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# Content validation of two SF-36 subscales for use in type 2 diabetes and non-dialysis chronic kidney disease-related anemia

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**Abstract**
*Purpose* This study aimed to evaluate the relevance and importance of two SF-36 subscales, Vitality (VT) and Physical Function (PF), to assess concepts of energy and physical function in patients with type 2 diabetes mellitus (DM) and non-dialysis CKD-related anemia.
*Methods* Patients with clinical history of DM and non-dialysis CKD-related anemia (n = 68) were identified as follows: 40 participated in concept elicitation (CE) interviews; 20 in cognitive interviews (CI), and 8 in pilot interviews. Relevance and importance ratings for SF-36 VT and PF items were obtained. Interviews were recorded, transcribed, and patient expressions of concepts coded. Inter-rater agreement was used to evaluate coding consistency. Concepts elicited were mapped to SF-36 VT and PF items.
*Results* Patients ($n = 64$) were 65.6% women, 42.2% Caucasian, with mean age of 66.1 ± 11.6 years. Of 830 coded concepts, 388 (47%) were "Energy" expressions and 287 (35%) were "PF limitations" expressions. Low energy was reported by 85% patients and rated as an important limitation by 88%. Limitations in PF were reported by 56–82% patients and rated important by 44–96%. CE and CI quotes correspond well to SF-36 VT and PF items.
*Conclusion* SF-36 VT and PF contents were suitable for assessing energy and physical function limitations, respectively, in this patient population.

**Keywords** Activities of daily living (MeSH) · Anemia (MeSH) · Diabetes mellitus · Type 2 (MeSH) · Questionnaires (MeSH) · Renal insufficiency (MeSH) · Validation studies (MeSH)

**Abbreviations**

| | |
|---|---|
| CKD | Chronic kidney disease |
| CI | Cognitive interview |
| CE | Concept elicitation |
| DM | Type 2 diabetes |
| eGFR | Estimated glomerular filtration rate |

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| | |
|---|---|
| HbA1c | Hemoglobin A1c |
| IRA | Inter-rater agreement |
| PF | Physical function |
| PRO | Patient reported outcome |
| SF-36 | Short-form 36 |
| VT | Vitality |

## Introduction

Anemia is a frequent complication related to chronic kidney disease (CKD), occurring in approximately 47% of patients who are not on dialysis [1, 2]. Patients with CKD develop anemia due to the inability to produce sufficient endogenous erythropoietin to stimulate the production of red blood cells [3]. Common symptoms of anemia include low energy, fatigue, weakness, shortness of breath, dizziness, and reduced exercise tolerance [4] with less common symptoms that include difficulty concentrating, leg cramps, and insomnia. These symptoms range in severity from mild to debilitating, with lack of energy and impaired physical function among the most common concerns [3–5]. The frequency and severity of these symptoms vary considerably from patient to patient. Patient-reported limitations of anemia on physical function and energy are well established in CKD patients receiving dialysis [6–13]. However, they have not been evaluated among patients with non-dialysis CKD-related anemia. Unlike CKD patients receiving dialysis who are generally debilitated from advanced kidney disease and associated comorbid conditions, those with CKD not yet on dialysis have a lower burden of illness overall and therefore might be expected to respond differently to the presence and extent of anemia. Type 2 diabetes is highly prevalent in this population [14], and even less is known about the effects of anemia treatment on energy and physical function in these patients.

Patient-reported outcomes (PROs) evaluate patients' perspectives on their disease and the treatment they receive; the importance of this information is widely recognized [15, 16]. Recent US FDA guidance discusses principles of PRO instrument development and validation of interest to reviewers when they consider evidence in support of a claim of treatment benefit. This guidance specifies that in order for an instrument to be considered sufficiently content valid to support a labeling claim, patients from the target population should be involved in the development process or be consulted in the evaluation of an existing instrument, including content relevance and interpretability.

Systematic reviews of literature indicate that the SF-36 is the most commonly used instrument in non-dialysis CKD studies to evaluate treatment-related changes in energy and physical function, using the Vitality (VT) and Physical Function (PF) subscales, respectively [17, 18]. Despite this, little is known about the content validity of these SF-36 subscales for evaluating treatment effects in patients with type 2 diabetes and non-dialysis CKD-related anemia. Therefore, the appropriateness of the Vitality (VT) and Physical Function (PF) subscales of the SF-36 needs to be evaluated in this specific patient population.

The assessment of content validity of an existing PRO measure addresses the extent to which the concept(s) presented in items comprising the measure are the right concept(s) for the target population and that these items adequately capture the concept(s) of interest. Evaluation procedures can also include information on the relative importance of the concept(s) of interest, as rated by individuals from the target population.

This study assessed the content validity of the SF-36 VT and PF subscales to assess the effects of treatment of anemia on two target concepts, energy, and physical function, in patients with type 2 diabetes and non-dialysis CKD-related anemia. To accomplish this objective, two specific challenges were addressed: (1) the need to establish whether the item-level concepts presented within subscales of a generic instrument were relevant and sufficiently comprehensive to measure the target concepts in a population with a specific health condition; and (2) the need to provide supporting evidence to underpin specific definitions of the target outcomes, without which results may not be interpretable within a formal research or regulatory context.

