

The Hyperhidrosis Disease Severity Measure-Axillary: Conceptualization and Development of Item Content

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ABSTRACT

Introduction: Patients with primary axillary hyperhidrosis (AHH) suffer from a variety of symptoms. Improved patient-reported outcome (PRO) measures are needed to better assess and categorize the severity of AHH symptoms experienced by patients because the widely used Hyperhidrosis Disease Severity Scale (HDSS) is a single-item measure that cannot capture the broad scope of disease impact.

Methods: The Hyperhidrosis Disease Severity Measure—Axillary (HDSM-Ax) was developed for determining the severity of excessive sweating in patients with primary focal AHH based on face-to-face concept elicitation interviews with 58 AHH patients, a literature review, and expert clinical input. Two waves of face-to-face cognitive interviews (n=26 and n=27) were conducted to evaluate HDSM-Ax clarity and relevance. Additional interviews (n=5) were conducted to confirm content. Adding Rasch Measurement Theory (RMT) analyses allowed for an iterative streamlined approach to documenting content validity and other cross-sectional measurement properties of the new HDSM-Ax measurement.

Results: The 11-item HDSM-Ax PRO scale (0-4 scale per item; 0-44 total scale) represents an AHH symptom range of 0 (no sweating) to 44 (worst possible sweating). Content validity of the HDSM-Ax was documented by showing that chronologically-grouped interviews demonstrated saturation in AHH symptom severity concepts. Cognitive debriefing interviews provided evidence that item content is complete, comprehensible, meaningful, and relevant. RMT-based exploration indicated that targeting of the HDSM-Ax was adequate, suggesting good matching between items and persons; item fit was adequate, suggesting a clinically cohesive scale; and items appeared to be stable between subgroups, thereby supporting a summary score.

Conclusions: The HDSM-Ax is a well-developed measure of AHH severity based on patient-reported signs and symptoms. It is a superior measure to the HDSS and can be used in clinical research and clinical practice to quantify changes in symptom severity in response to treatment.

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INTRODUCTION

Hyperhidrosis is a disorder of excessive sweating that can be idiopathic (primary) or secondary to medical conditions or medications.[1] Primary hyperhidrosis (axillae, hands, and feet) affects 3-5% of the US population and is believed to be caused by overactive cholinergic response of the sweat glands.[1,2] It has a significant effect on psychological and physical health, as well as work and daily activities.[3] Appropriate patient care requires the ability to accurately evaluate symptoms and treatment response. Given the difficulty of quantifying and interpreting laboratory-based measurements of hyperhidrosis, such as gravimetric sweat production,[4] assessing impact through patient-reported outcome (PRO) measurement is central to confirming the diagnosis, establishing the severity, and evaluating the treatment impact.

The widely used Hyperhidrosis Disease Severity Scale (HDSS) is a quick and easy PRO to administer. However, it consists of a single question. In assessing complex, clinically relevant domains, a single-item question cannot capture the broad scope of impact on a patient. These are scientifically weak measures with limited reliability, validity, and ability to detect change.[5] Additionally, the 4 possible responses to the HDSS incorporate 2 variables (tolerability and impact on daily life) in each response rather than separately assessing each variable. This does not allow for a different level of effect for each variable. Thus, the HDSS is a useful way of classifying subjects with hyperhidrosis, but it is inadequate for quantifying symptom severity[6] and measuring clinical trial outcomes. As such, the HDSS does not meet US Food and Drug Administration (FDA) requirements for well-defined and reliable outcome assessments in primary axillary hyperhidrosis (AHH) clinical trials.[7]

FIGURE 1. Hyperhidrosis Disease Severity Measure—Axillary (HDSM-Ax) version 1.1

INSTRUCTIONS: We are interested in finding out about your current experience with excessive **underarm** sweating.

- Please consider excessive sweating in your **underarms only** when selecting the answer to each question.
- For each statement, please provide the response that best describes your **experience since you woke up yesterday**.
- Please answer **ALL** questions even if some seem similar to others or seem irrelevant to you.

1. Since you woke up yesterday, how often did you experience the following while you were awake? (Please select the number that best describes your experience.)

