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Development of the Scalp Hair Assessment PRO™ measure for alopecia areata

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Summary

Background Valid patient-reported outcome (PRO) measures are required to evaluate alopecia areata (AA) treatments.

Objectives To develop a content-valid and clinically meaningful PRO measure to assess AA scalp hair loss with scores comparable with the five-response-level Alopecia Areata Investigator Global Assessment (AA-IGA™).

Methods A draft PRO measure was developed based on input from 10 clinical experts in AA. The PRO measure was cognitively debriefed, modified and finalized through two rounds of qualitative semistructured interviews with patients with AA who had experienced ≥ 50% scalp hair loss. Data were thematically analysed.

Results Adults (round 1: n = 25; round 2: n = 15) and adolescents aged 15–17 years (round 1: n = 5) in North America participated. All patients named scalp hair loss as a key AA sign or symptom. Patients demonstrated the ability to self-report their current amount of scalp hair using percentages. In round 1 not all patients interpreted the measurement concept consistently; therefore, the PRO was modified to clarify the measurement concept to improve usability. Following modifications, patients in round 2 responded without difficulty to the PRO measure. Patients confirmed that they could use the five-level response scale to rate their scalp hair loss: no missing hair, 0%; limited, 1–20%; moderate, 21–49%; large, 50–94%; nearly all or all, 95–100%. Almost all patients deemed hair regrowth resulting in ≤ 20% scalp hair loss a treatment success.

Conclusions The Scalp Hair Assessment PRO™ is a content-valid, clinically meaningful assessment of distinct gradations of scalp hair loss for evaluating AA treatment for patients with ≥ 50% hair loss at baseline.

What is already known about this topic?

- Assessing patient-reported outcomes is critical in patient-focused drug development.
- The patient perspective on their own signs, symptoms and unmet needs provides a key clinical trial data source for evaluating treatment outcomes.
- Clinically meaningful and content-valid patient-reported outcome (PRO) measures are required to collect these data in alopecia areata (AA) clinical trials.

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Conflicts of interest

H.K., S.K., N.V.J.A. and J.M. are employees of DRG Abacus, a health economics and outcomes research consultancy that consults with various pharmaceutical companies. K.W.W. was an employee and stockholder at Eli Lilly and Company when this research was conducted and is now an employee and stockholder at Pfizer Inc. F.P.N. and Y.D. are employees and stockholders at Eli Lilly and Company. B.A.K. has served on advisory boards and is a consultant and clinical trial investigator for Eli Lilly and Company; and is a consultant for Aclaris Therapeutics Inc., Eli Lilly and Company, Concert Pharmaceuticals Inc., Pfizer Inc. and Dermavant Sciences Inc. Eli Lilly and Company have commissioned DRG Abacus, J.M.K. and B.A.K. to consult on clinical outcomes assessment strategies for alopecia areata.

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What does this study add?

- This study developed a content-valid PRO measure for patients with AA to self-report the status of their scalp hair loss.
- This novel PRO measure allows scalp hair loss to be characterized into clinically meaningful gradations across the range of 0–100% missing scalp hair.

What are the clinical implications of this work?

- The Scalp Hair Assessment PRO™ provides a new clinical outcome assessment of AA scalp hair loss for use in both clinical trials to evaluate the efficacy of novel treatments and in clinical practice to obtain a patient-centred perspective on the key sign and symptom of AA.
- With corresponding response options to the newly developed Alopecia Areata Investigator Global Assessment (AA-IGA™), clinician and patient assessments are comparable to elucidate any perceived differences between respondents.

Patient-focused drug development requires the systematic collection of patient data to ensure that patients' experiences, perspectives, needs and priorities are meaningfully incorporated into drug development and evaluation.[1,2] This can include assessment of patients' disease signs and symptoms, quality of life, treatment experience, and preferences for outcomes and treatments, and the relative importance of these issues.[1] When patients can report directly on their condition, patient-reported outcome (PRO) assessments can provide a key source of data for evaluating treatment efficacy.[2]

Alopecia areata (AA) is associated with substantial impairment of patients' confidence, self-esteem and health-related quality of life.[3–8] AA is an autoimmune disorder that causes nonscarring hair loss.[9] The clinical spectrum of AA is broad and complex, ranging from isolated patches on the scalp or the face to complete baldness (alopecia totalis) or loss of hair on the entire body (alopecia universalis).[9,10] Scalp hair assessment in AA clinical trials has typically depended on clinician-reported outcomes, utilizing in particular the Severity of Alopecia Tool (SALT),[8,11] with varying dynamic thresholds for treatment success of 50–90% regrowth from baseline.[12–14] While clinician reports are important,[11] it is also important to obtain the patient's perspective on their own condition. Recording both clinician and patient reports can provide a comprehensive measurement approach.

