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Development and Content Validity of the Statin Experience Assessment Questionnaire (SEAQ)©

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Abstract

Introduction The National Lipid Association Statin Intolerance (SI) Panel recognized the need for better understanding of the patient SI experience.

Objective The objective of this research was to develop a patient-reported outcome (PRO) questionnaire to assess a patient's experience with SI.

Methods Questionnaire development was informed via a series of research activities: literature review, concept elicitation, item generation, and content evaluation. Following the literature review and concept elicitation, a draft questionnaire was constructed and subsequently modified based on feedback from therapeutic area experts and patients via cognitive debriefing interviews.

Results Muscle-related symptoms were the most commonly reported symptoms associated with SI in the

literature review (35 of 41 articles reviewed [85%]) and in semi-structured interviews with experts ($n = 5$ [100%]) and patients ($n = 17$ of 20 [85.0%]). Physical and other impacts of SI symptoms on daily activities were also frequently reported. A 17-item draft questionnaire was created, and cognitive debriefing with experts ($n = 5$) and patients ($n = 15$) was conducted. Overall, the items, response options, and instructions were comprehensible and positively reviewed; minor changes resulted in the 15-item Statin Experience Assessment Questionnaire (SEAQ)©. Using a 30-day recall period, the SEAQ© assesses the severity and impact of six SI symptoms (muscle ache, muscle pain, muscle cramps, muscle weakness, tiredness, and joint pain) on an 11-point numeric scale. Statin discontinuation and likelihood of discontinuation due to symptoms are assessed and scored on a yes/no and five-point verbal response scale, respectively.

Conclusion The SEAQ© is a novel content-valid PRO questionnaire that assesses patient SI experience and fosters dialogue about SI between patients and providers.

Electronic supplementary material The online version of this article (doi:[10.1007/s40271-016-0211-y](https://doi.org/10.1007/s40271-016-0211-y)) contains supplementary material, which is available to authorized users.

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Key Points for Decision Makers

Statins are widely prescribed and generally well tolerated for the treatment of hypercholesterolemia. However, statin intolerance has an estimated prevalence of up to 25% in the population.

The National Lipid Association Statin Intolerance Panel has emphasized statin intolerance as best understood from a patient-centric perspective. Furthermore, better communication between patients and providers regarding statin intolerance is needed. No validated tools that assess the patient experience with statin use currently exist.

This article describes the development of the content-valid Statin Experience Assessment Questionnaire[®] with the goal of identifying statin intolerance in clinical settings and fostering communication about statin intolerance between patients and providers. The use of this questionnaire will allow shared learning between patients and providers in identifying and evaluating statin intolerance.

1 Introduction

Hypercholesterolemia is a major risk factor for cardiovascular disease (CVD), which accounts for nearly one in three deaths in the USA [1]. The estimated annual costs associated with CVD in the USA are more than \$US320 billion (approximately \$US196 billion in direct costs and \$US124 billion in indirect costs). Statins, or 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, are recommended by current cholesterol management guidelines as the initial drug treatment of choice for individuals with elevated cholesterol levels and/or cardiovascular risk for whom lifestyle change alone is insufficient [2–6].

Despite the general tolerability and widespread use of statins, they can be associated with untoward side effects, including muscle symptoms, gastrointestinal symptoms, headache, and liver abnormalities [7, 8]. Statin intolerance (SI) can be associated with some of these side effects. It is estimated from randomized controlled trials, patient surveys, and retrospective studies that muscle-related symptoms occur in 5–25% of patients being treated with statins [9–15]. Furthermore, primarily as a result of muscle-related symptoms, SI is a major cause of nonadherence, dose reduction, and discontinuation of statins [16–18] and may

contribute to the high cost of CVD and affect clinical outcomes [19]. Thus, there is a need for a better understanding of the patient with SI [20].

In 2014, the National Lipid Association (NLA) SI Panel recognized this need for a better understanding of the SI experience, best defined in the context of a patient-centric perspective, as well as the need for appropriately developed SI scales that can assess the phenomenon and bothersome impacts of SI directly from the perspective of the patient [17]. The viewpoint is consistent with the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Performance Measures, which emphasized the importance of “shared accountability” among patients and providers and the impact this could have on treatment decisions and ultimately clinical outcomes [21]. Therefore, tools are needed to assess SI from the patient perspective, but—according to current literature—no such suitable measures exist. The objective of the current research activities was to develop a patient-reported outcome (PRO) questionnaire for use in real-world settings to evaluate patient-centric attributes of SI. The tool is intended to help foster communication between patients and providers and to construct a means by which the complaints about and patient burden of SI may be quantified. In addition, the questionnaire should aid in a better understanding and documentation of the experiences of patients with SI and allow the systematic collection of patient-centric data in research settings.

2 Methods

To identify and describe the symptoms and impacts that characterize SI, an empirical literature review of SI, advice meetings with SI experts, and interviews with patients who are statin intolerant were conducted. Results from these activities informed the selection of concepts for measurement and the construction of the PRO questionnaire. The questionnaire content was then assessed among clinical experts and patients with SI (Fig. 1).

