Kidney Symptom Questionnaire: Development, content validation and relationship with quality of life

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Abstract

Background : Chronic Kidney Disease (CKD) is associated with a range of symptoms, even at early stages. The importance of patient symptom experience is increasingly recognised, but validated symptom scores are lacking.

Objectives : This study aimed to refine an existing dialysis-patient symptom questionnaire for use with patients not requiring renal replacement therapy (RRT), carry out content validity testing, and explore convergent validity by comparing symptom scores with quality of life.

Design : A mixed-methods approach involving questionnaires, semi-structured interviews and a focus group.

Participants : Non-RRT CKD patients and expert health professionals.

Approach : Two hundred and nineteen non-RRT CKD patients completed an existing symptom questionnaire. The most commonly reported symptoms were identified, and descriptions refined in 11 semi-structured interviews. The questionnaire design was reviewed by a focus group. Content validity was established by a panel of expert health professionals. Seventy non-RRT CKD patients completed both the symptom questionnaire and a health-related quality of life questionnaire (EQ-5D-5L).

Results : Thirteen common symptoms were identified. During the content validity phase 13/16 experts responded (81%); 10/13 symptoms had “excellent” or “good” evaluation scores, and the content validity index of the whole questionnaire was 0.81, falling within the recommended threshold. Total symptom frequency scores, number of symptoms and the frequencies of 10/13 individual symptoms were all strongly associated with health-related quality of life (EQ-5D-5L index score; $p < 0.002$ for all).

Conclusion : This work has provided a new, validated symptom score for CKD patients not requiring RRT for clinical management and research purposes.

Introduction

Patients with chronic kidney disease (CKD) typically experience a range of symptoms, including fatigue, weakness, musculoskeletal pain, sleep problems, low libido, and skin discomfort (Brown et al 2017, van der Veer, Aresi & Gair 2017, Senanayake et al 2017, Pugh-Clarke, Read & Sim 2017, Gutierrez Sanchez, Leiva-Santos & Cuesta-Vargas 2017). Symptom burden is an important predictor of quality of life (QoL) (Almutary, Bonner & Douglas 2013, Almutary, Douglas & Bonner 2017), which can be reduced even in earlier stages of chronic kidney disease (Cruz et al. 2011). With CKD rising in prevalence, effective assessment and management of symptoms is vital (Eckardt et al. 2013). However, symptom experience is not directly related to clinical parameters such as renal function (Murphy et al. 2009, Brown et al 2017) and is often overlooked by clinicians or under-reported by patients (Weisbord et al. 2007, Pugh-Clarke, Read & Sim 2017).

The identification and assessment of patient symptoms is critical for good clinical management, and is of value for research (Abdel-Kader, Unruh & Weisbord 2009; Almutary, Bonner & Douglas 2013; Chambers, Brown & Germain 2010; Murphy et al. 2009; Murtagh, Addington-Hall & Higginson 2007). Inadequate attention to symptom burden has previously been highlighted as a particular concern by patients with CKD and reported as a priority for research (Kidney Health 2013). Furthermore, qualitative research has indicated that patients feel that identifying symptoms and responding appropriately is central to successfully managing their condition (Costantini, 2008). However, a recent qualitative study (Pugh-Clarke, Read & Sim 2017) showed that only 15 out of 18 non-RRT dependent CKD patients disclosed their symptoms to healthcare professionals, highlighting a need for improved attention to and communication about

symptom experience. Validated and population-appropriate symptom assessment tools are required to assist patient assessment for holistic service provision, and for research.

The majority of research into symptom experience in kidney disease has focussed on patients receiving dialysis, and there are a number of patient-reported outcome measures (PROMs) available for assessing symptom burden in this patient group (Aiyegbusi et al 2017). However, there is currently no validated symptom assessment tool widely available for, or systematically used in, patients with CKD who are not receiving renal replacement therapy (RRT). Research into non-RRT CKD symptoms has used a variety of assessment tools designed for other populations, but their applicability cannot be assumed without further research (Abdel-Kader, Unruh & Weisbord 2009; Almutary, Bonner & Douglas 2013; Murphy et al. 2009). A 2013 review of symptom tools showed that six quantitative studies of patients not receiving RRT each used different tools (Almutary, Bonner & Douglas 2013), resulting in great difficulty when comparing findings across studies. The available instruments differ in important ways, including varying symptom domains and numbers of symptoms considered. Questionnaires specifically designed or validated for the CKD population not on RRT are lacking. In a recent systematic review of CKD PROMs (Aiyegbusi et al 2017), only two symptoms scores for the non-RRT population were identified: that developed by Agarwal (2010) includes 37 symptoms, while the CKD-Symptom Burden Index (CKD-SBI) (Almutary, Bonner & Douglas 2016) has 32 items. The length of these questionnaires makes them impractical for clinical settings, and potentially burdensome for research participants. Therefore, development and validation of a short scale instrument is required for this population, an issue which was formally recognised and reported to the House of Lords in 2013 by the Kidney Alliance (Kidney Health, 2013).

