865-75
23. US Dept. of Health and Human Services. FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Silver Spring, MD, December 2009; Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM193282.pdf [Last accessed on July 15, 2010]
24. Patrick DL, Burke LB, Powers JH, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. Value Health 2007; 10(Suppl 2):S125-37
25. Ware J, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83
26. Scientific Advisory Committee of the Medical Outcomes Trust. Assessing health status and quality-of-life instruments: attributes and review criteria. Qual Life Res 2002;11:193-205
27. Guttman L. A basis for analyzing test-retest reliability. Psychometrika 1945; 10:255-82
28. Cohen JJ. Statistical Power Analysis for the Behavioral Sciences, 2nd edn. Hillsdale, NJ: Lawrence Erlbaum, 1988:8
29. Lysteda [package insert]. Newport, KY: Xanodyne Pharmaceuticals, Inc.; 2009
30. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 1989;10:407-15
31. Guyatt GH, Osoba D, Wu AW, et al. for the Clinical Significance Consensus Meeting Group. Methods to explain the clinical significance of health status measures. Mayo Clin Proc 2002;77:371-83
32. Patrick DL, Gagnon DD, Zagari MJ, et al. for the Epoetin Alfa Study Group. Assessing the clinical significance of health-related quality of life (HrQOL) improvements in anaemic cancer patients receiving epoetin alfa. Eur J Cancer 2003;39:335-45

Appendix A

In addition to the MIQ items listed in the table, patients described all activities that were limited by excessive bleeding (MIQ item 5). This information was not used for any formal statistical evaluations.

MIQ concept	MIQ item	Response scale
Perception of amount of blood loss	MIQ 1 'During your most recent menstrual period, your blood loss was':	1. Light 2. Moderate 3. Heavy 4. Very Heavy
Limitations in work outside or inside the home	MIQ 2 'During your most recent menstrual period, how much did your bleeding limit you in your work outside or inside the home?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in physical activities	MIQ 3 'During your most recent menstrual period, how much did your bleeding limit you in your physical activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in social or leisure activities	MIQ 4 'During your most recent menstrual period, how much did your bleeding limit you in your social or leisure activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Global assessment of change in blood loss	MIQ 6/6a/6b 'Compared to your previous menstrual period, would you say your blood loss during this period was':	0. About the same 1. Better (7-item scale): 1. Almost the same, hardly better at all 2. A little better 3. Somewhat better 4. An average amount better 5. A good deal better 6. A great deal better 7. A very great deal better 2. Worse (7-item scale): 1. Almost the same, hardly worse at all 2. A little worse 3. Somewhat worse 4. An average amount worse 5. A good deal worse 6. A great deal worse 7. A very great deal worse
Meaningfulness of perceived change in blood loss	MIQ 6c 'Was this a meaningful or important change for you?'	0. No 1. Yes

MIQ, Menorrhagia Impact Questionnaire.