2.1 Literature Review

Peer-reviewed literature regarding SI was limited to English-language studies published between 2006 and 4 November 2014. The search was conducted in MEDLINE, Embase, and PsycINFO using the OvidSP platform. Search queries included statin intolerance and these related terms: statin-intolerance, statin-induced, and statin therapy. Additionally, terms for signs, symptoms, side effects, impacts, and adverse events were used to narrow search results. The search was supplemented with

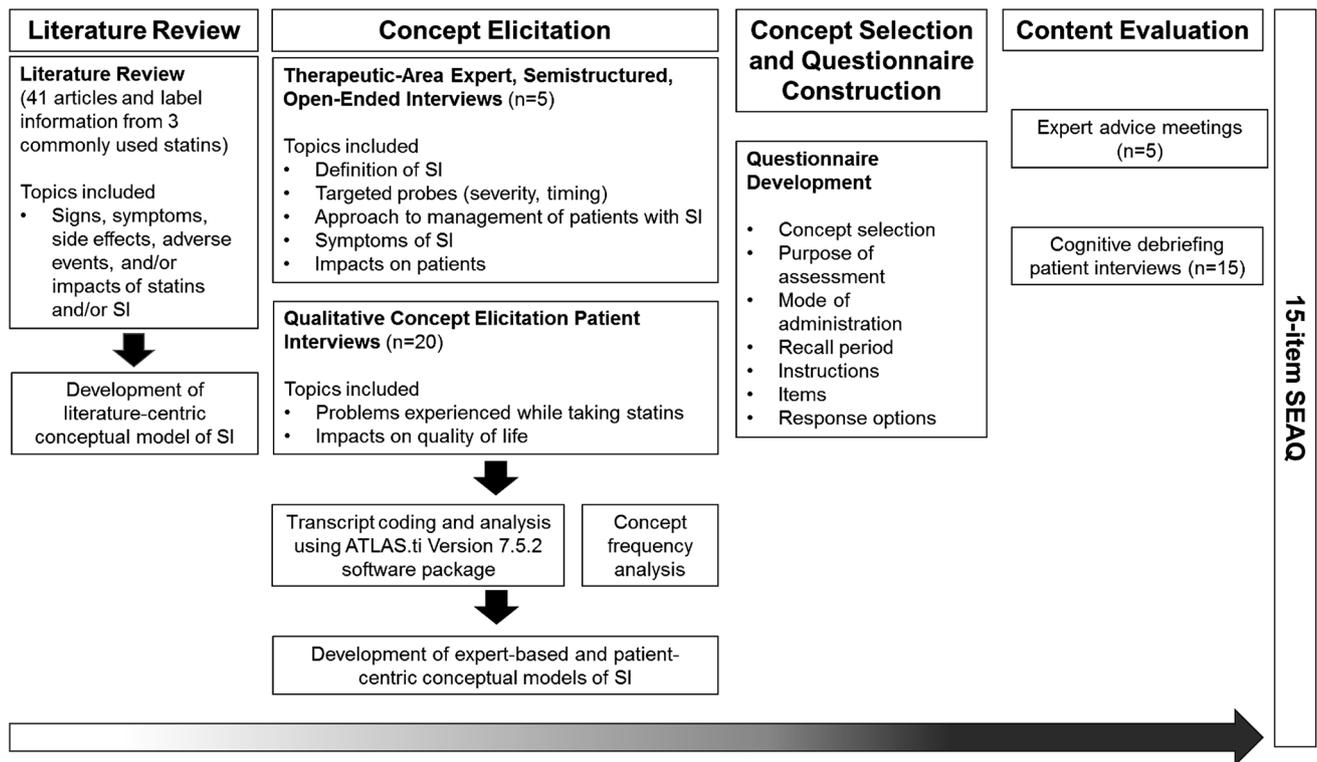


Fig. 1 Overall methodology schematic. *SEAQ*© Statin Experience Assessment Questionnaire, *SI* statin intolerance

articles identified by the members of the research team or manual review of reference lists that were not captured in the initial search. Relevant articles with a primary focus on signs, symptoms, side effects, adverse events, and/or impacts of statins and/or SI were identified and retrieved. Articles were excluded if they (1) primarily focused on the pathogenesis, genetics, or molecular biology of SI without discussion of signs, symptoms, side effects, adverse events, and/or impacts of statins and/or SI; (2) solely discussed statins used in combination with other non-statin drugs; or (3) solely discussed case studies of three or fewer patients. Key concepts associated with SI were extracted and informed the development of an SI conceptual model as well as documentation describing those concepts and justifying their relevance to the condition. The ‘Warnings and Precautions’ and ‘Adverse Reactions’ sections of the product labels for three commonly used drugs for the treatment of hypercholesterolemia, that is, atorvastatin (Lipitor), ezetimibe/simvastatin (Vytorin), and ezetimibe (Zetia), were reviewed for side effects. The targeted literature review was conducted early in the research process to document any untoward effects of lipid-modifying therapies assumed to be effective. All potentially effective lipid-modifying therapies were included in an effort to understand and document any similarities among or differences between therapies.

