Conceptual Framework for Patient-Reported Outcome Measures in Clinical Trials of Skeletal Muscle Cramping Experienced in Dialysis
A Kidney Health Initiative Workgroup Report


Abstract
Skeletal muscle cramping is a common and bothersome symptom for patients on maintenance dialysis therapy, regardless of modality, and it has not been prioritized for innovative assessments or treatments. Research to prevent or treat skeletal muscle cramping in patients receiving dialysis is hindered by poorly understood pathophysiology, lack of an accepted definition, and the absence of a standardized measurement method. The Kidney Health Initiative, a public-private partnership between the American Society of Nephrology and US Food and Drug Administration, convened a multidisciplinary workgroup to define a set of patient-reported outcome measures for use in clinical trials to test the effect of new dialysis devices, new KRTs, lifestyle/behavioral modifications, and medications on skeletal muscle cramping. Upon determining that foundational work was necessary, the workgroup undertook a multistep process to elicit concepts central to developing the basis for demonstrating content validity of candidate patient-reported outcome measures for skeletal muscle cramping in patients on dialysis. The workgroup sought to (1) create an accepted, patient-endorsed definition for skeletal muscle cramping that applies to all dialysis modalities, (2) construct a conceptual model for developing and evaluating a skeletal muscle cramping–specific patient-reported outcome measure, and (3) identify potential questions from existing patient-reported outcome measures that could be modified or adapted and subsequently tested in the dialysis population. We report the results of the workgroup efforts, provide our recommendations, and issue a call to action to address the gaps in knowledge and research needs we identified. These action steps are urgently needed to quantify skeletal muscle cramping burden, assess the effect, and measure meaningful changes of new interventions to improve the experience of patients receiving dialysis and suffering from skeletal muscle cramping.

Introduction
Skeletal muscle cramping is a common and bothersome problem for patients receiving dialysis, regardless of modality (1–5). Although skeletal muscle cramping was initially recognized as an intradialytic phenomenon associated with rapid fluid and electrolyte shifts during hemodialysis (HD) treatments (6,7), its pathophysiology remains largely unexplained and may include more complex neuromuscular signaling pathways; muscle fatigue; impaired oxygen delivery; and electrolyte, vitamin, or other dietary deficiencies (8,9). In patients receiving HD, skeletal muscle cramping rates range from 12% to 80%; anecdotally, its occurrence can contribute to early termination of dialysis (10–13). Monitoring and reporting skeletal muscle cramping are more challenging in the home dialysis setting because there is much less frequent interaction with the health care system. In general, studies of skeletal muscle cramping in patients receiving peritoneal dialysis are rare, have small sample sizes, and have methodologic flaws. However, at least one study has documented occurrence rates of up to 73% in these patients (14). Such a wide range of reported incidence highlights a fundamental issue: that there is neither an accepted definition nor standardized method to measure skeletal muscle cramping in patients receiving dialysis. An urgent need exists to derive a consensus definition and characterize skeletal muscle cramping. Once established, accurately determining skeletal muscle cramping epidemiology becomes possible. By necessity, patient-reported outcome measures (PROMs) are needed to capture patient experiences with skeletal muscle cramping particularly for evaluating efficacy in clinical trials.

The Kidney Health Initiative (KHI) was established in 2012 as a private-public partnership between the American Society of Nephrology, the US Food and Drug Administration (FDA), and over 100 organizations and companies (15). KHI was designed to “catalyze the development of safe and effective patient-centered therapies for people with kidney disease” through precompetitive collaboration. KHI aims to...
improve patient safety and foster innovation by breaking down barriers and addressing unmet needs (16). In 2016, KHI assembled a workgroup to (1) prioritize symptoms to target for therapeutic development among patients on in-center HD and (2) identify opportunities for targeted therapeutic development for the prioritized symptoms. Patients identified skeletal muscle cramping as one of the three most important unaddressed physical symptoms resulting from maintenance in-center HD (17). Another KHI workgroup worked with the FDA to (1) develop a conceptual framework for a health-related quality of life PROM; (2) identify and map existing PROMs to the conceptual framework, prioritizing them on the basis of their likely ability to support regulatory decision making; and (3) describe next steps for identifying PROMs for use in clinical trials of transformative KRT devices intended to support regulatory submissions (18). On the basis of these workgroups’ outputs and to further advance high-priority unmet needs (19), KHI followed procedures listed on their website (https://khi.asn-online.org/) to establish the current interdisciplinary Patient-Reported Outcomes for Muscle Cramping Workgroup to define a set of PROMs for use in clinical trials to test new interventions (e.g., dialysis devices, KRT technologies, lifestyle/behavioral modifications, and medications) on alleviating skeletal muscle cramping. However, as the workgroup evaluated needs and existing measures, we recognized (given the paucity of available evidence) that endorsing a definitive set of PROMs to assess skeletal muscle cramping in this population was premature. As a result, we undertook the process to elicit concepts central to developing the basis for demonstrating content validity of PROMs for skeletal muscle cramping in patients receiving dialysis.

