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

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# 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, patientendorsed 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.

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# 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 patientcentered therapies for people with kidney disease" through precompetitive collaboration. KHI aims to

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Dr. Michelle M. Richardson, William B. Schwartz Division of Nephrology, Tufts Medical Center, 800 Washington Street, Box 391, Boston, MA 02111. Email: mrichardson@ tuftsmedicalcenter.org 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

- Evaluated in patients on dialysis and captured effect of dialysis-related skeletal muscle cramping
- (2) Defined concepts/domains and attributes
- (3) Acceptable respondent and administrator burden
- (4) Acceptable psychometric characteristics
- (5) Available in the public domain

(6) Availability of translations, pediatric versions, computerized adaptive testing, or other administration modes

## 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."

Initial conceptualization of definition and model	<ul> <li>Solicited expert opinion from workgroup members</li> <li>Collated scientific literature related to skeletal muscle cramping in dialysis patients</li> <li>Conducted semi-structured, open-ended interviews with a convenience sample of patients</li> <li>Solicited keywords and experiences from members of the KHI Patient and Family Partnership Council</li> <li>Brainstormed proposed definition of skeletal muscle cramping and iterative development of 2 preliminary conceptual models</li> </ul>
Structured literature review with measure identification	<ul> <li>Conducted targeted search of published and gray literature</li> <li>Reviewed and considered elimination of tangentially relevant literature</li> <li>Evaluated PROMs identified based on agreed upon criteria (Box 1)</li> </ul>
Patient focus groups	Conducted 3 virtual focus groups (2 in-center, 1 home) following standardized procedures
Stakeholder feedback sessions	<ul> <li>Conducted 3 60-minute virtual stakeholder teleconferences to obtain feedback (clinical, regulatory, patients). Clinical group (2 nephrologists, 1 psychometrician with experience in kidney disease PROMs); regulatory science advisors (1 medical reviewer, 1 psychometrician, and 2 representatives from KHI's Board of Directors, both nephrologists); patient group (2 patient representatives from KHI Patient and Family Partnership Council, facilitated by the KHI Patient and Family Partnership Council representative on the workgroup. Three patients were invited but 1 was unable to attend the virtual session).</li> </ul>
Iterative revision	<ul> <li>Revised focus group moderator guides after first focus group to better understand the unexpected finding that patients did not feel the patient-facing conceptual model represented their experience</li> <li>Discussed and came to consensus on final prioritization of identified PROMs</li> <li>Revised conceptual model after focus groups and again after stakeholder feedback</li> </ul>
Final definition, model, and measure mapping	<ul> <li>Created a final definition and conceptual model based on input from all previous steps in the process</li> <li>Mapped items in the evaluated PROMs to main themes in the conceptual model</li> <li>Solicited consensus among workgroup members to finalize recommendations</li> </ul>

Figure 1. | Development steps and summary of key methods. 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.

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 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<sup>+</sup>, sodium.



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 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



Figure 4. | Literature search, review, and selection process. A systematic approach was taken to identifying PROMs in the literature.