2.2 Concept Elicitation

2.2.1 Patient Interviews

Patients were recruited by providers who were specialists in internal medicine ($n = 3$), cardiology ($n = 2$), or primary care ($n = 2$). Individual concept-elicitation interviews (CEIs) were conducted using a semi-structured interview guide to explore the concepts relevant and important to the patients who experienced SI. The guide served as a map rather than a verbatim script to be referenced during the interviews to capture complete and meaningful information related to the research questions while maintaining spontaneity. Patients were asked a series of open-ended questions about their experience with statins and associated impacts on quality of life. Open-ended follow-up questions were used to clarify concepts (e.g., concept severity, frequency, and duration) and to encourage elicitation of all pertinent concepts associated with SI. This method of inquiry avoids the use of leading questions that may bias patients’ responses and allows the experience to be described in the patient’s own language. Interviewers were trained in good interviewing practices, National Institutes of Health Participant Protection, sponsor adverse event reporting, and internal data protection. Mock interviews were conducted with the interviewers to ensure good interviewing practices and to identify any issues. The final

sample size was justified by achievement of saturation (i.e., the stage in the data assembly process when no new relevant information is obtained) [22–25]. Patients aged ≥ 18 years, having primary hypercholesterolemia (heterozygous familial hypercholesterolemia [FH] or non-FH) with moderate, high, or very high cardiovascular risk, and having the inability to tolerate one or more statin (i.e., modified statin dose level or frequency, recommended new statin, or discontinued statin) because of objectionable symptoms (real or perceived) within the 3 months prior to screening were included in the study. FH diagnosis and cardiovascular risk level were identified by the provider via a yes/no response and check box option, respectively. Patients with a diagnosis of fibromyalgia or a history of the following conditions were excluded from the study: severe neuropathic pain; rheumatological disease associated with symptoms that may be confounded by symptoms of SI (e.g., rheumatoid arthritis); myalgia or myopathy that began or increased during treatment with lipid-modifying therapy other than statin therapy and stopped when the lipid-modifying therapy was discontinued; myopathy, other than statin-associated myopathy; rhabdomyolysis (defined as evidence of organ damage with creatine kinase $>10,000$ IU/l); or homozygous FH. Interviews lasted approximately 1 h and were audio-recorded, transcribed verbatim by an independent transcription company, and analyzed as described subsequently. Before the study was conducted, all study documents were submitted to an ethics review board for consideration, and approval to execute the interviews was received from Copernicus Group Independent Review Board (CGIRB) on 3 February 2015.

2.2.2 Expert Advice Meetings

Individual expert advice meetings were conducted with physicians and nurse practitioners who were experienced with treating patients with SI and who were identified from peer-reviewed publications in cardiovascular and SI research. A semi-structured open-ended expert advice meeting guide was developed to reference during the interviews conducted between 1 December 2014 and 5 January 2015. As with the patient interviews, interviews were conducted by trained interviewers, and the guide served as a map rather than a verbatim script to encourage the spontaneous collection of relevant and complete information related to the research questions. Each expert was asked to define SI in his or her own words and given the opportunity to spontaneously describe the concepts that characterize SI. Each meeting lasted approximately 1 h and was audio-recorded, transcribed verbatim by an independent transcription company, and analyzed.

2.3 Concept Selection and Questionnaire Construction

The goals of the concept selection and questionnaire construction were to evaluate and select the primary SI-associated concepts for measurement based on the results from the literature review and concept-elicitation activities and to subsequently construct the first draft of the Statin Experience Assessment Questionnaire (SEAQ)[®], including specification of the mode of administration and recall period and development of the questionnaire instructions, items, and response options. The SEAQ[®] draft was initiated during a concept-selection and item-generation meeting of the questionnaire developers and subsequently finalized upon consensus. Informed by the harmonized results of the literature search, expert advice meetings, and patient interviews, concepts that best characterized the relevant symptom and impacts of SI were selected as measurement targets for the SEAQ[®]. The SEAQ[®] was developed after concept selection with the following aspects defined based on relevant information gathered from the concept-elicitation activities, as well as measurement-development best practices: purpose of assessment, mode of administration, recall period, instructions, items, and response options.

2.4 Content Evaluation

The purpose of the content evaluation was to assess the content of the SEAQ[®] among clinical experts and patients with SI in ways that were acceptable to patients and could generate results that were useful to both patients and providers. To achieve this goal, one-on-one meetings with experts ($n = 5$) were conducted to evaluate the relevance, comprehensiveness, and suitability of the SEAQ[®] and to modify the questionnaire, as necessary, based on these results. Next, cognitive debriefing interviews (CDIs) with 15 patients with SI were conducted to evaluate the SEAQ[®] with respect to their ability to read, understand, and complete the questionnaire (note that these were different patients from those who participated in the patient CEIs). Results from each of these activities informed subsequent modifications to the SEAQ[®], ultimately leading to the final tool.

During the expert advice meetings (conducted between 17 April 2015 and 1 May 2015), experts were provided the draft SEAQ[®] and asked open-ended questions to explore the main research questions using a semi-structured expert advice meeting guide. Verbatim interview transcriptions were coded and analyzed. Interim modifications to the SEAQ[®] based on expert feedback were made before the debriefing interviews with patients.

Individual patient CDIs were conducted following interim modifications using a semi-structured cognitive debriefing interview guide. Patients were included in this phase of the study if they met the inclusion criteria described previously for the concept-elicitation phase of the study. Interviews were audio-recorded, transcribed verbatim, and analyzed. After feedback from expert advice meetings and patient CDIs was received, the SEAQ[®] was modified to generate the final version. Before interviews, all study documents were submitted to an ethics review board for consideration. Approval to conduct the interviews was received from CGIRB on 8 April 2015.