## Methods

### Study design

This was a qualitative cross-sectional study of 68 patients with type 2 diabetes and non-dialysis CKD-related anemia recruited from a non-random convenience sample of 8 treatment clinics across the United States. The study was approved by the Essex Independent Review Board (IRB) (HRA 28-1100A 9/9/08) and conducted in accordance with the 1964 Declaration of Helsinki. Recruiting clinicians provided patients with a consent form explaining study procedures, compensation, and right to withdraw from the study without penalty or change in medical care. All study participants provided informed consent. Of the 68 patients enrolled, 40 patients participated in concept elicitation (CE) interviews and were asked to describe their experiences with anemia symptoms and impacts to identify relevant concepts and patient language. CE interviews included 32 individual interviews and two focus group interviews (4 patients each) to capture a full range of

patient responses. Twenty patients participated in cognitive interviews (CI) designed to evaluate patient comprehension and interpretation of SF-36 VT and PF items. Eight patients participated in pilot interviews (4 CE and 4 CI) to test the interview guide and train the interviewers, with an a priori decision these data would not be used to identify concept codes. At the end of each type of interview, patients also completed rating exercises to further address concept frequency, relevance, and importance.

## Study population

To be consistent with clinical trial enrollment criteria and to assure experience with anemia, patients with a clinical history of type 2 diabetes, non-dialysis CKD (defined as estimated glomerular filtration rate (eGFR) of 20 to 60 mL/min/1.73 $m^2$), and anemia within the past 12 weeks (hemoglobin $\leq$ 11 g/dL) were identified. Patients were excluded if they were pregnant, were treated with any erythropoietic agent in the 12 weeks prior to enrollment, or were scheduled to receive such treatment in the next 3 weeks. Patients currently on dialysis or expected to initiate dialysis within 4 weeks and those with the history of kidney transplant, cardiovascular events (within previous 12 weeks) were excluded. Each site clinician was asked to screen out patients with any other clinically relevant conditions that could potentially confuse the patient's ability to focus on symptoms of their anemia (this included depression, COPD, and other chronic conditions that affect energy levels). Patients participating in other research studies or clinical trials that included the use of investigational medications were also excluded.

## Qualitative interview process

Interviews were conducted using a semistructured interview guide. Four trained and experienced, interviewers were involved with the qualitative data collection process. Interviewer training included review of the interview guide, mock interviews with other interviewers, and pilot interviews on recruited patients who met the enrollment criteria. Small changes were made to the interview guide following the pilot interviews. Using the Day Reconstruction Method [19], patients were asked about their perceptions of the symptoms and effects of anemia and to describe how anemia impacted their daily activities. Participants were probed about several well-known effects of anemia, such as tiredness, and lower activity levels, if these impacts were not mentioned by patients spontaneously. Examples of some of the broad CE questions and subsequent probes are shown in Table 1.

The cognitive interviews were conducted using a "think aloud" exercise in which the patients were asked to respond to a specific set of interview questions regarding the instructions, questions, response options, and participants' recall time frames for the VT and PF scales of the SF-36 [20–23]. The "think aloud" technique is designed to help participants verbalize the thought process involved in understanding instructions and providing a response to each question in the instrument [24]. A standardized cognitive interview guide was developed to address the SF-36 VT and PF items for evaluating patient comprehension and interpretation of the concepts presented in the items. At the beginning of the interview, participants were asked to complete the SF-36v2 [25, 26]. Upon completion of the questionnaire, the participants were asked detailed questions about their understanding of the meaning of each item and response options in the SF-36 VT and PF subscales, and how they selected their responses. They were also asked about the importance and relevance of these items. Examples of some of the standard questions from the CI guide are shown in Table 2.

**Table 1** Examples of concept elicitation questions and subsequent probes

| |
|---|
| *1. How would you describe your usual level of energy?* |
| *2. Do you ever experience difficulty with having enough energy to do the things you want to or need to do?* |
| (Probe only those not already talked about) |
| What type of difficulty? |
| When does it happen? |
| Describe what it's like? |
| How does it make you feel? |
| *3. How does having anemia limit you in the various areas of your life?* |
| (Probe only those not already talked about) |
| Types of daily activities? |
| Usual chores or jobs around the house? |
| Ability to take care of yourself? |
| Mobility or getting around at home or at work? |
| Endurance or stamina? |
| Other? |

## Ratings of concept relevance, frequency, and importance

Ratings of the relevance, frequency, and importance to be free of limitations from the concepts present in the SF-36 VT and PF items were obtained from all 60 participants in the CE and CI interview sessions, as well as the four CI pilot interview participants. In these exercises, patients were asked to indicate whether they considered a list of limitations in energy and physical function to be *"not relevant at all, somewhat relevant, or highly relevant"* to

**Table 2** Examples of cognitive interview questions and subsequent probes

| |
|---|
| *Please look at the next two items in the Questionnaire (d and e)* |
| Actual Questionnaire text |
| The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? |
| d. climbing several flights of stairs? |
| e. climbing one flight of stairs? |
| Tell me in your own words what these questions are asking you about. |
| Describe any difficulty you had with the wording or in understanding the meaning of each item? |
| Do you have stairs in your environment that you normally need to climb? |
| Do you have difficulty climbing these stairs? (describe) |
| Are you able to climb at least one flight of stairs? About how many stairs would that be for you? |
| When you answered this question what time period were you thinking about? |

them personally. They were then asked to identify the frequency with which they experienced the limitation in the past week *("not at all, some of the time, all of the time")* and to indicate which limitations they considered as one of their top six most important ones to be rid of. The 4 items in the SF-36 VT subscale ask the respondent how much of the time they feel full of life, have a lot of energy, feel tired, and feel worn out. The 10 items in the SF-36 PF subscale ask how much of the time they are limited in activities (e.g., climbing stairs, bathing or dressing, moderate activities, and vigorous activities) because of their health.

