Development of the Alopecia Areata Patient Priority Outcomes Instrument: A Qualitative Study

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ABSTRACT

Introduction: Although alopecia areata (AA) profoundly impacts patients' physical appearance, emotional state, and daily activities, no treatment approved for AA currently exists. Patient-reported outcome (PRO) instruments currently used to capture patients' AA experiences do not meet the requirements to support claims of treatment benefit as described in the US Food and Drug Administration's 2009 PRO guidance. Our objective was to explore the consequences and priority treatment outcomes among individuals with AA and develop a PRO measure consistent with regulatory requirements that assesses these priorities and represents clinical benefit from the AA patient perspective.
Methods: Targeted literature and instrument reviews informed an initial concept set.

Concept elicitation interviews with 20 adults with AA confirmed the relevance and importance of the initial concepts, identified additional relevant concepts, and informed an AA consequence model. Thematic analysis yielded a draft item pool, which was evaluated through two iterative rounds of cognitive debriefing interviews with 16 patients with AA (9 adults; 7 adolescents).
Results: Hair loss was the primary consequence of importance to patients with AA. Patients emphasized the need to differentiate hair loss by location: scalp, eyebrows, eyelashes, and body. Consequences of AA include difficulty conducting daily activities, particularly outdoor activities and exercise, and emotional impacts such as sadness, frustration, and negative self-image. Following cognitive debriefing interviews, 11 items were included to form the Alopecia Areata Patient Priority Outcome (AAPPO), assessing AA-related symptoms and impacts over the past week.
Conclusions: The AAPPO is a novel, content-valid PRO that captures the consequences of AA of the highest priority to patients.

Keywords: Activity; Alopecia areata; Consequence; Development; Emotional; Hair loss; Impact; Patient-reported outcome; Qualitative; Symptom

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Key Summary Points

Patients with alopecia areata (AA) experience profound impacts on their physical appearance, emotional state, and daily activities and face unmet treatment needs. None of the available patient-reported outcome (PRO) measures currently used to evaluate patients' experiences with AA were developed in line with regulatory requirements.

Based on qualitative research with adults and adolescents with AA and a review of the published evidence, a novel AA-specific PRO measure was developed to capture the consequences and priority treatment outcomes of individuals with AA.

Cognitive debriefing interviews with patients confirmed the content validity of the measure, which was developed in a manner consistent with regulatory guidance.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14054123.

INTRODUCTION

Alopecia areata (AA), a T-cell-mediated disease characterized by nonscarring hair loss, is one of the most common autoimmune diseases for both men and women [1]. People living with AA are at a higher risk than the general population of developing depression, anxiety, and social phobia [2]. Living with AA has also been associated with much higher levels of body dissatisfaction and concern with general appearance due to the associated hair loss [2].

Treatment for AA typically involves off-label use of topical, intralesional, and systemic corticosteroids as well as non-steroidal treatments such as topical immunotherapy, topical minoxidil, topical irritants such as anthralin, and systemic immunosuppressants such as cyclosporine or methotrexate [3]. This strategy yields limited success, as most patients with AA relapse after therapy, and long-term use of these treatments is associated with concerns regarding tolerability and safety [4]. The symptomatic and emotional consequences of AA, coupled with a lack of highly effective treatment options, represent a significant unmet medical need [1].

In the age of patient-focused drug development (PFDD), instruments that assess benefit in clinical trials of investigational AA therapies must address outcomes and consequences of greatest priority to patients and adhere to regulatory requirements for development [5]. The objectives of this study were to (i) explore the consequences and priority treatment outcomes of adults and adolescents with AA and, if necessary, (ii) develop a patient-reported outcome (PRO) measure consistent with current regulatory expectations and representing clinical benefit from the AA patient perspective [6].

METHODS

This research was conducted in two stages: concept exploration and content confirmation. Following regulatory guidance on development of a PRO intended for use in a clinical trial setting to assess clinical benefit from the patient perspective (i.e., its context of use), concept exploration included reviews of existing data sources, followed by concept elicitation (CE) interviews with AA patients to identify patient priority concepts. Results from this first stage informed generation of a disease consequence model as well as a set of draft items. These items were then evaluated during content confirmation, which included cognitive debriefing (CD) interviews to ensure that the items assess patient priority outcomes in a manner reflective

of how they are experienced. The qualitative research study materials were reviewed and approved by the RTI Institutional Review Board (Approval No. 14241). The study complied with the Declaration of Helsinki, and all interview participants provided informed consent.