2.5 Qualitative Data Analyses

Verbatim transcripts were entered into ATLAS.ti Version 7.5.2 to facilitate the organization and analysis of qualitative data [26]. Transcript text germane to the research questions was identified, highlighted, and matched to a code from a codebook that best characterized the data. The codebook, a comprehensive list of all of the codes used to characterize important segments of transcript text, was used as a guide to organize the content and meaning of actual subject language. Several researchers or coders performed the coding by identifying transcript text in which a subject expressed an SI-related experience (i.e., a concept). When the data could not be matched to an existing code, a new code was created. The semi-structured CEI guide served as the basis for the preliminary coding scheme, which was updated as the coders analyzed the transcripts and added or modified codes. Codes added or modified were shared with all coders to maintain consistency with the scheme. A senior member of the project team reviewed the coding of every transcript to minimize variability across coders and to ensure inter-coder reliability. After completion of coding, data were pooled and qualitatively analyzed for common themes.

To facilitate coding in the concept-elicitation phase, the composition of each individual code followed this basic structure: domain::root concept::descriptor. ‘Domain’ conveyed the overarching general concept into which a specific root concept fell (e.g., symptom or impact). ‘Root concept’ was the unique characteristic of SI described by the expert or patient that was unlike any other concept (e.g., muscle pain). The ‘descriptor’ was intended to characterize, clarify, or otherwise describe some aspect of the root concept (e.g., a descriptor code may offer detail such as severity, frequency, duration, or location). Concept frequency was determined by counting the number of unique experts or patients who mentioned the concept at least once during an interview.

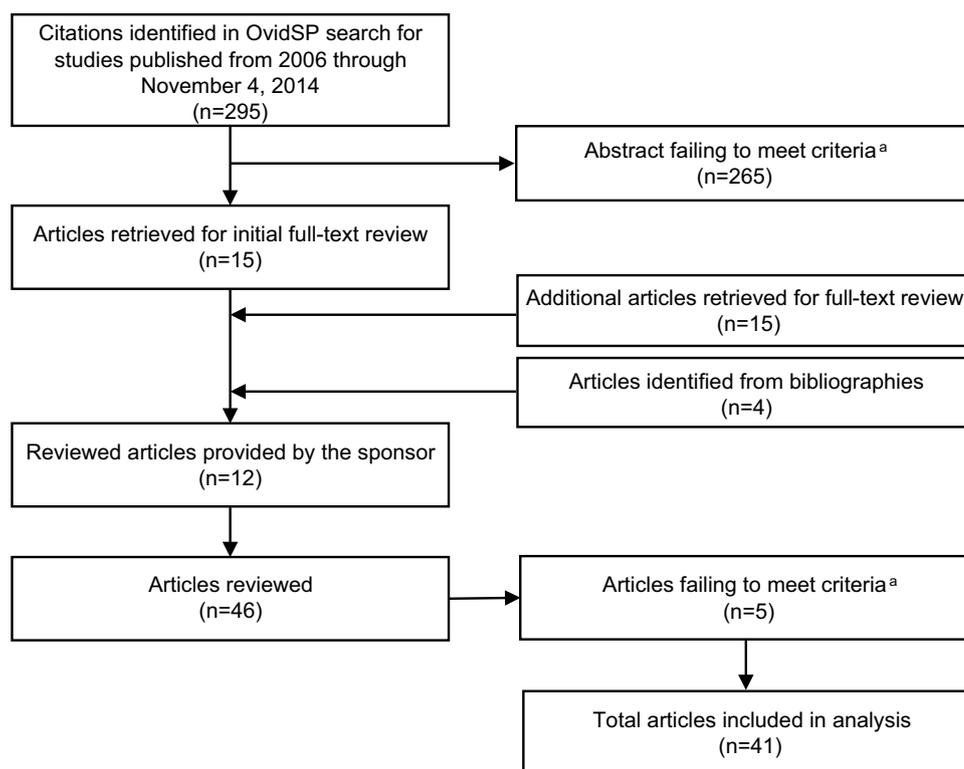
For the content-evaluation phase, a codebook organized feedback on the questionnaire. Coding was performed as described previously for the CEIs. The preliminary coding scheme was based on the semi-structured expert advice meeting guide or patient interview guide and was updated as transcripts were analyzed. Responses were compared and aggregated around themes associated with particular segments of the questionnaire (i.e., instructions, items, response options, and recall period) and more general topics such as the utility of the measure and overall format. A semi-quantitative analysis entailed counting the number of unique expert responses captured under a theme. Content analysis of patient responses consisted of evaluating patient interpretation of the instructions, items, and response options against their intended meaning.

3 Results

3.1 Literature Review

The literature review included 41 articles (19 review articles and 22 primary research articles) [9, 11, 15, 17, 27–63] (Fig. 2) and labels from three commonly prescribed lipid-modifying drugs [64–66]. Of the 41 articles reviewed, only four provided a working definition of SI [17, 51, 52, 63]. The literature described SI broadly as being any symptom significant enough to warrant a change in treatment. All three drug labels and 35 of the 41 articles reviewed reported muscle-related symptoms. SI concepts reported in the literature and labels included myalgia, myositis, myopathy, rhabdomyolysis, muscle atrophy, diminished muscle coordination, tendon pain/tendonitis, alopecia, renal impairment, liver enzyme abnormality, sleep disturbances, indigestion, headache, blisters, and nausea (Table 1 in the Electronic Supplementary Material [ESM]). The concepts identified in the literature review were organized into two conceptual models: one depicting SI (Fig. 1a in the ESM) and one depicting the side effects and adverse events associated with statins, as concepts specifically in the context of SI were often difficult to discern (Fig. 1b in the ESM). Conceptual models illustrate the relationship between a specified condition and its proximal to distal health outcomes [67]. These outcomes can be either unidimensional and have a direct relationship to the condition or multidimensional and indirectly relate to the condition. These models are not intended to be causal; arrows imply a dominant causal pathway, but a lack of arrows does not imply the absence of a relationship. The ultimate goal of this research was to generate a harmonized conceptual model incorporating the literature review and concept-elicitation activities.