Table 1.         Workgroup ass	essment of high- or medium-p	prioritization patient-reported o	outcome measures/articles	
Patient-Reported Outcome Measure Name or Study	Patient-Reported Outcome Measure or Study Purpose	Strengths	Weaknesses	Potential to Be Adapted
PROMs used in dialysis	3			
<i>Study-specific</i> <i>PROM, Lynch</i> <i>et al.</i> (23)	Evaluate patient's perception of frequency, severity, quality, and the effect that muscle cramps had on their prescribed treatment	<ul> <li>Asks about dialysis personnel who patients talk to about skeletal muscle cramping and what actions patients take when cramps happen</li> </ul>	<ul><li>Single center</li><li>Interview administered</li></ul>	Yes, questions on timing
PROMs not used in dialysis		1 11		
High prioritization Muscle and Joint Measure (24)	Four sections: muscle cramps, muscle weakness, myalgias, and arthralgias. Each section repeats items about temporal qualities, severity, and effect	<ul> <li>Self-administration</li> <li>Appropriate/reported survey development process—very specific to muscle pain</li> <li>Psychometric evaluated</li> <li>Measures effect</li> </ul>	<ul> <li>Format with skip questions may be a complicated pattern for patients</li> <li>English only</li> <li>No pediatric version</li> </ul>	Yes
Medium prioritization Brief Pain Inventory (25)	The Brief Pain Inventory rapidly assesses the severity of pain and its effect on functioning	<ul> <li>Has a diagram for indicating where pain is occurring</li> <li>Short form available</li> <li>Asks about relief from pain and pain effect on other areas of life</li> </ul>	<ul> <li>Not specific to cramping</li> <li>Available in multiple languages</li> </ul>	Possibly the diagram to indicate where cramping occurs, amount of relief item
<i>Study-specific</i> <i>PROM,</i> <i>Chatrath</i> <i>et al.</i> (26)	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	<ul> <li>Short</li> <li>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</li> </ul>	<ul> <li>Study specific</li> <li>Limited number of patients</li> </ul>	
Study-specific PROM, Mitsumoto et al. (27)	Assess muscle cramps in patients with amyotropic lateral sclerosis	<ul><li>Short</li><li>Psychometrics evaluated</li></ul>	<ul> <li>Limited number of patients</li> <li>Interview administered</li> <li>Full measure not reported</li> </ul>	
Multiple Sclerosis Spasticity Scale (28)	Self-assessment instrument to measure patients' perception and experiences of the effect of spasticity due to multiple sclerosis	<ul> <li>Six clinically relevant areas: three spasticity- specific symptoms (muscle stiffness, pain, and muscle spasms) and three areas of physical functioning (ADL, walking, and body movements), emotional health, and social functioning</li> <li>Psychometrics evaluated</li> <li>Available in multiple languages</li> </ul>	<ul> <li>Not all questions would pertain, not clear if this is reliable or has been validated even in the multiple sclerosis population</li> </ul>	Essentially changing "spasticity" to "cramping" would make several subsections pertinent
PROMIS Pain Behavior (29)	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	<ul> <li>Extensive development</li> <li>May be great for initial descriptions/response to cramp but not sure how it applies to cramps in the effect after (descriptors are excellent indicators of pain that may have use for our purpose)</li> <li>Translated into other languages</li> <li>Pediatric version</li> </ul>	• Not clear how pain behaviors relate to cramping with kidney failure and/or would be responsive to treatment	Pediatric version descriptors may be useful for caretakers of children or even older adults who cannot communicate well

Table 1. (Continued)				
Patient-Reported Outcome Measure Name or Study	Patient-Reported Outcome Measure or Study Purpose	Strengths	Weaknesses	Potential to Be Adapted
PROMIS Pain Interference (30) West Haven–Yale Multidimensional Pain Inventory (31)	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 Assesses chronic pain in individuals and is recommended for use with behavioral and psychophysiologic strategies	<ul> <li>Very standardized and methodical approach to development and testing</li> <li>Psychometrics evaluated</li> <li>Languages, pediatrics, and other administration modes available (including computerized adaptive testing)</li> <li>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</li> <li>Available in multiple languages</li> </ul>	<ul> <li>Long</li> <li>Not used in kidney failure</li> <li>Long</li> <li>Primary use is for chronic pain disorders (not acute cramping or sequelae)</li> <li>Use has been evaluated in temporomandibular disorder, cancer, chronic back pain</li> <li>No pediatric version</li> <li>Content validation was done by experts, not patients</li> </ul>	Yes. So, some questions could be adapted for our use, but the entire survey does not apply

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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

