

Research Submission

Determining Thresholds for Meaningful Change for the Headache Impact Test (HIT-6) Total and Item-Specific Scores in Chronic Migraine

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Objective.—The objective of the analyses described here was to develop thresholds defining clinically meaningful response on the total and item scores of the 6-item short-form Headache Impact Test (HIT-6) in a population of patients with chronic migraine (CM).

Background.—The HIT-6 is a short, easily understood, and useful measure of the impact of headache on daily life. Though widely used, limited literature supports a threshold value for clinically meaningful response within individuals over time for the HIT-6 total score and for the item scores, especially in the CM population.

Methods.—PROMISE-2 is a randomized, double-blind, multicenter study comparing intravenous eptinezumab 100 and 300 mg with placebo for the preventive treatment of CM. Responder definitions for HIT-6 total and items scores using data from PROMISE-2 study were calculated via distribution-based and anchor-based methods. Distribution-based methods included half of the baseline standard deviation and baseline standard error of measurement. The change from baseline to week 12 in HIT-6 scores was assessed using the following anchors: patient global impression of change, reduction in migraine frequency, and change in EuroQol 5 dimensions 5 levels visual analog scale. Values from the literature and PROMISE-2 analyses were plotted against the cumulative distribution function of change values (baseline to week 12) and used to triangulate to empirically support clinically meaningful change definitions for the HIT-6 total and item scores in patients with CM.

Results.—From the literature, 5 articles provided 7 candidate values for a responder threshold for the HIT-6 total score. From distribution- and anchor-based methods, 5 candidate values were derived from PROMISE-2 data. Using the median of all candidate values, a HIT-6 total score responder definition estimate of ≥ 6 (ie, ≥ 6 -point improvement in the total score) appears most appropriate for discriminating between individuals with CM who have experienced meaningful change over time and those who have not. For item-level analyses using anchor-based methods, the responder definition for items 1-3 (“severe pain,” “limits daily activities,” and “lie down”) was a 1-category improvement in response (eg, from Sometimes to Rarely); for items 4-6 (“too tired,” “felt fed up or irritated,” and “limits concentration”), a 2-category improvement in response (eg, from Always to Sometimes) was clinically meaningful.

Conclusions.—Using a multifaceted, statistically-based approach, the recommended responder definition for the HIT-6 total score in the CM population is a ≥ 6 -point decrease, consistent with previous literature. Anchor-based item-level responder thresholds were defined as a decrease of 1 or 2 categories, depending on the item. These CM-specific values will provide researchers and clinicians a means to interpret clinically meaningful change in the HIT-6 total and item scores and may facilitate the measurement of treatment benefits in specific functional domains of the HIT-6.

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[Corrections added on November 2, 2020, after online publication: the copyright has been updated.]

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Key words: 6-item short-form Headache Impact Test, minimal clinically important difference, responder definition, chronic migraine, PROMISE-2

Abbreviations: CDF cumulative distribution function, CM chronic migraine, EQ-5D-5L EuroQol 5 dimensions 5 levels, HIT-6 6-item short-form Headache Impact Test, MMD monthly migraine day, PGIC patient global impression of change, PROs patient-reported outcomes, SD standard deviation, SEM standard error of measurement, VAS visual analog scale

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INTRODUCTION

In recent years, headache clinicians, trialists, and researchers have emphasized the importance of moving beyond common primary endpoints such as migraine and headache days and assessing patient-reported outcomes (PROs).^{1,2} It is critical to understand not only whether a treatment or intervention reduces the number, severity, or duration of migraine attacks, but also if these reductions result in meaningful improvements in patients' lives. There are available tools for measuring an array of patient-reported domains, including patient and family burden, disability, quality of life, and functioning related to headache.¹⁻⁸ One of the most widely used tools in headache and migraine research is the 6-item short-form Headache Impact Test (HIT-6), a scale developed to measure the impact of headache on daily life in a general headache population.³ Although the HIT-6 has several strengths, including brevity, simple scoring, easy interpretability, and validity, it has been understudied in chronic migraine (CM).