## Analysis of the qualitative data

All interviews were recorded and transcribed. The CE sessions resulted in a total of 34 transcripts (32 individual interviews and two focus groups of 4 participants each). These transcripts were coded using ATLAS.ti software [27] to organize the coding framework to catalog patient descriptions of symptoms and impacts of anemia. The coding framework was structured according to the three main areas of inquiry: (a) description of symptoms related to anemia; (b) description of impacts experienced as a result of having anemia; and (c) general understandings participants had about their anemia. At the completion of the coding process, a code frequency list was generated indicating the frequency of codes in each transcript. Concept codes were grouped by concept (e.g., energy), subconcept (e.g., low energy), and unique patient expression (e.g., tiredness).

Patient quotes from the CI responses were organized into tables alongside the respective SF-36 subscale items and evaluated on the basis of content match to assess patient comprehension of content. Data from the relevance, frequency, and importance ratings were summarized using descriptive statistics to assist in the evaluation of conceptual fit between patient descriptions of energy and levels of physical function and the items in the SF-36 VT and PF subscales.

## Coding of qualitative data and inter-rater agreement

The initial list of concept codes was created by a trained and experienced coder using the transcript from the first interview site. This preliminary code list was expanded and modified as additional transcripts were reviewed and new codes identified. After the coding scheme and dictionary were established, 4 trained coders were assigned to the transcript coding process. Before initiation of transcript coding, all of the coders discussed the coding procedures and the intended content of the preliminary code list to increase their familiarity with, and ensure consistency in, the coding process.

The quality of coding was characterized by (1) recognition of concepts present in the transcript that need to receive a code, and (2) whether there was inter-coder agreement in the codes assigned to each patient mention of a concept. Agreement statistics such as Cohen's Kappa were not used for evaluating inter-rater agreement (IRA) of transcript coding because these statistics require a predefined (and finite) number of items to be rated and that the rating be ordinal or categorical. In the coding of transcripts, there are an infinite number of quotes that could be identified as concepts as well as an infinite number of codes that could be created and applied to each concept. To evaluate IRA, four transcripts (12% of the total number of CE transcripts) were selected (one from each chronological quartile), and each coded independently by a pair of coders. The resulting pairs of coded transcript files were then compared to indentify any differences in the assigned codes. IRA statistics were reported as percentage of agreement.

## Concept saturation

Concept saturation was used to identify and document the presence of sufficient qualitative data to capture important variations in patient experience with their condition and treatment. Concept saturation refers to the point in the qualitative data collection and analysis process when further data collection and analysis cease to generate any new or distinctive categories, high-level concepts, or substantive codes [28–30]. A 3-step process was used to evaluate saturation:

Step 1 The 34 transcripts were ordered chronologically and organized into four groups of 8 or 9 transcripts each

Step 2 Concepts appearing in the first group were identified using a saturation grid. The transcript group in which each concept first appeared is indicated by an "X"

Step 3 Each subsequent transcript group was compared to the previous group to identify appearance of new concepts based on the constant comparative method [31]. Saturation is reached when no new concepts appear in the final transcript group(s). Table 3 shows this process graphically

### Mapping qualitative results to existing SF-36 items

The process of concept mapping illustrates the conceptual fit between the patient experience (represented by the qualitative results) and the concepts being measured (individual items of the existing measure). The information for the mapping process comes from the following three sources:

1. concept elicitation interviews (demonstrating relevance of concept)
2. cognitive interviews (demonstrating comprehension of concept)
3. rating exercises (demonstrating concept relevance, frequency of concept experience, and importance of concept to patient)

**Table 3** Example quotes for frequency of symptom change

| Time frame | Patient quote |
|---|---|
| Change within months | "Energy changes every 2–3 months." |
| | "Energy level has gone down in the last 3 months." |
| | "In the last 6–7 months (energy level has gotten worse.)" |
| | "More sluggish now than a month ago." |
| Change within years | "Changed quite a bit in the last year." |
| | "Few years ago I worked the yard a lot more." |
| | "Last few years (low energy) started." |
| | "Tiredness began a few years ago." |
| Day-to-day change and change within a week | "Some days awake all day, other days need to nap." |
| | "Feel bad 3–4 days/week." |
| | "Twice out of a week, have to just sit there for a little while." |

### Evaluation of conceptual fit

In order to evaluate the conceptual fit between energy and PF-related concepts mentioned in the qualitative data and the content covered in the SF-36 VT and PF subscales, a 2-step mapping approach was used:

1. Matching of concept coded patient language from the CE process and patient quotes from the CI process to each existing SF-36 subscale item
2. Matching of results from ratings on relevance, frequency of limitation, and importance of concepts to each existing SF-36 subscale item.

During this process, other concepts expressed by patients, but not included in the SF-36 VT and PF subscales were noted, as well as any items in the two subscales that do not address patient experience in this population. Preliminary results of the concept matching were presented to a panel of three clinical and three methodological experts in order to assess the appropriateness of the matching results and obtain agreement that the results provide appropriate evidence for content validity from both clinical and research perspectives.

## Results

### Study sample

The mean age (SD) of the 64 participants was 66 (11.6) years, and they had been aware of having diabetes for an average of 14 (10.8) years. The majority of patients were women (65.6%), and 56.3% were African American. The mean (SD) body mass index at enrollment was 32.6 (7.1) kg/m$^2$, mean eGFR was 32.0 (10.9) mL/min/1.73 m$^2$, mean hemoglobin was 10.5 (0.6) g/dL, and mean hemoglobin A1c (HbA1c) level was 7.3 (1.7) %. A total of 13 participants had a hemoglobin level of between 8.2 and 9.9 and 49 were between 10.0 and 11.0, respectively. Table 4 shows the distribution of demographics, comorbidities, and clinical characteristics for the study sample.