This study describes the refinement of a symptom assessment tool called the Leicester Uraemic Symptom Score (LUSS). The LUSS was originally designed by author AGS for informal local use with peritoneal dialysis patients. The original LUSS tool asks the participant to indicate the “frequency” and “intrusiveness” of a list of 11 commonly reported renal symptoms (Table 1), which are scored by frequency (from 0 ‘never’ to 4 ‘every day’) and intrusiveness (from 0 ‘not applicable’ to 5 ‘extremely intrusive’).

[Table 1]

Subsequently, the LUSS was used by author ACS as a PROM in an interventional trial of exercise in non-RRT CKD, and found to be sensitive to change and to relate well to improvements in symptom experience (anecdotally reported by the participants). The results were also considered to be highly significant to quality of life and a strong motivator for continuing regular exercise after the end of the trial (Kosmadakis et al. 2012, Brown 2017). Therefore, the LUSS appeared to be a promising tool for adaptation to the specific requirements of the non-RRT CKD population.

Objectives

The current study aimed to refine the LUSS for use in non-RRT CKD, and to begin the improvement and validation process for this specific patient group. This work was used to develop an updated score, subsequently named the Kidney Symptom Questionnaire (KSQ).

The subjective nature of symptoms and their impact on the individual makes them difficult to assess objectively, and there is no obvious reference measure against which

to judge the concurrent validity of the questionnaire. However, given the established relationship between symptom burden and QoL (Almutary, Bonner & Douglas 2013), we explored convergent validity of the KSQ questionnaire by assessing the relationship between the new KSQ scores and health-related QoL. For this exercise, health-related QoL was measured using the EQ-5D-5L instrument (Euroqol 2011) in a sample of non-RRT CKD patients who completed both the KSQ and EQ-5D-5L.

Methods

Design

The study design involved five sequential stages: Stage 1: completion of the LUSS by non-RRT CKD patients to ascertain the most appropriate symptoms for inclusion in the new refined version; Stage 2: semi-structured interviews with non-RRT CKD patients to refine understanding and interpretation of symptom descriptions; Stage 3: a focus group with non-RRT CKD patients to review the design and layout of the KSQ questionnaire; Stage 4: a content validation exercise with an expert panel; and finally Stage 5: completion of the new revised KSQ and quality of life questionnaire (EQ-5D-5L) by non-RRT CKD patients.

Setting

The study was carried out in a single hospital nephrology outpatient clinic setting which is responsible for the secondary care of a large network of over 8,000 renal patients living in urban and rural areas. Stages 1-3 were completed sequentially between July 2013 and August 2014. Stage 4 was completed between September 2014 and January 2015, and Stage 5 between August and November 2016.

Participants

Patients with CKD stages 1-5 not on RRT attending routine nephrology outpatient clinic appointments were eligible for Stages 1-3 and 5 of this study. The only exclusion criterion was inability to give informed consent or to complete the questionnaires for any reason. The recruitment process and participant demographics for Stage 1 (LUSS completion) have been described elsewhere (Brown et al 2017). At the time of

recruitment to Stage 1, participants were provided with a brief outline of Stages 2 and 3 (interviews and focus group) and were asked to provide their contact details if interested in taking part. A purposive sample (to ensure diverse representation of gender, age and race) of patients who had provided contact details were then invited to participate in Stages 2 or 3.

Stage 4 (content validation) was carried out using an expert healthcare professional panel recruited by a researcher independent of the research team and comprised experts with: (i) 5+ years' experience in renal medicine; and (ii) extensive experience at a specialist level in kidney disease. The panel were identified via the UK CKD Forum and the research team's professional contacts with nationally-recognised renal clinicians. An initial covering email, copy of the KSQ, and a review proforma was sent to the selected clinicians. An additional follow up email was sent to non-responders one month later.

For Stage 5 (convergent validation), a consecutive sample of 100 patients was approached in general nephrology clinic waiting rooms and asked to complete a survey pack including the KSQ and the EQ-5D-5L. Participants gave written informed consent and were provided with the survey pack to complete at home, and a post-paid envelope in which to return it.

Outcome measures

For Stage 1, participants completed the LUSS tool, rating a list of 11 symptoms for "frequency" and "intrusiveness". For the purposes of this study, an additional 4 blank

rows were provided at the bottom of the LUSS form, with instructions to write in and rate any other symptoms experienced by the individual.

For Stage 2, cognitive interviews explored participants' responses as they considered each listed symptom (Knafl et al. 2007). Cognitive interviewing is a flexible tool widely used to assess patient completion of surveys and verbal probing is a commonly used direct questioning technique (Pope & Mays 2006, Collins 2003). The interviews were led by one of the research team (SAB), a white British female medical student who had received training in qualitative research techniques. Interviews lasted for 45-90 minutes. Cognitive probes were used to explore the participant's comprehension, retrieval and response of symptom descriptions. Scripted probes (provided as Supplementary Material), developed prior to interview in consultation with a patient involvement group, were used with spontaneous probes to seek clarification. Judgement and decision processes were explored using a card sorting task in which participants identified symptoms that related to each other e.g. pains in bones and pains in joints. The interviews were audio recorded, and transcribed verbatim.