The US Food and Drug Administration (FDA) have noted the need to develop endpoints for clinical trials to measure the aspects of AA of importance to patients.[6] Well-defined measures of the critical outcomes important to patients are needed to help identify treatment response or failure. While various PRO measures have been used to assess patients' overall health-related quality of life in AA clinical trials,[8] a simple PRO measure of disease severity does not exist, and no published studies have directly explored patients' perceptions of successful treatment as it relates to scalp hair growth. It is also beneficial for clinician-reported outcomes and PRO response scales to be similar to allow for comparison of data from each rater. Therefore, the first step in developing the PRO content was to develop the Alopecia Areata Investigator Global Assessment (AA-IGA™),[15] which builds from the SALT assessment.

This cross-sectional, noninterventional, qualitative interview study aimed to develop a content-valid and clinically meaningful PRO measure to assess scalp hair loss, with scores comparable with the AA-IGA™, to aid in understanding treatment success in AA.

Patients and methods

Qualitative approach and research perspective

This study was designed to elicit patient experience of the signs and symptoms of AA and to explore the content validity of a novel PRO measure through methodology aligned with the FDA PRO Guidance for Industry.[16]

Context of the research

Clinician interviews

Ten AA clinical experts practising in the USA participated in qualitative interviews to develop an IGA and a draft PRO measure, in part to design response categories that reflected clinically meaningful gradations of scalp hair loss. Utilizing cognitive interviewing techniques, the clinicians reviewed the PRO response category descriptors, provided corresponding percentage ranges of scalp hair loss, and identified the categories (and percentage ranges) that could indicate treatment success. The development of the AA-IGA™ and the corresponding five-level ordinal response scale for the draft Scalp Hair Assessment PRO were previously reported.[15]

Patient interviews

The content validity and appropriateness of the draft Scalp Hair Assessment PRO were tested in two rounds of

semistructured patient interviews. Firstly, open-ended and probing questions were included to explore systematically the patients' experiences of AA signs and symptoms, and the amount and type of scalp hair improvements they would consider meaningful following treatment (concept elicitation). Secondly, cognitive debriefing,[17] using 'think aloud' methodology and specific probes,[18] explored patients' acceptance, opinions and interpretation of the draft Scalp Hair Assessment PRO. Interviews were face to face, lasted 90 min and were conducted during October 2017 to March 2018 by a qualitative interviewer trained in PRO development techniques. All interviews were audio recorded and transcribed verbatim.

Sampling strategy

Clinicians at the University of California Irvine, Yale University and Northwest Dermatology Research Center in the USA, and the SKiN Centre for Dermatology in Canada identified eligible patients (Table S1; see Supporting Information). Patients successfully treated with oral Janus kinase inhibitors were purposively sampled to understand their perceptions of the amount of scalp hair that would represent treatment success. In round 2, the sampling strategy was adapted to increase the racial diversity and range of education levels within the sample to improve the generalizability of the findings.

Ethical review

The protocol was approved by Western Institutional Review Board (ref #20171820).

Analysis

Transcripts were reviewed in full, identifying information was removed, and codes were allocated to anonymize reporting. The codes indicated the participant number, sex and SALT score (clinician reported). For example, participant 33-F-100 was the 33rd interviewee, female, with complete (100%) hair loss.

Concept elicitation data

Transcripts were coded using ATLAS.ti version 7·5 (ATLAS.ti, Berlin, Germany). Thematic analysis[19] took a phenomenological approach, focusing on the perceptions, feelings and lived experiences of participants.[20]

Conceptual saturation analysis

Conceptual saturation, the point at which no new concept-relevant information emerges,[21] was explored to guide sampling and analysis.[22] A target sample size of 30 participants in round 1 was hypothesized as sufficient to assess saturation and achieve understanding of the conceptual experience of AA signs and symptoms, and to evaluate the content validity of the PRO.[17,23] Round 2 interviews were intended primarily to assess the PRO revisions. However, elicited concepts were reviewed against the conceptual saturation data from round 1.

Cognitive debriefing data

Data obtained via cognitive debriefing methods were subject to framework analysis,[24] whereby a predefined code list was applied to identify the relevance and appropriateness of item wording, response options and recall period. These data informed amendments of the PRO following round 1 of interviews.