As expected, patient scores on the SF-36 VT and PF subscales were well below the norm for the general US population. There were no significant differences in the key characteristics of the sample recruited for concept and cognitive interviews.

### Inter-rater agreement

IRA for the two pairs of raters was between 89% and 92% agreement for identification of concepts present in the transcripts, and there was between 85% and 100%

**Table 4** Patient demographic and clinical characteristics ($N = 64$)

| Demographic Characteristics | | | | | | | Mean (SD) |
|---|---|---|---|---|---|---|---|
| Age | | | | | | | 66.1 (11.6) |
| Education, years | | | | | | | 12.3 (3.0) |
| | | | | | | | *N* (%) |
| Gender | | | | | | | |
| Male | | | | | | | 22 (34.4) |
| Female | | | | | | | 42 (65.6) |
| Ethnicity | | | | | | | |
| White (non-Hispanic) | | | | | | | 27 (42.2) |
| Black/African American | | | | | | | 36 (56.3) |
| Asian/Pacific Islander | | | | | | | 1 (1.6) |
| Marital | | | | | | | |
| Married or living as married | | | | | | | 34 (53.1) |
| Widowed | | | | | | | 16 (25.0 |
| Separated | | | | | | | 1 (1.6) |
| Divorced | | | | | | | 6 (9.4) |
| Never married | | | | | | | 5 (7.8) |
| Employment status | | | | | | | |
| Full time | | | | | | | 9 (14.1) |
| 13 (20.3%) missing[a] | | | | | | | |
| Part time | | | | | | | 3 (4.7) |
| Retired | | | | | | | 36 (51.6) |
| Not employed | | | | | | | 6 (9.4) |
| Clinical characteristics | N | Missing | Mean | SD | Min | Max | Median |
| BMI (kg/m$^2$) | 52 | 8 | 32.6 | 7.1 | 18.8 | 48.1 | 31.6 |
| Fasting blood glucose | 54 | 10 | 146.0 | 77.4 | 38.0 | 465.0 | 104.5 |
| HbA1c (%) | 41 | 23 | 7.3 | 1.7 | 5.1 | 14.8 | 6.4 |
| Hemoglobin (g/dL)[b] | 62 | 2 | 10.5 | 0.6 | 8.3 | 11.6 | 10.2 |
| Hemoglobin 8.2–9.9 | 13 | | | | | | |
| Hemoglobin 10.0–11.0 | 49 | | | | | | |
| eGFR (mL/min/1.73m2) | 64 | 0 | 32.0 | 10.9 | 11.0 | 57.0 | 24.3 |
| Creatinine (mg/dL) | 63 | 1 | 2.2 | 0.8 | 1.2 | 5.2 | 1.6 |
| Time since diabetes dx (years) | 59 | 5 | 14.1 | 10.8 | 1.0 | 46.0 | 5.0 |
| SF-36 Physical Function[c] | 50 | 14 | 42.6 | 29.5 | 0 | 100 | 30.0 |
| SF-36 Vitality[c] | 48 | 16 | 44.6 | 24.7 | 0 | 100 | 37.5 |
| | | | | | | | N[a](%) |
| Comorbidities | | | | | | | |
| Hypertension | | | | | | | 59 (93.7) |
| Myocardial infarction (MI) | | | | | | | 9 (14.3) |
| Stroke | | | | | | | 6 (9.5) |
| Coronary artery disease (CAD) | | | | | | | 23 (36.5) |
| Peripheral artery disease (PAD) | | | | | | | 3 (4.8) |
| Angina | | | | | | | 5 (7.9) |
| Transient ischemia attack (TIA) | | | | | | | 3 (4.8) |
| Coronary artery bypass graft (CABG) | | | | | | | 23 (20.6) |
| Percutaneous coronary intervention | | | | | | | 10 (15.9) |
| Heart failure | | | | | | | 16 (25.4) |
| Neuropathy | | | | | | | 17 (27.0) |

$N = 64$ includes 4 additional pilot test patients who were not included in the CE transcript dataset but were included in the relevance and importance rating exercises

[a] $N = 63$, one patient in the CE group did not answer comorbidity items

[b] All 60 qualitative interview patients had hemoglobin values, plus two of the four pilot test patients, totaling 62 patients with values for hemoglobin

[c] The SF-36 scores reported here are from a separate task completed approximately a week after the interview

agreement in codes assigned to each patient mention of a concept.

### Concept saturation

Results of the saturation analysis for energy-related concepts showed 86% of the 14 concept codes first appeared in transcript group 1, and the remaining 14% of the 14 concept codes first appeared in group 2. The saturation analysis for physical function showed 89% of concept codes first appeared in transcript group 1, with 6% of new codes appearing in transcript groups two and three. These results show nearly all concepts to have come forward in the earliest interviews, and no new concepts were mentioned by patients in the final group of interviews. Therefore, we concluded that concept saturation was achieved in both domains (energy and physical function) that were assessed using these 34 transcripts. Any continuation beyond this number of interviews was not likely to provide any further new information.

### Qualitative results from CE interviews

Of the 830 coded concepts in the CE transcript database, 388 (47%) were expressions related to energy levels and 287 (35%) were expressions related to limitations in physical function.

Within the concept "Energy", several subconcepts were coded. A total of 235 (61%) of the energy-related expressions (concept mentions) were about low energy, while only 14 (2%) were about high energy. The most common patient language used to express low-energy levels was "tiredness". Other patient language included the following: not having energy; not capable of doing anything; being exhausted; and needing to sleep or rest all the time (Table 5).