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a) Damp or wet clothing caused by underarm sweating?	0	1	2	3	4
b) Underarm sweating for no apparent reason?	0	1	2	3	4

2. Since you woke up yesterday, how severe was your experience with the following? (Please select the number that best describes your experience.)

	I did not experience this	Mild	Moderate	Severe	Very severe
a) Underarm sweating when you felt nervous, stressed or anxious?	0	1	2	3	4
b) Damp or wet clothing caused by underarm sweating?	0	1	2	3	4
c) Underarm sweating after little or no physical exercise?	0	1	2	3	4
d) Underarm wetness?	0	1	2	3	4
e) Underarm sweating for no apparent reason?	0	1	2	3	4
f) Underarm sweating that was unmanageable?	0	1	2	3	4
g) Underarm sweating when you were cool?	0	1	2	3	4

3. Since you woke up yesterday, what was your experience with each of the following? (Please select the number that best describes your experience.)

	Not at all	Slight	Moderate	Strong	Very strong
a) Feeling the need to change clothes because of underarm sweating?	0	1	2	3	4
b) Feeling the need to wipe sweat from your underarms?	0	1	2	3	4

SUMMARY QUESTIONS (ANCHORS):

4. Since you woke up yesterday, how much of the time did you experience excessive underarm sweating while you were awake? (Please select the number that best describes your experience.)

0 None of the time
1 A little of the time
2 Some of the time
3 Most of the time
4 All of the time

5. How severe was your underarm sweating AT ITS WORST since you woke up yesterday? (Please select the number that best describes your experience.)

0 I did not have underarm sweating (i.e., completely dry)
1 I had underarm sweating but it was mild (i.e., moist)
2 I had underarm sweating and it was moderate (i.e., damp)
3 I had underarm sweating and it was severe (i.e., wet)
4 I had underarm sweating and it was very severe (i.e., soaking)

6. How normal was your level of physical exercise and stress since you woke up yesterday? (Please select all that apply.)

☐ It was a normal day in terms of physical exercise or stress.
☐ I experienced more physical exercise than usual.
☐ I experienced more nervousness, stress, or anxiety than usual.
☐ I experienced less physical exercise than usual.
☐ I experienced less nervousness, stress, or anxiety than usual.

The Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) Version 1.1 (Figure 1) is an 11-item (0-4 scale per item; 0-44 total scale) measure of the severity of excessive sweating in adult patients with AHH. It was developed for use as a primary or secondary endpoint measure in clinical trials, and to meet regulatory and scientific criteria as fit-for-purpose. Appended to the HDSM-Ax are 3 additional summary questions. These do not contribute to the HDSM-Ax score but rather are intended for use as anchors to interpret change in longitudinal studies.

Collaborating with the International Hyperhidrosis Society (IHS), subjects with AHH were identified and interviewed in a research study to develop valid item content. Combining that qualitative research with quantitative Rasch Measurement Theory (RMT),[8-10] psychometric analyses enabled an iterative streamlined approach to documenting content validity and other cross-sectional measurement properties of the new HDSM-Ax measurement. This paper describes the HDSM-Ax development and refinement process, which resulted in content validity being achieved.

METHODS

Overview

The FDA has provided guidance on developing PRO measures for use in clinical trials to support approval and labeling claims.[7] Pursuant to this guidance, qualitative data supporting the validity of HDSM-Ax content was developed using the following steps: review of targeted literature, development of a conceptual hypothesis for measurement of AHH symptom severity, interviews with expert clinicians experienced with diagnosis and treatment of AHH, patient concept elicitation (CE) interviews using an interview guide based on the conceptual hypothesis, and finalization of the instrument content with cognitive debriefing (CD) interviews in AHH patients.

Literature Review and Interviews With Expert Clinicians

A comprehensive literature review was conducted. Item concepts were identified and combined into an item set representing the hypothesized conceptual framework of a new measure that would provide a total score representing daily axillary sweating severity. These items were presented to clinical experts on treating patients with hyperhidrosis (Table 1).

Exploratory telephone interviews were conducted with 3 clinical hyperhidrosis experts, David Pariser, MD, Dee Anna Glaser, MD, and Lisa J. Pieretti, Executive Director of IHS. These experts expanded on knowledge provided by the literature review and provided feedback on the hypothesized conceptual framework and initial item set.