Content Exploration

Concepts that should be considered for inclusion in an AA-specific PRO were explored through targeted reviews of the literature and the ePROVIDE™ clinical outcomes assessment (COA) repository, as well as the 11 September 2017 FDA Patient-Focused Drug Development (PFDD) public meeting on AA [7, 8].

Literature, Instrument, and Patient-Focused Drug Development Meeting Materials Review

A literature search was conducted within PubMed to identify articles focusing on concepts and experiences associated with living with AA. The search (Table 1) targeted articles containing information on concepts of importance from the patient perspective. Articles were included if they contained the relevant patient population and data related to patient-reported symptom or impact concepts.

In addition, a desktop search of the ePRO-VIDE™ database of COA instruments was conducted to identify AA-specific PRO instruments to inform the list of relevant patient concepts further(ePROVIDE, 2018) [7]. Study staff also attended the 11 September 2017 FDA PFDD public meeting on AA and reviewed the meeting report [8] and transcript [9] to identify any additional priority concepts to persons with AA discussed during this meeting not represented in the literature and instrument reviews.

AA Consequence Model

An AA consequence model was drafted based on the literature and instrument reviews and the FDA PFDD meeting materials and refined based on data collected during the CE interviews. The model provided a framework for presenting the consequences of AA that represent priorities for treatment from the AA patient perspective.

CE Interviews

Patient interviews were conducted to confirm the AA consequence model and identify any missing concepts. Patient databases from two research organizations (L&E Research and Shifrin Hayworth) were utilized to identify participants for in-person CE interviews at three US locations (Charlotte, North Carolina; Tampa, Florida; and Southfield, Michigan). Medical recruiters employed a structured screening questionnaire to determine study eligibility. Eligible individuals were aged 12 years or older, were able to speak and read English, had self-reported a clinician diagnosis of AA, ≥ 50% hair loss, and had a sustained period of hair loss for ≥ 2 years. Although adolescents (aged 12–17 years) were eligible for the CE interviews, none could be recruited; however, adolescents did participate in a CE task during subsequent CD interviews. Individuals with other forms of alopecia (e.g., traction or scarring alopecia) or active forms of other inflammatory skin diseases (e.g., psoriasis, seborrheic dermatitis, lupus) were excluded.

The interviews were led by two experienced qualitative researchers (SM and NH, one of whom led the interviews and the other took notes) and followed a semi-structured interview guide. The interviews began with open-ended questions about participants' experiences with AA (e.g., the initial signs, symptoms, and how this onset of disease affected their daily life). Participants were then asked questions to elicit additional concepts that were found in other content exploration sources but not spontaneously reported during the open-ended portion of the interview. Each interview lasted approximately 60 min and was audio recorded and transcribed. Additional CE interviews were conducted until saturation was reached (i.e., no new concepts emerged).

Content Confirmation

Based on the CE findings from the content exploration stage of work and a review of existing instruments, de novo instrument generation work was deemed necessary. The consequences of AA that were most frequently