This report describes our methods and subsequent recommendations that establish a foundation for PROM development in skeletal muscle cramping, especially for use in clinical trials. The workgroup sought to create a standardized, patient-endorsed definition for skeletal muscle cramping that applies to all dialysis modalities, construct a patient-facing conceptual framework for developing and evaluating a skeletal muscle cramping-specific PROM, and identify potential questions from existing PROMs that could be modified or adapted and subsequently tested. This report culminates in a call to action for the nephrology community to address gaps in knowledge and future research needs identified by the workgroup as urgently needed to establish validated PROMs. Such PROMs would measure meaningful changes in patient experience of skeletal muscle cramping in the dialysis population and could be used in clinical trials of devices, pharmaceuticals, and/or behavioral therapies.

Materials and Methods

PROMs used as outcome assessments in clinical trials must meet rigorous criteria and be sensitive in detecting treatment effects (20). Hence, the workgroup followed recommended best practices (21) that included a systematic approach where each step informs the next. Figure 1 outlines the development steps and summarizes key methods. An iterative process was used throughout, and the workgroup revised its work products on the basis of feedback, giving particular attention to input from patients on dialysis who have experienced skeletal muscle cramping. A standardized patient-endorsed definition, final patient-facing conceptual framework, and related concept mapping were the workgroup deliverables designed to guide future skeletal muscle cramping PROM development and validation.

**Structured Literature Review**

**Measure Identification.** The American Institutes for Research (AIR), KHI’s partner, conducted a targeted search of published (i.e., PubMed/MEDLINE, Scopus, and Embase) and gray literature (e.g., reports, fact sheets, white papers, and conference proceedings) to identify PROMs that assess skeletal muscle cramping encompassing CKD and other chronic conditions with similar muscle cramping profiles and symptom burden (e.g., cirrhosis, amyotrophic lateral sclerosis, exercise induced, and electrolyte disorders) identified by the workgroup. The key content (e.g., domains, administration modes, language availability, and scoring) was abstracted to construct an annotated PROM inventory. Identified articles underwent a systematic, two-stage approach to include and exclude articles. First, a subteam eliminated measures that were deemed too general or were not available. Next, multiple subteams reviewed the remaining articles and conducted an in-depth analysis of their content. Articles that did not contribute to the workgroup’s goals were eliminated.

**Measure Evaluation and Prioritization with Measure Mapping.** After identifying relevant PROMs, the workgroup subteams evaluated and prioritized those using rank-ordered criteria (Box 1). The full workgroup subsequently discussed all measures and arrived at consensus on a final prioritization. The same subteams subsequently mapped the items or questions in the PROMs to main themes identified in the final conceptual framework.

**Box 1. Rank-ordered measure evaluation criteria**

<table>
<thead>
<tr>
<th>Rank-Ordered Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evaluated in patients on dialysis and captured effect of dialysis-related skeletal muscle cramping</td>
</tr>
<tr>
<td>2. Defined concepts/domains and attributes</td>
</tr>
<tr>
<td>3. Acceptable respondent and administrator burden</td>
</tr>
<tr>
<td>4. Acceptable psychometric characteristics</td>
</tr>
<tr>
<td>5. Available in the public domain</td>
</tr>
<tr>
<td>6. Availability of translations, pediatric versions, computerized adaptive testing, or other administration modes</td>
</tr>
</tbody>
</table>