Patient Referral and Screening

The IHS was responsible for identification of potential participants. The IHS invited adult participation by their membership

and screened them for participation according to the following enrollment criteria:

- Male or female, aged 18 years or older
- Clinical diagnosis of axillary hyperhidrosis (with or without other location involvement)
- Able to read and speak English
- Willing and able to provide written informed consent
- Willing and able to understand and comply with all study procedures
- Able to attend a 1-hour telephone interview

Screening results were reviewed by IHS to identify and select patients with a range of the demographic characteristics according to predefined categories. Consideration in the amount of $100 was provided to participants.

CE Interviews

Following referral and screening, 58 subjects were enrolled to participate in a 1-hour, one-on-one telephone interview conducted by an experienced qualitative researcher. In response to open-ended questions asking about AHH experiences, subjects were encouraged to provide spontaneous descriptions of their daily experience, variations in that experience, and how they perceived daily variations in their AHH severity. The recall period was defined as, "Since you woke up yesterday," in order to capture a minimum of 24 hours of experience. This language was probed in the interviews, with agreement that this was a meaningful recall period and would enable subjects to report on a full day of AHH experience.

TABLE 1.

Hyperhidrosis Disease Severity Measure—Axillary: Hypothesized Conceptual Framework	
Excessive underarm sweating (how long?)	Underarm Sweating Severity Score
Noticeable underarm sweating	
Worried about having an episode of sweating	
Embarrassed	
Depressed	
Avoided physical contact with others	
Changed my home activities for today	
Changed my work activities for today	
Changed my social activities for today	
Felt the need to change clothes	
Felt the need to shower during the day	

All 58 interviews were audio-recorded, transcribed, and coded by a LORA Group qualitative researcher using Atlas.ti software. Each code was assigned to one of the following 7 coding families: AHH Symptoms/Signs; Associated Symptoms/Signs; Symptom/Sign Severity; Coping; Treatment; Triggers; and Impact (including emotional, physical, financial, and social). This coding system distinguished the core symptoms and signs relevant to AHH severity from the more distal impacts of AHH. Codes assigned to the Coping, Treatment, Triggers, and Impact families were excluded from consideration for HDSM-Ax content because they were not specific to the concept of interest, i.e. AHH severity. Also excluded were any codes specific to non-axillary hyperhidrosis.

Iterative Rounds of Mixed Methods Research

Three stages of quantitative examinations of response data were performed using RMT. RMT was employed to incorporate more diagnostic details to refine the scale.[11,12] At each stage, RMT-based analyses were performed using RUMM2030 software.[9] There were 7 broad evaluations:

- Endorsement Frequencies (Stages 1-3);
- Targeting (Stages 1-3): comparison of person and item threshold distributions and estimates;
- Item and scale performance (Stages 1-3): ordering of item thresholds, mapping of measurement continuum, item fit statistics (fit residuals and chi-squared statistics); item scoring bias (item-level residual correlations);
- Person and sample measurement (Stages 1-3): reliability (Person Separation Index), Cronbach's alpha, item-total correlations, test-retest reproducibility;
- Stability (Stages 1-3): differential item functioning between defined groups (age, sex, race, HDSS);
- Construct Validity (Stage 3 only): convergent, discriminant, and known-groups validity examinations using the HDSM-Ax total score and key variables (age, sex, race, HDSS);
- Ability to Detect Change (Stage 3 only): continuum mapped by items and person separation reliability.

After each stage of analysis, the quantitative analysis results were reviewed in conjunction with the qualitative findings in order to guide thinking and consider potential changes to the item content, as well as to create a new draft item set for testing.

Finalization of the Instrument Content and CD Interviews

The CE phase of each patient interview was followed by probing questions to generate more opportunity for subjects to describe

TABLE 2.