Table 1 Literature search strategy

Search	Terms	Records
Disease		
#1	#1 "Alopecia Areata"[Mesh] OR "alopecia areata"[Title/Abstract] OR "alopecia circumscripta"[Title/Abstract] OR "alopecia totalis"[Title/Abstract] OR "alopecia universalis"[Title/Abstract]	1,457
Burden		
#2	#2 #1 AND ("Alopecia Areata/psychology"[Mesh] OR "Quality of Life"[Mesh] OR "Activities of Daily Living"[Mesh] OR "Stress, Psychological"[Mesh] OR "Patient Satisfaction"[Mesh] OR "Emotions"[Mesh] OR "Anxiety"[Mesh] OR "Depression"[Mesh] OR "Life Change Events"[Mesh] OR "quality of life"[Title/Abstract] OR stress*[Title/Abstract] OR burden[Title/Abstract] OR impact[Title/Abstract] OR psychologic*[Title/Abstract] OR psychiatric[Title/Abstract] OR psychosocial[Title/Abstract] OR capabilit*[Title/Abstract] OR embarrass*[Title/Abstract] OR emotion*[Title/Abstract] OR "self-conscious"[Title/Abstract] OR anxiety[Title/Abstract] OR depress*[Title/Abstract] OR neurotic*[Title/Abstract] OR "life quality"[Title/Abstract] OR "QoL"[Title/Abstract] OR "hrql"[Title/Abstract] OR "hrqol"[Title/Abstract] OR "well being"[Title/Abstract] OR "SF-6D"[Title/Abstract] OR "SF-36"[Title/Abstract] OR "activities of daily living"[Title/Abstract] OR "daily life activities"[Title/Abstract] OR "patient satisfaction"[Title/Abstract] OR patient experience*[Title/Abstract] OR patient's experience*[Title/Abstract] OR patients' experience*[Title/Abstract] OR "functional ability"[Title/Abstract] OR "functional capacity"[Title/Abstract] OR "functional status"[Title/Abstract] OR "social life"[Title/Abstract])	250
Patient's perspective		
#3	3 #2 AND ("Qualitative Research"[Mesh] OR "Focus Groups"[Mesh] OR "Interviews as Topic"[Mesh] OR "Patient Reported Outcome Measures"[Mesh] OR "Self Report"[Mesh] OR "Self-Assessment"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh] OR "Surveys and Questionnaires"[Mesh] OR qualitativ*[Title/Abstract] OR focus group*[Title/Abstract] OR interview*[Title/Abstract] OR oral histor*[Title/Abstract] OR self report*[Title/Abstract] OR self assess*[Title/Abstract] OR patient report*[Title/Abstract] OR proxy report*[Title/Abstract] OR patient perspective*[Title/Abstract] OR patient's perspective*[Title/Abstract] OR patients' perspective*[Title/Abstract] OR questionnaire*[Title/Abstract] OR survey*[Title/Abstract] OR diary[Title/Abstract] OR assessment*[Title/Abstract] OR scale[Title/Abstract] OR inventory[Title/Abstract] OR index[Title/Abstract] OR "Interview"[Publication Type])	113
Exclusions		
#4	"Animals"[Mesh] NOT "Humans"[Mesh] 1,042,774	1,042,774
#5	"Comment"[Publication Type] OR "Letter"[Publication Type] OR "Editorial"[Publication Type]	646,283
Total		
#6	(#3 NOT (#4 OR #5))	108

endorsed by participants and described as most impactful were selected for inclusion in a draft PRO measure. The draft set of items was tested during CD interviews with adult and adolescent participants to confirm that they adequately captured the concepts of priority to AA patients.

CD Interviews

Participants in the CD interviews were identified and recruited by a board-certified practicing dermatologist based in Fairfield, Connecticut. The CD interviews were conducted via telephone so that the interviews could be scheduled at the participants' convenience and to expedite collection of content confirmation evidence so that the measure could be finalized for inclusion in a planned clinical trial. Enrolled participants resided in Connecticut ($n = 8$), New York ($n = 5$), Ohio ($n = 1$), Massachusetts ($n = 1$), and Pennsylvania ($n = 1$). Inclusion and exclusion criteria were identical to those for recruiting the CE sample, with the exception that all CD participants had a dermatologist-confirmed diagnosis of AA and had experienced a sustained period of hair loss for ≥ 6 months.

The same interviewers (SM and NH) conducted the CD interviews following a semistructured interview guide. The adult interviews began with a brief exploration of the participant's experiences with AA and the consequences considered to be of highest priority. As the initial CE set was composed solely of adults, the adolescent participants (i.e., those aged 12–17 years) in this set of interviews first engaged in a detailed CE discussion. All CD participants were debriefed on the draft items using a "think aloud" format that allowed interviewers to gather information about participants' interpretations of each item [10]. Specifically, after providing their feedback on the title and instructions, participants read each item while describing their thought processes out loud (i.e., understanding of the question and reasons for selecting a specific response option). Interviewers also asked probing questions about participants' interpretation of the questions, recall period, and response options to identify any need for modifications to improve comprehension and ease of response. Upon completion of the measure, participants were asked whether any item(s) could be omitted and whether any important concepts were missing from the draft item set. The wording and response options of the draft items were refined after the first set of CD interviews. Adult interviews lasted approximately 60 min and adolescent interviews lasted approximately 90 min due to the inclusion of the CE portion; all interviews were audio recorded and transcribed.

Data Analysis

Thematic analysis of the qualitative data was conducted in a standard, systematic manner. For CE interviews, the symptom and impact consequences described during each interview were tabulated, with the aim of documenting concept saturation (i.e., the point at which no new priority consequences emerged) [6, 10]. In addition, participant quotations characterizing the symptom and impact consequences to be included in the item set were documented.

