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ORIGINAL RESEARCH

A Qualitative Study to Develop and Evaluate the Content Validity of the Vitiligo Patient Priority Outcome (ViPPO) Measures

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ABSTRACT

Introduction: Vitiligo can be associated with a psychological burden, stigmatization and impaired quality of life. Tools to assess the impact of vitiligo exist; however, none were developed in line with the FDA's patient-reported outcome (PRO) Guidance for Industry. This study aimed to explore the content validity of two newly developed PRO measures to assess the impact of facial and total body vitiligo on how patients feel and function.

Methods: Draft PRO measures were developed from existing literature and input from PRO experts, a patient advocate and a clinical expert. Qualitative interviews were conducted with US participants living with vitiligo and international dermatologists with vitiligo expertise. Concept elicitation methodology explored the relevance of concepts in the draft PRO, while cognitive debriefing assessed conceptual relevance and understanding/interpretation. Items were iteratively amended/added throughout the interview study.

Results: The 60 participants included adults (n = 48, 63% female, 18–62 years old) and adolescents (n = 12, 67% female, 12–17 years old) with Fitzpatrick Skin Types I–VI. Expert dermatologists from the US (n = 8), EU (n = 4), India (n = 1) and Egypt (n = 1) participated. Concept elicitation was utilized to confirm the signs/symptoms of vitiligo and the associated impact on emotional/psychological wellbeing, social functioning, daily life and work/school. Conceptual saturation was achieved. Most participants reported impacts on their emotional/psychological wellbeing (n = 57, 95%), e.g. feeling self-conscious (n = 35, 58%). Participants reported impacts on social functioning (n = 53, 88%), e.g. vitiligo being noticed by others (n = 42, 70%). There was general consensus between participants and expert dermatologists. Cognitive debriefing confirmed that the items were well understood. Most items were conceptually relevant; feeling self-conscious and feeling frustrated were highly endorsed. Items were removed based on low conceptual relevance (feeling abandoned, skin

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roughness) and expected redundancy (four items), resulting in two measures with three proposed domain scores: Emotional/Psychological Wellbeing; Social Functioning; and Physical Sensation. No comprehension concerns were observed in relation to the 7-day recall period or the item response scale/options. Eight dermatologists reviewed the PRO measures, confirming comprehensiveness and relevance.

Conclusion: The draft Vitiligo Patient Priority Outcomes (ViPPO) measures evaluate the impact of facial (ViPPO-F) and total body (ViPPO-T) vitiligo on emotional/psychological and social functioning. The ViPPO measures are well understood, comprehensive and content valid for adults and adolescents with vitiligo.

Keywords: Vitiligo; Quality of life; Qualitative research; Outcome measurement; Vitiligo Patient Priority Outcome

Key Summary Points

Individuals living with vitiligo experience depigmentation on the skin, which can occur at multiple locations on the body. Vitiligo may be associated with a psychological burden, stigmatization and impaired quality of life.

Assessing patient-reported outcomes (PROs) is essential in patient-focused drug development. Although PROs to assess the impact of vitiligo on quality of life do exist, none have been developed in line with the FDA PRO Guidance for Industry.

This qualitative interview study with individuals living with vitiligo and expert dermatologists developed a vitiligo consequence model and two content-valid PRO measures. The draft Vitiligo Patient Priority Outcomes (ViPPO) measures evaluate the impact of facial (ViPPO-F) and total body (ViPPO-T) vitiligo on emotional/psychological and social functioning.

The ViPPO measures are well understood, comprehensive, content valid and relevant for adults and adolescents with non-segmental vitiligo. The measures can be used in interventional clinical trials and in observational/real-world settings to evaluate patient-relevant experiences related to their vitiligo.

INTRODUCTION

Vitiligo is an autoimmune skin condition that is clinically characterized by white macules and patches due to the loss of functioning melanocytes in the skin [1, 2]. Vitiligo can be segmental (confined to the dermatome; usually a unilateral, localized presentation [3]) or, more commonly, non-segmental or generalized vitiligo (wide distribution; symmetrical distribution of depigmented lesions) [1, 4]. Approximately 80–90% of patients have non-segmental vitiligo. Non-segmental vitiligo is the subject of the work presented here.

Vitiligo signs (i.e. depigmentation and the body surface area affected) can be evaluated via clinician-reported outcomes (ClinROs) such as the Vitiligo Area Scoring Index (VASI) [5]. However, the impact of vitiligo on how patients feel and function is best understood via self-report. These data can be systematically collected through patient-reported outcome (PRO) measures implemented in clinical trials and in clinical practice.

The US Food and Drug Administration (FDA) PRO Guidance and draft Patient-Focused Drug Development (PFDD) Guidance provide standards for sponsors to achieve when selecting, developing or validating PRO measures for use in pharmaceutical clinical trials [6, 7]. Considering the known and considerable psychological burden [8], distress [9], stigmatization [9], uncertainty around disease progression [10, 11] and impairment of quality of life [8] associated with vitiligo, it is important to have valid, reliable and responsive PRO measures to evaluate patient-relevant experiences in clinical trials

and allow patients to report directly on their wellbeing. Ultimately, PRO data can facilitate our understanding of the efficacy of investigational treatments and inform clinical decision making.

Existing PRO measures used in vitiligo include the Self-Assessment Vitiligo Extent Score (SA-VES [12]), the Vitiligo-Specific Quality of Life (VitiQoL [13]), the Vitiligo Impact Patient Scale (VIPs [14]) and the Vitiligo Noticeability Scale (VNS [15]). The existing PROs have strengths in assessing specific aspects of vitiligo; e.g. the SA-VES provides a self-assessment of vitiligo involvement ('no involvement' to 'severe involvement') across 12 body areas. Similarly, the VNS item specifically evaluates the noticeability of vitiligo. However, neither measure assesses the *impact* of vitiligo on how patients feel. The VitiQoL and VIPs measures assess the impact of vitiligo on quality of life, including aspects of how patients feel and function. However, the VitiQoL (16 items) assesses the impact of vitiligo over the past month, which is longer than typically recommended for PRO measures in clinical trials due to a potential for recall bias [16]. Furthermore, the VIPs total score includes items around economic constraints, which limits its utility for clinical trials where the relationship between treatment efficacy and economic constraints is distal. Research is ongoing to support the use of a 12-item short form of the VIPs; however, both the fair skin (VIPs-12-FS) and dark skin (VIPs-12-DS) versions retain items regarding the economic constraints of treatment [17].