Few studies have focused on the properties of the HIT-6 in CM, a prevalent and severely disabling condition, defined as having 15 or more headache days per month with at least 8 headache days showing features of migraine with or without aura.⁹ CM has been

linked to a variety of negative health and life outcomes, including increased levels of disability (eg, missed work/school, activities, and reduced effectiveness), poor social and emotional functioning, and elevated family burden.¹⁰⁻¹⁵ Fortunately, several new and efficacious treatment options have become available for CM; these treatments reduce the number of monthly migraine and headache days over time. With the development of these treatments for CM, there is a need to incorporate patient experience measures like the HIT-6 to assess improvements in patients' lives via reliable and validated PRO measures.

Existing research has largely focused on the HIT-6 total score (summing over the 6 individual items) in general headache and migraine populations, with little work in CM. The HIT-6 total score is generally higher in patients with CM than in patients with episodic migraine.¹² To our knowledge, no previous research studies have investigated the specific items of the HIT-6, which potentially provide valuable insight to clinicians and researchers on how headache and migraine impacts specific areas, such as severe headache pain, limitations to usual daily activities, the wish to lie down, fatigue, negative affect, and limitations to concentration. As a result, there is a clear need for better understanding of how longitudinal fluctuations in

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HIT-6 total and item-level scores relate to clinically meaningful change. Responder definitions are thresholds for determining meaningful change within individuals over time. Several previous studies have published responder definitions for the HIT-6 total scores, most of which were derived from general headache and migraine samples.¹⁶⁻¹⁹

The goals of the current study were 2-fold: first, to use a multifaceted approach that integrates new findings from a large CM clinical trial with the existing literature to triangulate on a robust HIT-6 total score responder definition for individuals with CM; second, to develop novel responder definitions for each of the individual HIT-6 items that can be used in research and clinical practice. This study used multiple analytical approaches (distribution-based, anchor-based, visualization of cumulative distributions) and previous research findings to determine a single set of empirically supported thresholds that can be easily applied at the total score and individual item level.

METHODS

Study and Data Source.—Data came from the PROMISE-2 study (*ClinicalTrials.gov* Identifier: NCT02974153).²⁰ Study approval was provided at each study site by the corresponding independent ethics committee or institutional review board. The research was conducted in accordance with current Good Clinical Practices per the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, the principles of the Declaration of Helsinki, and local regulatory requirements. Each patient provided written informed consent prior to their participation.

PROMISE-2 was a phase 3, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of eptinezumab, a humanized monoclonal antibody targeting calcitonin gene-related peptide, for the preventive treatment of CM in adults. Patients were randomized to receive eptinezumab 100 mg, eptinezumab 300 mg, or placebo by 30-minute intravenous administration once every 12 weeks. To be eligible for the trial, patients had to meet the diagnosis criteria for CM detailed earlier. This study uses all available data from baseline and week 12, pooling across the 3 treatment arms.

Measures.—The HIT-6³ is a patient-reported outcome measure used to measure the impact and effect of headache on the ability to function normally in daily life (Fig. 1). The HIT-6 consists of 6 questions, all using 5 ordered response categories with verbal labels ranging from “never” to “always.” A total summed score for the HIT-6 is obtained, using the following values to weight response categories for each item: never = 6, rarely = 8, sometimes = 10, very often = 11, and always = 13; these values were specified by the HIT-6 authors so that summed scores from the items would match item response theory-based scores as closely as possible. Using these weights, HIT-6 total scores may range from 36 to 78. When relevant for item-level analyses (eg, providing descriptive statistics [means, standard deviations], computing change scores), the ordinal HIT-6 responses were coded as never = 1, rarely = 2, sometimes = 3, very often = 4, and always = 5.

The patient global impression of change (PGIC) includes a single question concerning the patient’s impression of the change in their disease status since the start of the study. Responses were provided on a 7-category scale, with verbal labels ranging from “very much improved” to “very much worse.” Due to the large placebo effect often seen in migraine research, the “improved” group based on the PGIC was defined using the 2 highest PGIC response categories (ie, “very much improved” and “much improved”), which was compared to a “not improved” group combining 5 responses from “minimally improved” to “very much worse.”

