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Review Article

Review article: Patient-level outcomes: the missing link

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SUMMARY: Treatment of chronic kidney disease (CKD) may be life-saving, but can disrupt every aspect of a patient's life and the lives of family members. Many patients with CKD are elderly with significant comorbidities and sometimes therapies to improve survival may be less important than those that improve or maintain quality of life. In this setting, patient-level benefits become particularly important goals of therapy. Randomized controlled trials (RCT) are also essential to justify expensive therapies, such as medications used in the treatment of CKD mineral and bone disorders. Surprisingly, data to support the efficacy of these drugs for patient-level outcomes remains limited. In fact, fewer RCT are conducted in renal medicine than in any other medical specialty and reliance is often placed on association data and the assessment of intermediate and biochemical end-points. While some of these may prove to be valid surrogates for clinically important outcomes, some may not. Inclusion of patient-level outcomes in clinical research provides a missing link that can inform a more comprehensive approach to clinical practice and patient care. Incorporating measures of health-related quality of life into clinical trials can make outcomes more relevant and may be relatively simple. This paper provides examples of reliable, validated instruments to measure health-related quality of life domains and functional status, together with practical instructions for their use. Most could be incorporated into RCT of CKD mineral and bone disorder treatments. Inclusion of outcomes that are perceived by patients to be significant should become standard practice in renal medicine and in clinical renal research.

KEY WORDS: **functional domains, health-related quality of life, patient-level outcomes, testing instruments.**

Patients with chronic kidney disease (CKD) have extremely high mortality compared with the general population and morbidity associated with CKD is accompanied by a host of physical, psychosocial and emotional disturbances. Despite significant advances that include improved dialysis efficiency and improved control of hypertension and electrolyte disturbances, mortality remains high and in most cases quality of life is compromised. Among risk factors for morbidity and reduced survival, a number of observational studies have indicated consistent associations with levels of serum phosphate, calcium and parathyroid hormone,[1–7] which can be influenced by the choice of phosphate binder, the use of calcitriol and its analogues, calcimimetics therapy and dialysate calcium concentration. Surprisingly, few prospective studies have addressed the impact of altering these variables on mortality and other patient-level outcomes[8,9] and those randomized controlled trials (RCT) that have been performed, tend to concentrate on short-term changes to laboratory parameters. While adverse events and mortality are generally evaluated, other patient-level domains such as physical and social functioning, perceived health, mental health, role limitation, vitality, sexual function and pain are rarely assessed and constitute a missing link between clinical research and nephrology practice. In fact, should treatments improve survival without improving symptoms and quality of life, delaying death may sometimes contribute to prolonged suffering. Similarly, better laboratory values without patient-level benefits might improve the contentment of physicians but not patients.

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PITFALLS OF ASSUMPTION AND EXTRAPOLATION

It has generally been assumed that improving risk factors that influence mortality in the general population, or normalizing parameters such as levels of haemoglobin should improve survival or quality of life for patients on dialysis. Some observational studies have shown promise for such

interventions: for example, the 2002 USRDS Morbidity and Mortality Study Wave 2 reported that the risk of cardiovascular death decreased by 36% for patients receiving statins.[10] Observational studies in patients with CKD have also identified associations between abnormal parameters of bone and mineral metabolism and mortality, particularly for levels of phosphate, calcium, parathyroid hormone and recently alkaline phosphatase. These parameters have the advantage of being rapidly and easily measured and modulated over relatively short time frames. Providing they are valid surrogates for patient-level outcomes, their use should also assist pharmaceutical companies to expedite regulatory approval – an important consideration when research, development and marketing are expensive and when profits may be limited by patent expiry or the discovery of adverse events not recognized in pre-marketing studies. According to a January 2007 report by the Tufts Center for the Study of Drug Development, the average cost of developing a new biotechnology product is $1.2 billion (Pharmaceutical Representative 1 January 2007. http://www.highbeam.com/doc/1P3-1220805141.html, accessed 24 November 2008).

However, intermediate end-points (such as vascular calcification or bone mineral density) and biochemical endpoints require validation in prospective treatment trials before their use as surrogates for patient-level outcomes can be justified. Surrogates also require validation for the particular population at risk.