Furthermore, many of the existing PRO measures were not developed or refined through concept elicitation and cognitive debriefing with patients, as recommended in the FDA PRO Guidance for Industry. This evidence gap could be filled with a retrospective content validation study. However, PROs must also measure conceptually relevant outcomes that are important to the patients, taking into consideration inherent clinical and demographic characteristics. In vitiligo, facial lesions are often more bothersome to patients than areas that can be concealed with clothing [18]. In recent clinical trials [19], improvement in facial vitiligo has been a primary endpoint (assessed by the Facial VASI [F-VASI]) separate to improvement in total-body vitiligo. This is supported by the clinical rationale that the face is dense with hair follicles that are considered a reservoir of melanocytes, and it is therefore least resistant to repigmentation, provided there is no presence of follicular leukoderma [20]. Thus, in addition to an assessment of the extent of facial depigmentation, a PRO measure that can evaluate the specific impact of facial vitiligo (independently of total body vitiligo) will be valuable for assessing overall treatment benefit in future clinical trials. A problem with using current vitiligo measures for this evaluation is that items that are of low relevance to the face (e.g. those related to clothing choices) may dilute the change in score resulting from an improvement in facial vitiligo.

The present study aimed to develop two content-valid PRO measures to assess the impact of vitiligo involving the face and total body and provide two separate scores. PRO development follows a mixed-methods process [6, 21]. The first step comprises iterative item generation (e.g. from a review of the existing qualitative literature, expert input and/or qualitative interviews) and testing the draft item wording, response scales and recall period. A draft conceptual framework is developed which proposes instrument scoring (e.g. domain/total scores). This first step focuses on documenting the *content validity*. The next step in PRO development comprises quantitative data collection to test the psychometric performance of the measure; this step focuses on documenting the *reliability*, *construct validity*, and *responsiveness to change*, ultimately to confirm the conceptual framework and scoring. The first step in the development of the Vitiligo Patient Priority Outcomes (ViPPO) measures is described here.

METHODS

This study comprised a cross-sectional, non-interventional, qualitative interview study with individuals living with vitiligo and dermatologists with expertise in vitiligo (referred to as 'expert dermatologists' throughout).

PRO Development

The ViPPO measures were drafted in a stepwise approach. First, the project team reviewed existing qualitative research on vitiligo [22] to generate a list of draft concepts. The draft concepts were then developed into PRO items during an item generation meeting attended by experts in PRO development techniques. The resulting draft items were then reviewed by a study-specific steering committee (comprising a patient advocate and a clinical expert).

Two draft measures were developed to assess the impact of facial vitiligo only (ViPPO-F) and total body vitiligo including the face (ViPPO-T). The ViPPO items were refined iteratively, with items added or removed throughout the development process (Fig. 1).

A 7-day recall period ('in the past 7 days') was tested throughout, as is typically acceptable for impact measures for use in clinical trials. A 7-day recall period is recommended to help standardize reporting and ensure that respondents are able to adequately recall the information. Although vitiligo itself is a chronic condition, the concepts assessed with the ViPPO measures (e.g. emotional wellbeing, social functioning) are expected to occur frequently and may fluctuate over longer time periods.

Two four-point Likert response scales were drafted (Fig. 2). Both scales were tested in the qualitative interviews to understand whether one was better understood, preferable, or more relevant to the measurement concepts.