Patient Characteristics	
Characteristic	**N (%) (N=58)**
Gender	
Female	38 (65.5)
Male	20 (34.5)
Race	
White	42 (72.4)
African American	6 (10.3)
Asian	4 (6.9)
Hispanic/Latino	2 (3.4)
Native American	1 (1.7)
Other (mixed race)	3 (5.2)
Age	
18-19	2 (3.4)
20-29	13 (22.4)
30-39	26 (44.8)
40-49	11 (19.0)
50-59	6 (10.3)
Age of Onset	
<30	58 (100.0)
Education	
Completed High School	14 (24.1)
Bachelors Degree	28 (48.3)
Graduate Degree	16 (27.6)
Geographic Region	
Northeast	14 (24.1)
West	13 (22.4)
Midwest	12 (20.7)
Southeast	10 (17.2)
Southwest	9 (15.5)

their experience. In order to provide an efficient path to the generation of a valid, sensitive, reliable, and interpretable measure of AHH severity across the full range of severity experienced by AHH patients, the draft item set was expanded and reduced based on CE interview findings and analysis for saturation.

The qualitative transcripts were ordered chronologically, based on interview completion date, and then grouped into quintiles. The codes that were derived from the second quintile were compared with the codes that appeared in the transcripts from the first quintile. If new codes appeared in the second quintile, it would suggest that saturation had not been achieved. This evaluation and comparison was repeated for each of the 3 remaining quintiles to ensure that no additional codes appeared that had not already been identified in the qualitative analysis of the previous quintiles.

Following the probed portion of the interview, patients were given access to a password protected website to read and complete the HDSM-Ax draft item set, followed by the HDSS, and respond to CD queries by the interviewer. The CD included participant descriptions with probing for difficulties in understanding, meaning and relevance of items, alternative wording, and additional suggested items.

RESULTS

Demographic Characteristics

The demographic characteristics of those interviewed are summarized in Table 2. Ages ranged from 18 to 59, 65.5% of the patients were female, and most (72.4%) were Caucasian.

Item Generation

The Saturation Grid (Table 3) identifies the patient group from which each new concept was initially elicited. The stepwise analysis showed that after the fourth group of interviews, no additional AHH severity-related concepts were elicited. Only one new concept was elicited in the fourth group (feel need to change clothing). No AHH severity-related concepts were elicited in either the third or the fifth groups. Therefore, we concluded further interviews were unlikely to result in additional concepts being identified, and that the dataset had achieved saturation of AHH severity-related concepts.

After saturation was established with the first 26 interviews (Patients 1-26), a subsequent 27 interviews (Patients 27-53) were structured with both CE and CD to further confirm saturation and to modify the content of the item stems and response options. Based on patient input, the draft item set was reduced from 25 to 13 for one or more of the following reasons:

- Inconsistent with the goal of a patient-reported assessment of sweating severity over the past 24 hours (eg, change over time, seasonal);
- Excessive variability may be seen due to patient personality traits (eg, compare to others, think about sweating/don't think about sweating, sweating without being aware of sweating);
- Not proximal to the concept of interest (skin rash/infection, dehydration, nausea, flushing);
- Decision to exclude nighttime sweating (eg, sweating/not sweating at night when asleep) because it was inconsistently reported and not thought to be a part of the AHH syndrome according to the experts; and
- Ambiguity (eg, sweating in one location linked to sweating in other location).

TABLE 3.

New AHH Severity Codes by Patient Group (n=26)					
	Group 1 n=5	Group 2 n=5	Group 3 n=5	Group 4 n=5	Group 5 n=6
Clothing looks/feels wet	X				
Frequency	X				
Change over time	X				
Think about sweating/don't think about sweating	X				
Sweating with little or no exertion	X				
Compare to others	X				
Episodes	X				
Seasonal	X				
Sweating seems continuous, constant	X				
Sweat running (trickling, dripping) down sides/arms	X				
Duration	X				
Sweating when cold, cool	X				
Feeling warm/hot	X				
Wiping sweat away	X				
Sweating for no apparent reason	X				
Sweating does not stop, unable to stop sweating	X				
Odor	X				
Skin rash/infection	X				
Can feel self sweating	X				
Tingling	X				
Sweating less with exertion than at rest	X				
Sweating without being aware of sweating	X				
Dehydration	X				
Quantity of sweat	X				
Dry skin	X				
Flushing	X				
Nausea	X				
Amount of sweat in short period of time	X				
Armpits feel moist, damp, wet, soggy, swampy		X			
Sweating in one location linked to sweating in other locations		X			
Sweating/not sweating at night, when asleep		X			
Feel need to change clothing				X	