For the frequency of migraine days, baseline monthly migraine days (MMDs) was defined as the number of migraines during the 28-day screening period. MMDs at week 12 were computed as the number of migraine days in the previous 28 days (weeks 9-12); missing MMD values were imputed as previously reported.²⁰ Change from baseline was the differences in frequency between baseline and week 12 MMD values. Migraine frequency response at the 75% threshold was used to define the “improved” – or “meaningful change” – group for this anchor variable (meaningful change: $\geq 75\%$ reduction in MMDs, vs no meaningful change: $< 75\%$ reduction in MMDs). Historically, a 50% threshold has been used for migraine/headache days, but recent clinical trials of preventive treatment

HIT-6™

HEADACHE IMPACT TEST

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please check one box for each question.

1. When you have headaches, how often is the pain severe?

Never Rarely Sometimes Very Often Always

2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

Never Rarely Sometimes Very Often Always

3. When you have a headache, how often do you wish you could lie down?

Never Rarely Sometimes Very Often Always

4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

Never Rarely Sometimes Very Often Always

5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

Never Rarely Sometimes Very Often Always

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

Never Rarely Sometimes Very Often Always

Fig. 1.—Headache Impact Test (HIT-6). Headache Impact Test™ (HIT-6™) © 2001, 2015 QualityMetric Incorporated and the GlaxoSmithKline group of companies. All rights reserved. HIT-6™ United States (English) version.

have evaluated more stringent thresholds (eg, 75 and 100% reductions) and researchers have proposed a “tipping point” for patients with a 75% response.^{21,22} Given these recent trends, the stringent 75% threshold was chosen to ensure that substantial improvement had been realized which, in turn, would lead to a robust responder definition candidate value for the HIT-6 scores.

The EuroQol 5-dimension, 5-level scale (EQ-5D-5L)²³ is a descriptive system of health-related quality of life states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with 5 levels of severity (“no problem” to “extreme problem”). This tool also has a visual analog scale (VAS) in which patients are asked to rate their overall health with scores ranging from 0 = “the worst health you can imagine” to 100 = “the best health you can imagine.” The subgroup for “meaningful

change” was defined as an increase of 10 points on the VAS from the beginning of the treatment period to week 12, and the “no meaningful change” subgroup was defined as less than a 10-point increase. Ten points was selected to define meaningful change in the VAS values as it represents an increase of 10% of the possible range of VAS values.

Analytic Strategy.—Candidate responder definition values were derived using a multifaceted approach that is consistent with recommended best practices in the field.^{24,25} For the HIT-6 total score responder definition, several distribution-based and anchor-based approaches were used to determine a single responder definition. Item-specific HIT-6 responder definitions were derived using anchor-based approaches. Distribution-based approaches for the item-level analyses were not considered because they are inappropriate for single items (ie, standard error of measurement [SEM] could not be

Table 1.—Previously Reported HIT-6 Total Score Responder Definitions

Source	Sample	Reported Decrease Needed	Ceiling Rounded Value
Bayliss and Batenhorst ²⁷	Unspecified (HIT-6 User Guide)	5	5
Castien et al ¹⁹	186 patients with chronic tension-type headache	8	8
Coyteaux et al ¹⁸	71 patients with chronic daily headache	5	5
Rendas-Baum et al ¹⁶	1384 patients with CM	3.7	4
Smelt et al ¹⁷	368 patients with migraine	7	7
		2.5	3
		6	6

Rounded values are reported as HIT-6 scores (and therefore change scores) and may only take integer values. Ceiling rounding was used to make candidate values more conservative. Some sources conducted more than 1 analysis to determine a responder threshold.

calculated because coefficient alpha is not applicable for a single item). All analyses were conducted with SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Distribution-Based Approaches.—For the distribution-based estimates, 2 typical values for total scores are reported for the HIT-6 total scores: (1) one-half standard deviation (SD) of baseline scores and (2) the SEM at baseline (defined as SD at baseline multiplied by the square root of [1–reliability]) where coefficient alpha of the scale from baseline was used as the reliability estimate for the total score. It is important to note that given the homogeneous patient populations observed in clinical trials, these distribution-based methods were expected to underestimate responder definitions because, given the homogeneity of patients meeting the trial inclusion and exclusion criteria and the severity of CM, the variability within the sample at pretreatment timepoints was expected to be attenuated.²⁶ For this reason, anchor-based approaches were also considered.