For Stage 3, a focus group led by SAB reviewed the updated KSQ and assessed the layout and design for ease of use.

For Stage 4 (content validity), the expert panel completed a review proforma which described the purpose of the questionnaire (to encapsulate symptoms that non-RRT CKD patients experience and find important, regardless of whether they are "caused by" or related to kidney disease). Experts were asked to assess: (i) relevance of each item to the target population on a 4-point Likert scale (not relevant; somewhat relevant; quite

relevant; highly relevant); (ii) clarity of items; (iii) overall comprehensiveness; and (iv) any missing key symptoms.

Stage 5 (convergent validity): Participants were provided with a survey pack containing some brief demographic questions and a series of questionnaires including the KSQ and the EQ-5D-5L. The EQ-5D-5L assesses quality of life across 5 dimensions (mobility, self care, usual activities, pain/discomfort, anxiety/depression) according to 5 levels (where 1 indicates no problem and 5 indicates an extreme problem). The accompanying visual analogue scale (VAS) records the individual's self-reported health on a vertical scale from 0 (the worst health you could imagine) to 100 (the best health you could imagine).

Ethical considerations

Stages 1-3 of this work were derived from the CKDSX trial which was given a favourable opinion by the NHS Research Ethics Committee – Derby on 16th May 2013 (ref 13/EM/0155). Stage 5 was derived from the ADAPT-CKD trial which was given a favourable opinion by the NHS Research Ethics Committee – London Queen Square on 6th June 2016 (ref 16/LO/0980).

All participants provided written, informed consent to participation after explanation of the study by a member of the research team, reading the Information Sheet, and having the opportunity to ask questions. The questionnaire used in this study was brief and simply required ticking boxes, but the subject matter is potentially sensitive and the study setting (clinic waiting rooms) may have discouraged some individuals from taking part. In Stage 5, this issue was avoided by allowing participants to complete the survey pack at home and providing a post-paid envelope for its return.

Stage 2 involved qualitative discussion of individual symptom experiences. The interviews were held in a quiet, comfortable private room away from clinical areas to minimise distress or embarrassment, and participants were provided with contact numbers for clinical or emotional support should they need it. No identifiable information was included in the audio-recordings or transcripts to preserve anonymity and confidentiality.

Stage 3 involved a focus group with a group of patients previously unknown to one another. Ground rules for respect and confidentiality were agreed before the audio-recording commenced.

Participation in this study required the ability to communicate well enough in English to converse with the researcher, read the study documentation and complete the written forms. This unfortunately excluded those with severe hearing or visual impairment, learning difficulties or insufficient English.

Statistical and Analytical Methods

Stage 1 : The additional symptoms written in the provided blank rows were grouped into themes and those mentioned by several participants were further explored in the qualitative stages 2 and 3 with a view to including them in the refined questionnaire if appropriate.

Stages 2 and 3 : Qualitative analysis of the semi-structured interview transcripts was facilitated by the use of the qualitative software NVivo. Interview data were compiled into a pre-defined matrix informed by the cognitive appraisal stage 'comprehension' which was broken down into a list of possible errors including: description of term; difficulty understanding; ambiguous concept and synonyms or other terms for symptoms. For the purpose of questionnaire improvement, a tailored approach to interview response analysis was taken (Blair & Brick 2010) using formation of a matrix display to compile data; a process described by Knafl et al when improving their specific instrument (Knafl et al 2007). Using NVivo analysis software, discussion about each symptom was coded and grouped allowing the patient views to be summarised in a purposely-designed matrix.

Stage 4 : The KSQ was assessed using the content validity index (CVI) to quantify the proportion of agreement between experts for each item (I-CVI) and for the overall questionnaire (S-CVI) (Polit, Beck & Owen, 2007). Modified kappa statistics (Polit et al. 2007) were used to measure agreement by chance, interpreted using guidelines developed by Cicchetti et al (1981) (Cicchetti & Sparrow 1981) and Fleiss (1981) (Fleiss 1981) as poor ($k^* < 0.40$); fair ($k^* 0.40-0.59$); good ($k^* 0.60-0.74$) and excellent ($k^* > 0.74$). We considered the potential removal of any items falling in the 'fair' or 'poor' content validity threshold (i.e. $k^* < 0.60$). Similarly, we chose a S-CVI of less than 0.80 for the whole questionnaire as unacceptable, as recommended (Davis 1992; Polit & Beck 2004).

Stage 5 : Country-specific EQ-5D-5L health states were converted into single index values (van Hout et al. 2012). The index scores and VAS scores were compared with KSQ scores: (a) individual and total frequency scores; (b) individual and total importance scores; and (c) number of symptoms, in the KSQ. The relationships between frequency and importance symptom scores in the KSQ and EQ-5D-5L index scores and VAS

scores were assessed using Spearman's rho correlations and applying a Bonferroni-corrected probably significance level of $p < 0.002$ (28 tests for each hypothesis).