RMT-based Examinations

Stage 1 (n=19 HDSM-Ax completions) findings indicated that targeting was adequate, suggesting a good match between item and person location ranges; item fit was adequate for most items, suggesting the clinically cohesive item set was also cohesive statistically; and the items appeared to be stable between subgroups, thereby supporting a summary score. However, there were a high number of items with disordered thresholds, implying the response categories might not have worked as intended. A high number of pairs of items with high residual correlations suggested some content overlap, which can falsely elevate reliability.

Stage 2 (n=34) findings indicated that targeting of the item set was adequate, suggesting that there was good matching between items and persons; item fit was generally adequate,

suggesting a clinically cohesive item set; and the items appeared to be stable between subgroups, thereby supporting a summary score. However, although the number of disordered thresholds was improved compared to Stage 1, the data suggested that the response option structures could be sub-optimal. The number of pairs of items with high residual correlations was also improved, but still suboptimal.

Stage 3 (*post hoc* analysis of the same n=34 patient interviews) indicated that targeting of the HDSM-Ax was adequate, suggesting good matching between items and persons; item fit was adequate, suggesting a clinically cohesive item set; and the items appeared to be stable between subgroups, thereby supporting a summary score. However, the number of disordered thresholds remained high (8/11 items), still suggesting that the response option structures could be sub-optimal. The number of pairs of items with high residual correlations was markedly improved (2 pairs).

At this stage comparison was made between the HDSM-Ax and the HDSS, a single-item, 4-level indicator of symptom severity. The correlation between the 2 scales was 0.80, indicating that they measured a related concept (64% shared variance). However, for 3 of the 4 HDSS scores, HDSM-Ax measurements ranged widely, which meant that patients with the same HDSS grade had notable variability in HDSM-Ax score. This indicates that the HDSM-Ax had a superior ability to detect differences and changes in symptoms and their severity.

Finalization of the Instrument Content and Cognitive Debriefing Interviews

The last 5 patient interviews (patients 54-58) were completed and analyzed as a small CD study to provide confidence that the final draft version was complete, understandable, meaningful, and representative of the daily AHH severity experience. This CD study determined that all items were understood and were deemed complete and meaningful in describing the daily experience of subjects with AHH.

Overall, feasibility of the HDSM-Ax was strong, and administrative burden was minimal. However, the CD interviews revealed that 2 items (internal feelings of hotness, and tingling before sweating) were not endorsed as daily symptoms and were experienced by very few patients. These 2 items were deleted, resulting in Version 1.0 of the 11-item HDSM-Ax. The 11 signs and symptoms listed in the HDSM-Ax Version 1.0 conceptual framework (Table 4) generate a single estimate of disease severity, where 0 represents no sweating, and 44 represents the worst possible sweating.

The final item content was reviewed by the same hyperhidrosis clinical experts that were interviewed at the beginning of the HDSM-Ax development process. They found the item content to be clinically relevant and meaningful, but requested the addition of a general item that asks subjects to describe how "normal" the 24-hour reporting period was for them. This item was added, resulting in the HDSM-Ax Version 1.1. The general item does not contribute to the 11-item HDSM-Ax total score. It was the experts' opinion that this exploratory item may be useful in interpreting HDSM-Ax score results in the clinical setting.

TABLE 4.

Hyperhidrosis Disease Severity Measure—Axillary Version 1.0 (11 Items): Conceptual Framework	
Damp or wet clothing (frequency)	Daily Underarm Sweating Severity Score
Sweating for no apparent reason (frequency)	
Sweating when felt nervous, stressed or anxious	
Damp or wet clothing (severity)	
Sweating after little or no physical exercise	
Underarm wetness	
Sweating for no apparent reason (severity)	
Sweating that was unmanageable	
Sweating when you were cool	
Felt the need to change clothes	
Felt the need to wipe sweat from underarms	

A Child Version was also created because a 10-year-old had difficulty with some of the words used in Version 1.1. The Child Version is a parallel measure with the same item concepts but revised wording having a Flesch-Kincaid Grade Level of 5.2. The Child Version was subject to further cognitive debriefing interviews in children 10 to 12 years of age.