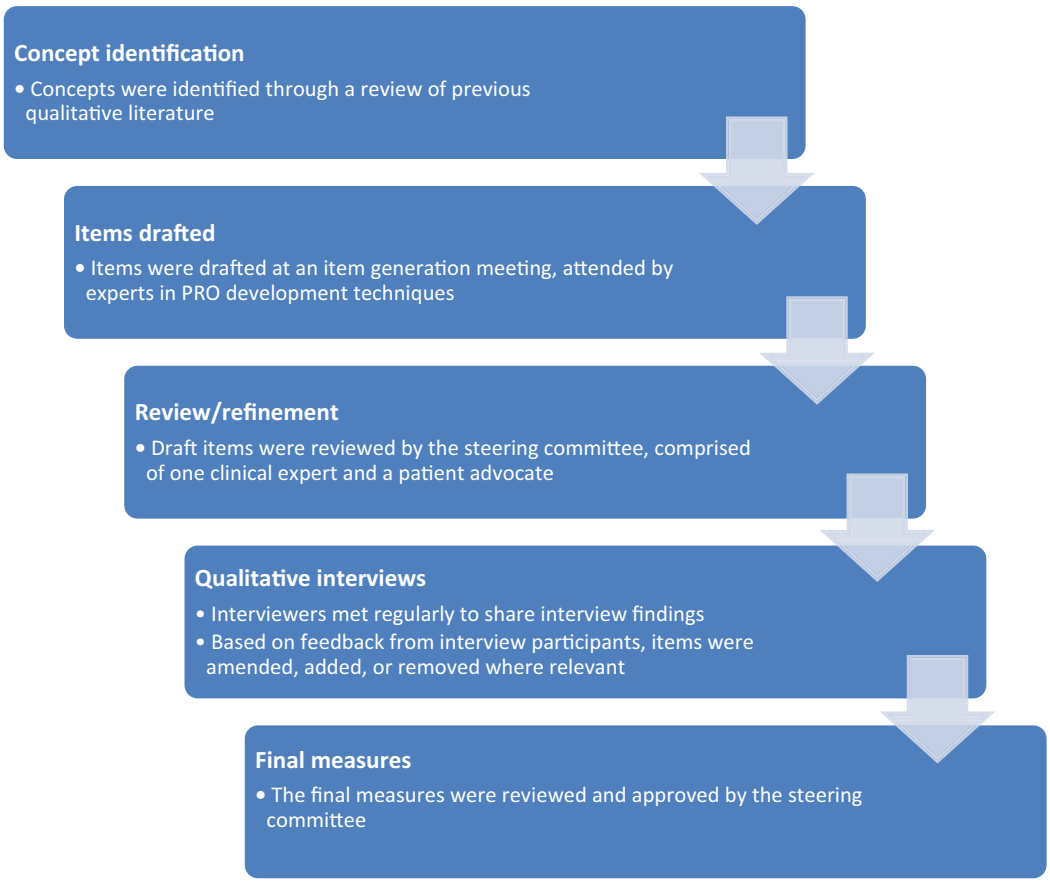

Fig. 1 ViPPO item development and refinement

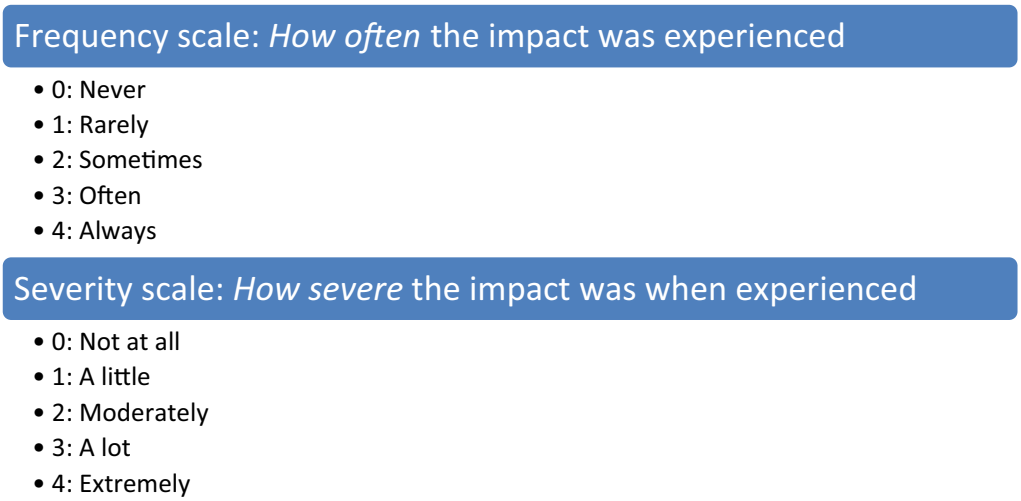

Fig. 2 ViPPO response scales shown during debriefing

Steering Committee

A steering committee comprising a clinical expert in vitiligo (referred to as the 'clinical expert' throughout) and a patient advocate was established to guide this research and/or interpret findings. The steering committee reviewed the patient interview guide, clinician interview guide and study results.

Interviews with Individuals Living with Vitiligo

The study protocol was approved by the WIRB-Copernicus Group® independent review board (WCG-IRB). Individuals were eligible to participate if they were aged ≥ 12 years, US residents, and had non-segmental active vitiligo with lesions on the face and/or body affecting 4–60% of their total body surface area (BSA) and at least 0.25% BSA on their face, according to their most recent clinician assessment. Individuals were excluded if they had segmental or mixed vitiligo, were enrolled in a vitiligo clinical trial, or had active comorbid inflammatory skin disease. Following 4 months of recruitment, the eligibility criteria were amended to include adolescents with either 4–60% of their BSA impacted by vitiligo or ≥ 0.25% BSA on their face. Vitiligo can be more visible on some skin types and thus it is sometimes assumed that the psychological burden of vitiligo is greater in individuals with darker skin. However, several studies have noted that all individuals may experience a psychosocial burden, regardless of skin type [8, 23]. Therefore, an important consideration in this study was to include input from a sample where all six Fitzpatrick skin types (FST) were represented.

Participants were identified via specialist recruiters or clinical sites (Northwest Dermatology Institute, Oregon and Dawes Fretzin Dermatology, Indianapolis). The Global Vitiligo Foundation also advertised the study. Individuals provided written informed consent/assent before eligibility and clinical history were confirmed via a clinician-completed case report form (CRF). Demographic information was collected via a self-report screener.

Interviews took place between November 2020 and March 2021, during the COVID-19 pandemic, and thus were conducted remotely. Interviews were conducted by one of six trained qualitative interviewers who met weekly to share findings to aid consistency and allow adjustments to be made to the ViPPO measures and/or interview guide.

All interviews included concept elicitation and cognitive debriefing. This combined approach has been undertaken in PRO development studies [24], particularly where expert input or existing literature was used to develop

the draft items [25, 26], in order to maximize qualitative data collection. Combined interviews allowed for a post-hoc comparison of the concepts identified during concept elicitation with the PRO measures. Importantly, the researcher ensured that the individuals with vitiligo did not view the ViPPO items until after the concept elicitation discussion to avoid biasing the discussion.

Concept elicitation (~ 30 min) comprised open-ended questions to elucidate concepts relevant to the experience of living with vitiligo. Concepts were elicited spontaneously (e.g. 'Tell me about the vitiligo on your face?'), followed by in-depth probe questions (e.g. 'How does having vitiligo on your face affect you emotionally/socially/your daily activities/at work or school, if at all?'). Questions focused on the locations of vitiligo lesions, the impact of vitiligo on social and emotional functioning, physical sensations experienced, and the relative importance of these (i.e. which locations and impacts of vitiligo were most bothersome). The interviewer then explored meaningful treatment outcomes (reported elsewhere [27]).

Cognitive debriefing (~ 40 min) involved the participants completing each ViPPO measure using a 'think aloud' technique in which they spoke their thoughts aloud while reading the questions and selecting an answer. Participants were asked direct and specific questions to establish the content validity of the ViPPO measures (Table 1).