Results

Participants

In Stage 1, 219 patients with non-RRT CKD Stage 1–5 (response rate 80.8%) completed the LUSS questionnaire and were sampled to take part in the interview phase (subsequently, an additional 64 individuals were included in further analysis (Brown et al. 2017)). Of these, 113 participants (51.6%) agreed to further involvement.

Using purposive sampling, Stage 2 interviews were arranged with 11 individuals: 55% ($n=6$) were male; mean age was 61 years (range 28–78) and all were White British.

An additional focus group (Stage 3) was arranged with 5 individuals: 80% ($n=4$) were male; mean age was 59 years (range 35–93), 60% ($n=3$) were White British and 40% ($n=2$) were of South Asian descent.

The Stage 4 content validity expert panel included 16 experts (11 renal physicians and 5 renal nurses or dieticians) from across England.

In Stage 5, 70 individuals agreed to complete the EQ5D and KSQ as part of a larger survey pack (70% response rate). The sample comprised 42 men (60%) and 26 women (81%) between the ages of 18 and 86 years (mean 59.9). Participants were mostly white (81%; 8% South Asian; 5% other/not known) and had been diagnosed with CKD for, on average (median), 8 years (IQR 2–13.5 years).

Bias

The potential for bias in the Stage 1 sample population has been reported previously (Brown et al 2017). We compared the Stage 5 sample population with general

nephrology patients seen in 2013 (n=8414). We found that the sample had a greater proportion of men (60% in our sample compared with 51%), were slightly younger (mean age 60 years in our sample compared with 64) and had a lower proportion of patients of South Asian descent (8% in our sample compared with 11%).

Main results

Stage 1 : Analysis of the LUSS responses revealed that additional symptoms reported were diverse. The most common symptoms added were: the need to urinate more often (n=44/283); feeling cold (n=23/283); back pain (n=10/283); and cramp (n=10/283).

The Stage 2 interview data on descriptions of the symptom and understanding of the terminology for existing and new symptoms were analysed to assess understanding. In general, interviewees had a similar, shared, understanding of the existing symptoms from LUSS. The most commonly reported additional symptoms, 'the need to urinate more often' and 'feeling cold', were well understood and justified addition to the questionnaire. The symptom 'cramp' was more complex. Patients linked this to 'muscle spasm', but found the term 'cramp' easier to relate to and understand. Indeed, many could not differentiate between 'spasms' and 'cramp'. Thus we kept the original item on muscle spasm but replaced 'spasm' with 'cramp'. 'Back pain' was interpreted in different ways by patients, and as only 10 reported it in phase 1, we did not add it to the questionnaire. The findings for each symptom are summarised in Table 2, and the recommendations arising from this exercise are summarised in Table 3.

[Table 2]

[Table 3]

Informed by this analysis, amendments were made to the questionnaire terminology, design and layout. This included re-naming of the questionnaire to the Kidney Symptom Questionnaire (KSQ).

In Stage 3, focus group participants felt that the new KSQ symptom list was comprehensive and covered the symptoms they experienced; they approved the final symptom list chosen for the questionnaire, including the extra symptoms. Each phrase was well understood by the group and the wording approved. In terms of the time frame for reporting symptoms, the group agreed that 2 weeks was an appropriate time period as it was long enough to capture the experience (yet not too long to forget). The patients said they found the questionnaire an acceptable length, saying that it would take about 5 minutes to complete in total. The group also approved the new questionnaire design and suggested no changes to the layout or format. Focus group comments are summarised in table 4.

[Table 4]

In the Stage 4 content validation exercise, 13 of the 16 experts returned the review proforma for the KSQ (81.3% response rate). Table 5 shows the mean relevance ratings, I-CVI values and modified kappa coefficients. None of the items received a poor relevance rating, but three ('pain in bones or joints', 'poor concentration', 'loss of sex drive/difficulty becoming sexually aroused') had fair content validity. All experts judged 'itching' and 'shortness of breath' as relevant. The average of I-CVI scores (S-CVI) for

the KSQ as a whole was 0.81, falling within the recommended threshold of 0.80 (Davis 1992; Polit & Beck 2004).

[Table 5]

Comments related to the items with poor or fair content validity broadly referred to the item not being adequately specific (i.e. the symptom was so common in those without kidney disease that it was perceived to be irrelevant, e.g. “Non-specific, usually associated with tiredness”) and not being adequately sensitive (i.e. the symptom was not common at all in general nephrology patients, e.g. ““In my experience this is unusual in people not on dialysis”).

Eleven (85%) experts described the KSQ as clear. Two experts felt that the questionnaire was not clear; one suggested improving the lack of concentration item as it was too ‘vague’; the other felt that the last question on additional symptoms needed more focus in terms of their perceived relationship to the kidney problem - so as to avoid an exhaustive list. Five (38%) experts described the KSQ as comprehensive. The most common suggested additions to the questionnaire were nausea/sickness (n=5), ankle/leg swelling (n=4) and mood/psychological effects (n=3). As these were not specifically identified by the service users themselves, we chose not to add these items, but instead to allow for them by retaining an additional free text category in the KSQ.