Table 2. Measure mapping t	o universally	and variably ex	perienced co	mponents of s	keletal muscl	e cramping of	high- or me	dium-prio	ity articles/r	neasure	s		
	Universally	' Experienced ?	Skeletal Muse	cle Cramping	Attributes		Variably	Experience	ed Skeletal	Muscle	Cramping	Attributes	
PROM Name or Study	Frequency	Acute Pain Severity or Intensity	Duration	Location	Timing	Residual Pain (Sore, Stiff, Achy Muscles)	Gross Motor Effect	Fine Motor Effect	Avoid Activity/ Movement	Effect on Sleep	Effects on Mood and/or Affect	Personal Interactions	Pain Avoidance Behaviors
PROMs used in dialysis Study specific, Lynch <i>et al.</i> (23)	Yes	Yes—NRS	No	YesNRS	Yes	No	No	No	No	No	No	No	No
Study-specific PROM, Miterimoto <i>et al.</i> (77)	Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No
Study-specific PROM, Chatrath <i>et al.</i> (26)	Yes	YesVAS	Yes	Yes	Yes—time of day	No	No	No	No	No	No	No	No
Brief Pain Inventory (25)	No	YesNRS	No	Yes—uses diagram	No	Yes	Yes	No	No	Yes	Yes	Yes	No
PROMIS Pain Interference (30)	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Muscle and Joint Measure (24)	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes
PROMIS Pain Behavior (29)	No	No	No	No	No	No	No	No	No	No	No	No	No
Multiple Sclerosis Snasticity Scale (28)	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No
West Haven-Yale Multidimensional Pain Inventory (31)	No	Yes—NRS	No	No	No	Yes	YesNRS	(es—NRS	No	Yes	Yes—NRS	YesNRS	No
NRS, numeric rating scale; $V_{I}$	AS, visual and	alog scale; PRC	MIS, Patient	-Reported Ou	tcomes Measi	urement Infor	mation Syst	em.					



**Figure 5.** | **Final conceptual framework for assessing skeletal muscle cramping in patients treated with dialysis**. Based on the entirety of the workgroup's efforts, the final conceptual model was created to represent the totality of impact of skeletal muscle cramping and present the information in a format that could be used by a variety of stakeholders. Symptoms were divided into acute cramping episode and residual cramping effects (top darker tan boxes). Under those categories, the lighter peach boxes indicate the specific symptoms. Proximal effects are closer to the cramping episode, and moving down the framework results in more distal effects. All symptoms listed are important to patients, but selective measurement may be necessary based on the user's goals.

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 modalityspecific 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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The views and opinions expressed in this publication are those of the authors and do not necessarily reflect the official policies of any KHI member organization or the US Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organization imply endorsement by the US Government. The authors of this paper had final review authority and are fully responsible for its content. KHI makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the members of the workgroup. More information on KHI, the workgroup, or the conflict of interest policy can be found at www. kidneyhealthinitiative.org. The content of this article does not reflect the views or opinions of ASN or *CIASN*.

#### **Author Contributions**

A. Grandinetti, T.S. Hilliard-Boone, S. Keller, E. Lacson, M.M. Richardson, W.L. St. Peter, F. Tentori, M. West, K.R. Wilund, and R. Wingard conceptualized the study; A. Grandinetti, T.S. Hilliard-Boone, E. Lacson, M.M. Richardson, W.L. St. Peter, F. Tentori, and R. Wingard were responsible for data curation; A. Grandinetti, T.S. Hilliard-Boone, S. Keller, E. Lacson, D. Logan, M.M. Richardson, W.L. St. Peter, F. Tentori, M. West, K.R. Wilund, and R. Wingard were responsible for investigation; A. Grandinetti, T.S. Hilliard-Boone, E. Lacson, D. Logan, M.M. Richardson, W.L. St. Peter, F. Tentori, K.R. Wilund, and R. Wingard were responsible for formal analysis; A. Grandinetti, T.S. Hilliard-Boone, S. Keller, E. Lacson, D. Logan, M.M. Richardson, W.L. St. Peter, F. Tentori, M. West, K.R. Wilund, and R. Wingard were responsible for methodology; T.S. Hilliard-Boone, E. Lacson, M.M. Richardson, and M. West were responsible for project administration; T.S. Hilliard-Boone and M. West were responsible for funding acquisition; M.M. Richardson wrote the original draft; and A. Grandinetti, T.S. Hilliard-Boone, S. Keller, E. Lacson, D. Logan, M.M. Richardson, W.L. St. Peter, F. Tentori, M. West, K.R. Wilund, and R. Wingard reviewed and edited the manuscript.