Some recent RCT have identified problems caused by extrapolating from the general population to patients on dialysis. The 4D study compared atorvastatin with placebo in 1255 patients with type 2 diabetes on maintenance haemodialysis, followed for a median period of 4 years.[11] In contrast to observational and general population studies, atorvastatin did not significantly affect cardiovascular outcomes and was associated with a higher rate of fatal strokes. While the conclusions remain controversial, the authors recommended that patients with diabetes who have commenced dialysis should not be initiated on statin therapy. Similar results were reported in a study that assessed traditional risk factor modification in CKD.[12] Aggressively treated aspects of care were hypertension, dyslipidaemia (using atorvastatin), reduction of homocysteine (using folic acid, vitamin B12 and pyridoxine), haemoglobin levels, phosphate levels (using predominantly calcium-based phosphate binders), cessation of smoking and the use of aspirin unless contraindicated. Over a mean follow-up period of 1.8 years, levels of cholesterol (total and low-density lipoprotein), homocysteine, phosphate, aspirin use and smoking differed in favour of the aggressively treated group, but the groups did not differ in cardiac events or all cause mortality. Independent predictors of new ischaemic events were older age, systolic blood pressure and lower low-density lipoprotein–cholesterol but not treatment group. These interesting data do not negate the argument to treat, but point to the potential impact of non-targeted factors and the need to test hypotheses by undertaking RCTs.

Recent publications addressing haemoglobin levels also serve as warnings that intuitive targets need careful assessment. Although vitality and exercise tolerance improved with normalization of haemoglobin levels in one study, left ventricular function and mortality did not.[13] Similarly a Cochrane review reported that patients with cardiovascular disease and haemoglobin levels less than 120 g/L had lower mortality than those with levels over 130 g/L.[14] Two prospective studies assessed optimal haemoglobin targets in patients with CKD not yet on dialysis.[13,15] In one, haemoglobin levels of 130–150 g/L did not reduce cardiac events compared with levels of 105–115 g/L, although general well-being did improve. In the other, patients with haemoglobin levels of 135 g/L had no improvement in quality of life, but a higher risk of death, myocardial infarct, hospitalization for cardiac failure and stroke when compared with levels of 113 g/L.

Finally, the results of two studies evaluating dialysis efficiency emphasize the complexity of risk factors in CKD and the importance of RCTs to support treatments. Inefficient dialysis has been associated with increased mortality, but two studies that assessed a change in dialysis prescription did not demonstrate an influence on survival: the Adequacy of Peritoneal Dialysis Mexico (ADEMEX) study, in which peritoneal small solute clearance was increased and the Hemodialysis (HEMO) study, in which the dialysis dose was increased and dialysis membrane characteristics were altered.[16,17]

PATIENT-LEVEL OUTCOMES FOR THERAPY OF CKD MINERAL AND BONE DISORDERS

Regulatory bodies such as the Australian Therapeutic Goods Administration (TGA) and the US Food and Drug Administration must justify public expenditure on new therapies and evaluate claims relating to the use, safety and effectiveness of medical products. A number of newer drugs used in the management of CKD mineral and bone disorders (CKD-MBD) are registered in Australia. These include paricalcitol, lanthanum, sevelamer and cinacalcet. While the TGA considered proof of patient-level benefits was not yet conclusive, the latter three drugs have been funded under the Pharmaceutical Benefits Scheme, because of the excessive mortality of patients on dialysis. Therapeutic outcomes of calcimimetic and vitamin D therapy have recently been assessed in Cochrane reviews, the Caring for Australasians with Renal Disease guidelines and proposed Kidney Disease Improving Global Outcomes guidelines. The Cochrane meta-analysis of calcimimetic therapy[8] did show improvements in biochemical parameters that are associated in observational studies with increased mortality, cardiovascular risk and osteitis fibrosa. But despite some positive data, it remains inconclusive whether calcimimetic use will translate into improved patient outcomes of mortality, hospitalization, pain, fracture or levels of activity. In the case of vitamin D therapy, recent retrospective, observational studies suggest a survival advantage over no vitamin D therapy[5,18–20] and a more pronounced effect for the vitamin D_2 derivative paricalcitol than for calcitriol.[21] However, this advantage was not confirmed after adjustment for laboratory values and clinic standardized mortality in a report that also assessed the vitamin D_2 derivative doxercalciferol[19] and in a recent Dialysis Outcomes and

Practice Patterns Study analysis of over 38 000 patients,[22] no relationship was detected between the use of vitamin D and outcome, using an instrumental variable approach. This suggests that a significant degree of residual confounding may have influenced the conclusions of observational studies.