Techniques to reduce bias

Interview conduct by a single interviewer kept interviewer effects consistent. Several analysts coded the first two transcripts and developed a preliminary codebook of interview themes to facilitate consistent analysis. Additionally, the findings were interpreted by the multidisciplinary research team.

Results

Sample

Patients aged 15–72 years participated in round 1 (n = 30) and round 2 (n = 15) of the study (Table 1). Efforts to recruit more patients who were not white and patients with lower educational levels in round 2 provided an overall diverse sample.

Concept elicitation

Scalp hair loss is an important sign and symptom in alopecia areata

Scalp hair loss was the most bothersome symptom for most patients (n = 35, 78%). Some patients described constantly assessing the amount of hair they had: 'I can't describe it, it's almost like becomes an obsession. [. . .] I am personally constantly checking and self-checking what's going on with my head' (10-F-10). Patients described feeling self-conscious or insecure (n = 25), feeling embarrassed or ashamed (n = 10) and lack of confidence (n = 9), which lead them to conceal their AA: 'I don't leave the house without a wig on' (45-F-64) and/or avoid social situations: 'I don't like being around people in the daytime. [. . .] so I just choose to work at night' (01-M-100).

Patient descriptions of scalp hair

Patients with SALT score < 100% (n = 26, 58%) primarily described their scalp hair in terms of coverage or amount (n = 21) and density (n = 11), which included the areas of the scalp currently with or without hair, for example, 'It's about half of what I used to have' (34-F-54). Sixteen patients spontaneously used percentages or fractions to describe the quantity of scalp hair. Most viewed their scalp using mirrors (15 of 20) and/or photographs or videos (nine of 20).

Table 1 Clinical and demographic characteristics for Scalp Hair Assessment PRO interviewees

Clinical or demographic characteristic	Round 1 (n = 30)	Round 2 (n = 15)	Total (n = 45)
Clinical description, n (%)			
AA with ≥ 50% scalp hair loss and no experience of eyebrow or eyelash loss[a]	6 (20)	4 (27)	10 (22)
AA with ≥ 50% scalp hair loss and experience of partial or full eyebrow and/or eyelash loss[a]	24 (80)	11 (73)	35 (78)
Time since diagnosis (years), mean ± SD (range)	11·7 ± 12·0 (1–47)	12·1 ± 10·1 (2–39)	11·8 ± 11·3 (1–47)
Most recent SALT score (%), mean ± SD (range)	57·9 ± 40·4 (0–100)	85·9 ± 20·3 (50–100)	67·2 ± 37·2 (0–100)
JAKi exposure, n (%)			
JAKi experienced	18 (60)	2 (13)	20 (44)
JAKi naive	12 (40)	11 (73)	23 (51)
Unknown,[b] either JAKi or placebo	0 (0)	2 (13)	2 (4)
Current treatment, n (%)			
Oral JAKi	15 (50)	0 (0)	15 (33)
Other treatment(s)[c]	4 (13)	3 (20)	7 (16)
Unknown,[b] either JAKi or placebo	0 (0)	2 (13)	2 (4)
No treatment	13 (43)	10 (67)	23 (51)
Sex, n (%)			
Male	13 (43)	6 (40)	19 (42)
Female	17 (57)	9 (60)	26 (58)
Age (years), mean ± SD (range)	35·2 ± 16·9 (15–72)	29·5 ± 8·4 (18–43)	33·3 ± 14·8 (15–72)
Ethnicity/race, n (%)			
Asian	5 (17)	4 (27)	9 (20)
Black or African American	1 (3)	1 (7)	2 (4)
White	21 (70)	4 (27)	25 (56)
Hawaiian or Pacific Islander	0 (0)	1 (7)	1 (2)
Hispanic	0 (0)	5 (33)	5 (11)
Other	3 (10)	0 (0)	3 (7)
Education, highest certificate achieved			
No high school diploma	6 (20)	3 (20)	9 (20)
High school diploma or equivalent	8 (27)	7 (47)	15 (33)
Associate's degree	2 (7)	0 (0)	2 (4)
Bachelor's degree or higher	14 (47)	5 (33)	19 (42)

AA, alopecia areata; JAKi, Janus kinase inhibitor; SALT, Severity of Alopecia Tool. [a]Some round 1 patients had successful JAKi treatment but SALT score ≥ 50% prior to treatment. [b]Two round 2 patients were in a current clinical trial, and it was unknown whether they were receiving a JAKi or placebo. [c]Two patients received a JAKi and 'other treatments'. Other treatments included Biotin Forte with zinc (n = 1), clobetasol 0·05% ointment (n = 2), diphenylcyclopropenone (n = 2), excimer (n = 1), intralesional triamcinolone (n = 3), Luxiq foam (n = 1), minoxidil (n = 1), Rogaine (n = 1), slow-release iron (n = 1) and vitamin E (n = 1).