Fig. 2 Literature search flow diagram. ^aArticles were included if they focused on the signs, symptoms, side effects, adverse events, and/or impacts of statins, and/or statin intolerance and excluded if they focused on pathogenesis, genetics, or molecular biology of statin intolerance, or solely discussed statins used in combination with other drugs, in a non-adult population (i.e., aged <18 years), and/or in case studies. ^bFollowing review of statin intolerance-related articles, an additional 15 articles that primarily focused on the side effects or adverse events of statins were selected from the initial list of 295 abstracts for full-text review



3.2 Concept Elicitation

Five experts (four physicians and one nurse practitioner) from diverse geographical areas in the USA and with a reported patient treatment experience of 19–29 years agreed to participate (Table 2 in the ESM). Each expert provided a unique definition of SI, and four (80.0%) reported that SI is different from experiencing side effects with statins. A total of 13 concepts reflecting the patient experience with SI were identified: muscle pain ($n = 5$ [100.0%]), muscle weakness ($n = 4$ [80.0%]), and forgetfulness ($n = 2$ [40.0%]), with burping, constipation, diarrhea, fatigue, gas, headache, indigestion, muscle cramps, reflux, and upset stomach being reported by one expert each. Experts frequently reported impacts on physical activity and daily living (e.g., inability to get out of bed or chair [$n = 3$ (60.0%)], difficulty walking [$n = 3$ (60%)], and impact on general daily activities [$n = 3$ (60.0%)]). The concepts generated from these meetings were organized into a conceptual model (Fig. 2 in the ESM).

Table 1 describes the characteristics of the 20 patients who participated in CEIs, including demographics, general health, and statin therapeutic history. Patients were nearly evenly divided on whether they were familiar with the term ‘statin intolerance’ (55.0% familiar vs. 45.0% unfamiliar). The majority of patients who were familiar with the term ($n = 7$ [63.6%]) reported that SI was related to experiencing side effects. The saturation analysis of SI-related

symptom data concluded that saturation was achieved (i.e., no new symptoms were elicited during the final quartile of interviews; Table 3 in the ESM). Patients reported 37 impact-level SI concepts across the following ten domains: emotional ($n = 15$ [75.0%]), activities of daily living ($n = 13$ [65.0%]), physical ($n = 11$ [55.0%]), social ($n = 7$ [35.0%]), sleep ($n = 6$ [30.0%]), work ($n = 3$ [15.0%]), cognitive ($n = 2$ [10.0%]), leisure ($n = 2$ [10.0%]), attire ($n = 1$ [5.0%]), and identity ($n = 1$ [5.0%]). Generated concepts were organized in a conceptual model (Fig. 3 in the ESM).

3.3 SEAQ© Development

Harmonized concepts from the literature review and the concept elicitations (Table 2) were utilized to generate a 17-item draft questionnaire (Fig. 4 in the ESM). One set of items assesses the level of severity for each symptom, and the second set assesses each symptom’s interference in daily life. To assess severity and interference, 11-point numeric rating scales (NRSs) were selected. The Symptom Severity Scale uses an NRS ranging from 0 (none) to 10 (as bad as you can imagine), and the Symptom Interference Scale ranges from 0 (not at all) to 10 (extremely). A recall period of ‘the past 30 days’ was deemed clinically appropriate to capture the patients’ experiences between visits with their providers, which typically occur about 1 month after initiating statin treatment and gradually decrease over time.

Table 1 Provider- and patient-reported demographic and health information of patients who participated in concept-elicitation interviews and cognitive debriefing interviews

Characteristic	CEIs (<i>N</i> = 20)	CDIs (<i>N</i> = 15)
Age, years		
Range	55.9–78.9	48.2–74.2
Mean ± SD	65.6 ± 7.4	62.9 ± 9.1
Sex, female	13 (65.0)	9 (60.0)
CV risk		
Moderate	7 (35.0)	5 (33.3)
High	8 (40.0)	5 (33.3)
Very high	5 (25.0)	5 (33.3)
Currently taking a statin	17 (85.0)	13 (86.7)
No lactose intolerance	20 (100.0)	14 (93.3)
No vitamin D deficiency	19 (95.0)	13 (86.7)
Hypothyroidism		
Yes (currently controlled)	3 (15.0)	1 (6.7)
No	17 (85.0)	14 (93.3)
Health in general		
Excellent	0 (0.0)	NR
Very good	2 (10.0)	1 (6.7)
Good	10 (50.0)	7 (46.7)
Fair	6 (30.0)	5 (33.3)
Poor	2 (10.0)	2 (13.3)
Patient-reported statin medication history ^a		
Type(s) of statin medication had been changed	11 (55.0)	NR
Statin medication had been discontinued	5 (25.0)	NR
Dosage(s) of statin medication had been changed	4 (20.0)	NR
Statin medication dose/type had not been changed	2 (10.0)	NR
Medications other than statins ^a		
Antihypertensive medications	6 (30.0)	12 (80.0)
Diabetes medications	2 (10.0)	3 (20.0)