The ViPPO items drafted by the project team (following a review of existing qualitative research and expert input) were implemented in the first interviews. Items were added between interviews based on feedback (Table 2). Items were only removed at the end of the study to allow for maximum data collection throughout the interviews.

Table 1 Example cognitive debriefing questions

Concept	Example interview questions
Understanding of item wording	What does the question mean to you?
	How would you say this in your own words?
Interpretation of the measurement concept	What does [self-conscious] mean to you?
Relevance of the measurement concept	Have you ever experienced this?
	Can you give me an example?
Item redundancy	Do you think feeling [embarrassed] and [self-conscious] are the same or different?
Relationship between items	Is it important to ask about feeling [sad] and feeling [depressed] separately? Or could the questions be combined?
Comprehensiveness	Was there anything missing from the questionnaire?
Suitability of the different response scales/options	What are your thoughts on the response scale?
	Which scale do you prefer?
Relevance of the recall period to the measurement concepts	How easy or difficult was it to answer thinking about the past 7 days?
	Would a different timeframe be easier to think about?

Interviews with Expert Dermatologists

International expert clinicians were selected from a list provided by the study sponsor (Pfizer) based on their experience in vitiligo research and clinical trials. All clinicians signed an information and consent form (ICF) before participating. The dermatologist interviews (~ 1 h) were conducted remotely in English, and included discussion of the clinical signs of vitiligo (reported in this publication), vitiligo assessment, and appropriate methods to measure treatment success (published elsewhere). Interviewers used a semi-structured interview guide including open-ended questions with

Table 2 ViPPO item tracking table

Original item wording (November 2020)	Items added based on interview findings (December 2020)	Items added following interim report (February 2021)	Final item recommendations (March 2021)
Emotional/psychological functioning			
1. I felt self-conscious	*No change*	*No change*	*No change*
	1. I felt self-conscious	1. I felt self-conscious	1. I felt self-conscious
2. I felt insecure	*No change*	*No change*	*Remove (item redundancy with 'I felt self-conscious')*
	2. I felt insecure	2. I felt insecure	
3. I felt embarrassed	*No change*	*No change*	*Renumbered, but no change*
	3. I felt embarrassed	3. I felt embarrassed	2. I felt embarrassed
4. I felt sad	*No change*	*No change*	*Renumbered, but no change*
	4. I felt sad	4. I felt sad	3. I felt sad
–	*New item added*	*No change*	*Removed (item redundancy with 'I felt sad')*
	5. I felt depressed	5. I felt depressed	
5. I felt worried	*Renumbered, but no change*	*No change*	*Renumbered, but no change*
	6. I felt worried	6. I felt worried	4. I felt worried
6. I felt frustrated	*Renumbered, but no change*	*No change*	*Renumbered, but no change*
	7. I felt frustrated	7. I felt frustrated	5. I felt frustrated
7. I felt overwhelmed	*Renumbered, but no change*	*No change*	*Renumbered, but no change*
	8. I felt overwhelmed	8. I felt overwhelmed	6. I felt overwhelmed
8. I felt abandoned	*Renumbered, but no change*	*No change*	*Removed (low conceptual relevantce*
	9. I felt abandoned	9. I felt abandoned	
–	–	*New item added*	*Removed (item redundancy with 'I felt frustrated')*
		10. I felt angry	
–	–	*New item added*	*Minor wording change suggested by steering committee*
		11. I felt like vitiligo occupied my thoughts	
			7. I felt that vitiligo occupied my thoughts
Social functioning			
9. My relationships with family were affected	*Renumbered, but no change*	*Renumbered, but no change*	*Renumbered, but no change*
	10. My relationships with family were affected	12. My relationships with family were affected	8. My relationships with family were affected

Table 2 continued

Original item wording (November 2020)	Items added based on interview findings (December 2020)	Items added following interim report (February 2021)	Final item recommendations (March 2021)
10. My relationships with friends were affected	*Renumbered, but no change* 11. My relationships with friends were affected	*Renumbered, but no change* 14. My relationships with friends were affected	*Renumbered, but no change* 9. My relationships with friends were affected
11. My romantic relationships were affected	*Renumbered, but no change* 12. My romantic relationships were affected	*Renumbered, but no change* 15. My romantic relationships were affected	*Renumbered, but no change* 10. My romantic relationships were affected
12. My relationships with partners/potential partners were affected	*Renumbered, but no change* 13. My relationships with partners/potential partners were affected	*Renumbered, but no change* 16. My relationships with partners/potential partners were affected	*Removed (item redundancy with "My romantic relationships were affected")*
13. I avoided social situations	*Renumbered, but no change* 14. I avoided social situations	*Renumbered, but no change* 17. I avoided social situations	*Renumbered, but no change* 11. I avoided social situations
14. I limited interactions with other people	*Renumbered, but no change* 15. I limited interactions with other people	*Renumbered, but no change* 18. I limited interactions with other people	*Renumbered, but no change* 12. I limited interactions with other people
15. I felt that other people treated me differently	*Renumbered, but no change* 16. I felt that other people treated me differently	*Renumbered, but no change* 19. I felt that other people treated me differently	*Renumbered, but no change* 13. I felt that other people treated me differently
16. I spent too much time trying to hide the vitiligo on my face (e.g. with make-up, facial hair or hairstyles)/on my body (e.g. with make-up, clothing choices)	*Renumbered, but no change* 17. I spent too much time trying to hide the vitiligo on my face (e.g. with make-up, facial hair or hairstyles)/on my body (e.g. with make-up, clothing choices)	*Renumbered, but no change* 20. I spent too much time trying to hide the vitiligo on my face (e.g. with make-up, facial hair or hairstyles)/on my body (e.g. with make-up, clothing choices)	*Renumbered, but no change* 14. I spent too much time trying to hide the vitiligo on my face (e.g. with make-up, facial hair or hairstyles)/on my body (e.g. with make-up, clothing choices)
17. My work or school was affected	*Renumbered, but no change* 18. My work or school was affected	*Renumbered, but no change* 21. My work or school was affected	*Renumbered, but no change* 15. My work or school was affected