**Skeletal Muscle Cramping Definition and Conceptual Framework**

Given the lack of a standardized definition of skeletal muscle cramping in dialysis (19), the workgroup reviewed existing skeletal muscle cramping literature specific to dialysis and solicited input from experts and members of the KHI Patient and Family Partnership Council to develop a proposed skeletal muscle cramping definition (22). The workgroup initially defined skeletal muscle cramping as follows: “Muscle cramps are involuntary painful skeletal muscle contractions anywhere on the body, occurring during or between dialysis treatments, day or night.”
The hypothesized conceptual framework (Figure 2) was initially organized on the basis of symptoms occurring before, during, and after dialysis and included considerations relating to patient-related behaviors and functioning independent symptom timing. A workgroup subteam and a graphic designer collaborated to create a patient-facing version of the framework that illustrated the main concepts using plain language and easily understood graphics. The patient-facing conceptual framework (Figure 3) was organized into three main areas indicating changes in the (1) “things I can do,” (2) “way I feel,” and (3) “way I act.” Concepts from the hypothesized framework were classified into one of these three main areas.

**Patient Focus Groups**

AIR conducted three 90-minute virtual focus groups to gather feedback on the proposed definition and conceptual framework and assess patients’ experiences with skeletal muscle cramping (two for in-center HD and one for home HD or peritoneal dialysis) with English-speaking adult patients on dialysis who had experienced muscle cramping in the past month. Because of the coronavirus disease 2019 pandemic, we partnered with a recruitment firm, L&E Research, to identify participants from their diverse panel of patients with CKD and those treated by dialysis. An experienced moderator from AIR (T.S.H.-B.) led all focus groups using tailored moderator guides developed in collaboration with workgroup members. The audio-recorded and professionally transcribed sessions were reviewed and coded systematically. Themes and patterns within and across focus groups were identified. The workgroup reviewed focus group results, which led to conceptual framework revisions.

**Stakeholder Feedback**

After conducting the focus groups, three 60-minute stakeholder feedback sessions were held via videoconferencing software; each one was dedicated to a defined group of clinicians, patients, and regulators. Specifically, we inquired whether the symptoms and domains in the iteratively revised conceptual framework reflected patient priorities and would be of value to developers of new therapies for skeletal muscle cramping. We further solicited input for identifying potential gaps and/or improvements to the

![Figure 1. Development steps and summary of key methods.](image-url)

Workgroup members completed each of the major areas (defined in dark blue) using the methods summarized in this figure and described in detail in the methods. An iterative process was followed where the experience and information gained from each step informed the next. KHI, Kidney Health Initiative; PROM, patient-reported outcome measure.
During cramping

Patient-related behaviors
- e.g., anxiety, fear in anticipation of cramping, prodromal symptoms (severity, frequency, duration, bother and/or impact*)

Patient-related functioning
- e.g., pain, stiffness, sleep disruption (location, severity, frequency, duration, relationship to dialysis, bother and/or impact*)

Post-cramping sequelae
- e.g., fatigue, muscle tenderness, depression, sleep (quantity and/or quality) (location, severity, frequency, duration, relationship to dialysis, bother and/or impact*)

Pre-cramping

Patient-related behaviors
- e.g., pain, stiffness, sleep disruption
- (location, severity, frequency, duration, relationship to dialysis, bother and/or impact*)

Patient-related functioning
- “Impact on life” (hand cramp–writing)
- Ability to be active (physical functioning, leg/foot cramp–walking)
- Intrusion on family and social life
- Mental functioning and well-being

Changes in the way I act
- I change the way I act
- I change the amount I drink
- I change the amount of salt I eat
- I change the amount I take my blood pressure medicine

Changes in the way I feel
- I’m afraid
- I’m in pain
- I feel bad for no reason
- I just don’t feel right most of the time
- I feel sad
- I feel upset
- I can’t fall asleep or stay asleep
- I’m tired all the time

Changes in the things I can do
- I’m not able to go to work
- Going out or seeing friends and/or family is hard
- I am less active
- I have trouble walking
- I can’t do simple things like writing

How does dialysis cramping change your life?

This picture shows a way to think about muscle cramping that may occur in dialysis patients. The changes described may apply to muscle cramps that occur before, during, or after treatment. A muscle cramp can also be described by the location, how severe it is, how often and how long it occurs, how much it bothers you, and how much it impacts your life.

Figure 2. | Initial hypothesized conceptual framework as envisioned early on in the workgroup’s efforts. Initially, the workgroup organized the concepts (blue boxes) based on when symptoms of muscle cramping could occur (before a cramp, during a cramp, or after a cramp). The workgroup also hypothesized that there would be an impact from patient-related behaviors and/or functioning (green boxes). The arrows indicate hypothesized, directional relationships. Na⁺, sodium.