Understanding successful treatment

Patients were asked to identify the percentage of scalp hair that they would need to have to consider a treatment successful (Figure S1; see Supporting Information). Patients deemed treatment success at a median 80% in round 1 (range 30–99%; n = 26) and median 75% in round 2 (range 50–100%; n = 15).

Quantity was the single most important factor for determining meaningful growth. While the location of growth was important for some patients, a sufficient quantity of hair could cover missing patches of hair. Most patients considered a treatment successful even if the newly grown hair was different in colour, quality or thickness from their original hair (round 1, 15 of 20; round 2, 13 of 15): 'I [...] feel like any hair is a win, so I mean, if it's not exactly the way it was before, that's okay with me [...] I'd feel a bit more normalcy if I just had hair at all' (44-F-100).

Saturation analysis

Saturation was reached in round 1: all signs and symptoms concepts were identified prior to completion of the interviews and resulted in a comprehensive and in-depth understanding of AA signs and symptoms. No new concepts emerged in the round 2 sample, which comprised greater ethnic diversity and lower educational levels, further confirming saturation.

Development of the Scalp Hair Assessment PRO™

To explore patients' familiarity with percentages, iterative versions of the Scalp Hair Assessment PRO™ were cognitively debriefed in both rounds. An initial version included five response category descriptors (Figure S2; see Supporting Information), a second version prompted patients to provide percentage ranges for each response category, and a third version included percentage ranges based on earlier clinician input.[15]

Round 1 (n = 30)

Seventeen patients correctly interpreted 'hair loss' to mean hair currently missing from the scalp. However, 13 were confused by or misinterpreted the meaning of 'hair loss'. Some interpreted this to mean the hair that was lost or shed on that day (n = 5), while others incorrectly rated their hair loss before recent growth or treatment (n = 5), rated their full-body hair loss (n = 2) or described their level of concern about scalp hair loss (n = 1).

Few patients suggested changes to improve the PRO. The most common suggestions related to the response categories. Three patients spontaneously suggested adding percentage ranges to the category descriptors to make assessment easier or more accurate. All patients provided percentage ranges that they associated with each response category descriptor. Most differences appeared regarding the thresholds between the 'moderate'/'large' and 'large'/'very large' categories (Figure S3; see Supporting Information). Three patients suggested that a sixth category should be added to describe hair loss of 80–100%, as this amount was more severe than the descriptor 'very large'. Six patients suggested that a sixth category could be added to represent total hair loss.

The patients were then shown percentage ranges proposed by clinicians (Figure S4; see Supporting Information). Most patients agreed with the proposed ranges for the 'no hair loss', 'limited' and 'moderate' categories. Twelve patients agreed with the 'large' and 'very large' ranges of 50–94% and 95–100%, respectively. While seven patients agreed that the 'very large' category descriptor corresponded to 95–100%, five patients suggested alternative descriptors (e.g. 'complete', 'total', 'extreme').

Interim analysis and modifications between round 1 and round 2 interviews

Given the importance of consistent interpretation of the measurement concept,[16,22] a second round of interviews was considered necessary to test revised wording. The term 'hair loss' was rephrased as 'missing hair', each percentage range was followed by the phrase 'of my scalp is missing hair', and additional wording in the first response category anchored the meaning of 'a full head of hair' (Figure 1). To address patients' concerns, the 'very large' category was renamed as 'nearly all or all'. Additionally, while most patients did not include vellus hair in their assessment, instructions were added to rate 'vellus hair' (i.e. baby hair or 'peach fuzz') as 'missing hair' to improve clarity. Finally, an instruction to use mirrors to view the entire scalp was added to aid accurate completion.

Round 2 (n = 15)

All 15 patients interpreted the measurement concept as intended and understood the vellus hair explanation and instruction: 'I understand that anything that's just like fuzzy hair is not included as hair growth' (44-F-100).