Of the 287 physical function-related concepts, patients expressed 128 (45%) concepts related to difficulties with walking, climbing stairs, bending, lifting, and carrying. Another 125 (44%) were related to difficulties carrying out daily tasks, such as home maintenance, work, physical activities, and personal care (Table 6).

**Table 5** Summary of energy-related concept expressions

| Energy | | Number of patient expressions of concept | % of patient expressions within concept group | % patient expressions of total 388 energy-related expressions | % patient expressions of all 830 in CE transcript database |
|---|---|---|---|---|---|
| Concept | Further concept description | | | | |
| Low energy | | 235 | 100 | 61 | 28 |
| | No activity | 39 | 17 | 10 | 5 |
| | No energy | 40 | 17 | 10 | 5 |
| | Tiredness | 74 | 31 | 19 | 9 |
| | Exhaustion | 26 | 11 | 7 | 3 |
| | Sleep all the time | 42 | 18 | 11 | 5 |
| | Other expressions of low energy | 14 | 6 | 4 | 2 |
| High energy | | 14 | 100 | 4 | 2 |
| | High energy | 14 | 100 | 4 | 2 |
| Changes in energy | | 58 | | 15 | 7 |
| | Association | 3 | 5 | 1 | 0 |
| | Changes in energy (days/weeks) | 16 | 28 | 4 | 2 |
| | Changes in energy (months/years) | 30 | 52 | 8 | 4 |
| | Changes in energy (no change) | 9 | 16 | 2 | 1 |
| Energy levels (attribution) | | 49 | 100 | 13 | 6 |
| | Due to anemia (maybe) | 18 | 37 | 5 | 2 |
| | Due to anemia (yes) | 20 | 41 | 5 | 2 |
| | Due to anemia (non-anemia attribution) | 11 | 22 | 3 | 1 |
| Energy levels (description) | | 32 | 100 | 8 | 4 |
| | Descriptions of good day (doing things) | 22 | 69 | 6 | 3 |
| | Descriptions of good day (feelings) | 7 | 22 | 2 | 1 |
| | Descriptions of good day (other) | 3 | 9 | 1 | 0 |

**Table 6** Summary of physical function-related concept expressions

| Physical function and activity | | Number of patient expressions of concept | % of patient expressions within concept | % patient expressions of total 287 physical function-related expressions | % patient expressions of all 830 in CE transcript database |
|---|---|---|---|---|---|
| Concept | Further concept description | | | | |
| Physical function/ activity: movement (1) | | 64 | 100 | 22 | 8 |
| | Walking (cannot) | 7 | 11 | 2 | 1 |
| | Walking (difficulty with distance) | 20 | 31 | 7 | 2 |
| | Walking (difficulty physically) | 20 | 31 | 7 | 2 |
| | Walking (difficulty with time) | 4 | 6 | 1 | 0 |
| | Walking (difficulty for other reasons) | 13 | 20 | 5 | 2 |
| Physical function/ activity: movement (2) | | 64 | 100 | 22 | 8 |
| | Difficulty with stairs | 29 | 45 | 10 | 3 |
| | Difficulty bending | 17 | 27 | 6 | 2 |
| | Difficulty with lifting and carrying | 12 | 19 | 4 | 1 |
| | Difficulty with balance | 6 | 9 | 2 | 1 |
| Physical function/ activity: housework | | 83 | 100 | 29 | 10 |
| | Difficulty with cooking | 6 | 7 | 2 | 1 |
| | Difficulty with vacuuming | 9 | 11 | 3 | 1 |
| | Difficulty shopping | 2 | 2 | 1 | 0 |
| | Difficulty with chores | 29 | 35 | 10 | 3 |
| | General difficulty | 37 | 45 | 13 | 4 |
| Physical function/ activity: self-care | | 22 | 100 | 8 | 3 |
| | Difficulty bathing | 11 | 50 | 4 | 1 |
| | Other self-care difficulties | 11 | 50 | 4 | 1 |
| Physical function/ activity: work | | 17 | 100 | 6 | 2 |
| | Work performance difficulty | 17 | 100 | 6 | 2 |
| Physical function/ activity: activity changes | | 3 | 100 | 1 | 0 |
| | Difficulty with activity levels | 3 | 100 | 1 | 0 |
| Physical function/ activity: limitation due to anemia | | 37 | 100 | 12 | 4 |
| | Activity level due to anemia (don't know) | 13 | 38 | 5 | 2 |
| | Activity level due to anemia (partly) | 3 | 9 | 1 | 0 |
| | Activity level due to anemia (yes) | 12 | 35 | 4 | 1 |
| | Activity level due to anemia (other) | 9 | 26 | 3 | 1 |