Figure 3. | Patient-facing conceptual framework. After developing the hypothesized conceptual framework in Figure 2, the workgroup developed a patient-facing version that could be used in the focus groups. The organization of the patient-facing framework did not follow the pre-, during, or post-cramping episode, but rather focused on changes in the way patients may act, feel, or do.
work products. Detailed notes were taken during these sessions by workgroup cochairs and administrative staff, and later, they were shared with workgroup members.

Results

Literature Review

Measure Identification. The literature review (Figure 4) ultimately identified 37 PROMs; 17 (46%) were cramping-specific PROMs or subscales, 17 (46%) were other PROMs with questions to assess cramping or muscle pain, and three (8%) were qualitative assessments. Only six (16%) PROMs identified were used in patients with kidney disease or those treated with dialysis.

Measure Evaluation and Mapping. Box 1 summarizes the criteria workgroup members used to rank the PROMs. No PROMs met all of the predefined criteria (23–31). As listed in Table 1, a few PROMs had medium- to high-priority rankings (23–31), and there were several PROMs that contained questions with the potential to be adapted and evaluated for skeletal muscle cramping in dialysis. PROMs with low or no ranking are listed in Supplemental Table 1 (32–46).

Table 2 represents measure mapping from the questions within the high- and moderate-priority PROMs to universally and variably experienced skeletal muscle cramping attributes. Supplemental Table 2 contains the measure mapping for the low- or no-prioritized PROMs (32–46). Categorizing our findings was an iterative process. After significant discussion and debate, we ultimately chose two categories in which the attributes of skeletal muscle cramping could be organized. Supplemental Table 3 includes examples of existing PROM questions that could potentially be adapted to measure skeletal muscle cramping in patients treated by dialysis. These questions cannot be extracted as is from their current source. Although the workgroup identified that these questions had the potential to be adapted, most require consideration of the recall period (assessing the response options), and overall, they require formal psychometric evaluation, including reliability, validity, and responsiveness in this patient population.

Focus Group

A total of 20 patients participated: 13 on in-center HD and seven on home dialysis. Purposive sampling resulted in a heterogeneous distribution of age, sex, race, education, time on dialysis, and self-reported comorbidities. We organized the focus group themes of skeletal muscle cramping that arose as universally and variably experienced attributes applicable to either in-center or home dialysis treatment location. The universally experienced skeletal muscle cramping attributes are onset, location, severity, proximity.

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**Figure 4. | Literature search, review, and selection process.** A systematic approach was taken to identifying PROMs in the literature.
<table>
<thead>
<tr>
<th>PROMs used in dialysis</th>
<th>Patient-Reported Outcome Measure or Study Purpose</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Potential to Be Adapted</th>
</tr>
</thead>
<tbody>
<tr>
<td>High prioritization</td>
<td>Study-specific PROM, Lynch et al. (23)</td>
<td>• Asks about dialysis personnel who patients talk to about skeletal muscle cramping and what actions patients take when cramps happen</td>
<td>• Single center</td>
<td>Yes, questions on timing</td>
</tr>
<tr>
<td></td>
<td>PROM, Mitsumoto et al. (26)</td>
<td>• Self-administration</td>
<td>• Format with skip questions may be a complicated pattern for patients</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Muscle and Joint Measure (24)</td>
<td>• Appropriate/reported survey development process—very specific to muscle pain</td>
<td>• English only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brief Pain Inventory (25)</td>
<td>• Psychometric evaluated</td>
<td>• No pediatric version</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Slightly modified a published questionnaire including description of muscle cramps (onset, precipitating events, frequency, duration, relief, and localization) and severity of pain by the Wong–Baker FACES Pain Rating Scale</td>
<td>• Measures effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low prioritization</td>
<td>Study-specific PROM, Mitsumoto et al. (27)</td>
<td>• Short</td>
<td>• Limited number of patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple Sclerosis Spasticity Scale (28)</td>
<td>• Additional questions include aggravating factors, what do you do to get relief from your muscle cramps, and has quality of life deteriorated because of muscle cramps</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PROMIS Pain Behavior (29)</td>
<td>• Limited number of patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The table above is a comprehensive list of patient-reported outcome measures/articles used in dialysis, both high and medium prioritization. It includes details on the measure, strengths, weaknesses, and potential for adaptation. The measures are designed to assess various aspects of patients' experiences, including pain, muscle cramps, dialysis, and quality of life. Each measure is evaluated for its comprehensiveness, reliability, and linguistic adaptation.
to dialysis treatment, time of day, duration, and cause. Variably experienced skeletal muscle cramping attributes include both gross and fine motor physical function, sleep, mood effects, avoidance or adaptive behaviors, and remedies.