Data are presented as *n* (%) unless otherwise indicated

CDI cognitive debriefing interview, CEI concept-elicitation interview, CV cardiovascular, NR not reported, SD standard deviation

^a Counts not mutually exclusive

3.4 Content Evaluation

The initial 17-item draft SEAQ© was debriefed with the same experts who participated in the concept elicitation. Expert feedback received after review of the draft SEAQ© confirmed the relevance of the muscle-related items in the questionnaire (*n* = 5 [100.0%]); however, two experts (40.0%) disagreed on the relevance of non-muscle-related items. All experts agreed on the severity and interference assessment of symptoms, and all but one expert (80.0%) indicated that the 30-day recall period was appropriate. Experts also made suggestions regarding the instructions, NRS, overall format, and additional information to be collected from the questionnaire. As a result of the feedback, two additional items were added to the SEAQ© during an interim modification before conducting CDIs

with patients: one item asking patients whether they stopped taking their statin because of symptoms (using a dichotomous yes/no response scale) and another item asking patients how likely they would be to stop taking their statin because of symptoms (rated on a five-point verbal response scale).

The patients who participated in the CDIs were unique from those who participated in the CEIs, but their characteristics were similar (Table 1). A summary of results from the patient CDIs is included in Table 4 in the ESM. All patients (*n* = 15) reported that the SEAQ© was easy to read and answer. All patients for whom data were collected (*n* ≥ 13 [100.0%]) interpreted the instructions and response scales as intended; data were not available for patients who were not asked a specific question and/or who provided a response that was not sufficient for analysis. At

Table 2 Harmonization of results from concept-elicitation phase

Reported by three perspectives	Reported by two perspectives	Reported by patients only	Reported by experts only	Reported by literature only
Muscle cramps	Muscle spasm ^b	Jitteriness	Constipation	Diminished muscle coordination
Muscle weakness	Body ache ^c	Lightheaded	Gas	Tendon pain/tendonitis
Muscle ache	Indigestion	Swelling		Alopecia
Muscle pain	Forgetfulness			Blisters
Headache	Diarrhea			
Nausea	Runny nose ^d			
Tiredness				
Joint pain or joint stiffness ^a				

^a Described as joint pain by patients and in the literature. Expert-reported ‘muscle pain’ around the joints

^b Described similarly by patients as muscle cramps; however, patients who reported this symptom indicated the two were distinct based on duration

^c Patient-reported ‘body ache’. Expert-reported ‘muscle ache’ sometimes described by patients as ‘body ache’

^d Patient-reported ‘runny nose’. Sinusitis reported as a side effect or adverse event in the product label for ezetimibe

least 93% of patients for whom data were collected interpreted each item as intended. The majority of patients found the muscle-related items (as well as joint pain and tiredness items) relevant to their experience with SI (ranging from $n = 10$ [66.7%] to $n = 15$ [100.0%] patients), whereas headache and nausea were experienced by less than half of the patients for whom data were collected ($n = 6$ [40.0%] and $n = 2$ [13.3%], respectively). The removal of nausea and headache from the SEAQ© as target measurement concepts was the only change based directly on patient feedback. All experts ($n = 5$ [100.0%]) and patients ($n = 15$ [100.0%]) indicated that the SEAQ© would aid in facilitating patient–provider communication.

Based on expert feedback and CDIs with patients, the following modifications were made to the SEAQ© instructional text: indication that some people have no negative or unwanted symptoms (60.0% of experts agreed); adjustment to the NRS to include a middle anchor to represent the severity/interference of moderate symptoms (80.0% of experts agreed); reordering of muscle-related symptoms from least invasive (based on one expert recommendation); and removal of nausea and headache from the questionnaire as target concepts based on irrelevance to SI according to some experts ($n = 2$ [40.0%]) and the majority of patients (headaches and nausea were not relevant to 7 [53.8%] and 12 [80.0%] patients, respectively). Figure 3 presents the final 15-item SEAQ©. After finalization of the SEAQ©, a conceptual framework was constructed to depict the relationship between the concepts and subsequent items in the instrument (Fig. 4) [68].

Scoring of the SEAQ© is based on the conceptual framework, which hypothesized a symptom severity scale (items 1–6), a symptom interference scale (items 7–12), and three additional items assessing ‘overall impact’

(item 13), whether the respondent stopped taking statins as prescribed (item 14), and intention to stop taking statins (item 15). A symptom severity scale score is created by summing and averaging responses to items 1 through 6, and a symptom interference scale score by summing and averaging responses from items 7 through 12. Additionally, a combined total score can be created by averaging the scores of all items from both the symptom severity and the symptom interference scales (items 1–12). Finally, the items assessing overall impact (item 13) and whether the respondent stopped taking statins as prescribed (item 14) or intends to stop taking statins (item 15) are scored independently. For the dichotomously scored item 14, we recommend a 0 (no) and 1 (yes) scoring method. Item 15 may be scored from 0 (very likely) to 4 (very unlikely).