Anchor-Based Approaches.—Responder definition analyses were conducted using 3 anchor variables (PGIC, MMDs, and EQ-5D-5L VAS), with improved and not improved groups as previously defined. For each anchor variable, a candidate responder definition was estimated as the mean HIT-6 baseline to week 12 change score of individuals deemed to have exhibited meaningful change, as defined earlier.

To “triangulate” to a final CM-specific responder definition value, the cumulative distribution function (CDF) of the HIT-6 change scores from baseline

to week 12 were plotted as a function of the PGIC anchor groups, and all candidate values were considered along with values from the existing literature. A CDF plot provides a graphical representation of the percent change (or absolute change) from baseline on the horizontal axis and the cumulative percent of patients experiencing up to that change on the vertical axis. Such figures allow for a collection of candidate response threshold values to be examined simultaneously and collectively; a well-chosen responder definition value should show noticeable separation between groups included as separate curves on the plot.

Missing Data.—Analyses were based on all available data and missing data were rare. For the distribution-based methods, there were no missing data because only baseline data were used (n = 1072). The anchor-based methods required data at week 12, but the retention rate was high (96% of patients; n = 1024). For the measures used as anchors at week 12, the analyses involving PGIC and EQ-5D-5L were based on n = 1023 subjects each.

RESULTS

Previously Proposed HIT-6 Responder Definitions.—A literature review was undertaken to find previously reported candidate values for HIT-6 meaningful within person change values. In total, 7 values for a HIT-6 total score responder were obtained from 5 different peer-reviewed publications,^{16-19,27} with no literature evaluating responder definitions for the

individual HIT-6 items. The suggested HIT-6 total score responder definition values from all 5 articles are provided in Table 1.

PROMISE-2 Analyses.—Table 2 provides the demographic characteristics from PROMISE-2.²⁰ Patients were primarily female (over 88%) and identified as not Hispanic or Latino (92%) and white (91%). The mean age at baseline was approximately 40 years.

HIT-6 Total Score Responder Definitions.—Descriptive statistics for the HIT-6 total score showed that, at baseline, headache impact scores were high (mean of 65.0) but decreased by week 12 (mean of 58.6) (Table 3). Using the distribution-based candidate values of $0.5 \times SD$ of baseline scores and the baseline SEM, candidate responder definition values were found to be -2.6 and -2.2 , respectively. Thus, rounding down to a larger, more stringent change showed that the distribution-based methods both produced candidate HIT-6 total score responder definitions of -3 .

Candidate responder definition values were also found through an anchor-based approach (Table 4). Results showed the mean HIT-6 total score changes were -10.0 (PGIC), -10.8 ($\geq 75\%$ MMD response), and -9.4 (EQ-5D-5L VAS) for the 3 anchors of meaningful change. Rounding these values down corresponded to candidate responder definition values of -10 , -11 , and -10 , respectively.

Table 2.—Demographic Characteristics for the Full Sample Pooling Across the Active and Placebo Groups (N = 1072)

Variable	Mean (SD)/n (%)
Age (years)	40.5 (11.2)
Gender	
Female	946 (88.2%)
Male	126 (11.8%)
Race	
White	975 (91.0%)
Black or African American	82 (7.6%)
Multiple	7 (0.7%)
American Indian or Alaska native	3 (0.3%)
Asian	3 (0.3%)
Native Hawaiian or other Pacific Islander	1 (0.1%)
Other	1 (0.1%)
Ethnicity	
Hispanic	86 (8.0%)
Not Hispanic or Latino	986 (92.0%)

SD = standard deviation.