#### Supplemental Material

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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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# **Supplemental Material Table of Contents**

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Supplemental Table 3: Examples of Potential PROM Question Adaptations to Capture Skeletal Muscle Cramping Attributes

# Supplemental Table 1: Low or No Priority PROM Measures/Articles

PROM Name or Study	PROM or Study Purpose	Strengths	Weaknesses	Potential to be Adapted
PROMs Used in Dialysis				
Low Prioritization				
Numeric Rating Scale (NRS) for Pain (Multiple studies) <sup>32</sup>	Unidimensional measure of pain intensity in adults and is segmented numeric version of the visual analog scale	<ul> <li>Short</li> <li>Interview or self-administration</li> <li>Psychometrics evaluated</li> <li>Evidence for use in dialysis<sup>33</sup></li> <li>Can be used for both severity ratings and average pain ratings</li> <li>Cross-cultural adaptations available</li> <li>Responsive to treatment</li> </ul>	<ul> <li>Unidimensional – only measures pain</li> <li>Chronic back pain and symptomatic hip and knee osteoarthritis have found it to be inadequate to capture complexity and idiosyncratic nature of pain</li> <li>No pediatric version</li> </ul>	No
PROMs Not Used in Dia	lysis			
Low Prioritization				
JOA Back Pain Evaluation Questionnaire (JOABPEQ) <sup>34</sup>		<ul> <li>Could be useful to get at impact Asks emotional questions</li> <li>not just physical aspects</li> <li>Translations available</li> </ul>	<ul> <li>Needs to be evaluated whether it could be translated into muscle cramping – written for low back pain</li> <li>Similar to PROMIS Pain Behavior although seems to have more impact questions</li> <li>Mostly yes/no response options</li> </ul>	
Abd-Elsalam, 2018 <sup>35</sup> (modification of the questionnaire proposed by Chatrath et al., 2012 <sup>26</sup> )	The aim of this study was to assess the safety and efficacy of orphenadrine in the treatment of muscle cramps in cirrhotic patients	<ul> <li>Captured differences in baseline muscle cramps, frequency, severity, duration, timing, location, aggravating factors, relieving factors, or quality of life</li> <li>Detailed description of muscle cramps (onset, precipitating events, frequency, duration, relief, and localization) and severity of pain</li> </ul>	<ul> <li>Telephone interview</li> <li>Psychometrics unknown</li> </ul>	
Rajabally, 2018 (cited Johnson 2015 <sup>36</sup> as the development article) <sup>37</sup>	To assess muscle cramp frequency, location, severity, duration and triggering factor	<ul> <li>Short, easy to answer</li> <li>Determined specific anatomical location of cramp.</li> <li>Asks about cramps interfering with sleep, daily activities, exercise and quality of life</li> </ul>	Psychometric data not available	Muscle cramp frequency, location, severity, duration and triggering factors
Study-specific PROM - Wake Forest Cramp/ Fasciculation Survey: Caress, 2016 <sup>38</sup>	To assess the experiences patients with early stage ALS have with muscle cramps	<ul> <li>Cramp index score can be calculated</li> <li>Measures difference over time.</li> </ul>	<ul> <li>Small sample size.</li> <li>Psychometrics unknown</li> </ul>	