Stage 5

[Table 6 here]

Table 6 shows the relationship between the EQ-5D-5L index scores and frequency and severity of symptoms. At a p-value of <0.002 , the frequency of 10 out of 13 symptoms (itching, difficulty sleeping, loss of appetite, feeling tired, pain in bones or joints, poor concentration, loss of muscle strength, shortness of breath, muscle cramps or stiffness and feeling cold) were all negatively associated with the EQ-5D-5L index score (i.e. the greater the frequency of symptoms, the poorer the health-related and self-perceived quality of life). The remaining symptoms were also associated with EQ-5D-5L index score at the 5% level ($p<0.05$) but did not reach statistical significance under the Bonferroni correction. The strongest relationship was observed between the frequency of pain in bones and joints and EQ-5D index score ($\rho=-0.709$; $p<0.001$). Six of the symptom frequencies were also associated with the VAS score. A strong association was also found between total frequency score and EQ-5D-5L index score and VAS ($\rho=-0.647$ and -0.573 respectively; $p<0.001$ for both). However, in terms of importance, we only observed a relationship between one of the symptoms (pain in bones and joints) and the EQ-5D-5L index score. We also found that the total number of symptoms reported (median 8.5; IQR 6 – 11) was strongly associated with quality of life ($\rho = -0.528$ and -0.425 respectively for EQ-5D-5L index score and VAS; $p<0.001$ for both).

Discussion

This study presents the development, content validity and convergent validity of the KSQ for patients with CKD not on renal replacement. The KSQ was developed in collaboration with both clinicians and patients to ensure relevance and acceptability. Our findings show the KSQ to be a potentially useful instrument in assessing symptom burden. Patients described how the KSQ was relatively quick and simple to complete and, as such, has the potential to be incorporated into routine clinical assessment, thus addressing the need for a PROM in this patient group.

In Stage 5 of this study, we had a 70% response rate for the KSQ which was completed independently at home, indicating a high level of patient acceptability. Furthermore, the observed relationships between health-related QoL and the majority of the individual KSQ symptoms provides additional evidence of the importance of the symptoms selected and the relevance of the tool to patient experience. Therefore, although further interventional studies are required to indicate sensitivity of the KSQ to detect meaningful change, it shows promise as a useful PROM that, if incorporated into systematic data collection, could potentially contribute to patient-centred care and increase patient engagement (Caskey 2013).

Active patient engagement behaviour, e.g. asking questions during consultations, has been associated with higher levels of patient satisfaction, better adherence to treatment and improved health outcomes (Hibbard, 2013; Greene, 2012; Marshall, 2013). However, a qualitative study aiming to explore barriers to effective communication among CKD patients found that a number of patients described their role to be listening

(Lederer, 2015). These patients displayed greater levels of dissatisfaction with their physician relationship and less CKD knowledge in comparison to patients adopting a more active role (Lederer, 2015). We suggest that the KSQ could be a useful tool to initiate discussions about symptom experiences between patients and clinicians, thus improving communication around this overlooked topic.

The final version of the KSQ included 13 items and three domains: (a) number of symptoms (0–13); (b) total frequency score (0–52); and (c) total importance score (0–65). We would recommend the first of these domains be used as a simple descriptive measure of symptom burden for clinicians to engage patients in discussion around symptom experience and quality of life, and the second two as a potential research tool.

This study involved patients from one centre and so may not reflect the symptom experience of other patients across the UK. The purposive sampling for the qualitative component of the study comprised a relatively small sample, although a range of male and female participants with a median age close to the whole regional CKD population were included. The subjective nature of symptoms makes them difficult to assess objectively; however, patient insight gained throughout the mixed-methods process informed the tool development and therefore maximises its relevance. Whilst we believe that we have developed a useful symptom burden questionnaire for clinicians and researchers, we recognise that it is not possible to apply the same stringent psychometric property testing as some other measures. There is no reference ('gold') standard for symptom burden in the target population on which to compare our questionnaire and internal consistency cannot be tested because the symptoms do not represent a homogenous construct. It is also important to note that the relationship found

between symptoms and health-related quality of life does not fully demonstrate convergent validity because symptom burden is too narrow a concept to measure overall quality of life. However, the observed relationship does highlight the adverse effect that symptoms have on a person's quality of life and the need to take account of these symptoms in the clinical setting.

In summary, there is a need to standardise the approach taken nationally to address the lack of understanding and recognition of CKD symptoms (Kidney Health, 2013), which emphasises the need for validated tools that are practical to integrate into regular measurement. Symptom tools are useful as PROMs and, if incorporated into systematic data collection, could potentially contribute to patient-centred care and increase patient engagement (Caskey 2013). The KSQ offers an assessment tool option which can be used to address this need and further increase understanding of symptomatology in early CKD stages. Both patients and expert clinicians were involved in the process of face and content validation, and criterion validity was assessed. This has led to an updated questionnaire that addresses the need for a PROM in this patient group.