After each round of CD interviews, the interviewers analyzed their field notes to identify any potential problems within the questionnaire. Specifically, the results of the first round of CD interviews were reviewed to summarize and identify patterns in the way participants interpreted and responded to each item and determine how well the items captured consequences of priority to the participants. The authors then implemented revisions to the draft questionnaire based on the interview results. The revised questionnaire was evaluated in the second round of interviews. An itemtracking matrix was also produced for each round of interviews to document revisions made to the items and the rationale for the revisions.

RESULTS

Content Exploration

Literature, Instrument, and Patient-Focused Drug Development Meeting Materials Review.

Of 108 abstracts found in PubMed, 43 were deemed potentially relevant and reviewed in full-text form. Ultimately, 25 articles were included, most of which were observational studies, while 4 included a qualitative component. In addition to the hallmark symptom of hair loss, a broad range of potential impacts of AA were reported, including emotional symptoms (e.g., bullying, perceived stigma, and functional limitations such as difficulty engaging in daily activities).

Across all of the observational and mixed methods studies reviewed, the most commonly utilized COA measures were the Dermatology Life Quality Index (DLQI) [11] (*n* = 7), Skindex (*n* = 6; includes the 16-item [*n* = 3], 17-item [*n* = 1], and 29-item [*n* = 2] versions) [12–14], and the 36-item Short Form Health Survey (SF-36) [15, 16] (*n* = 5). Importantly, none of these measures were developed to capture the AA patient experience. The first two were designed to assess general dermatologic skin conditions and thus have item wording that is not appropriate for the AA patient (e.g., items ask about "skin" rather than "hair"). The SF-36 is a generic measure of health status and does not fully capture the range of concepts that are likely of priority to the AA patient. Full-text article review and a desktop search of ePROVIDE™ revealed three additional measures that were developed specifically for the AA population: the Alopecia Areata Symptom Impact Scale (AASIS) [17], the Alopecia Areata Quality of Life (AAQ) [18], and the Alopecia Areata Quality of Life Index (AA-QLI) [15, 16, 19].

Findings from the PFDD meeting revealed the most significant AA symptoms to be hair loss on the scalp, hair loss on other areas of the body, and sensitivity to sun [7]. Impacts of AA included activity limitations and emotional symptoms such as depression, anxiety, and perceived stigma [7].

CE Interviews

A total of 20 patients participated in the CE interviews. Average age of these participants was 52 years, and participants had been experiencing AA for an average of nearly 20 years. Most CE interview participants were female (*n* = 16; 80%), and 60% were African American

(*n* = 12). Participants ranged in disease severity (Table 2).

During the CE portion of the second set of interviews, adolescents provided feedback similar to that provided by adult CE participants. Descriptions of the onset of AA included an initial experience of diffuse hair thinning or discrete patches of complete hair loss. Participants detailed the marked emotional impact of both the diagnostic process as well as experiences with treatments (both prescribed and nonprescribed) and noted that treatment had little to no positive effect on their hair loss. When exploring beyond the initial scalp hair loss, participants spontaneously reported very few additional symptoms or signs (Table 3). Loss of eyebrow and eyelash hair were the most common spontaneously reported signs (*n* = 6 for each). When discussing hair loss, participants emphasized the need to differentiate each location separately, including scalp hair, eyebrows, eyelashes, and body hair. Other scalp hair signs—such as white hair and patchy hair regrowth—were less frequently reported and considered less bothersome than scalp hair loss. Although itch was endorsed by 15 patients, only one did so spontaneously. Also, patients noted difficulty in differentiating itch related to disease and treatment versus itch related to other factors (e.g., application of AA treatments, wearing wigs). When discussing other signs and symptoms of AA, painful/sensitive skin was endorsed as a bothersome symptom but only by three participants when probed.

Participants also described the consequences of AA in their daily lives (Tables 4 and 5). Among the 20 adult participants, impacts on self-image (*n* = 12) as well as on social interactions and relationships (*n* = 12) were spontaneously endorsed by over half of participants. When probed, frustration was also endorsed by over half of the sample (*n* = 14) (Table 4). When spontaneous and probed reports were combined, the most frequent additional impacts reported were those affecting daily activities, including outdoor activities (*n* = 12), feelings of sadness (*n* = 11), and sexual function or intimacy (*n* = 11). When asked to identify the impact of AA that bothered them the most, adult participants reported altered self-image,