DISCUSSION

The HDSM-Ax reflects the experiences of patients who suffer from hyperhidrosis and the clinical experts who treat them. The qualitative research plan was based on the hypothesis that a combination of items could be identified that would represent the most important and frequent signs and symptoms that define the range of AHH severity from the patient perspective. Furthermore, that a single score could be generated from these items that summarized and represented the daily severity of AHH in an individual.

We used iterative rounds of qualitative and small sample quantitative research to develop the content validity of the HDSM-Ax. This approach is not yet widely used but is clinically logical, scientifically sensible, and recommended by the FDA because neither qualitative nor quantitative research alone is necessary and sufficient to achieve validity.[13] Some may question the use of small sample psychometric analyses. The aim

of these analyses is to inform and guide thinking that is taken forward into the next stage of qualitative research rather than dictate irreversible changes.

There are a number of reasons why we used RMT rather than other available psychometric paradigms.[14] First, RMT, as articulated by Rasch,[8] and Andrich,[9] is an hypothesis-testing paradigm. Specifically, the Rasch measurement model (a mathematic model) provides a criterion against which the measurement hypothesis (observed data using a version of the scale) is tested. Second, parameter separability, an inherent mathematic property of the Rasch model means the item parameter estimates are freed up from, and therefore not dependent upon, the distributional properties of the sample.[10] Third, the pairwise conditional estimation method of RUMM2030 maximizes the data enhancing the stability of the estimates.[15] We recommend this approach to be used by others.

The concept measured and represented by the HDSM-Ax score is "daily AHH severity." The AHH severity score is generated from subject responses to a set of 11 items that represent the core disease-defining experience, including both signs and symptoms, of primary AHH. These 11 signs and symptoms generate a single estimate of disease severity, from no sweating (score of 0) to the worst possible sweating (score of 44). The HDSM-Ax response categories capture the patient experience in terms of both the severity and the frequency of the most important aspects of the AHH experience that define severity to the patient. The recall period for each item is the previous 24 hours ("since you woke up yesterday"). AHH impact on daily activities or on physical, emotional, and social functioning is not measured by the HDSM-Ax. By examining each sign and symptom separately, the HDSM-Ax provides a more nuanced and robust assessment of a patient's hyperhidrosis severity than the single-item HDSS.

If adequate and well-controlled studies demonstrate a statistically significant treatment effect using the HDSM-Ax, the content validity evidence generated by the qualitative research used to develop and test the HDSM-Ax supports a claim that the treatment reduces the severity of excessive sweating due to AHH. The clinical meaningfulness of a change in the HDSM-Ax score can be interpreted using the 2 additional general questions as anchors in longitudinal studies.

CONCLUSION

The HDSM-Ax is an 11-item PRO designed to measure the severity of primary axillary hyperhidrosis in everyday clinical practice or clinical research and is a superior measure to the HDSS. HDSM-Ax generates a single estimate of disease severity ranging from no sweating to the worst possible sweating. The HDSM-Ax can be administered by an interviewer or completed in writing by the patient to assess patient-reported axillary hyperhidrosis severity based on sweating-related daily experience. The instrument was highly acceptable to patients and was complete, understandable, meaningful, and representative of daily AHH symptom severity. As a multi-item scale developed in accordance with FDA guidance documents, the HDSM-Ax is a superior measure of patient-reported signs and symptoms of axillary hyperhidrosis to HDSS, and we anticipate it will become the new gold standard assessment tool for clinical trials and clinical practice.

DISCLOSURES

Drs. Walker and Kirsch are employees and stockholders of Brickell Biotech, Inc., and Dr. Angulo is a stockholder and former employee of Brickell Biotech, Inc. Ms. Burke and Dr. Hobart are consultants to Brickell Biotech, Inc. Ms. Burke is the Founder of LORA Group, LLC and Affiliate Associate Professor at the University of Maryland School of Pharmacy. Dr. Hobart is Professor of Clinical Neurology and Health Measurement at Plymouth University Peninsula Schools of Medicine and Dentistry. LORA Group contracted with the University.

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