Most (n = 12) patients agreed with the percentage ranges derived from the prior clinician and patient interviews (Figure 2). All patients could use both the descriptor and percentage range (n = 11), or just the percentages (n = 4) to select a category. Patient comments on the use of percentages to aid completion are summarized in Table S2 (see Supporting Information).

Meaningful change

Most of the patients in round 1 and round 2 who were asked (34 of 35, 97%) indicated that treatment would be successful if they moved from ≥ 50% missing hair at baseline to the 'limited' category (≤ 20% missing hair) on the Scalp Hair Assessment PRO™. Indeed, many patients commented that achievement of the 'moderate' (n = 11) or 'large' (n = 2) categories would also be successful (i.e. ≤ 49% and ≤ 94% missing hair, respectively). Patients perceived ≤ 20% hair loss as an amount that would have a positive impact on their daily lives: 'I would feel a lot more confident about meeting new people' (35-M-89) and '[I'd feel] a lot better, happier, satisfied' (34-F-54). Additionally, most of the patients who were asked (10 of 14) confirmed that it was important to record patients' and clinicians' assessments during clinical trials.

Discussion

This qualitative study confirmed that scalp hair growth is an important AA treatment outcome. The Scalp Hair Assessment PRO™ was developed in line with FDA PRO Guidance for Industry[16] and is a content-valid (i.e. interpretable, relevant and usable) measure of scalp hair loss.[17,22,25] Importantly, all patients could provide ratings using the percentages and/or descriptors. While some patients were familiar with using percentages to describe their scalp hair, likely due to them discussing the amount of hair in these terms with their doctors, other patients who did not spontaneously use percentages noted that they were helpful. Ultimately, the PRO allows patients to decide whether to use the percentage range, the descriptor, or both, to rate their scalp hair.

Throughout the development process, modifications were made to reduce inconsistent interpretation and ensure that patient perspectives were reflected in the response category descriptors and corresponding percentage ranges. There was agreement among patients that successful treatment would result in ≤ 20% hair loss (the categories no or limited area of missing hair). No comparable studies exist, to date, to contextualize this result further.

The Scalp Hair Assessment PRO™ was developed to fulfil the need for a simple PRO measure to assess disease severity, as other PRO measures used in AA clinical trials comprise multiple items that assess health-related quality of life alongside signs and symptoms.[8] Thus, the Scalp Hair Assessment PRO™ provides single-item assessment of quantity, which the

Use mirrors to look at your entire scalp.

Please rate **the total area of your scalp that is missing hair right now.**

Areas of *vellus* hair (peach fuzz or baby hair) should **also** be considered as missing hair.

Please select **one** answer.

❑$_0$ **No missing hair** (0% of my scalp is missing hair; I have a full head of hair)

❑$_1$ **A limited area** (1–20% of my scalp is missing hair)

❑$_2$ **A moderate area** (21–49% of my scalp is missing hair)

❑$_3$ **A large area** (50–94% of my scalp is missing hair)

❑$_4$ **Nearly all or all** (95–100% of my scalp is missing hair)

Abbreviations: PRO, patient-reported outcome.

Figure 1 Version 2 of the Scalp Hair Assessment PRO™.