Using the current analyses values and the previously cited values from the literature to triangulate to a final value, a responder definition estimate of -6 appears most appropriate for discriminating between individuals with CM who have experienced meaningful change over time and those who have not. This suggested value is the rounded median (-5.5) of all responder definition candidate values, including the results of the current analysis (-3 , -3 , -10 , -10 , and -11) and 7 values found in the literature (see Table 1).^{16-19,27} The CDFs of the change in HIT-6 total scores by the PGIC-defined groups from Table 4 are plotted in Figure 2. The CDF of the change scores includes reference lines denoting the candidate responder definition values from both the current distribution- and anchor-based methods as well as values found in the literature. Examination of Figure 2 finds that the proposed CM responder definition of -6 (decrease of ≥ 6 points; red vertical reference line) occurs at a point on the plot where the difference between the group (minimally improved or worse vs much or very much improved) functions are well separated but is not so stringent that very few patients would be considered responders.

HIT-6 Item-Level Responder Definitions.—HIT-6 item-specific candidate responder definition values were found through anchor-based approaches (Table 3). Results showed the mean HIT-6 item-specific (rounded down) score changes were -1 (reducing by 1 response category; items 1-3: “severe pain,” “limits daily activities,” “lie down”) and -2 (reducing by 2 response categories; items 4-6: “too tired,” “felt fed up or irritated,” “limits concentration”). The CDFs of the item-specific change scores by the PGIC-defined responder definition provided visual support for these item-level responder definitions. As with the total score plot, the proposed CM responder definition for each item (red vertical reference line, Fig. 3) generally occurs at a point on the plot where the functions of the 2 groups (minimally improved or worse vs much or very much improved) are well separated but is not so stringent that very few patients would be considered responders.

DISCUSSION

The evaluation of clinically meaningful within-person change plays an important role in headache research, clinical trials, and

Table 3.—Summary of HIT-6 Item and Total Scores by Visit, Pooling the Active and Placebo Groups

Item	Content	Mean (SD)	Response Categories n (%)				
			Never	Rarely	Sometimes	Very Often	Always
Baseline (n = 1072)							
1	Severe pain	3.7 (0.6)	0 (0.0%)	28 (2.6%)	350 (32.6%)	626 (58.4%)	68 (6.3%)
2	Limits daily activities	3.6 (0.7)	3 (0.3%)	51 (4.8%)	377 (35.2%)	535 (49.9%)	106 (9.9%)
3	Lie down	4.2 (0.8)	4 (0.4%)	22 (2.1%)	135 (12.6%)	461 (43.0%)	450 (42.0%)
4	Too tired	3.5 (0.8)	11 (1.0%)	94 (8.8%)	379 (35.4%)	506 (47.2%)	82 (7.6%)
5	Felt fed up or irritated	3.7 (0.9)	18 (1.7%)	86 (8.0%)	304 (28.4%)	461 (43.0%)	203 (18.9%)
6	Limits concentration	3.6 (0.8)	9 (0.8%)	74 (6.9%)	334 (31.2%)	540 (50.4%)	115 (10.7%)
	Total score	65.0 (5.1)	—	—	—	—	—
Week 12 (n = 1024)							
1	Severe pain	3.1 (0.9)	30 (2.9%)	207 (20.2%)	421 (41.1%)	322 (31.4%)	44 (4.3%)
2	Limits daily activities	3.1 (0.9)	30 (2.9%)	225 (22.0%)	445 (43.5%)	270 (26.4%)	54 (5.3%)
3	Lie down	3.8 (1.1)	23 (2.2%)	110 (10.7%)	223 (21.8%)	374 (36.5%)	294 (28.7%)
4	Too tired	2.8 (1.0)	118 (11.5%)	283 (27.6%)	371 (36.2%)	228 (22.3%)	24 (2.3%)
5	Felt fed up or irritated	2.8 (1.1)	149 (14.6%)	298 (29.1%)	301 (29.4%)	205 (20.0%)	71 (6.9%)
6	Limits concentration	2.8 (1.0)	103 (10.1%)	274 (26.8%)	394 (38.5%)	217 (21.2%)	36 (3.5%)
	Total score	58.6 (7.9)	—	—	—	—	—

The mean and standard deviation for the HIT-6 items are provided for descriptive purposes only and were calculated by scoring the ordinal responses with integer scores from 1 = never to 5 = always. Exact sample sizes vary slightly between 1024 and 1072 across items and visits due to missing data.