Study-specific, Nocturnal Cramps Sleep Diary <sup>39</sup>	Combined adaptation of the "assessment, Espie diary form," and the Two Week Sleep Diary	Specific to cramps, but only nocturnal	<ul> <li>Only asks questions about sleep</li> <li>Focused on patients with multiple nocturnal cramps and may not be relevant to dialysis patients</li> <li>Self-report diary</li> </ul>	Yes. Serial measures, day of week – could be adapted to dialysis and non-dialysis days
Study Specific, Weiker, 2017 <sup>40</sup>	Evaluate if correction of vitamin D insufficiency relieved muscle cramps in postmenopausal women	<ul> <li>Short</li> <li>Asks questions about cramps affecting ability to fall asleep and about waking during night</li> </ul>	<ul> <li>Single center</li> <li>Limited number of questions with yes/no response options</li> </ul>	Possibly
Visual Analogue Scale (VAS) of Pain	Unidimensional measure of pain intensity which is a continuous scale comprised of a horizontal or vertical line, usually 10 centimeters in length, anchored by 2 verbal descriptors, one for each symptom extreme.	<ul> <li>Used in dialysis<sup>41,42</sup></li> <li>Cross-cultural adaptations available</li> <li>Pediatric version available</li> </ul>	<ul> <li>Unidimensional – only measures severity</li> </ul>	No
Fear of Pain Questionnaire (FPQ- III) <sup>43</sup>	Assesses fear associated with situation- specific medical, minor, or severe pain.	Psychometrics evaluated	<ul> <li>Only 1 question relevant to muscle cramping "I fear the pain associated with having a muscle cramp"</li> </ul>	Could inform new question development related to fear of activities around dialysis or activities of daily living
Guy's Neurological Disability Scale <sup>44</sup>	Clinical disability scale capable or embracing the whole range of disabilities which could be encountered in the course of multiple sclerosis.	<ul> <li>Subscales for fatigue and other disabilities.</li> <li>Overall score can be calculated</li> <li>Each domain graded according to severity and impact</li> <li>Psychometrics evaluated</li> </ul>	<ul> <li>Focused on multiple sclerosis</li> <li>One question addresses pain, spasms, or dizziness.</li> <li>Long, administration by health care personnel</li> <li>No translations</li> <li>No pediatric version</li> </ul>	Potentially
No Prioritization				
Pain Catastrophizing Scale (PCS) <sup>45</sup>	To quantify pain catastrophizing characterized by magnification and rumination of pain beliefs.	<ul> <li>Short</li> <li>Multiple languages available</li> <li>Computerize Adaptive Testing available</li> </ul>	Pain only	
Disabilities of the Arm, Shoulder and Hand (DASH) <sup>46</sup>	The DASH is designed to evaluate disorders and measure disability of the upper extremities, and monitor change or function over time.	<ul> <li>Short</li> <li>Self-administered</li> <li>Other languages available</li> </ul>	No pediatric version	Yes (Conceptually to develop measure that relates cramping and activities of daily living)

PROM - Patient-reported Outcome Measure

Supplemental Table 2: Measure Mapping to Universally- and Variably-Experienced Components of Skeletal Muscle Cramping from Low or No

# Prioritized Measures

PROM Name or Study	Universal	lly-experienced S	Skeletal Muscl	e Cramping At	tributes		Vá	ariably-exp	erienced Skelet	al Muscle C	ramping Attri	butes	
	Frequency	Acute Pain Severity Or Intensity	Duration	Location	Timing	Residual Pain (Sore, Stiff, Achy Muscles)	Gross Motor Impact	Fine Motor Impact	Avoid Activity/ Movement	Impact on Sleep	Effects on Mood and/or Affect	Personal Interactions	Pain Avoidance Behaviors
PROMs Used In Dialysi	s												
Numeric Rating Scale (NRS) for Pain <sup>32</sup>	No	Yes	No	No	No	No	No	No	No	No	No	No	No
PROMs Not Used In Di	alysis												
Study-specific PROM Weiker, 2017 <sup>40</sup>	Yes	Yes	No	No	No	No	No	No	No	Yes	No	No	No
Study-specific PROM Rajabally 2018 <sup>37</sup> ; cited Johnson 2015 <sup>36</sup> as development article	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No	No	No
Study-specific PROM Abd-Elsalam, 2018 <sup>35</sup> ; modification of the questionnaire proposed by Chatrath et al., 2012 <sup>26</sup>	Yes	Yes - VAS	Yes	Yes	Yes	No	No	No	No	No	No	No	No
Wake Forest Cramp/Fasciculation Survey Caress, 2016 <sup>38</sup>	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	No
Nocturnal Cramps Sleep Diary <sup>39</sup>	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes	No	No	No
Visual Analogue Scale (VAS) of Pain (Multiple studies)	No	Yes	No	No	No	No	No	No	No	No	No	No	No
Pain Catastrophizing Scale (PCS) <sup>45</sup>	No	No	No	No	No	No	No	No	No	No	Yes	No	No