**Skeletal Muscle Cramping Definition for Patients Receiving Dialysis.** Generally, participants agreed with the proposed definition. They suggested explicitly using words like annoying, aggravating, intense, and painful. They affirmed that skeletal muscle cramping could occur anytime or anywhere, was part of dialysis or their reality, and is one of the most challenging parts of dialysis. On the basis of this feedback, we revised the definition to “[m]uscle cramps that maintenance dialysis patients experience are involuntary, painful, sometimes intense, skeletal muscle contractions anywhere on the body, occurring at any time, day or night.”

**Skeletal Muscle Cramping Patient-Facing Conceptual Framework.** Overall, focus group participants did not feel that the patient-facing conceptual framework represented their experiences with skeletal muscle cramping and thought that it was more representative of dialysis overall. Some items were not consistent with their experience of skeletal muscle cramping (e.g., difficulty going out/seeing friends and changing intake of BP medicine). Participants did like how the information was laid out and suggested that it could be an effective educational tool particularly for patients new to dialysis treatment.

**Stakeholder Feedback**

All stakeholders supported the workgroup process, and their respective perspectives were meaningfully represented. No gaps and/or significant improvements were identified. However, stakeholders, particularly the clinicians and regulators, recommended emphasizing the universally experienced attributes of the acute muscle cramping episode (i.e., severity, frequency, location, duration, and timing) versus variably experienced attributes in alignment with outcomes of primary interest in clinical trials. Several participants across all three groups suggested using the universally experienced attributes as a minimum requirement and having the option of including variably experienced attributes and the health-related quality-of-life effects for a more complete picture. The patient stakeholders agreed with the focus group participants that the patient-facing conceptual framework was more applicable to the entire dialysis experience and not specifically to skeletal muscle cramping. They endorsed its use as an educational tool and made suggestions on how the workgroup could partner with other organizations toward further refinement and implementation.

**Final Conceptual Framework**

The final conceptual framework (Figure 5) incorporated the literature review, focus group results, and stakeholder discussions. The workgroup reconciled attributes of the acute cramping episode with the residual effects of the episode identified by patients. Potential PROM questions from the measure mapping process were linked, allowing for flexibility to incorporate variably experienced skeletal muscle cramping attributes. This final conceptual framework is designed to append the symptom section of the “flexible, device-specific domain(s)” created by a previous KHI workgroup (18).

**Summary**

The workgroup followed a rigorous process designed to focus on the perspectives of skeletal muscle cramping from

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**Table 1. (Continued)**

<table>
<thead>
<tr>
<th>Patient-Reported Outcome Measure Name or Study</th>
<th>Patient-Reported Outcome Measure or Study Purpose</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Potential to Be Adapted</th>
</tr>
</thead>
</table>
| PROMIS Pain Interference (30)                 | Assess self-reported consequences of pain on relevant aspects of one’s life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities | - Very standardized and methodical approach to development and testing  
  - Psychometrics evaluated  
  - Languages, pediatrics, and other administration modes available (including computerized adaptive testing)  
  - Three domains: the pain experience, the responses of others to the patient’s communicate pain, and the extent to which patients participate in daily activities  
  - Available in multiple languages | - Long  
  - Not used in kidney failure | Yes. So, some questions could be adapted for our use, but the entire survey does not apply |
| West Haven–Yale Multidimensional Pain Inventory (31) | Assesses chronic pain in individuals and is recommended for use with behavioral and psychophysiologic strategies | - Long  
  - Primary use is for chronic pain disorders (not acute cramping or sequelae)  
  - Use has been evaluated in temporomandibular disorder, cancer, chronic back pain  
  - No pediatric version  
  - Content validation was done by experts, not patients | | |
Table 2. Measure mapping to universally and variably experienced components of skeletal muscle cramping of high- or medium-priority articles/measures