Conclusion

The KSQ is short to complete, has acceptable content validity and has a strong relationship with health-related quality of life. The KSQ can support regular symptom measurement in routine clinical practice and can potentially be used as a resource to improve and develop effective future treatment and management in CKD patients - through symptom assessment. With involvement from both patients and healthcare professionals, the questionnaire is both relevant and user-friendly. Further work is

required to extend the content validation to include allied health professionals, assess the test-retest reliability of the KSQ, and investigate whether and how symptoms vary over time.

Conflict of Interest Statement

None of the authors of this manuscript have any conflicts of interest to declare. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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Tables

Table 1: Symptoms in the Leicester Uraemic Symptom Score (LUSS)

LUSS symptoms
Itching
Sleep disturbance
Loss of appetite
Excessive tiredness
Pain in bones / joints
Poor concentration / mental alertness
Impotence / lack of sex drive
Loss of muscle strength / power
Shortness of breath
Muscle spasm / stiffness
Restless legs

Table 2: Understanding of symptom terminology among participants interviewed

Symptom	Understanding	Recommendations
Itching	Similar descriptions given for symptoms <i>“needing to scratch”</i> <i>“skin being irritated”</i> differed only in location of sensation. Easily understood, <i>“Well itching it means itching”</i> .	None.
Sleep disturbance	Varied descriptions given including: <i>“Not be able to sleep”</i> , <i>“Getting up to go to the toilet coming back and not getting off again because you don’t drop off”</i> , <i>“You wake up every ten minutes”</i> <i>“Difficulty getting to sleep”</i> , <i>“Insomnia”</i> . Overall patients appeared to find the phrase quite straightforward; however, many stages of sleep were described.	Addition of ‘insomnia’ (as mixed description) to incorporate both getting to sleep and staying asleep.
Loss of appetite	Eating less or reduced desire to eat was described: <i>“You are not eating as normal as you would do”</i> , <i>“Not eating as much as you used to do”</i> or <i>“Don’t enjoy food”</i> , <i>“Don’t fancy food”</i> The phrase was clear and well understood.	None.

Excessive tiredness	<p>Descriptions included sleep and physical perspectives: <i>"I am nearly always feeling as though I didn't have enough sleep or I ought to be going to sleep soon"</i> and <i>"everything is heavy, and you feel tired with it"</i> Patients raised issues surrounded the use of 'excessive' and many were unsure of how to gauge their experience. The use of 'excessive' was an issue when qualifying tiredness.</p>	Modification of symptom to 'feeling tired' or 'exhaustion'.
Pain in bones/ joints	<p>The feeling of pain was described in numerous ways using words such as, <i>"ache"</i>, <i>"hurts"</i>, <i>"sore"</i>. Although the descriptions and experiences did vary greatly, the widely recognised idea that pain is a 'highly unpleasant physical sensation' (Oxford University Press 2014) was reflected in the patient experiences with 'pain in the bones/ joints' proving to be an understandable and straightforward phrase.</p>	None.
Poor concentration/ mental alertness	<p>Poor concentration was mainly seen from a functional viewpoint as not being able to achieve what was normal or needed during the day, e.g. reading a book, watching TV, keeping their mind on a subject to follow a thought through.</p>	None.

	<p>Mental alertness was interpreted more variably, from being aware, keeping up with a conversation or solving problems in an effective way. The term 'concentration/ mental alertness' was easy to comprehend and patients were able to expand on it with their personal experiences.</p>	
<p>Impotence/lack of sex drive</p>	<p>Differences were found between the views of the male and female participants. Women saw impotence as a symptom experienced by males and often felt that it did not apply to them at all. The women seemed to relate to 'lack of sex drive' more, "<i>When you say impotent that's referring to a man isn't it?</i>". The phrase seemed well understood and relatable to the male participants but female participants were put off by the word 'impotence'. The phrase 'impotence/lack of sex drive' was found to be uncomfortable for some patients and avoiding the word 'sex' could reduce this embarrassment.</p>	<p>Future modification may benefit from separate male and female responses for this particular symptom to make it more relevant to both genders.</p> <p>Potential substitute of 'impotence' for 'erectile dysfunction'.</p>
<p>Loss of muscle strength/ power</p>	<p>Patients used examples of functional decline of everyday activities to illustrate their understanding of the phrase e.g. "<i>A suitcase seems twice as heavy now.</i>" Although many other</p>	<p>None.</p>

	terms were used to describe the experiences such as ' <i>muscle wasting</i> ', ' <i>shrinking muscles</i> ', ' <i>weakness</i> ' and ' <i>not being able to lift as much</i> ', the participants found it easy to relate to the phrase and it was well understood.	
Shortness of breath	Various alternative definitions were provided which included, being " <i>out of puff</i> ", " <i>breathing heavily</i> " and " <i>can't breathe properly</i> ". While some gave examples of the consequences of feeling short of breath such as going weak and trembling or needing to sit down or rest, others described the situations in which they felt breathless including after walking up the stairs, after physical activity or walking round the house. The phrase appeared to be easily and well understood.	None.
Muscle spasm/ stiffness	Patients mostly separated spasm and stiffness describing them as two different experiences. Muscle stiffness was found to be fairly straightforward for patients and descriptions often involved the timing or location of the sensation. It was often associated with activity when people noticed it more or compared it to the feeling of sore tight muscles after not	Separation into two single-barrelled responses. Substitution of 'spasms' for 'cramps'