Table 2 Participant Characteristics

Characteristic	Concept elicitation Adults (*n* = 20)	Cognitive debriefing		Total (*N* = 36)
		Adults (*n* = 9)	Adolescents (*n* = 7)	
Age, years				
Mean, range[a]	52.3, 29–70	31.5, 20–56	15.0, 12–17	38.6, 12–70
Sex, *n* (%)				
Female	16 (80)	7 (78)	3 (43)	26 (72)
Race/ethnicity				
White	7 (35)	9 (100)	6 (86)	22 (61)
Black	12 (60)	0 (0)	1 (14)	13 (36)
Hispanic	1 (5)	0 (0)	0 (0)	1 (3)
Time since diagnosis, years				
Mean, range[b]	19.9, 2–52	14.6, 7–23	7.9, 1–16	15.8, 1–52
Severity, *n* (%)				
< 50% hair loss[c]	1 (5)	0 (0)	0 (0)	1 (3)
50–99% hair loss	11 (55)	5 (56)	4 (57)	20 (56)
Totalis (complete loss of hair on the scalp)	3 (15)	0 (0)	2 (29)	5 (14)
Universalis (complete loss of hair on the scalp, face, and body)	5 (25)	4 (44)	1 (14)	10 (28)

All data were self-reported

[a] Mean age across the 29 adult participants was 46 years (range 20–70 years)

[b] Mean time since diagnosis across the 29 adult participants was 18 years (range 2–52 years)

[c] Participant had previous diagnosis of alopecia universalis

emotional impacts, and impacts on social interactions and relationships.

Among adolescents (*n* = 7), impacts on participation in outdoor activities, often sports or water activities, were endorsed by nearly all participants (*n* = 6; Table 4). Impacts on self-image/feeling self-conscious were also endorsed by nearly all participants (*n* = 6). When probed, emotional impacts of feeling sad (*n* = 6), frustrated (*n* = 5), embarrassed (*n* = 5), and worried (*n* = 5) were endorsed by nearly all adolescents. When asked to identify the impact of AA that bothered them the most, adolescent participants endorsed impacts on physical activities as well as emotional impacts.

Across the adult and adolescent participants, similar consequences of AA emerged in spontaneous and probed reporting, including self-consciousness, impacts on social interactions, and frustration. Proportionally more adolescents than adults reported impacts relating to daily or outdoor activities; embarrassment, which was not separately probed among the adult participants, was endorsed by five of seven adolescent patients.

Review of Content Exploration Findings

Across the sources that informed content exploration, there was general consensus

Table 3 Alopecia areata symptoms and signs reported by participants

Symptom or sign	Adults (n = 20)		Adolescents (n = 7)	
	Spontaneous	Probed	Spontaneous	Probed
Loss of scalp hair[a]	20	–	7	–
Loss of eyelashes	6	4	–	1
Loss of eyebrows	6	6	–	2
White hair regrowth	2	11	–	–
Itching	1	10	–	4
Tingling	1	7[b,c]	–	1
Loss of body hair	1	8	1	2
Fingernail/toenail issues	1	4	–	1
Hair growing back patchy	1	5	–	6
Pain	–	3	–	–
Numbness	–	3	–	–
Burning	–	2[a]	–	–
Loss of nose hair	–	2	–	1
Stinging	–	1	–	1

Signs/symptoms reported spontaneously by one participant each (and not probed upon) included tiredness, lightheadedness, hunger, and headache (due to the scalp being exposed)

Bleeding was probed of all participants, but none endorsed this symptom

[a] Scalp hair loss, as an eligibility criterion, was required of all participants

[b] One participant considered symptom to be a result of scratching

[c] One participant also reported a cold feeling on their scalp that would precede additional hair loss

regarding the priority symptoms and impacts of AA. Table 6 provides an overview of concepts endorsed by five or more patients during CE interviews, and further supported by patient testimonials given during the FDA PFDD meeting, the qualitative literature, and existing COA measures. In addition to the hallmark symptom of scalp hair loss, activity limitations were consistently reported across sources, particularly those pertaining to social interactions and daily activities. Various emotional symptoms, including altered self-image, frustration, and sadness, were reported in multiple sources.

The AA consequence model is represented in Fig. 1 and incorporates information from the existing data sources and the qualitative patient interviews. The model further served to identify content for inclusion in an instrument representing clinical benefit from the patient perspective.

Review of the priority concepts alongside the existing AA measures confirmed that the existing instruments are missing concepts of priority to individuals with AA and/or employ response options and recall periods which are not likely to capture the impacts of disease and treatment in the context of an AA clinical trial. Based on this assessment, the team initiated de novo development of an AA-specific PRO measure.