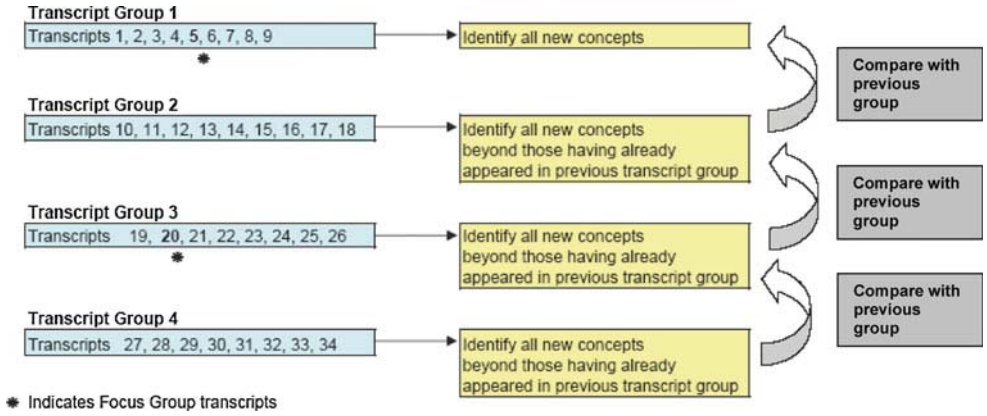


**Fig. 1** Process for determining saturation of concept

**Table 7** Relevance rating of health limitations

| Experiencing limitations in the following areas because of health | How relevant is this issue for you? | | | |
|---|---|---|---|---|
| | % Not at all relevant | % Relevant[a] | % Somewhat relevant | % Highly relevant |
| Vigorous activities (running, lifting heavy objects, strenuous sports) | 43.8 | 56.2 | 31.2 | 25.0 |
| Moderate activities (bowling, playing golf, pushing a vacuum) | 28.1 | 71.9 | 48.4 | 23.4 |
| Lifting or carrying groceries | 23.4 | 76.6 | 50.0 | 26.6 |
| Climbing stairs | 18.0 | 82.0 | 44.3 | 37.7 |
| Bending, kneeling, stooping | 22.2 | 77.8 | 33.3 | 44.4 |
| Walking | 17.5 | 82.5 | 39.7 | 42.8 |
| Bathing or dressing | 42.8 | 57.2 | 28.6 | 28.6 |
| Feeling tired or worn out | 14.3 | 85.7 | 39.7 | 46.0 |
| Feeling low in energy | 14.5 | 85.5 | 33.9 | 51.6 |
| Being limited in your work because of your health | 31.2 | 68.8 | 37.5 | 31.3 |
| Being limited in other activities because of your health | 18.7 | 81.3 | 51.6 | 29.7 |

[a] Computed: includes "Somewhat relevant" and "Highly relevant"

During the CE interviews, 27 of the 40 patients provided information on variations in their energy. Figure 1 shows examples of the responses for short-term and long-term symptoms change. Of these 27 patients, 20 (74%) reported energy levels had changed over previous months or years, but not recently. Of the 20 who reported long-term changes in energy, 5 patients also indicated fluctuations in daily/weekly energy, but in patterns that were consistent over time. For example: "*Changed in past year, but in afternoon I slow down*".

Another 4 patients (15%) indicated change in energy levels from day to day or week to week, and three patients (11%) had no reportable time-linked change in their energy levels.

## Ratings of concept relevance and importance

Table 7 lists the relevance ratings for energy and physical function concepts. A total of 85.5% of the patients indicated that the two high-energy items were either "somewhat relevant or highly relevant" to their disease experience, and 85.7% of the responses indicated the low-energy items (tired and worn out) to be either somewhat relevant or highly relevant. Table 7 also shows the most relevant physical function concepts to be walking (82.5%) and climbing stairs (82.0%). The less relevant concepts were engaging in vigorous activities (56.2%) and bathing/dressing (57.2%).

Table 8 provides information on the degree of importance patients assign to the energy and physical function concepts items. Bathing or dressing limitations were rated by 96.4% patients as the most important limitation to be rid of, followed by walking (95.6%), feeling low in energy (89.4%), feeling tired or worn out (87.8%), and lifting or carrying groceries (78.9%). Fewer patients (44%) rated limitations in vigorous activities as the most important limitation to be rid of.

**Table 8** Importance Rating of Health Limitations

| SF-36 Items | N (%) Indicated "Most Important" to patients to be rid of |
|---|---|
| Bathing or dressing | 96.4 |
| Walking | 95.6 |
| Feeling low in energy | 89.4 |
| Feeling tired or worn out | 87.8 |
| Lifting or carrying groceries | 78.9 |
| Being limited in your work because of your health | 69.4 |
| Bending, kneeling, stooping | 66.7 |
| Climbing stairs | 64.2 |
| Being limited in other activities because of your health | 62.8 |
| Moderate activities (such as bowling, playing golf, pushing a vacuum) | 56.5 |
| Vigorous activities (such as running, lifting heavy objects, strenuous sports) | 44.0 |

**Table 9** Mapping of Low Energy Item

| Concept: Tiredness<br>SF-36 item: Did you feel worn out?<br>Response Options: All of the time/Most of the time/Some of the time/ A little of the time/None of the time | |
|---|---|
| Patient quotes from CE interviews | Patient quotes from cognitive interviews for item |
| *Weak/weakness*<br>*overall fatigue*<br>*energy zapped/zapped all my strength*<br>*lethargic*<br>*feel drained*<br>*extreme tiredness*<br>*feel terrible*<br>*terribly tired*<br>*exhausted*<br>*I give out*<br>*I was worn out..it had me beat down*<br>*wiped out*<br>*like a drug I'm wiped out*<br>*so tired my legs are going to give out on me* | Quote: *Just so tired that you can't go no more.*<br>Quote: *Do you have the want or desire to do things or do you want to take a nap all the time. Don't have energy to do anything at all.*<br>Quote: *Being very tired, just making it to the couch to sit down or to bed. Every bone in your body needs to sit down and relax.*<br>Quote: *That means do you have the energy, do you feel tired.*<br>Quote: *Did you feel worn out, did you feel tired. You're wiped out. You don't feel like doing nothing. You don't want to think about nothing. All your energy is gone. It is zapped out.*<br>Quote: *Worn out, you don't even want to get out of the bed or out of the chair. Worn out means you just feel bad all the time.*<br>Quote: *Not having any energy, just not wanting to do anything.*<br>Quote: *I just don't have the energy to do a lot of things. Worn out you just don't have the energy to sit.* |

### Mapping qualitative data to existing PRO items

One mapping table was created for each existing SF-36 subscale item. Due to space limitations, an example of the mapping for an Energy subscale item and a Physical Function subscale item is shown in Tables 9 and 10.