4 Discussion

The primary purpose of the development of the content-valid SEAQ© is to facilitate clinically meaningful communication between patients and their providers to improve the understanding of SI and its associated patient experience. To date, no validated scales accurately assess the patient SI experience in the clinic. Although new and proposed tools for providers are becoming available, they do not allow for direct input from the patient, an important component of SI diagnosis and management. The statin myalgia clinical index (SMCI) score proposed by the NLA provides weighted values based on the distribution of muscle complaints, information on the temporal pattern of onset and improvement after withdrawal from statins, and reoccurrence on rechallenge [69]. Additionally, the ACC has implemented an SI app to help guide providers through

Fig. 3 Final 15-item Statin Experience Assessment Questionnaire©

Statin Experience Assessment Questionnaire (SEAQ) (© 2015)

A statin is a medication used to lower cholesterol and sometimes people will have negative or unwanted experiences because of these medications and some people do not. This questionnaire asks about your experiences with taking statins. Please select only one answer for each question by circling the number that best describes your experience **over the past 30 days**. There are no right or wrong answers to any of the questions.

	None ▼			Moderate ▼				As bad as you can imagine ▼			
1. Rate the severity of your <u>muscle aches</u> (for example, muscles feeling sore, strained or stiff).	0	1	2	3	4	5	6	7	8	9	10
2. Rate the severity of your <u>muscle pain</u> (for example, a throbbing or shooting pain in the muscles).	0	1	2	3	4	5	6	7	8	9	10
3. Rate the severity of your <u>muscle cramps</u> .	0	1	2	3	4	5	6	7	8	9	10
4. Rate the severity of your <u>muscle weakness</u> (for example, a feeling of heaviness or tiredness in the muscles).	0	1	2	3	4	5	6	7	8	9	10
5. Rate the severity of your <u>tiredness</u> (or lack of energy).	0	1	2	3	4	5	6	7	8	9	10
6. Rate the severity of your <u>joint pain</u> .	0	1	2	3	4	5	6	7	8	9	10
7. How much has <u>muscle aches</u> (for example, muscles feeling sore, strained or stiff) interfered with your daily life?	0	1	2	3	4	5	6	7	8	9	10
8. How much has <u>muscle pain</u> (for example, a throbbing or shooting pain in the muscles) interfered with your daily life?	0	1	2	3	4	5	6	7	8	9	10

	None ▼			Moderate ▼				As bad as you can imagine ▼			
9. How much has <u>muscle cramps</u> interfered with your daily life?	0	1	2	3	4	5	6	7	8	9	10
10. How much has <u>muscle weakness</u> (for example, a feeling of heaviness or tiredness in the muscles) interfered with your daily life?	0	1	2	3	4	5	6	7	8	9	10
11. How much has <u>tiredness</u> (or lack of energy) interfered with your daily life?	0	1	2	3	4	5	6	7	8	9	10
12. How much has <u>joint pain</u> interfered with your daily life?	0	1	2	3	4	5	6	7	8	9	10
13. Overall, how much have your <u>statin medication symptoms</u> interfered with your daily life?	0	1	2	3	4	5	6	7	8	9	10
14. Have you <u>stopped taking your statin as prescribed</u> because of your medication symptoms?	<input type="checkbox"/> Yes						<input type="checkbox"/> No				
15. Overall, <u>how likely are you to stop taking your statin medication</u> because of the symptom(s) you experience?	<input type="checkbox"/> Very likely		<input type="checkbox"/> Likely		<input type="checkbox"/> Unsure		<input type="checkbox"/> Unlikely		<input type="checkbox"/> Very unlikely		

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	Item	Concept	General Concept
Rate the severity of the symptom over the past 30 days	Item 1: Muscle aches (for example, muscles feeling sore, strained or stiff)	Severity of muscle aches	Symptom severity
	Item 2: Muscle pain (for example, a throbbing or shooting pain in the muscles)	Severity of muscle pain	
	Item 3: Muscle cramps	Severity of muscle cramps	
	Item 4: Muscle weakness	Severity of muscle weakness	
	Item 5: Rate the severity of your tiredness (or lack of energy)	Severity of tiredness	
	Item 6: Rate the severity of your joint pain	Severity of joint pain	
How much has the symptom interfered with your daily life over the past 30 days	Item 7: Muscle aches (for example, muscles feeling sore, strained or stiff)	Impact of muscle aches	Symptom impact
	Item 8: Muscle pain (for example, a throbbing or shooting pain in the muscles)	Impact of muscle pain	
	Item 9: Muscle cramps	Impact of muscle cramps	
	Item 10: Muscle weakness (for example, a feeling of heaviness or tiredness in the muscles)	Impact of muscle weakness	
	Item 11: Tiredness (or lack of energy)	Impact of tiredness	
	Item 12: Joint pain	Impact of joint pain	
	Item 13: Overall, statin medication symptoms	Overall impact	
Overall, how likely are you to stop taking your statin medication because of the symptom(s) you experience?	Item 14: Have you stopped taking your statin as prescribed because of your medication symptoms over the past 30 days?	Stopped statin medication	Statin persistence
	Item 15: Overall, how likely are you to stop taking your statin medication because of the symptom(s) you experience?	Likelihood of stopping statin medication	

Fig. 4 Statin Experience Assessment Questionnaire[©] conceptual framework. The *left column* ('Item') lists the specific items from the SEAQ[©], the *middle column* ('Concept') lists the specific concept

of measurement as related to the item, and the *right column* ('General Concept') is the targeted measurement domain. SEAQ[©] Statin Experience Assessment Questionnaire[©]

the process of identification, management, and treatment of patients reporting muscle-related symptoms while taking statins [70]. There is the potential to combine the SEAQ[©] with specific symptom evaluation tools such as the SMCI as a way to use both clinical and patient-centric approaches to assess the SI experience.