Table 2 continued

Original item wording (November 2020)	Items added based on interview findings (December 2020)	Items added following interim report (February 2021)	Final item recommendations (March 2021)
18. I avoided sharing photos of myself on social media	*Renumbered, but no change* 19. I avoided sharing photos of myself on social media	*Renumbered, but no change* 22. I avoided sharing photos of myself on social media	*Minor wording change suggested by steering committee* 16. I avoided sharing photos of myself (e.g. on social media, with friends and family)
Physical sensations			
19. The skin on my face/my skin felt itchy	*Renumbered, but no change* 20. The skin on my face/my skin felt itchy	*Renumbered, but no change* 23. The skin on my face/my skin felt itchy	*Renumbered, but no change* 17. The skin on my face/my skin felt itchy
20. The skin on my face/my skin felt rough to touch	*Renumbered, but no change* 21. The skin on my face/my skin felt rough to touch	*Renumbered, but no change* 25. The skin on my face/my skin felt rough to touch	*Removed (low conceptual relevance)*

follow-up probes to explore clinicians' experience treating individuals with vitiligo.

All clinicians discussed the impact of vitiligo on patients (concept elicitation) and, time permitting, reviewed the ViPPO measures. Questions explored comprehensiveness ('Do you feel anything is missing from the two draft measures?'), relevance ('Do you think that the measures are relevant to assess vitiligo?') and item redundancy ('Do you feel there are any questions included in either measure that are not needed/relevant?'). The interviewer also cross-checked with previous statements made by the dermatologists ('You told me earlier that patients say [concept] is a problem for them. Do you feel that is adequately assessed by these measures?').

Analysis

Weekly interviewer meetings were held to discuss interview methods and findings, aid consistency in approach, and make changes when needed (e.g. interview guide updates). All interviews were audio-recorded and transcribed verbatim. Transcripts were analysed using ATLAS.ti v7.5. Each transcript was coded by one analyst, with codes and quotations reviewed by the project lead at regular intervals. The project team revisited the verbatim quotes when summarizing the findings.

Concept elicitation analysis took a phenomenological interpretative approach, seeking to understand the multiple realities of individuals rather than one 'true' reality, and focusing on the perceptions, feelings and lived experiences of the individuals [28]. A vitiligo consequence model was developed as a visual representation of patient experience, supported by data contained in the interview transcripts. The concepts included in the ViPPO measures were continually mapped against the vitiligo consequence model to ensure the measures demonstrated conceptual coverage of the concepts important to individuals with vitiligo. As noted in Table 2, items were added iteratively to the ViPPO measures throughout the conduct of

the interview study to reflect the concept elicitation findings.

Conceptual saturation is defined as the point at which no new concept-relevant information emerges [29]. When reached, this suggests that a comprehensive understanding of the patient experience has been achieved and no further interviews are required. As recommended in the Best Practice Guidelines for Establishing Content Validity of PRO Instruments [30] and FDA PFDD Draft Guidance 2 [7], interview transcripts were grouped into four equal sets in chronological order, and the elicited concepts were compared between sets.

Data obtained via cognitive debriefing were subject to framework coding [31], whereby a predefined code list was applied to identify the relevance and appropriateness of item wording, response options and the recall period.

RESULTS

Sample

Sixty individuals with vitiligo (n = 48 adults, n = 12 adolescents) and 14 expert dermatologists participated in the interview study. Sample demographic characteristics are reported in Supplementary Material 1. In the individuals with vitiligo, representation of lower education levels (n = 9 adults with a high school diploma or equivalent) and some cultural diversity (n = 8 who were first/second-generation individuals living in the US) were achieved. No FST group was significantly over- or under-represented.

Concept Elicitation

The vitiligo consequence model is presented in Supplementary Material 2; example quotes are provided in Supplementary Material 3.

Signs/Symptoms of Vitiligo

All individuals living with vitiligo (n = 60/60, 100%) and expert dermatologists (n = 14/14, 100%) reported that vitiligo involved depigmentation on the skin. The symptoms (or physical sensations) most frequently reported by individuals living with vitiligo were itching (n = 28/60, 47%) and roughness (n = 7/60, 12%).

Individuals with vitiligo frequently identified their face (n = 52/60, 87%), hands (n = 42/60, 70%) and legs (n = 21/60, 35%) as among the most bothersome locations of vitiligo; the face was considered the most important area for a treatment to improve (n = 40/54, 74%). Expert dermatologists also identified the face (n = 14/14, 100%) and hands (n = 13/14, 93) as the areas perceived to be most bothersome to individuals.

Impact on Emotional and Psychological Wellbeing

Fifty-seven individuals living with vitiligo (n = 57/60, 95%) and all expert dermatologists (n = 14/14, 100%) described an emotional or psychological impact of vitiligo. Impacts most frequently reported by individuals were feeling self-conscious (n = 35/60, 58%), anticipating the reactions of others (n = 27/60, 45%), feeling sad/upset (n = 19/60, 32%) and self-stigma (e.g. feeling that the vitiligo 'looks ugly'; n = 18/60, 30%).

Impact on Social Functioning

Fifty-three individuals living with vitiligo (n = 53/60, 88%) described at least one way in which their social life had been impacted by vitiligo. The most frequently reported impacts were the vitiligo being noticed by others (n = 42/60, 70%) and avoiding social interactions (n = 26/60, 43%). Six dermatologists (n = 6/14, 43%) described impacts on social functioning, including times where individuals avoid socializing and/or feel less confident in social situations.

Sixteen individuals (n = 16/60, 27%) reported that their romantic relationships had been affected by vitiligo and/or that they had experienced difficulties with intimacy. Eleven dermatologists (n = 11/14, 79%) also described the impact of vitiligo on current and future romantic relationships.

Impact on Daily Life

Forty-one individuals (n = 41/60, 68%) described at least one way that their daily life had been impacted by vitiligo. The most frequently reported impacts were the need to use sun protection or to avoid sun exposure (n = 28/60, 47%), the additional time taken to conceal vitiligo lesions (n = 13/60, 22%) and impacts on sports/exercise (n = 12/60, 20%).

