

BACKGROUND

- ATTR amyloidosis (ATTR) is a serious, debilitating, and rare disease in which the protein transthyretin (TTR) becomes unstable, misfolds, and deposits in various organs, primarily the heart and/or nervous system
- While ATTR can be categorized into 2 types: hereditary (hATTR) and wild-type (ATTRwt), it is a multi-systemic, heterogeneous condition
- Patient-reported outcome measures (PROs) are a key aspect of patient-focused drug development and clinical care
- Currently, there is no single, comprehensive, and validated ATTR-specific PRO available, making it difficult to fully capture the disease experience
- Best practices for development of an ATTR-specific PRO dictate using input from the literature, experts, and patients to ensure the inclusion of relevant, comprehensive, and understandable concepts¹
- This study presents findings from a literature review and interviews with key opinion leaders (KOLs) conducted as part of a larger effort to develop an ATTR-specific PRO measure

OBJECTIVE

- This qualitative study used a literature review and interviews with KOLs to identify important concepts for inclusion in an ATTR disease-specific PRO meant for use in clinical practice and clinical trials

METHODS

Literature Review

- Conducted 2 searches to 1) identify the signs, symptoms, and impacts on health-related quality of life (HRQoL) experienced by patients with ATTR (Search 1); and 2) identify the PROs that have been or are being used in ATTR research and clinical practice (Search 2)
- Examined peer-reviewed manuscripts, gray literature, clinical trial descriptions, and other resources

KOL Interviews

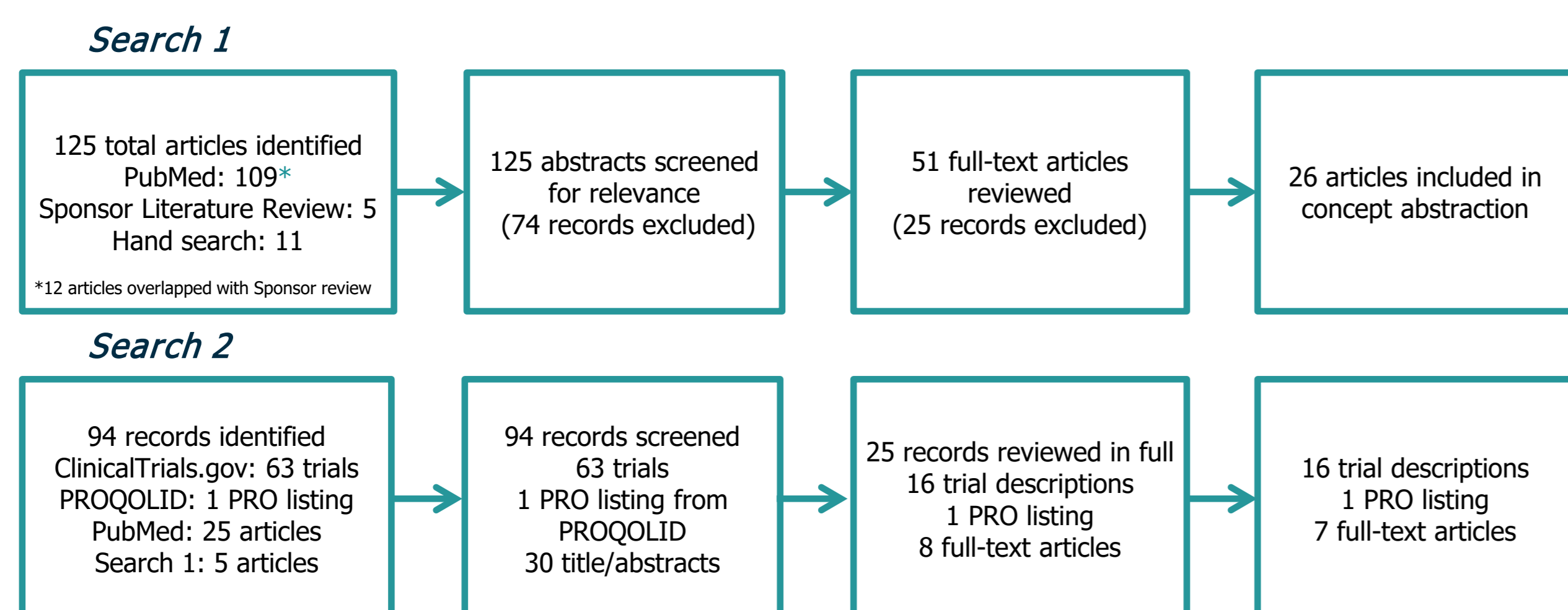
- Invited KOLs (clinicians specializing in hematology/oncology, cardiology, gastroenterology, and neurology; and patient advocates) working in ATTR to participate in one-on-one interviews
- Developed study materials using information gathered from the literature search:
 - Semi-structured interview guide tailored to the participant type (clinician vs. patient advocate)
 - Worksheet listing common ATTR symptoms, which KOLs were asked to complete and return prior to the interview
- Conducted 60-minute concept elicitation interviews by telephone or webcam in which KOLs:
 - Reflected on the comprehensiveness of the symptom worksheet, including any missing or misrepresented symptoms
 - Described the various ways their patients report that ATTR impacts their lives
 - Provided insights into PRO elements (e.g., recall period) and administration (e.g., mode)
- Transcribed interview recordings and quality checked transcripts to ensure accuracy
- Coded transcripts to identify key concepts related to the experience of ATTR and preferences regarding PRO elements and administration