— = not applicable/not relevant.

clinical practice. The headache community has begun to recognize the importance of evaluating treatments and interventions using PRO measures, such as the HIT-6, that capture the impact of migraine on a patient's daily life.^{1,2} Though CM is more burdensome and disabling compared to other headache disorders, such as episodic migraine,¹⁰⁻¹⁵ most of these headache-focused PRO measures have not been rigorously evaluated in CM samples; only Rendas-Baum et al¹⁶ examined the HIT-6 total score responder definition in a CM sample previously. The current study aimed to address this shortcoming by cumulatively building on the existing literature and establishing robust responder definitions for the HIT-6 total score and item-specific scores.

Using a multifaceted approach, the recommended responder definition for the HIT-6 total score was ≥ 6 -point decrease, which is consistent with previous literature in migraine patients. In the CM-focused study of over 1300 patients, a decrease of at least 7 points was considered necessary to demonstrate meaningful individual change, based on results from anchored analyses using a 50% reduction in headache days and a

50% reduction in cumulative headache hours to define responders.¹⁶ When examined in a sample of general migraine patients, Smelt et al¹⁷ found that an appropriate within-person change of 2.5 on HIT-6 total scores is needed for meaningful response, an estimate obtained from 2 separate anchored analyses. Smelt et al¹⁷ also reported a possible responder definition of 6 points based on a receiver-operator curve analysis, which they suggested was more reasonable given the total range of the HIT-6 scores.

Other analyses in the literature evaluated responder definitions in unspecified or other types of headache disorders. The HIT-6 User Guide²⁷ states that a change of 5 points or more is clinically meaningful and a change of 3-5 points is "noteworthy," but provides no reference or evidence to support these statements and does not define the population evaluated. Coeytaux et al¹⁸ suggested an individual change of approximately 3.7 points, which was the average HIT-6 change value associated with patients who reported being "somewhat better" on a patient impression of change item; this estimate was derived

Table 4.—Mean (SD) HIT-6 Change Scores (Baseline to Week 12) by Anchor Variable Groups

Measure	n	Item 1 Severe Pain	Item 2 Limits Activities	Item 3 Lie Down	Item 4 Too Tired	Item 5 Fed Up Irritated	Item 6 Limits Concentration	Total Score
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Patient global impression of change								
Very much improved or much improved	525	-0.8 (0.9)	-0.8 (1.0)	-0.7 (1.1)	-1.2 (1.1)	-1.4 (1.1)	-1.3 (1.0)	-10.0 (7.2)
Minimally improved or worse	498	-0.3 (0.7)	-0.2 (0.7)	-0.2 (0.8)	-0.3 (0.8)	-0.4 (1.0)	-0.3 (0.8)	-2.5 (4.9)
75% migraine responder rates								
Met 75% reduction	317	-0.9 (1.0)	-0.9 (1.0)	-0.8 (1.2)	-1.3 (1.1)	-1.4 (1.2)	-1.3 (1.1)	-10.8 (8.0)
Did not meet 75% reduction	707	-0.4 (0.8)	-0.4 (0.8)	-0.3 (0.9)	-0.5 (0.9)	-0.7 (1.1)	-0.6 (0.9)	-4.3 (5.9)
EQ-5D-5L VAS								
≥10-point increase	324	-0.8 (0.9)	-0.9 (1.0)	-0.8 (1.2)	-1.1 (1.1)	-1.3 (1.2)	-1.2 (1.0)	-9.4 (8.0)
<10-point increase	699	-0.4 (0.8)	-0.4 (0.8)	-0.3 (0.9)	-0.6 (1.0)	-0.8 (1.1)	-0.6 (1.0)	-4.9 (6.4)

The mean and standard deviation for the HIT-6 items are provided for descriptive purposes only and were calculated by scoring the ordinal responses with integer scores from 1 = never to 5 = always.