Item Development

Based on concepts endorsed across the reviewed sources, six symptoms and seven impacts (a

Table 4 Impacts of Alopecia Areata Reported by Participants

Impacts	Adults (n = 20)		Adolescents (n = 7)	
	Spontaneous	Probed	Spontaneous	Probed
Hard to participate in daily or outdoor activities (sports, swimming)	8	4	5	1
Sadness	3	8	–	6
Self-image/self-consciousness	12	3	3	3
Frustrated	–	14	–	5
Social interactions	12	3	1	4
Embarrassed[a]	4	–	–	5
Worry	2	4	3	2
Anxiety	–	8	–	3
Anger	2	5	–	3
Bullied	–	–	–	2
Depressed	2	4	–	2
Work or school productivity	4	2	–	1
Sexual function/intimacy[b]	4	7	–	–
Concerned about passing condition on to children[b]	1	7	–	–
Thoughts of self-harm[c]	–	1	–	–

Table summarizes all probed impacts across both adults and adolescents

[a] Not probed for adult patients

[b] Not probed for adolescent patients

[c] Self-harm was probed upon but not endorsed by any of the adolescent participants

total of 13 concepts; Table 7) were selected as candidate items. Priority was given to concepts that were endorsed by a majority of CE participants and were issues that are able to be improved with treatment in the time frame of a clinical trial. Items were drafted employing a recall period and language reflective of how CE and CD participants described their experiences with AA.

Content Confirmation

A total of 16 patients participated in two iterative rounds (n = 8 in each round) of CD interviews: 9 adults (round 1, n = 5; round 2, n = 4) and 7 adolescents (round 1, n = 3; round 2, n = 4). The average participant age was 32 years

for the adults and 15 years for the adolescents. Most participants were white (n = 15; 93.8%) and female (n = 10; 62.5%), with adults having been diagnosed with AA for an average of just under 15 years and adolescents for nearly 8 years. All participants had experienced a fixed period of hair loss of at least 6 months. Participants ranged in disease severity (Table 2).

Results and feedback were consistent across the adolescent and adult participants and thus are presented together. Response options for Items 1–4 on hair loss were changed from a numeric to a verbal response scale, and the wording of several items was modified to improve clarity. When reviewing the items, round 1 participants generally reported that the measure covered all relevant concepts and that no important concepts were missing. Items 5

Table 5 Patient Quotes Regarding the Impact of Alopecia Areata

Adults

I'm real self-conscious over it. Even with me brushing back with a ponytail, I'm looking in the mirror to make sure that that spot is not seen. [Female, aged 61 years]

[I feel] extremely sad. Like, I broke down a couple times in front of my husband. [Female, aged 49 years]

I can't really go anywhere without someone staring or someone laughing at me, and depending on the day, it does upset me…it still never feels good when someone laughs about you being bald. [Female, aged 20 years]

A big thing for me is sometimes I don't feel comfortable exercising and like going to the gym because I don't want to have to deal with my hair if I get sweaty or something. [Female, aged 21 years]

When I was first diagnosed, I still liked going out. I would still go out and I wanted to. But now I don't want to. [Female, aged 29 years]

I didn't want to go out anywhere. Yeah. Blasted my ego and it, you know, here I was a model and a ladies' man and now I'm this guy with this bald head. I looked like a cue ball because of the loss of the eyebrows. [Male, aged 61 years]

It's sad when you see…I mean, I see people, the way people treated me with hair, without, with hair, without, and it was, it just sucked. I mean, it's a huge difference. [Male, aged 38 years]

Adolescents

I feel embarrassed because I look different than other people. [Male, aged 15 years]

I can't put my hair up in a ponytail and I have to have it in a certain style and I'm worried that people notice and I can't swim. And now that it's summer, that's kind of rough for me. [Female, aged 15 years]

[I] just like wanted to not be involved as much. Wanted to, like, hide myself and, like, not have attention on me. Because I felt like…people would, like, judge more because I look different. [Male, aged 17 years]

and 6 (fingernail/toenail issues and itch) were not widely endorsed as part of patients' experience with AA and were flagged for potential elimination.

Following the round 2 interviews, further refinements were implemented to yield the final item set. When queried about any concepts missing from the round 2 item set, participants generally reported that the items covered all relevant concepts. As expected, items addressing fingernail/toenail issues and itch were not widely endorsed and were thus removed from the final instrument content.