JOA Back Pain Evaluation Questionnaire (JOABPEQ) <sup>34</sup>	No	No	No	No	No	No	Yes	No	Yes	Yes	No	Yes	No
Disabilities of the Arm, Shoulder and Hand (DASH) <sup>46</sup>	No	Yes	No	No	No	Yes	No	Yes	No	No	No	No	No
Fear of Pain Questionnaire (FPQ- III) <sup>43</sup>	No	No	No	No	No	No	No	No	No	No	Yes (fear)	No	No
Guy's Neurological Disability Scale44	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No

NRS – Numeric Rating Scale; VAS – Visual Analog Scale

Supplemental Table 3: Examples of Potential PROM Question Adaptations to Capture Skeletal Muscle Cramping Attributes

Original PROM Source	Original PROM Question	Example of Potential Adaptations	Comments
nced Skeletal Muscle	Cramping Attributes		
West Haven-Yale Pain Inventory <sup>31</sup>	Question 7. Section A. "On the average, how severe has pain been during the last week? <u>Response Options</u> O=Not at all severe to 6=Extremely	On the average, how severe has pain from skeletal muscle cramping been during the last week? Potentially keep response options Even simple quantification of "How	Ideal recall period needs to be determined. Unclear if "last week" is the correct recall period for skeletal muscle cramping experienced by patients receiving dialysis.
		long does each skeletal muscle cramping episode last on average? Longest?" with open ended answers in minutes or as categories may be tested.	The workgroup recommends asking about both average or usual pain and most severe. There were no specific questions for duration of the cramping episode which may affect the perceived severity of the pain.
Study-specific PROM, Lynch <sup>23</sup>	Question 3:"How often do you get muscle cramps?"Response Options Greater than 5 times a day Twice a day Daily Every other day Twice a week Once a week Twice a month Once a month		Used in dialysis patients and have face validity, but needs to be psychometrically evaluated. Original response option intervals need to be more inclusive and specific. For example, it is not clear how to answer Question 3 if patient has skeletal muscle cramping more than twice a day but less than 5 times a day Response options are more
	Original PROM Source Meed Skeletal Muscle Pain Inventory <sup>31</sup> Study-specific PROM, Lynch <sup>23</sup>	Original PROM SourceOriginal PROM Questionnced Skeletal Muscle Cramping AttributesWest Haven-Yale Pain Inventory31Question 7. Section A. "On the average, how severe has pain been during the last week?Response Options 0=Not at all severe to 6=ExtremelyStudy-specific PROM, Lynch23Question 3: "How often do you get muscle cramps?"Response Options Greater than 5 times a day Twice a day Daily Every other day Twice a month Once a month Less than once a month	Original PROM Source         Original PROM Question         Example of Potential Adaptations           Acced Skeletal Muscle Cramping Attributes         Attributes         Image: Comparison of the average, how severe has pain lowentory <sup>31</sup> On the average, how severe has pain been during the last week?         On the average, how severe has pain been during the last week?         Image: Comparison of the average, how severe has pain been during the last week?         Image: Comparison of the average, how severe has pain from skeletal muscle cramping been during the last week?         Potentially keep response options         Even simple quantification of "How long does each skeletal muscle cramping episode last on average?         Even simple quantification of "How long does each skeletal muscle cramping episode last on average?         Doge each skeletal muscle cramping episode last on average?           Study-specific         Ouestion 3:         "How often do you get muscle cramps?"         Response Options Greater than 5 times a day Twice a day Daily         Response Options day Twice a week         Image: Comparison day Twice a week         Image: Comparison day Twice a month Unce a month         Image: Comparison day Twice a month

				PROMs which may be better for
				dialysis patients.
Location	Study-specific	Question 8:	Response Options should also	Used in dialysis patients and have
	PROM, Lynch <sup>23</sup>	"Where do you get muscle	include:	face validity, but requires
		cramps?"	Hands	psychometric evaluation.
			Fingers	
		Response Options	Forearms	A few focus group participants
		Leg	Feet	reported having cramps in
		Arm		multiple places. The response
		Chest		options should allow for
		Abdomen		respondents to indicate more
		Neck		than one area, potentially
		Head		ranking from #1 as most common
		Back		up to least common.
		Shoulder		
				Consider offering more specific
				locations such as thigh or calf.
Timing	Study-specific	Question X:		Used in dialysis patients and have
	PROM, Lynch <sup>23</sup>	"What time of day do you get		face validity, but needs
		muscle cramps?"		psychometric evaluation
		Bespense Options		Compared to other DDOMs these
		Marning		compared to other PROIVIS these
		Afternoor		questions seem more specific.
		Alternoon		No odko oli prve for previlstvolo
		Evening		Need to allow for multiple
		Night		choices of times; consider
		Output in M		ranking with #1 as most likely,
		Question X:		and so on as applicable.
		vvnich days do you get muscle		
		cramps?		
		Response Options		
		Dialysis days		
		Non-Dialysis days		
		Both		
		Question X:		