RESULTS

Literature Review

- 26 articles were included in the final review from Search 1; 16 clinical trial descriptions, 1 PRO listing, and 7 full-text articles were included in the final review from Search 2 (see **Figure 1**)
 - Articles and trial descriptions were excluded if they were duplicates, not in English, did not include relevant content, focused on AL, or did not list a PRO as an endpoint

Figure 1. Literature search screening results



- Patients with ATTR experience a diverse number of symptoms that vary by patient² and type (hATTR vs. ATTRwt) making measurement challenging
- Important concepts related to the ATTR patient experience include signs and symptoms, impacts on HRQoL, and treatment experience
 - Quantifying disease burden is challenging because no single PRO covers the “constellation of symptoms” patients experience³
 - As the disease progresses and symptoms worsen, HRQoL decreases⁴⁻⁹
 - Published literature on HRQoL often focuses on the impact of neuropathy, cardiac health, mobility, and gastrointestinal symptoms specifically on patients’ perceived HRQoL
 - Patients receiving treatments such as liver transplant,^{4-5,10} inotersen,¹¹⁻¹² patisiran,¹³ and tafamidis¹⁴ report improved or stabilized quality of life after starting/undergoing treatment
- There is a paucity of literature on the social, emotional, and financial impacts of ATTR
- Trials using PROs as endpoints use multiple instruments to capture neuropathy, cardiac disturbances, or general health/HRQoL (see **Table 1**)
 - Validation of these instruments in ATTR patients is incomplete; for example, the Norfolk QOL-DN has had some psychometric testing, but content validity has not been established in patients with ATTR

Table 1. PROs in use in ATTR trials, by focus area

Focus Area	Norfolk QOL-DN	KCCQ	R-ODS	COMPASS-31	EQ-5D	SF-36 / SF-12	HADS	WPAI	HRUS	GIQLI
Cardiac disturbances										
GI disturbances										
Neuropathies										
Autonomic function										
General health status										
Physical functioning										
Mental health										
Health care utilization										
Work impacts										
Utility score										

Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Neuropathy; KCCQ: Kansas City Cardiomyopathy Questionnaire; R-ODS: Rasch-built Overall Disability Scale; COMPASS-31: Composite Autonomic Symptom Score 31; EQ-5D: EuroQol EQ-5D; HADS: Hospital Anxiety and Depression Scale; WPAI: Work Productivity and Activity Impairment Questionnaire; HRUS: Health Resource Use Survey; GIQLI: Gastrointestinal Quality of Life Index

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RESULTS (cont.)

KOL Interviews

Sample

- 16 KOLs participated in individual interviews, representing a mix of clinical and patient advocacy perspectives (**Table 2**)

Important Concepts for Measurement

- There is a need to track not only symptoms, but also the ways in which the disease impacts patients’ lives, including changes in social, emotional, and financial well-being and functional ability
- Symptoms, impacts, and treatment experience should be considered for inclusion in an ATTR-specific PRO