No participants reported difficulty with the contemporaneous recall period and understood that they were responding based upon their impression of their hair loss (scalp, eyebrow, eyelash, body) currently. Participants confirmed their ability to recall over the 1-week period for the remaining emotional symptoms and

activity limitation items and that these item concepts were appropriate for assessment referencing a past-week time frame.

The 11 items in the final version of the measure, the Alopecia Areata Patient Priority Outcomes (AAPPO) (see Table 7), were interpreted consistently, deemed relevant, and easily understood and answered by interview participants. The CD interviews confirmed the content and led to refinements to the wording and response options of the final questionnaire.

DISCUSSION

This study explored the consequences and priority treatment outcomes to individuals with AA, revealing the need for a novel PRO measure developed according to regulatory requirements and expectations for use in a clinical trial

Table 6 Concepts elicited across sources during content exploration

Symptom or impact	Qualitative		Qualitative literature (N = 4)	Existing measures (N = 6)
	Interviews (N = 27)	AA PFDD public meeting		
Hair loss				
Loss of scalp hair	27	✔	4	2
Loss of eyebrows	14	✔	–	1
White hair regrowth	13	✔	–	
Loss of body hair	12	✔	–	1
Hair growing back patchy	12	✔	–	1
Loss of eyelashes	11	✔	–	1
Other physical signs and symptoms				
Itching	15	✔[a]	–	4
Tingling	9		–	1
Fingernail/toenail issues	6	✔	–	
Activity limitations		✔		
Social interactions	20	✔	4	4
Hard to participate in daily or outdoor activities	18	✔	3	3
Sexual function/intimacy	11	✔	-	4
Work or school productivity	7	✔	1	5
Emotional symptoms				
Self–image/self-consciousness	21	✔	4	
Frustrated	19	✔	–	1
Sadness	17	✔	1	3
Worry	11	✔	1	3
Anxiety	11	✔	3	2
Anger	10	✔	1	1
Embarrassed	9	✔	1	3
Depressed	8	✔	3	2
Concerned about passing condition on to children	8	✔	–	1

PFDD patient-focused drug development

Reported by at least one participant during the PFDD meeting on September 11, 2017

[a] Participant quotes from the PFDD meeting described itch as a side effect of treatment for alopecia areata and not as a symptom of the disease itself
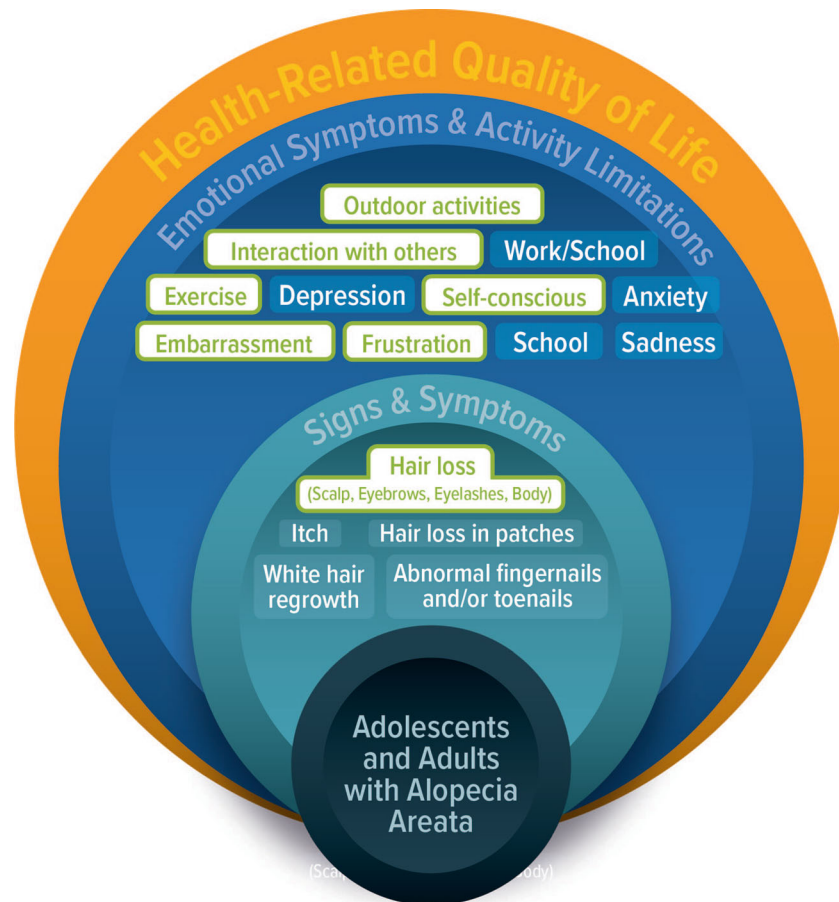
Fig.1 Alopecia Areata Consequence Model. The alopecia areata consequence model was developed iteratively. A literature and instrument review informed the initial list of concepts for the model, which was updated based on results from qualitative interviews with adults and adolescents with alopecia areata. Concepts with a green box correspond to items that were ultimately included in the Alopecia Areata Patient Priority Outcomes instrument