		"When you get cramps on your dialysis day, when do they occur?" <u>Response Options</u> Before dialysis		
		During dialysis After dialysis Not applicable		
Variably-experience	d Skeletal Muscle Cra	amping Attributes		
Sleep	Joint and Muscle Measure <sup>24</sup>	Question X: "Do cramps or spasms wake you when you are sleeping or make it difficult to get to sleep?" <u>Response Options</u> Rarely or not at all Less than once a week One to 2 times a week 3 to 5 times a week, or more Question X: "Do muscle aches or pains, stiffness or other problems wake you when you are sleeping or make it difficult to get to sleep?" <u>Response Options</u> Rarely or not at all Less than once a week One to 2 times a week, or more	Do skeletal muscle cramps wake you when you are sleeping or make it difficult to get to sleep? <u>Response Options</u> Rarely or not at all Less than once a week One to 2 times a week 3 to 5 times a week, or more Do muscle aches or pain, stiffness from skeletal muscle cramping wake you when you are sleeping or make it difficult to get to sleep? <u>Response Options</u> Rarely or not at all Less than once a week One to 2 times a week, or more	Ideal recall period needs to be determined for skeletal muscle cramping impacts on sleep in dialysis patients and also if the frequency pattern in the response options is relevant to this patient population

Avoidance Physical Activity/Movement	Multiple Sclerosis Spasticity Scale <sup>28</sup>	Question, Sections 7 & 8:"As a result of your musclespasticity, how much in the past 2weeks have you been botheredby: Feeling reluctant to go out?"Response Options1=Not at all bothered2=A little bothered3=Moderately bothered4=Extremely bothered	As a result of your <i>skeletal muscle</i> <i>cramping</i> , how much in the past 2 weeks have you been bothered by: Feeling reluctant to go out? <u>Response Options</u> 1=Not at all bothered 2=A little bothered 3=Moderately bothered4=Extremely bothered	Ideal recall period needs to be determined for skeletal muscle cramping. Two 2 weeks may or may not be appropriate. 4-item bother response options may be limited in detecting a difference when evaluating treatment. This type of question could enhanced understanding of reluctance to go out may be connected with avoiding physical
Residual Pain (achy, sore, stiff muscles)	Multiple Sclerosis Spasticity Scale <sup>28</sup>	Question, Section 1:"As a result of your musclespasticity, how much in the past 2weeks have you been botheredby:02. Stiffness anywhere in yourlower limbs?07. Stiffness when standing up?08. Tightness in your muscles?Response Options1=Not at all bothered2=A little bothered3=Moderately bothered4=Extremely bothered	As a result of your <i>skeletal muscle</i> <i>cramping</i> , how much in the past 2 weeks have you been bothered by: 02. Stiffness anywhere in your lower limbs? 07. Stiffness when standing up? 08. Tightness in your muscles? <u>Response Options</u> 1=Not at all bothered 2=A little bothered 3=Moderately bothered 4=Extremely bothered	activity or movement.Ideal recall period needs to bedetermined Two weeks may ormay not be appropriate.4-item response options may belimited in detecting a differencewith treatment.This type of question couldprovide further understanding onwhether reluctance to go out isconnected with avoiding physicalactivity or movement.
Gross Motor. Potentially avoidance of movement	JOA Back Pain Inventory <sup>34</sup>	Q2-1 "Because of the low back pain, you sometimes ask someone to help you when you do something."	Because of pain <i>from skeletal</i> <i>muscle cramping</i> , you sometimes ask someone to help you when you do something.	Needs psychometric evaluation for use in patients on dialysis. Yes/No response options provide limited information.