SD = standard deviation; VAS = visual analog scale.

from a study of 71 patients with chronic daily headache. In examining meaningful change in 186 chronic tension-type headache patients, Castien et al¹⁹ suggested a decrease of 8 points is the minimum change value necessary, based on a stringent anchored analysis defining groups using a patient perceived improvement response of “much improved” or “very much improved,” and at least a 50% reduction in headache days. Using the noted anchors individually (ie, using only perceived improvement or 50% reduction in headache days) resulted in a responder definition of 5 points.

Taken together, the current CM-specific results are consistent with values derived from general headache/migraine samples and suggest that a decrease of 6 points or more on the HIT-6 total score would be considered meaningful to CM patients. This would translate to approximately a 4-category change on a single item, change on 2 items of approximately 2 and 3 categories, or a 1-category change on 3 or 4 of the 6 items, depending on the initial category. Responder definition estimates for individual HIT-6 items from these analyses were either a 1-category improvement (items 1-3) or a 2-category improvement (items 4-6). No previous studies have proposed responder definitions for the individual HIT-6 items. These values appeared most appropriate for identifying patients with CM who have experienced meaningful change over time at the item level. While we believe these item-level thresholds for within person meaningful change will likely be informative for researchers and practitioners – providing a more nuanced understanding of individual patient improvement – we do caution against overinterpreting such change. While single items can be face valid assessments of straightforward topics, statistically speaking, the information available from individual items will always be less (and therefore estimates less precise) than from a composite measure.

A potential limitation of the current study was that the study sample came from a clinical trial where patients tended to report similar, high levels of headache impact at baseline and were primarily female and/or white. Results suggested that this limited baseline variability resulted in lower distribution-based candidate responder-definition values for the HIT-6 total

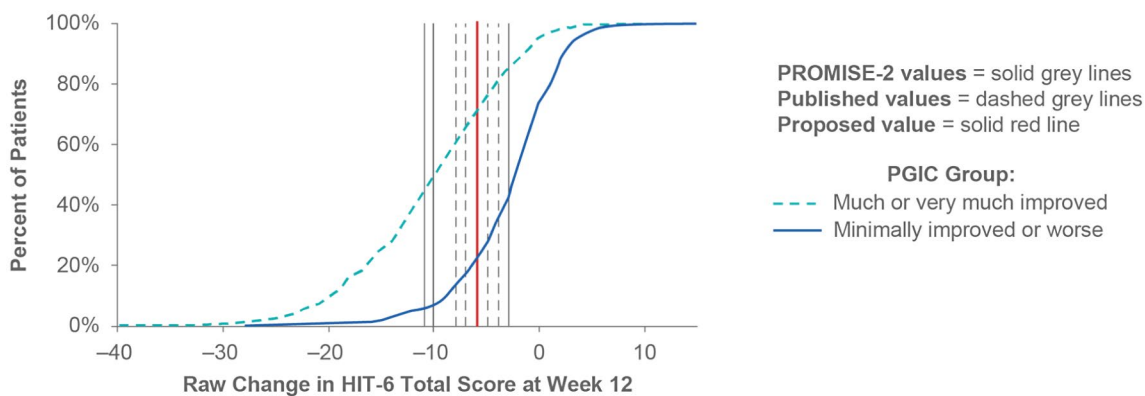


Fig. 2.—Cumulative distribution function (CDF) of total 6-item short-form Headache Impact Test (HIT-6) change scores at week 12, grouped by patient global impression of change (PGIC) responder groups with candidate responder definition values as reference lines. Candidate responder definition values as vertical reference lines – solid gray lines (—) are from current analyses, dashed gray lines (---) are from literature, and the solid red line (—) is the proposed chronic migraine responder definition for HIT-6 total score.