Impacts on daily activities were rarely described by dermatologists, likely because individuals with vitiligo tend to be able to complete daily activities (e.g. household chores and self-care). However, four dermatologists (n = 4/14, 29%) mentioned impacts such as going out for dinner or to the supermarket and impacts on sports/exercise.

Impact on Work or School

Seventeen individuals (n = 17/60, 28%) described at least one way in which their work or school activities had been impacted by vitiligo. The most frequently reported impacts were thinking about vitiligo while working (n = 6/60, 10%) and missing meetings/days due to the vitiligo (n = 5/60, 8%).

Seven dermatologists (n = 7/14, 50%) described the impact of vitiligo on work/school, including feeling self-conscious in public-facing activities/roles (e.g. presenting, shaking hands), participating in gym class, being bullied at school, and experiencing or perceiving opportunity loss.

Conceptual Saturation

Conceptual saturation [29] was achieved in the adult sample and adolescent sample, with the exception of the following concepts (spontaneously reported for the first time in the final 'set' of interviews): 'relationships with family' in adults (although discussed by n = 7 participants when probed) and 'roughness/dryness' in adolescents.

Exploratory Sub-Group Analyses

To ensure that the ViPPO concepts were appropriate and relevant across key sub-groups, the sample was grouped according to FST and age. There were no substantial differences in the patient's experience of vitiligo symptoms and/or impacts according to FST group. Some social and work-related concepts (e.g. intimacy, difficulty finding a job) were only reported by the adult participants interviewed, as denoted in Supplementary Material 3.

Comparisons were made between the concepts reported by individuals living with vitiligo and dermatologists. Individuals living with vitiligo provided more detailed and varied insights into the impacts experienced. However, some concepts (loss of cultural identity, difficulty seeking romantic partners) were discussed by dermatologists only, perhaps due to the international representation achieved in the clinician sample. Dermatologists also noted suicidal ideation as an impact of vitiligo, which was not directly discussed by individuals in the sample.

Cognitive Debriefing of the ViPPO Measures

Understanding

The ViPPO items were well understood by all participants, including adolescents (Supplementary Material 4). The instructions were largely understood (n = 55/60, 92%). Five participants initially considered their total body when completing the ViPPO-F but understood the intention when the interviewer repeated the instruction.

Item Changes

Table 2 is an item tracking table that presents changes made to the ViPPO measures. Items were added to the measures between interviews, based on feedback. Items were only removed at the end of the study to allow for maximum data collection throughout the interviews.

ViPPO-F Conceptual Relevance

The ViPPO-F was debriefed with almost all participants (n = 59/60, 98%; one participant debriefed the ViPPO-T as they did not have vitiligo on their face). Items added during the study were only debriefed with the remaining sample: 'I felt depressed' (debriefed by n = 47), 'I felt angry' (n = 12) and 'I felt like vitiligo occupied my thoughts' (n = 12).

Each item in the ViPPO-F was considered relevant now or in the past to at least 15% of the participants asked. Most items (n = 15/23, 65% of the measure) were considered relevant to $\geq$ 50% of the sample (Fig. 3; Supplementary Material 4).

ViPPO-T Conceptual Relevance

As the ViPPO-F and ViPPO-T measures assessed the same concepts, participants only completed a top-line review of the ViPPO-T. Most participants asked (n = 39/55, 71%) felt that their responses to the ViPPO-T would be the same as those to the ViPPO-F.

Fifteen (n = 15/55 asked, 27%) reported that $\geq$ 1 response on the ViPPO-T would 'increase.' The most common items to change