	<p>stretching properly following exercise. The phrase ‘muscle spasms’ was less clear. Although some patients did provide a definition including those of “<i>cramp</i>” or muscles “<i>locking up</i>”, “<i>jerking and tensing</i>” or “<i>moving on their own in an unexpected way</i>”, most were unsure of the definition and felt they hadn’t experienced it so couldn’t explain. Participants felt that the phrases were different that separating them out could improve the clarity. There was also confusion surrounding the difference between ‘muscle spasm’ and ‘cramp’.</p>	
Restless legs	<p>Patients either described location of the sensation or compared it to a movement such as “<i>It’s inside your legs</i>” or “<i>I have got to keep twitching or moving it</i>”. The phrase ‘restless legs’ was the symptom which seemed to have the greatest difference in understanding not only throughout the interviews, but also when completing questionnaires with patients in clinic in phase 1 of the study. Some were found to immediately relate to the experience where as many weren’t sure what it was and asked for clarification.</p>	<p>Potential change in phrase to ‘Restless legs or difficulty keeping the legs still’ in line with other scores, e.g. DSI (Weisbord et al. 2004).</p>

<p>The need to urinate more often</p>	<p>Many patients felt that they experienced the problem at night time where they noticed in particular because of the disturbance. Other patients noticed it throughout the day as well, needing urinate frequently – some every few minutes. Other patients noticed it throughout the day as well, needing to urinate frequently – some every few minutes. A minority described that for them, it wasn't the frequency, it felt more urgent. Using a more general statement such as 'the need to urinate more often' rather than a time specific phrase such as 'getting up to go to the toilet at night' seems to apply to more patients. However, it was suggested adding 'day/night' for clarity and also to jog the memory may be useful. The symptom 'need to urinate more often' was experienced commonly and the phrase is well understood by the participants.</p>	<p>Improvements could be made including adding 'day or night' for clarity.</p>
<p>Feeling cold</p>	<p>Descriptions of 'feeling cold' included the need to put the heating on more, being cold compared to others around them and even feeling cold in the summer sat in the sunshine.</p>	<p>None.</p>

	<p>Patients found it easy to understand and few alternative descriptions were raised in discussion and no recommendations for changes were made. The phrase ‘feeling cold’ is relatable for many of the patients, easy to comprehend.</p>	
Cramp	<p>Description of ‘cramp’ included those who said it was when the muscle went “<i>stiff</i>” or “<i>tight</i>” and those who explained the need to “<i>move it</i>” or “<i>straighten it out</i>” for relief. The term ‘cramp’ was easily understood and there seemed no need to change the wording. Despite this, there was great confusion and overlap between cramp and muscle spasm.</p>	See ‘muscle spasm/stiffness’ recommendation
Back pain	<p>‘Back pain’ was considered quite differently by participants and descriptions ranged from feeling like a “<i>toothache</i>” to like “<i>being wrapped in a vice and squeezed</i>”. Description varied depending on the attributed cause given to the symptom which varied from spine to kidney related issues and wasn’t considered as a result of their renal condition by many.</p>	Different interpretations. Not recommended for inclusion in updated questionnaire.

	Synonyms for back pain included ache, back ache and kidney pain.	
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Table 3: Summary of changes to questionnaire

Itching	No change
Sleep disturbance	Sleep disturbance / insomnia
Loss of appetite	No change
Excessive tiredness	Feeling tired
Pain in bones/ joints	No change
Poor concentration/ mental alertness No change	No change
Impotence/ lack of sex drive	Females: Loss of libido Males: Loss of libido/ erectile dysfunction
Loss of muscle strength/ power	No change
Shortness of breath	No change
Muscle spasm/ stiffness	Cramp/ Muscle stiffness
Restless legs	Restless legs or difficulty keeping the legs still
New item	The need to urinate more often (night/day)
New item	Feeling cold
New item	Space to add additional symptoms

Table 4: Example quotes from focus group participants

Aspect of questionnaire	Patient Quotes
Symptom wording	<ul style="list-style-type: none"> • Sleep disturbance to sleep disturbance/ insomnia: <ul style="list-style-type: none"> ○ “that extra little bit clarified that one up” <i>Male, 35y</i> • Excessive tiredness to feeling tired: <ul style="list-style-type: none"> ○ “I think that’s better” <i>Female, y</i> • Impotence/ lack of sex drive to erectile dysfunction for males and loss of libido for both males and females: <ul style="list-style-type: none"> ○ “I think that is straight forward, that’s fine” <i>Male, 50y</i> ○ “We all know what libido is surely don’t we.” <i>Male, 77y</i> • Muscle spasm/ stiffness to cramp/ muscle stiffness: <ul style="list-style-type: none"> ○ “I think you need to expand on it, so to start off you need to address it as muscle and then give a few more options.” <i>Male, 50y</i> • Restless legs to restless legs or difficulty keeping the legs still: <ul style="list-style-type: none"> ○ “The chap across here he gets it and straight away he knew what we were talking about so that says quite a bit doesn’t it.” <i>Male, 35y</i> ○ “People who don’t have a very high understanding of the English language would also be able to understand how it’s been set out and it would be easy for them as well I think to use.” <i>Female, 43y</i>
Timing	<ul style="list-style-type: none"> • “I think it’s good as it is, two weeks. I think it would make it difficult to extend it to months” <i>Male, 77y</i> • “” think two weeks is spot on personally.” <i>Male, 93y</i>