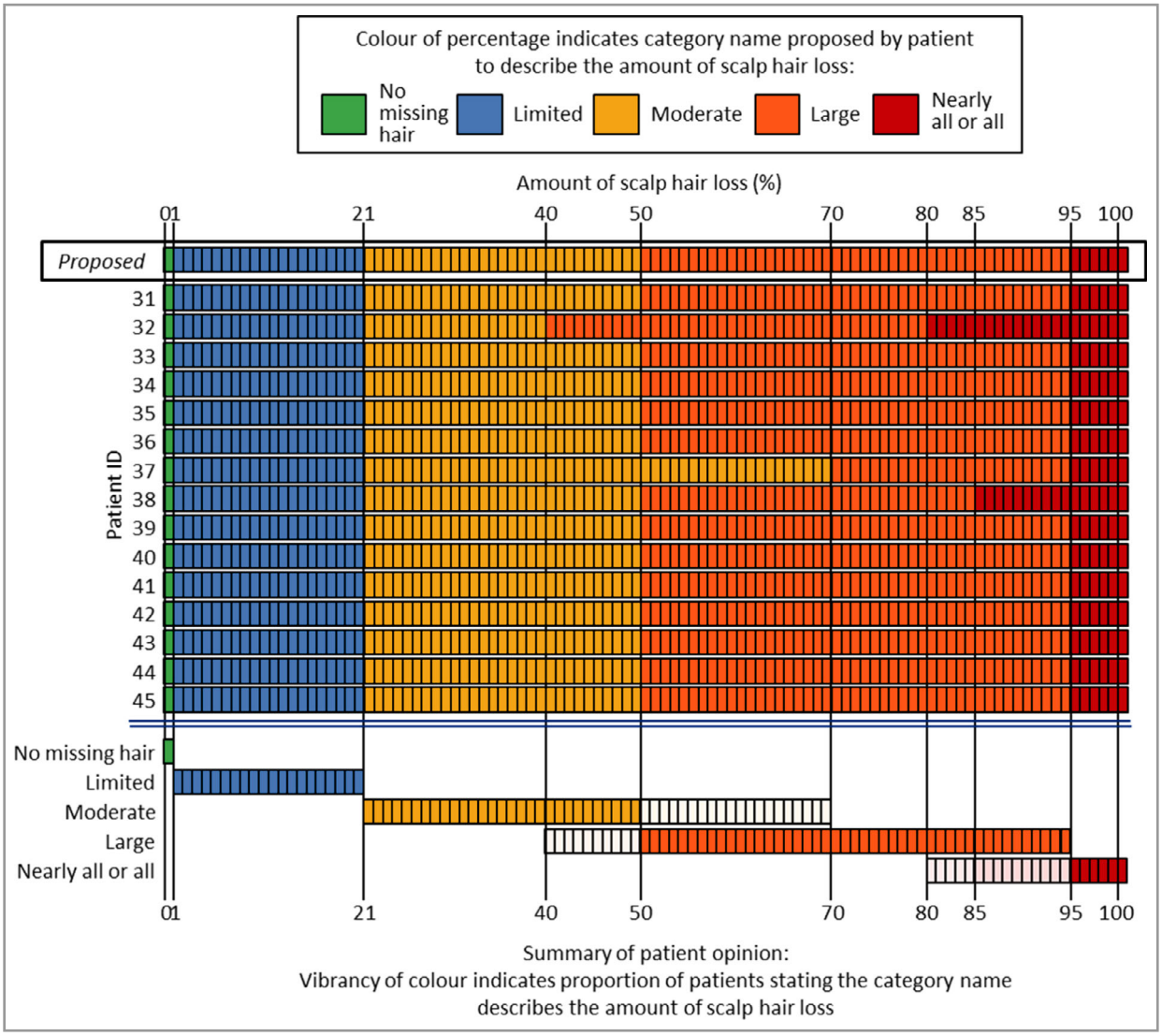

Figure 2 Round 2 patients' agreement with the percentage ranges associated with each category.

results of this study indicated was the most critical aspect of scalp hair loss to patients. Importantly, the PRO can provide a complementary score to a clinician report, which patients confirmed as important. The AA-IGA™,[15] which is based on the clinician's SALT score, and Scalp Hair Assessment PRO™ will permit comparable assessments with minimal completion burden. While the Scalp Hair Assessment PRO™ was developed to inform clinical trial endpoints, this measure has potential utility in clinical practice to understand hair loss status prior to treatment, to facilitate discussion between patients and clinicians, and to achieve a shared understanding of treatment goals.

Limitations of this study are acknowledged. Participants were included only if they had experienced ≥ 50% scalp hair loss, and all were recruited in North America, and thus the findings may not be generalizable to other populations, cultures and countries without further confirmation. Although scalp hair loss was the most bothersome sign or symptom of AA, patients identified other important signs and symptoms including eyebrow and eyelash loss, eye irritation and nail damage, for which novel measures have been developed.[26] Additionally, while the Scalp Hair Assessment PRO™ is content valid, further quantitative research will be undertaken to validate its psychometric properties (e.g. reliability, and ability to detect change).[16]

In conclusion, the Scalp Hair Assessment PRO™ is a content-valid, clinically meaningful measure that reflects patients' and clinicians' perspectives and treatment expectations for AA.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1 Scalp hair percentage needed for patients with alopecia areata (n = 41) to deem a treatment successful.

Figure S2 Version 1 of the Scalp Hair Assessment PRO (shown to round 1 patients).

Figure S3 Percentage ranges suggested by round 1 patients for each response category.

Figure S4 Round 1 patients' agreement with percentage ranges proposed by clinicians for each category.

Table S1 Patient interview inclusion and exclusion criteria.

Table S2 Inclusion of percentages in version 2 of the Scalp Hair Assessment PRO™.