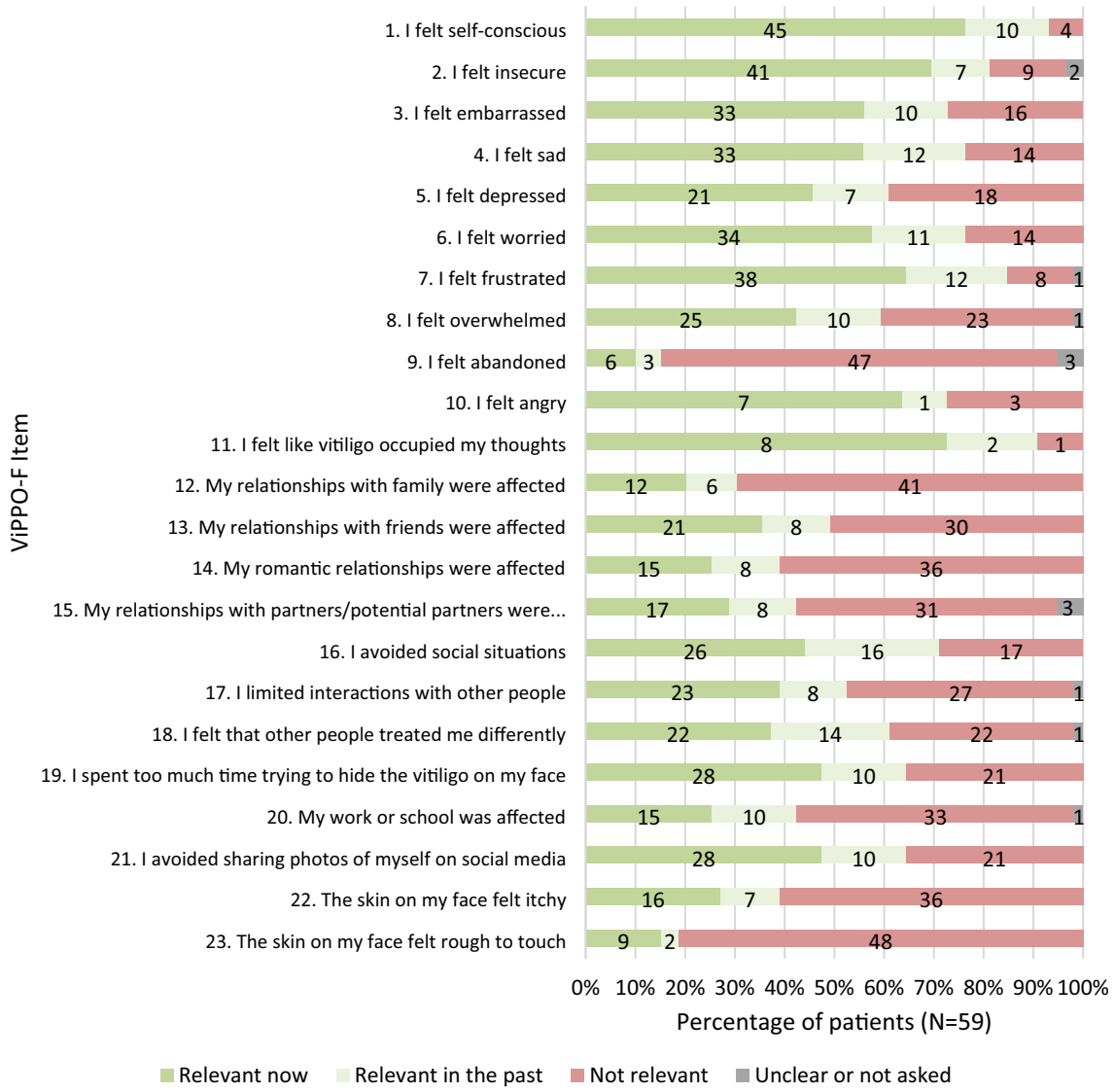

Fig. 3 ViPPO-F conceptual relevance (N = 59)

were feeling self-conscious ($n = 8$), insecure ($n = 6$) or itchy ($n = 5$). An additional adolescent participant provided lower responses to the ViPPO-T; it appears that she had not considered her facial vitiligo when responding.

Response Options

No participants experienced difficulty understanding either response scale:

- "I think it's good. I think it gives you plenty of choices, um, to, like, measure exactly where you feel about it." (Female, 51 years old; 'frequency' responses)
- "I think they were a good choice of answers to pick out of." (Female, 13 years old; 'severity' responses)

When asked which response scale they preferred (Fig. 2), over half ($n = 33/58$, 57%) preferred 'frequency'; 18 ($n = 18/58$, 31%) preferred 'severity'; six ($n = 6/58$, 10%) had no preference; while an additional participant ($n = 1/58$, 2%) felt that their preference changed for each domain.

Recall Period

Fifty-three participants ($n = 53/59$, 90%) discussed the recall period. Of these, 24 ($n = 24/53$, 45%) understood and used the recall period correctly throughout:

- "I'm thinking in the last seven days […] I kept saying that was the last seven days because some of my answers would be different if you would have asked me in the past, you know, six months." (Female, 37 years old)

Twenty-nine participants ($n = 29/53$, 55%) acknowledged that they were thinking back over a longer timeframe while completing the ViPPO-F. It is important to note that interviews were conducted when the US was under restrictions due to the COVID-19 pandemic. Eleven participants specifically mentioned how the pandemic had influenced their responses to certain items, as they had not had the opportunity to be around others in the past 7 days due to lockdown/social distancing:

- "COVID or whatnot, past seven days I haven't done too much, besides, like, Zoom classes. Um, I really haven't had any thing, err, vitiligo wise to be embarrassed about." (Male, 22 years old)

Thirty-seven participants ($n = 37/59$, 63%) were asked whether it would be easy or difficult to recall the past 7 days, regardless of whether they had used the recall period correctly. Most ($n = 29/37$, 78%) felt that it would be easy. Eight ($n = 8/37$, 22%) felt that it would be difficult, half of whom ($n = 4/8$, 50%) suggested that the activities on the ViPPO-F are unlikely to have happened over a 7-day period, particularly the concepts included in the social functioning domain.

Missing Concepts from the ViPPO-F and ViPPO-T

Twenty-five participants ($n = 25/59$, 42%) identified concepts that they felt were missing from the ViPPO-F. Four concepts were reported by > 1 participant: risk of sunburn/use of sun protection ($n = 7$); anxiety ($n = 2$); anger ($n = 2$; added as an item during interviewing); and pain/discomfort ($n = 2$).

Fifteen participants ($n = 15/60$, 25%) identified concepts that they felt were missing from the ViPPO-T, including risk of sunburn/use of sun protection ($n = 4$) and clothing choices ($n = 2$).

Given the seasonal nature of sunburn/use of sun protection (e.g. a change in the perceived risk of sunburn may be due to the season as opposed to vitiligo itself), the researchers did not develop an item to assess this concept. Items were not developed for the other suggestions, as the concepts were not frequently reported in concept elicitation.

Feedback from Dermatologists

Eight dermatologists reviewed the ViPPO measures, commenting on the relevance and appropriateness of the items. All ($n = 8/8$, 100%) indicated that the measures were comprehensive and measured the key concepts relevant to vitiligo.

- "I think this is actually great […] I'm happy that you're doing this." (US Clinician)
  Six dermatologists (75%) suggested the removal of the 'skin felt rough to touch' item.. One dermatologist (13%) noted item redundancy with the items assessing romantic relationships, relationships with a partner/potential partner, and the items assessing feeling sad and feeling depressed.
- "Just going through these, so, looks quite good, comprehensive. Except for this last one, 'The skin on face felt rough to touch', but, err – I mean, most of the time, roughness or dryness is not related to vitiligo." ('Rest of the world' clinician)

Dermatologists noted that the following concepts may be missing: impact on sports/physical activities (n = 2); impact on sex life (n = 2) [one felt that 'My romantic relationships were affected' would capture this, but the other felt that a separate item would be needed]; and feeling angry, sunburning easily, and treatment side effects (all n = 1).

DISCUSSION

This non-interventional, cross-sectional, qualitative interview study included N = 60 individuals living with vitiligo and aged $\geq$ 12 years in the US. The sample included a broad representation of clinical and demographic characteristics, including a range of ages, FSTs, education levels, and a representation of first- or second-generation immigrants to the US from Asia, the Middle East and Africa.