setting. Not surprisingly, the primary consequence of importance to individuals with AA was scalp hair loss. Additional consequences included hair loss from other areas (e.g., eyebrows), emotional impacts (e.g., sadness), and activity limitations (e.g., interactions with others).

Results from the CE interviews confirmed the relevance and priority of concepts identified in existing data sources and confirmed that no existing measure adequately captures the AA patient experience. Across adults and adolescents, the CE results indicate that the priority impacts of AA were relevant to both adult and adolescent participants. The priority concepts

reported by adolescents with AA were consistent with those reported by adults with AA, indicating that a single measure is appropriate for both subgroups.

After two iterative rounds of CD interviews, both adolescent and adult participants found the items comprehensive, easy to understand, and simple to answer. Participants were able to respond using the specified recall periods. Participants did not identify any concepts relating to key impacts of AA that were missing from the item set, supporting the content validity of the measure. These results provide evidence that the final item set adequately and appropriately

Table 7 Alopecia areata patient priority outcomes instrument concepts

Draft concepts evaluated in cognitive debriefing interviews	Final concepts in pilot questionnaire
Item 1. Hair loss, scalp	Item 1. Hair loss, scalp
Item 2. Hair loss, eyebrows	Item 2. Hair loss, eyebrows
Item 3. Hair loss, eyelashes	Item 3. Hair loss, eyelashes
Item 4. Hair loss, body hair	Item 4. Hair loss, body hair
Item 5. Problems with fingernails or toenails	
Item 6. Itching on scalp	
Item 7. Self-consciousness about hair loss	Item 5. Self-consciousness about hair loss
Item 8. Embarrassed about hair loss	Item 6. Embarrassed about hair loss
Item 9. Sad about hair loss	Item 7. Sad about hair loss
Item 10. Frustrated about hair loss	Item 8. Frustrated about hair loss
Item 11. Limited outdoor activity because of hair loss	Item 9. Limited outdoor activity because of hair loss
Item 12. Limited physical activity because of hair loss	Item 10. Limited physical activity because of hair loss
Item 13. Limited interactions with others because of hair loss	Item 11. Limited interactions with others because of hair loss

assesses priority consequences of AA to adolescents and adults.

Some limitations of this study should be noted. An important limitation is that adult participants in the CE interviews self-reported having a clinician diagnosis of AA, and clinical characteristics were not physician confirmed. However, clinical confirmation of diagnosis was an inclusion criterion for the CD portion of this study, and the priorities of the CE sample were acknowledged as relevant and comprehensive by the clinically confirmed CD participants. For both rounds of CD interviews, the researchers prioritized obtaining patients who had a confirmed diagnosis from an expert in dermatology, although this limited recruitment to a single clinical site. With 36 participants, the sample size of the study was small, although sufficient to accomplish the study objectives and achieve concept saturation. While CE and CD participants resided in five separate states, the overall geographic diversity of the patient sample was limited. An additional limitation is that CD interviews were conducted via telephone. Additional analyses are planned with a larger population to evaluate the AAPPO's structure, scoring, and measurement properties and establish that it is a fit-for-purpose measure of the impacts of AA from the patient perspective.

CONCLUSIONS

The AAPPO instrument is a content-valid PRO measure that contains 11 items assessing hair loss and key impacts of importance to both adults and adolescents with AA. The AAPPO employs a contemporaneous recall period for the four hair loss items and a 1-week recall period ("over the past week") for seven items addressing emotional consequences and activity limitations. Future research will evaluate the structure of the AAPPO, establish scoring and further support its use in AA clinical trials as a fit-for-purpose assessment of treatment benefit from the patient perspective. In addition, to enable use in global studies of AA, the measure

should undergo linguistic validation for use in other countries and to ensure that its content is meaningful and representative of priority AA consequences to other cultures.

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