		Q2-2"Because of the low back pain, you refrain from bending forward or kneeling down."Q2-3Q2-3Because of the low back pain, you have difficulty in standing up from a chair.Q2-4"Because of the low back pain, turning over in bed is difficult.Response Options 1) Yes 2)No	Because of pain <i>from skeletal</i> <i>muscle cramping</i> , you refrain from bending forward or kneeling down. Q2-3 Because of pain <i>from skeletal</i> <i>muscle cramping</i> , you have difficulty in standing up from a chair. Because of pain <i>from skeletal</i> <i>muscle cramping</i> , turning over in bed is difficult.	
Fine Motor	Disorders of Arm, Shoulder and Hand <sup>46</sup>	Question:1. Open a tight or new jar.2. Write.3. Turn a key.4. Prepare a meal.10. Carry a shopping bag or briefcase.17. Recreational activities which require little effort (e.g., card playing, knitting, etc.)Response Options 1=No difficulty 2=Mild difficulty 3=Moderate difficulty 4=Severe difficulty 5=Unable		Could potentially select certain items of relevance. Also has questions on other activities including sports, work etc that could be potentially modified to address computer use, gaming, fishing, etc Needs to be psychometrically evaluated in dialysis patients Question lead in would need to specifically refer to muscle cramping in fingers or hands.
Mood	Multiple Sclerosis Spasticity Scale <sup>28</sup>	Question, Section 7: <u>"</u> As a result of your muscle spasticity, how much in the past 2	As a result of your <i>skeletal muscle</i> <i>cramping,</i> how much in the past 2 weeks have you been bothered by:	Ideal recall period needs to determined.

		weeks have you been bothered by: 77. Feeling frightened, 79. Feeling panicky, 80. Feeling nervous." <u>Response Options</u> 1=Not at all bothered 2=A little bothered 3=Moderately bothered 4=Extremely bothered <u>Question, Sections 7 &amp; 8</u> : "As a result of your muscle spasticity, how much in the past 2 weeks have you been bothered by: 68. Feeling frustrated, Feeling reluctant to go out?" <u>Response Options</u> 1=Not at all bothered 3=Moderately bothered 4=Extremely bothered 4=Extremely bothered	<ul> <li>77. Feeling frightened, 79. Feeling panicky, 80. Feeling nervous.</li> <li>As a result of your <i>skeletal muscle cramping</i>, how much in the past 2 weeks have you been bothered by:</li> <li>68. Feeling frustrated, Feeling reluctant to go out?</li> </ul>	May be important to not only ask about amount of bother but also impact.
Personal Interactions	West Haven-Yale Multidimensional Pain Inventory <sup>31</sup>	Question:"indicate how often yoursignificant other generallyresponds to you in that particularway when you are in pain."1. Ignores me.2. Asks me what he/she can do tohelp.4. Expresses irritation at me.6. Talks to me about somethingelse to take my mind off the pain.7. Expresses frustration at me.8. Tries to get me to rest.	<ul> <li>indicate how often your significant other/care giver/dialysis staff generally responds to you in that particular way when you are in pain due to skeletal muscle cramping.</li> <li>1. Ignores me.</li> <li>2. Asks me what he/she can do to help.</li> <li>4. Expresses irritation at me.</li> <li>6. Talks to me about something else to take my mind off the pain.</li> <li>7. Expresses frustration at me.</li> </ul>	Needs formal psychometric evaluation for use in dialysis patients. Potentially more useful in clinical practice than for research purposes evaluating new devices or therapies for skeletal muscle cramping. Need to determine specifically who want to assess (care giver, spouse, significant other, dialysis

9. Tries to involve me in some	8. Tries to get me to rest.	staff) and not clump all three
activity	9. Tries to involve me in some	together in one question.
10. Expresses anger at me.	activity	
11. Gets me some pain	10. Expresses anger at me.	Consider revising question #11 to
medications.	11. Gets me some pain	dialysis staff intervenes with pain
	medications.	medication, adjusting dialysis
Response Options		machine, etc.
0=Never to 6= Very often		
		Need to assess if never to very
		often constitute the appropriate
		response options.