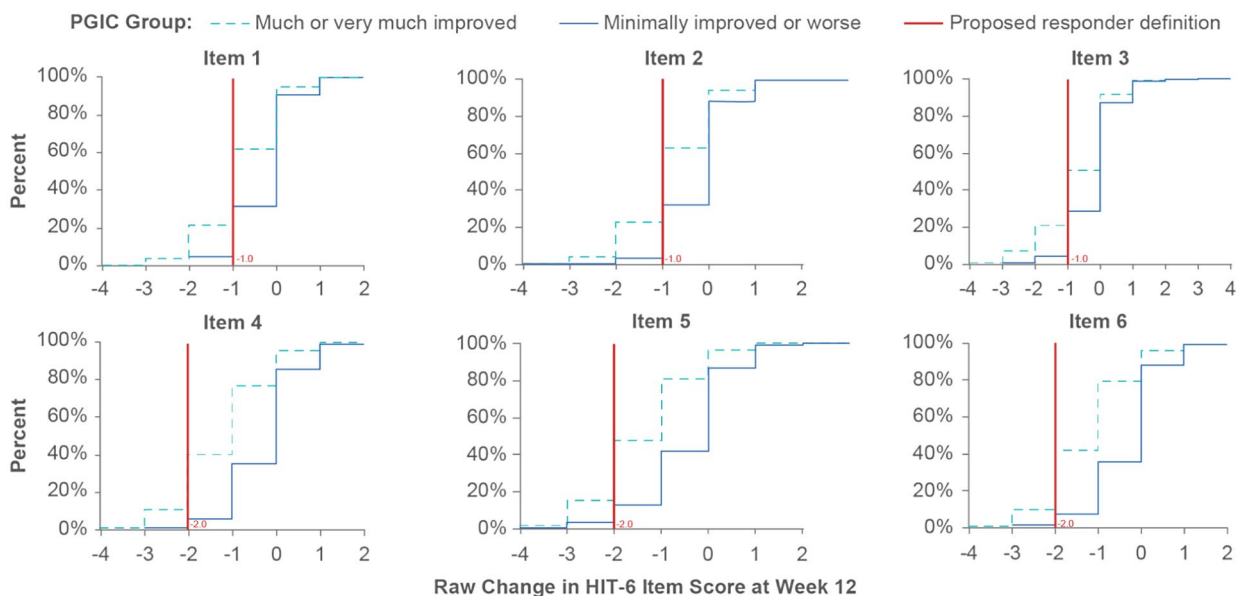


Fig. 3.—Cumulative distribution function (CDF) of item-specific 6-item short-form Headache Impact Test (HIT-6) change scores at week 12, grouped by patient global impression of change (PGIC) responder groups and with candidate responder definition values as reference lines. Candidate responder definition values as reference lines (—).

score, but the impact of this shortcoming was limited because final responder values were determined using both distribution- and anchor-based derived values, as well as values from the existing literature. Also, because the analysis sample was from a clinical trial, it is possible the results do not fully generalize to all patients with CM. The current work considered candidate responder definitions from prior studies, which did not always consist solely of individuals with CM. Given the scarcity of studies in this area,

it was determined to be beneficial to include all relevant information for making decisions. Additionally, not all possible or commonly employed preventive trial endpoints were used as anchors (eg, most bothersome/troublesome symptom); the inclusion of additional candidate values from alternate anchors could result in a modified recommended responder definition value. The current work used a multitude of methods applied to a large, rich clinical trial dataset to provide recommendations for determining

within-person meaningful change thresholds for the HIT-6. The findings provide valuable information for the headache community, but rigorous and programmatic studies in this area are necessary to replicate and possibly refine the suggested thresholds. The reported values should not be used to determine clinically meaningful difference between treatment groups; future work, similar to that reported here, will identify a CM-specific clinically meaningful difference between treatment groups value.

Conclusion.—This study builds on the existing HIT-6 literature focused on meaningful within-person change. In general, the recommended HIT-6 total score responder definition is consistent with other studies and provides strong support for use in clinical practice and research focused on CM. The item-specific responder definitions give clinicians and researchers the ability to evaluate and track the impact of headache on specific item-level areas of patients' lives. These responder definitions provide practical and easily interpreted results that can be used to evaluate treatment benefits over time and to improve clinician-patients communication focus on improvements in key aspects of functioning in individuals with CM.

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