The SEAQ[©] was developed following best practices established by the US FDA and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) PRO Good Research Practices Task Force [24, 68]. Best practice guidance from the FDA for developing PRO measures designates that content validity be supported by evidence from qualitative studies demonstrating that the items in a questionnaire are appropriate and comprehensive relative to the intended measurement concept, population, and application [68]. Patient input to item generation and evaluation of comprehension of the questionnaire also contribute to content validity. Patients with SI provided input that was an integral part of the SEAQ[©] development. Evidence from the patient CDIs indicates that the SEAQ[©] was easy to complete, comprehensive, and interpreted as intended. All patients who participated confirmed that the resulting SEAQ[©] would aid in the dialogue with their providers. The concept-elicitation activities for the

SEAQ[©] development demonstrated saturation, which indicates that these results are robust and reliable. Research establishes that qualitative data should be gathered to the point of saturation to ensure that the items in a PRO questionnaire represent the 'universe of content' for a given concept [24, 25, 71–74]. According to the ISPOR PRO Task Force, saturation should be documented when developing a new instrument [24].

The resulting SEAQ[©] emphasizes that the patient SI experience is multifaceted and primarily characterized in the context of muscle pain and weakness. Removal of headache and nausea from the draft SEAQ[©] aligned with the proposed SI definitions from the NLA, International Lipid Expert Panel, and European Atherosclerosis Society, which primarily focus on muscle-related symptoms and recognize these symptoms as the main reason for discontinuation of therapy [17, 18, 75]. The SEAQ[©] also underscores that SI is best assessed from the patient perspective. This is consistent with the recommendations of the NLA SI Panel, which highlights the importance of collaboration between patients and providers through effective communication for the management of SI. According to the ACC/AHA Task Force on Performance Measures, active engagement of patients in self-care,

defined by their ability to perform activities necessary to attain, preserve, and encourage best health, leads to greater success in achieving treatment goals. For optimal shared accountability with their providers, patients would ideally be aware of symptoms, discuss any symptoms with their providers, become educated about the condition, execute a treatment plan, and follow up to assess outcomes.

The methodology utilized for the development of the SEAQ[©] had several strengths. First, by obtaining data via research interviews that allowed spontaneous responses, experts' definitions and characterizations of SI were not limited to prespecified concepts about the topics. Second, the nature of the qualitative research allowed for collection of more in-depth data and deeper understanding of the experts' perspectives of SI. The experts who were interviewed provided detailed input and are likely to partner with patients to utilize the final SEAQ[©] for a better understanding of the patient-centric SI experience. Third, items in the questionnaire were rated on an 11-point NRS, suggested by researchers and measurement development specialists because of its relative advantages in minimization of missing data, patient preference, and ease of recording and implementation in research settings [76]. Finally, the research activities followed the guidelines provided by the FDA and ISPOR for the development of PRO questionnaires.

There were also limitations in the activities leading to the generation of the SEAQ[©]. First, because of the small sample size of experts and patients, additional research would be necessary to gain further consensus on clinical perspectives related to SI and to ensure that results are generalizable. Second, the recall period was set to 30 days because the questionnaire was intended to document patient experiences between visits with their providers. This would preclude the assessment of SI among patients who are no longer taking statins but who had experienced symptoms characteristic of SI in the past (i.e., longer than 30 days prior to assessment). In an effort to minimize the burden on study participants, limited demographic and health information was collected. In particular, detailed information regarding the history of statin use and associated statin-related problems was lacking. The limited demographic information collected could impair the utility of the SEAQ[©] in the general population. Specifically, the lack of information regarding education and reading levels of those patients who participated in the CDIs makes it difficult to determine whether a broader group of patients might find the questionnaire comprehensible and easy to read. The last limitation is the lack of a patient review of the final SEAQ[©]. However, changes made to the questionnaire following patient CDIs were minor. In other words, the most substantial changes to the SEAQ[©] were made after the expert advice meetings and, therefore, were

evaluated by patients. Thus, we are confident that the current version of the SEAQ[©] will be easily comprehended by future patients completing the questionnaire.

As a measure of SI, the SEAQ[©] is a content-valid PRO questionnaire that has been developed and documented in accordance with measurement-development best practices. The SEAQ[©] can be utilized in clinical practice for shared learning of the patient SI experience, for facilitating communication between patients and providers about patient health status, and potentially for informing treatment decisions regarding the use of statins. In a research setting, the SEAQ[©] can be used as a means to gather patient-centric data. Future research is needed to quantitatively evaluate the psychometric properties and interpretability of the scores and to assess the impact of the SEAQ[©] on treatment decision making.

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Compliance with Ethical Standards

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Conflict of interest T. A. Jacobson is a consultant for Amgen, Amgen, AstraZeneca, Merck, Sanofi US, and Regeneron Pharmaceuticals, Inc. S.V. Edelman is a consultant for Sanofi US and Merck. N. Galipeau and A.L. Shields were consultants for Sanofi US at the time this research was conducted. U.G. Mallya and A. Koren are employed by and have ownership interest in Sanofi US. M.H. Davidson is a consultant for Sanofi US and Amgen.

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