	<ul style="list-style-type: none"> • “Psychologically you find that most people are happy to give five minutes” <i>Male, 50y</i>
Response options	<ul style="list-style-type: none"> • Frequency <ul style="list-style-type: none"> ○ “They are understandable aren’t they and not confusing” <i>Male, 93y</i> ○ “I would leave it as it is myself” <i>Male, 73y</i> • Intrusiveness <ul style="list-style-type: none"> ○ “Some people may not understand intrusiveness’ <i>Female, 43y</i> ○ “Impact on daily life, that to me would be the one” <i>Male, 35y.</i>
Clarity and Layout of KSQ design	<ul style="list-style-type: none"> • “I think the way it’s set out using the colour bars that does make a difference” <i>Female, 43y</i>

Table 5: Content validity of items on the KSQ

Item	Experts rating item as relevant (total N)	Mean relevance score*	I-CVI†	k‡	Evaluation
Itching	13 (13)	3.53	1.00	1.00	Excellent
Difficulty sleeping	9 (13)	3.00	0.69	0.66	Good
Loss of appetite	12 (13)	3.69	0.92	0.92	Excellent
Feeling tired	12 (13)	3.69	0.92	0.92	Excellent
Pain in bones or joints	8 (13)	2.46	0.62	0.54	Fair
Poor concentration	8 (13)	2.46	0.62	0.54	Fair
Loss of sex drive or difficulty becoming sexually aroused	7 (13)	2.69	0.54	0.42	Fair
Loss of muscle strength	11 (13)	2.77	0.85	0.84	Excellent
Shortness of breath	13 (13)	3.53	1.00	1.00	Excellent
Muscle cramps or stiffness	11 (13)	2.77	0.85	0.84	Excellent
Restless legs or difficulty keeping the legs still	12 (13)	3.43	0.92	0.92	Excellent
The need to urinate more often (night and/or day)	9 (13)	3.00	0.69	0.66	Good
Feeling cold	12 (13)	3.46	0.92	0.92	Excellent

* mean of relevance rating scores (1=not relevant; 2 = somewhat relevant; 3 = quite relevant; 4 = very relevant) † I-CVI = item-specific content validity index ‡ k* = Modified Kappa

Table 6: Relationship between frequency and importance of symptoms on the KSQ and quality of life (EQ-5D-LD index score and VAS) among adults seen in general nephrology clinics

Symptom	Frequency				Importance			
	Number	Median (IQR)	EQ-5D	VAS	Number	Median (IQR)	EQ-5D	VAS
Itching	66	2 (0–3)	-0.427*	-0.254	66	2 (1–3)	-0.267	-0.079
Difficulty sleeping	67	2 (0–3)	-0.373*	-0.257	67	4 (1–4)	0.075	-0.019
Loss of appetite	66	0 (0–1)	-0.537*	-0.315	66	2 (1–3)	-0.141	-0.015
Feeling tired	68	3 (2–4)	-0.564*	-0.514*	68	4 (3–5)	-0.223	-0.222
Pain in bones or joints	67	2 (0–4)	-0.709*	-0.291	67	3 (2–4)	-0.478*	-0.123
Poor concentration	69	1 (0–3)	-0.408*	-0.386*	69	4 (2–4)	- 0.196	-0.137
Loss of sex drive or difficulty becoming sexually aroused	64	0.5 (0–4)	-0.275	-0.247	64	2 (1–4)	-0.002	0.001
Loss of muscle strength	65	2 (0–3)	-0.519*	-0.427*	65	3 (2–4)	-0.180	-0.349
Shortness of breath	68	1 (0–2.5)	-0.474*	-0.530*	68	3 (1–4)	-0.104	-0.038
Muscle cramps or stiffness	68	2 (1–3)	-0.435*	-0.520*	68	3 (2–4)	-0.199	-0.283
Restless legs or difficulty keeping the legs still	67	1 (0–2)	-0.317	-0.262	67	2 (1–4)	-0.096	-0.036

The need to urinate more often (night and/or day)	69	3 (1–4)	-0.248	-0.218	69	4 (2–4)	-0.105	-0.127
Feeling cold	58	2 (0–4)	-0.424*	-0.339	58	3 (1–4)	-0.153	-0.099
Total score**	63	23 (14–29)	-0.648*	-0.573*	63	39 (29–46)	-0.180	-0.154

IQR Interquartile range; EQ-5D Health-related quality of life index score for the EQ-5D-5L; VAS Visual Analogue Scale

* $p < 0.002$

** For the total score, one missing symptom was treated as absence of that symptom (i.e. score=0). Where more than one symptom was missing, this was treated as missing data.