The second step of the mapping process was to match data from the rating exercises for relevance, frequency, and importance with each of the SF-36 subscale items. Table 11 shows that between 56.2 and 85.7% of patient responses indicated relevance of the SF-36 Vitality and Physical Function items. A high proportion of patients reported limitations either "some of the time" or "most of the time" in "feeling low in energy" (86.7%), and "feeling tired or worn out" (85.7%), in comparison with those reporting limitations in moderate or vigorous activities (65%). Only 45% patients reported experiencing limitations either "some of the time" or "most of the time" in bathing or dressing. A high proportion of patients (approx 95%) rated "walking limitations" and "bathing/dressing" as the most important limitations to be rid of, followed by "feeling low in energy" (89%) and "feeling tired or worn out" (88%). Limitations in vigorous activities were rated by 44% as the most important limitations to be rid of.

Other symptoms and impacts reported by patients during their interviews that did not map to the SF-36 VT and PF subscales were largely related to comorbidities. For example, a variety of expressions related to arthritis or musculoskeletal problems were mentioned ("*aching joints, back aches, gout, stiff and hurting*"). A number of symptoms specifically related to diabetes were also mentioned by patients, but were not useful in supporting content validity of the two subscales ("*feel dizzy when blood sugar is high, numbness and burning sensation in feet*").

## Discussion

The findings of this study provide qualitative and quantitative evidence that the concepts of energy and physical function and the item-level concepts included in the SF-36 VT and PF subscales are relevant to patients with type 2 diabetes and non-dialysis CKD-related anemia. Results suggest SF-36 VT and PF subscales represent the concepts of energy and physical functioning limitations, respectively, based on data from three evaluative approaches: (1) concepts contained in patient expressions in the interview transcripts, coded and then mapped to each item; (2) patient responses to direct questions regarding the degree of relevance they felt each item had to their disease experience; and (3) patient quotes from the cognitive interviews, mapped to each item, to provide evidence of comprehension of concept. Coverage of the concepts in

**Table 10** Mapping Physical Function: Moderate Activity Item

| Concept: Moderately intensive activity<br>SF-36 Item: Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf<br>Response Options: Yes, limited a lot/Yes, limited a little/No, not limited at all | |
|---|---|
| Patient Quotes from CE Interviews | Patient Quotes from Cognitive Interviews for Item |
| General | Quote*: I'd say it's asking me what kind of activities I can do, such as bowling, anything like that, such as moving a table, pushing a vacuum cleaner, playing golf, that's what it's asking me.* |
| *it's a very long period of time before I get any housework done* | |
| *some days leave it until I feel better* | |
| *everything takes longer/can't do it as fast* | Quote: *Could I possibly move tables or push a vacuum cleaner around, or going outside to participate in activities or to go bowling and doing things that's not quite so hard to do.* |
| *do a little [housework] then sit down/rest* | |
| *doing a lot less around house* | |
| *lean against cabinet or take a break when standing and chopping for a long time* | Quote: *It's asked me can I move objects around like pushing things towards things, vacuuming, cleaning house, vacuuming, stuff like that, the house, a car, going bowling.* |
| Vacuum | |
| *I get tired and have to sit down and rest* | |
| *can hardly vacuum* | Quote: *Moderate activity –could be moving furniture in the house.* |
| *worn out with vacuuming* | |
| Cooking | Quote: *I push a vacuum cleaner. Like maybe reading, doing something simple like that. Just sitting and watching TV.* |
| *don't have much umph to get dinner ready but I do it* | |
| *don't do it everyday, just when I feel like it* | |
| *don't feel like it some days* | |

these two SF-36 subscales was complete and relevant to this patient population in reflecting the symptoms and impacts of their condition.

The mapping method used in this study provides evidence that qualitative results from the interview data matched the content in existing items of the SF-36 VT and PF subscales. The only exception was the vigorous activity item in the PF subscale. Patients did not report performing any vigorous activities during the concept elicitation interviews. Patient quotes from cognitive interviews indicate good understanding and comprehension of this item and provide further explanation that they no longer engage in activities that are too physically demanding for them. Among the ratings, the least relevant concept mentioned was engaging in vigorous activities (56%), with 66% patients being limited in vigorous activities "some or most of the time". These findings are consistent with lower ratings of importance being reported for inability to engage in vigorous activities. The fact that patients understand the item and respond that they are unable to perform this activity suggest the item serves as a useful anchor, much like "0" and "100" on a 0 to 100 scale, and, as such, may be useful for documenting improvements in physical function due to an effective treatment in these patients.

Another item with low relevance was "bathing or dressing" (43% patients indicating not at all relevant), with 45% being limited in bathing or dressing activities "some or most of the time". However, this item received the highest importance ratings (96.4%). We interpret this difference between relevance and importance ratings as the patients' recognition of the importance of not losing the ability to tend to their own personal care.