There was a general consensus regarding the key symptoms and impacts of vitiligo reported by individuals living with vitiligo and expert dermatologists, which corroborated the concepts included in the draft ViPPO measures. The study highlighted the importance of obtaining the perspective of individuals living with vitiligo when assessing the impact of the vitiligo, beyond the visible signs of depigmentation.

Almost all individuals described ways that vitiligo impacted their emotional and psychological wellbeing, including feeling self-conscious. The fear or anticipation of others noticing vitiligo resulted in social impacts; some avoided social situations, including posting photos on social media, and reported impacts on their social interactions. Romantic relationships and intimacy could be affected. Relationships with family and friends could also be affected due to negative comments and a lack of understanding; however, others described friends and family being supportive.

A vitiligo consequence model was developed to further understand the patient experience of vitiligo, including signs/symptoms and impact on psycho-social functioning. Understanding the patient experience is important in clinical trials to ensure that the outcome measures (including ClinROs and PROs) evaluate what is most important to individuals with vitiligo. The concept elicitation findings and consequence model confirmed the relevance of the concepts assessed in the newly developed ViPPO measures. Conceptual saturation was largely achieved in the sample, suggesting that the sample was sufficient to understand the patient experience of vitiligo. There were no notable differences in the patient experience of vitiligo between the sub-groups explored.

Cognitive debriefing confirmed that adults and adolescents living with vitiligo found the ViPPO items easy to understand and conceptually relevant. Use of the frequency response scale is recommended, based on the preferences of the individuals interviewed, although both response scales were understood. The 7-day recall period will be retained, in line with FDA guidance, but it should be highlighted through format changes and training when these measures are implemented into future studies. A quarter of the participants (n = 15/55, 27%) reported that their responses on the ViPPO-F would change if they were asked to consider their total body, highlighting the value in developing separate PRO measures for the face and total body.

A strength of this study is that it involved a multidisciplinary team including experts in PRO development and a steering committee of a clinical expert and a patient advocate to oversee this research. Steering committee engagement is recommended to ensure the research remains patient focused, to identify any knowledge gaps

or sensitive topics and to mitigate potential researcher bias when developing study documents [32]. A methodological strength was the use of concept elicitation and cognitive debriefing in line with industry standards for selecting, developing and validating COA measures [21, 33]. Insights from individuals living with vitiligo and expert dermatologists contributed to the refinement of the draft ViPPO measures, including the iterative addition and removal of items based on item relevance.

Some limitations of this qualitative interview study are noted. Interviews were conducted with a sample of individuals living with vitiligo in the US only. The impact of vitiligo may be in part influenced by cultural and societal norms. For example, in the context of arranged marriages, women with vitiligo in India are described as having a lower chance of getting married [9]. Those who are already married when they develop vitiligo are reported to experience marital problems and potentially divorce [9, 34]. In a recent Saudi Arabian study, participants reported that they would not marry an individual with vitiligo (42.8%) or even shake hands with an individual with vitiligo (69.5%) [35]. A study in Iran highlighted the continued stigma around vitiligo, perceived as a punishment for moral or spiritual 'sins' [34]. The inclusion of dermatologists outside of the US was an attempt to increase diversity in cultural perspectives but was not sufficient for the measure to be assumed relevant globally. Further investigation including linguistic/cultural validation and translation is required before the use of the measure outside of the US.

The next step is to evaluate the psychometric properties of the ViPPO measures (including reliability, validity and responsiveness to change) to confirm the conceptual framework, conceptual relevance of items and scoring. This requires the ViPPO measures to be included in longitudinal, interventional or observational studies to collect quantitative data. Following the confirmation of these measurement properties, interpretation of the ViPPO scores should be explored to estimate the score change or thresholds that define a within-patient meaningful change.

CONCLUSION

This study obtained qualitative insights from individuals living with vitiligo and expert dermatologists to understand the patient experience and identify priority outcomes. These insights can inform patient-focused drug development and outcome measurement in future clinical trials.

The content validity of the ViPPO-F and ViPPO-T has been established in this study. The measures were developed to primarily evaluate emotional and social functioning in individuals with vitiligo and appear to be well understood, relevant and comprehensive in a US adult and adolescent sample. Future research to evaluate the psychometric properties and interpretation thresholds are needed to inform their use in vitiligo clinical trials.

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currently an employee of Janssen Pharmaceuticals Group of Companies of Johnson and Johnson and holds stock/stock options of Johnson and Johnson. Kathleen Wyrwich is a former Pfizer Inc. employee and holds Pfizer stock and stock options and Eli Lilly and Company stock. She is currently employed at Bristol Myers Squibb Company. Tatjana Lukic is a salaried employee and holds stock shares and/or options in Pfizer Inc. Hannah Pegram was an employee of Clarivate at the time this work was conducted. Sharon King is founder and executive director of the Litty Ligo Network. Brett King has served on advisory boards and/or is a consultant and/or is a clinical trial investigator for AbbVie, AltruBio Inc., Almirall, AnaptysBio, Arena Pharmaceuticals, Bioniz Therapeutics, Bristol Myers Squibb, Concert Pharmaceuticals Inc., Equillium, Horizon Therapeutics, Eli Lilly and Company, Incyte Corp, Janssen Pharmaceuticals, LEO Pharma, Otsuka/Visterra Inc., Pfizer Inc., Regeneron, Sanofi Genzyme, TWi Biotechnology Inc. and Viela Bio. He is on speaker bureaus for AbbVie, Incyte Corp, LEO Pharma, Pfizer Inc., Regeneron and Sanofi Genzyme.

Compliance with Ethics Guidelines. The study protocol was reviewed and approved by the WIRB-Copernicus Group® independent review board (WCG-IRB) on 20 October 2020. Written and verbal informed consent was obtained from every participant before each interview was conducted and before any other study activities.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request, and with permission from the study sponsor.

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