<table>
<thead>
<tr>
<th>PROM Name or Study</th>
<th>Universally Experienced Skeletal Muscle Cramping Attributes</th>
<th>Variably Experienced Skeletal Muscle Cramping Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Acute Pain Severity or Intensity</td>
</tr>
<tr>
<td>PROMs used in dialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study specific, Lynch et al. (23)</td>
<td>Yes</td>
<td>Yes—NRS</td>
</tr>
<tr>
<td>PROMs not used in dialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study-specific PROM, Mitsumoto et al. (27)</td>
<td>Yes</td>
<td>Yes—VAS</td>
</tr>
<tr>
<td>Study-specific PROM, Chatrath et al. (26)</td>
<td>No</td>
<td>Yes—NRS</td>
</tr>
<tr>
<td>Brief Pain Inventory (25)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>PROMIS Pain Interference (30)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Muscle and Joint Measure (24)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>PROMIS Pain Behavior (29)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Multiple Sclerosis Spasticity Scale (28)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>West Haven–Yale Multidimensional Pain Inventory (31)</td>
<td>No</td>
<td>Yes—NRS</td>
</tr>
</tbody>
</table>

NRS, numeric rating scale; VAS, visual analog scale; PROMIS, Patient-Reported Outcomes Measurement Information System.
patients on dialysis and incorporate viewpoints of clinicians and regulators to produce its recommendations (Box 2). The standardized, patient-endorsed definition of skeletal muscle cramping is the first step to harmonize the uncoordinated approach to describe, evaluate, and address this problem. The final conceptual framework will facilitate a standardized, minimum set of universally experienced attributes of skeletal muscle cramping, and its successful application should allow for epidemiologic evaluation to include longitudinal changes as part of natural history or pathobiology. Furthermore, this work facilitates systematic evaluation of response(s) to novel treatments, including for clinical trials designed to obtain regulatory approval for devices or pharmaceuticals.

Initially, we focused on skeletal muscle cramping attributes to inform PROM development for regulatory submissions. However, the totality of our findings led us to recognize that patients receiving dialysis who experience skeletal muscle cramping were affected by more than just the clinical characteristics of the acute skeletal muscle cramping episodes, but that not all patients were affected in the same way. Thus, we classified skeletal muscle cramping attributes as universally or variably experienced. The research goal should dictate which attributes are assessed. A modular approach to PROM development and validation may be adopted on the basis of interest or necessity. Ultimately, the elucidation of all of these attributes—universally and variably experienced—will be

Box 2. Summary of workgroup recommendations

(1) The workgroup recommends a standardized definition of skeletal muscle cramping in patients requiring maintenance dialysis therapy: “Muscle cramps that maintenance dialysis patients experience are involuntary, painful, sometimes intense, skeletal muscle contractions anywhere on the body, occurring at any time, day or night.”

(2) The workgroup recommends assessing universally experienced and variably experienced attributes for a comprehensive view of patients’ skeletal muscle cramping experience.

(a) Universally experienced skeletal muscle cramping attributes are timing (i.e., when cramping occurs both in time of day and in relation to dialysis therapy), frequency at least over the span of a week or longer, severity of pain both on average and at its worst, duration of acute skeletal muscle cramping (on average and at its worst), location of affected muscle groups, and, if applicable, accounting of aggravating circumstances and/or various remedies utilized to alleviate skeletal muscle cramping.

(b) The variably experienced attributes proximally related to acute skeletal muscle cramping include effect on sleep, effects on mood and/or affect, dysfunctional personal interactions, residual pain, transient gross or fine motor disability, and/or avoiding specific activity during a variable length of a postskeletal muscle cramping period.

(c) From the patient perspective, more distal residual effect of the skeletal muscle cramping episode(s) that requires further elucidation may include lingering pain, ongoing fear or anxiety, adaptive behaviors to avoid muscle cramping, and patient-associated gross and/or fine motor physical sequela.

(d) An overall skeletal muscle cramping burden score may provide an estimate of how the combination of universally and variably experienced attributes affect patients’ lives.
essential to fully understanding skeletal muscle cramping in dialysis.