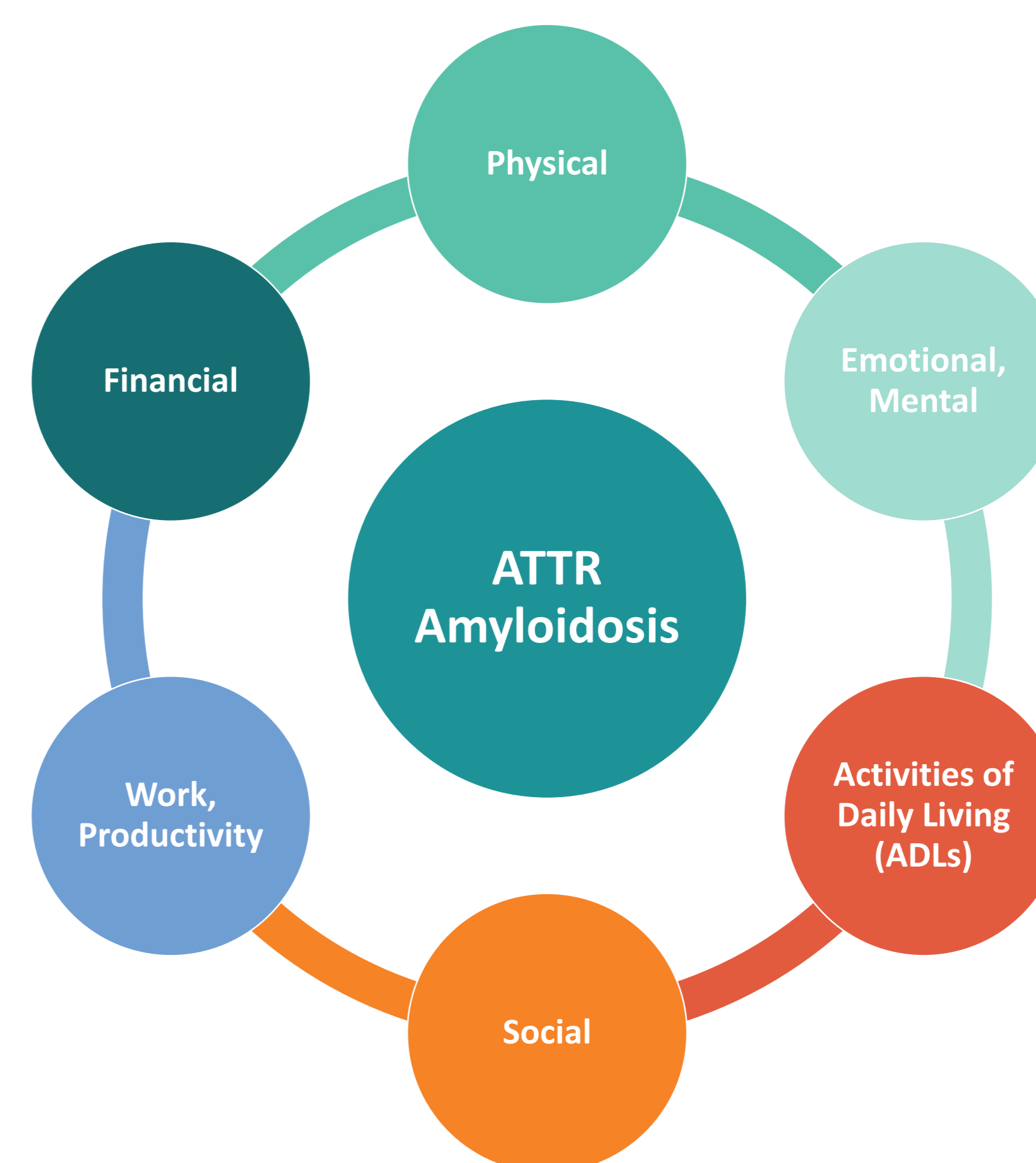
Symptoms

- KOLs confirmed that patients with ATTR experience a wide variety of symptoms, largely dependent on type
 - Confirmed that all 23 symptoms from the literature-informed worksheet were important and relevant
 - Identified the following symptoms missing from the worksheet they reviewed: fecal incontinence, syncope, difficulty swallowing
 - Suggested patient-friendly language for all symptoms; for example, “orthostatic hypotension” should be revised to “dizziness upon standing”
- KOLs indicated that in clinical practice symptom frequency and severity are best measured by asking patients to characterize their experience of the symptoms, including physical and functional impacts

Impacts

- KOLs described many different ways their patients report being impacted by the disease (see **Figure 2**)

Figure 2. Areas of patients’ lives impacted by ATTR, according to KOLs



PRO Elements and Administration

- KOLs recommended the ideal ATTR-specific PRO would be: available in paper and electronic format, brief (not more than 20 minutes), and able to be taken at home prior to a doctor visit
- PRO should ideally be administered every 3-6 months to capture change
- No consensus was reached on the appropriate recall period
 - Recommendations for the recall period ranged from “the last week” to “the past year”; most KOLs felt the recall should focus on anywhere from the last 3-6 months or “since your last [doctor] visit”
 - KOLs noted that the recall period might differ by symptom, depending on how frequently symptoms fluctuate or how quickly they progress
- KOLs preferred a non-modular PRO structure, wherein all patients answer all items regardless of ATTR type or primary manifestations (i.e., polyneuropathy vs. cardiomyopathy)
 - A non-modular approach ensures the collection of comprehensive symptom and impact data and allows for tracking disease progression over time
- KOLs felt that scores for individual domains—including symptoms by organ involvement (e.g., neurological, cardiovascular, gastrointestinal) and impacts—would be more useful than an overall score

CONCLUSIONS

- This qualitative study confirmed the large number of symptoms and impacts experienced by patients with ATTR
- Results from this study indicate that an ATTR-specific PRO should measure symptoms and functional impairment as it pertains to physical, social, emotional, and financial well-being as well as activities of daily living
- These findings will inform the next phase of PRO development in which the research team will conduct a focus group and interviews with patients with ATTR to further explore the key concepts for inclusion in an ATTR-specific PRO and identify any additional, important aspects of the patient experience
- The use of an iterative process that incorporates input from the published literature, clinicians and advocates, and patients themselves helps ensure that the resulting PRO and its conceptual framework are well-researched, rooted in the evidence, and accurately incorporate the patient perspective

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