All patients interviewed in this study had multiple morbidities (e.g., type 2 diabetes, CKD, anemia), which may have made it difficult for them to specifically attribute their symptoms to anemia. Nevertheless, they reported often being extremely tired, a known correlate of anemia. Therefore, the negative aspect of the energy concept ("not having lots of energy") was a large focus. Only 4% of patient mentions of energy were expressions of "high energy levels". When asked to identify how much of the time they experienced limitations from their low-energy levels, 87.3% of patients-reported feeling tired "some or most of the time" while 85.7% experienced being worn out "some or most of the time". Patient reports of day-to-day fluctuations in energy, which would have supported the use of shorter recall periods, were infrequent. The majority of patients described their energy levels as constantly low or changing slowly. Patient reports about the variation in their energy levels support the use of a long recall period for measuring energy in patients with type 2 diabetes and non-dialysis CKD-related anemia.

A limitation of this study was the non-random convenience sampling of patients, which may not be representative of all patients with type 2 diabetes and non-dialysis CKD-related anemia. Qualitative research by its nature generally involves small sample sizes, limiting the generalizability of the findings. However, all of the patients had physician-confirmed diagnosis of type 2 diabetes and non-dialysis CKD-related anemia. In addition, the achievement of saturation for concepts corresponding to the SF-36 VT and PF items suggests that our sample size was adequate to meet the study objectives.

## Conclusion

The results from this qualitative study enhance our understanding of patient perceptions of energy and physical function in patients with anemia. The study data also supported the specific relevance of low energy as well as a pronounced limitation in everyday physical function,

**Table 11** Mapping relevance, frequency, and importance of concepts to SF-36 v2 Items

| **Relevance to Patients** *(How relevant this issue is – not at all/ somewhat/highly)* | **Frequency of Limitation** *(How often in past week the limitation was experienced – most of the time/ some of the time / none of the time)* | **Importance to Patients** *(Which limitations are important, and which limitations are among top 6 most important)* |
|---|---|---|
| SF-36 Item: **Do you feel full of life?**<br>SF-36 Item: **Did you have a lot of energy?**<br>Response Options: All of the time/Most of the time/Some of the time/A little of the time/None of the time | | |
| "feeling low in energy"<br><br>Highly relevant = 51.6%<br>Somewhat relevant = 33.9%<br>Not at all relevant = 14.5%<br>} 85.5% | "feeling low in energy"<br><br>Most of the time = 33.3%<br>Some of the time = 54.0%<br>None of the time = 12.7%<br>} 87.3% | "feeling low in energy"<br><br># patients marking as important = 47<br># patients ranking in top six = 42 / 47 (89%) |
| SF-36 Item: **Do you feel tired?**<br>SF-36 Item: **Do you feel worn out?**<br>Response Options: All of the time/Most of the time/Some of the time/A little of the time/None of the time | | |
| "feeling tired or worn out"<br><br>Highly relevant = 46.0%<br>Somewhat relevant = 39.7%<br>Not at all relevant = 14.3<br>} 85.7% | "feeling tired or worn out"<br><br>Most of the time = 39.7%<br>Some of the time = 46.0%<br>None of the time = 14.3%<br>} 85.7% | "feeling tired or worn out"<br><br># patients marking as important = 49<br># patients ranking in top six = 43 / 49 (88%) |
| SF-36 Item: **Climbing one flight of stairs**<br>SF-36 Item: **Climbing more than one flight of stairs**<br>Response Options: All of the time/Most of the time/Some of the time/A little of the time/None of the time | | |
| "Being limited in climbing stairs because of their health"<br><br>Highly relevant = 37.7%<br>Somewhat relevant = 44.3%<br>Not at all relevant = 18.0%<br>} 82.0% | "limitations climbing stairs because of their health"<br><br>Most of the time = 49.2%<br>Some of the time = 31.7%<br>None of the time = 19.1%<br>} 70.9% | "Being limited in climbing stairs because of their health"<br><br># patients marking as important = 53<br># patients ranking in top six = 34 / 53 (64%) |
| SF-36 Item: **Bathing or dressing**<br>Response Options: All of the time/Most of the time/Some of the time/A little of the time/None of the time | | |
| "Being limited in bathing or dressing because of their health"<br><br>Highly relevant = 28.6%<br>Somewhat relevant = 28.6%<br>Not at all relevant = 42.9%<br>} 57.2% | "limitations in bathing or dressing because of their health"<br><br>Most of the time = 15.6%<br>Some of the time = 29.7%<br>None of the time = 54.7%<br>} 45.3% | "Being limited in bathing or dressing because of their health"<br><br># patients marking as important = 28<br># patients ranking in top six = 27 / 28 (96%) |
| SF-36 Item: **Vigorous activities**<br>Response Options: All of the time/Most of the time/Some of the time/A little of the time/None of the time | | |
| "Being limited in vigorous activities because of their health"<br><br>Highly relevant = 25.0%<br>Somewhat relevant = 31.3%<br>Not at all relevant = 43.8%<br>} 56.3% | "limitations in vigorous activities because of their health"<br><br>Most of the time = 43.8%<br>Some of the time = 21.9%<br>None of the time = 34.3%<br>} 65.7% | "Being limited in vigorous activities because of their health"<br><br># patients marking as important = 50<br># patients ranking in top six = 22 / 50 (44%) |

suggesting that the concepts are meaningful to this patient population. Further, using a multimethod approach, data suggest the items comprising the SF-36 VT and PF scales adequately capture the concepts of energy and physical function limitations in these patients. It is important to note that this research focuses only on the relevance of these two specific concepts to the target population; it does not suggest that these two concepts are the only concepts of importance for this particular population.

These findings support the content validity of the SF-36 VT and PF items among patients with type 2 diabetes and non-dialysis CKD-related anemia and indicate that these subscales are suitable for the assessment of energy and physical function in this patient population. Future studies should evaluate the measurement properties of these two subscales and their ability to detect changes in response to treatment in this patient population.

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