We cannot overemphasize the importance of the “patient-reported” aspect of this project. The inherently intense personal experience and effect of skeletal muscle cramping require direct patient input. Even when skeletal muscle cramping is witnessed by a medically trained observer, the assessment is at best incomplete and at worst inaccurate when the patient’s experience and the effect on their life are not systematically recorded, hence the value of and need for a skeletal muscle cramping PROM specific to patients on dialysis. The workgroup endorses a call to action for the nephrology community to address skeletal muscle cramping as a top priority for innovation.

The workgroup accomplished significant foundational work, yet there is still much work to be completed to produce a high-quality, psychometrically sound PROM for skeletal muscle cramping in patients on dialysis. PROM questions need to be adapted and/or developed, tested, and validated using accepted psychometric approaches. The testing and validation of questions we identified were beyond the scope of this workgroup. In addition, once such questions are developed, it will be important to consider how these instruments would be implemented in clinical trials. We recognize that pharmaceutical and device manufacturers may decide to measure only universally experienced attributes, pursuant to the indications they are targeting. In contrast, researchers and/or clinicians may be interested in specific aspects of skeletal muscle cramping in dialysis (e.g., effect on sleep and restfulness) such that they may pursue validating metrics for these variably experienced attributes in addition to those universally experienced. The workgroup encourages evaluating more distal sequelae of skeletal muscle cramping, such as effects on mood and emotional well-being along with avoidance and adaptive behaviors. Future work may also investigate the prevalence and effectiveness of remedies as well as the effect that various skeletal muscle cramping experiences have on patient interactions. These steps are urgently needed to quantify skeletal muscle cramping burden and assess the effect of new interventions.

The workgroup recommends that high-quality PROMs for skeletal muscle cramping be developed for patients receiving dialysis. Patients’ input is vital to that effort, as is rigorous psychometric testing and validation. Ideally, PROMs would be applicable to dialysis regardless of setting, although staged development and/or modality-specific PROMs may be necessary.

Disclosures

A. Grandinetti reports employment with Goldfinch Bio; consultancy agreements with AstraZeneca; honoraria from CareDx for Patient Summit January 2019; serving as a KHI Patient and Family Partnership Council Vice Chair; and other interests/relationships as a Getting On With Your Life With a Transplanted Kidney (GETONTRAK) study content developer for the website and reviewer and Vice Captain of the Kidney Action Committee Region 3 National Kidney Foundation (NKF). T.S. Hilliard-Boone, S. Keller, and D. Logan report employment with AIR. E. Lacson reports employment with and other interests/relationships with Dialysis Clinic, Inc. (a nonprofit dialysis provider). M.M. Richardson reports employment with Tufts Medical Center; ownership interest in Integra Life Sciences; honoraria from Letters & Sciences for participating as a faculty member in a continuing education program; and other interests/relationships with Dialysis Clinic, Inc. Dialysis Clinic, Inc. contracts with Tufts Medical Center to pay the salary for M.M. Richardson’s role as Director of the Outcomes Monitoring Program. W.L. St. Peter reports consultancy agreements with Total Renal Care, Inc.; honoraria from the American Nephrology Nursing Association, Integritas Group, Letters and Sciences, and OptumLabs; serving as a scientific advisory board member for NKF; and other interests/relationships with the American Society of Nephrology Task Force on eGFR and Race, the Centers for Medicare & Medicaid Services Technical Expert Panel on Development of a Quality Measure Assessing Delay in Progression of Chronic Kidney Disease, NKF, and the Technical Expert Panel for Quality Insights Kidney Care Pilot project. F. Tentori reports employment with DaVita Clinical Research and serving on the Ardelyx Medical Advisory Board. M. West reports employment with the American Society of Nephrology. K.R. Wilund reports honoraria from NKF and Renal Research Institute, Inc. and serves as a scientific advisor or member of Journal of Renal Nutrition. R. Wingard reports employment with Fresenius Medical Care North America; stock options in Fresenius Medical Care North America; and serving as a member of the KHI Muscle Cramping Patient-Reported Outcomes Project and as a volunteer of Welcome Home of Chattanooga (nonprofit).

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Supplemental Material
This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.11980921/-/DCSupplemental.

Supplemental Table 1. Low-priority or no-priority PROMs/articles.

Supplemental Table 2. Measure mapping to universally and variably experienced components of skeletal muscle cramping from low- or no-priority measures/articles.

Supplemental Table 3. Examples of potential PROM question adaptations to capture skeletal muscle cramping attributes.

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