Even with carefully performed studies, results may prove difficult to interpret. The Dialysis Clinical Outcomes Revisited trial was a large, randomized, multicentre, open-label, industry sponsored study to assess the effect of sevelamer hydrochloride- versus calcium-based phosphate binders on mortality and hospitalization in haemodialysis patients.[23] Over 1068 patients were followed for a mean of 20 months with no significant differences detected for all-cause or cause-specific mortality. However, patients older than 65 years did show a significantly lower overall (but not cardiovascular-linked) mortality in the sevelamer group, while younger patients with lower event rates showed a tendency to benefit from calcium-based phosphate binders. A secondary analysis concluded that treatment with sevelamer- versus calcium-based binders did not affect the primary outcome of overall mortality, or cause-specific mortality, morbidity and first or cause-specific hospitalization, which were secondary outcomes.[24] There was evidence for a beneficial effect on multiple all-cause hospitalizations and hospital days.

DEFINING 'PATIENT-REPORTED OUTCOMES' AND 'HEALTH RELATED QUALITY OF LIFE'

'Patient-reported outcomes' encompass satisfaction with treatment, discomfort, and functional status and productivity performance measures. 'Health-related quality of life' (HRQOL) comes under this umbrella and is used to describe health status, well-being and quality of life. HRQOL is a multidimensional, subjective and ideally self-administered construct, although in the case of elderly or disabled subjects, assessment can be made via an interviewer. HRQOL is composed of a core set of 'domains' or 'dimensions' (the attributes being measured) and is generally structured as a questionnaire (the 'instrument'). The core domains are physical function and role functioning, psychological well-being, social functioning and for specific instruments, disease and treatment-related symptoms. Other domains such as general health perception, pain, vitality, sexual function and sleep may also be evaluated. HRQOL is subjective because it seeks to assess a person's perception of the impact of disease and treatment on their health, influenced by experience, beliefs and expectations.

HRQOL DOMAINS AS TRIAL END-POINTS

Health-related quality of life should always refer to the impact of treatment or symptoms on the different domains of life and is not a proxy for adverse event reporting. Taken together, the following domains contribute to a HRQOL assessment (but any one alone cannot assess it): a disability scale, an anxiety or depression scale, a fatigue or pain scale, a symptom bother scale. So, a clinical trial that assesses HRQOL should include in its design a definition of what is being measured, which domains are covered and the intended HRQOL claim.[25] HRQOL precision should be quantified in the same way as precision is quantified for a biochemical marker.

Health-related quality of life is a relevant trial end-point for illnesses such as CKD. This is particularly the case when there are few objective markers of disease activity or when a disease is characterized by a variety of clinical features or is expressed by many symptoms. HRQOL assessment is also important when treatment may extend life, but at the expense of well-being, increased morbidity, functional or psychological impairment and side-effects. At other times, treatment may have little impact on survival but a positive impact on HRQOL. HRQOL assessment may also be important in equivalence trials, when drugs are anticipated to have similar efficacy but may display HRQOL differences. Encouragingly, some recent studies to assess the effectiveness of erythropoietic agents have incorporated measures of HRQOL and functional capacity such as the SF-36, Kidney Disease Quality of Life (KDQOL), muscle strength and functional capacity testing.[26]

INCLUDING PATIENT-LEVEL OUTCOMES IN CLINICAL STUDIES AND NEPHROLOGY PRACTICE

In the CKD population, the effect of an intervention on cardiovascular events, hospitalization, fracture or mortality may require extended follow up and high patient numbers. But other patient-level outcomes that should not be overlooked include physical, psychological and social domains that can be measured by HRQOL instruments or that may be functionally tested (e.g. muscle strength, ability to walk and carry out activities of daily living). A significant challenge in this area is fragmentation of literature on the subject. Nevertheless, these dimensions should be considered routine study inclusions, because they measure outcomes that matter to people with CKD. They can also be incorporated into regular patient follow up; and perhaps one reason they feature infrequently in study protocols is that clinicians have rarely appreciated their value in routine clinical care.

APPLICATION OF HRQOL INSTRUMENTS TO CKD

A psychometric or functional HRQOL instrument needs validity (i.e. measures what it is supposed to measure), reliability (accuracy, precision and reproducibility), sensitivity and an easily interpretable scoring system. Selection of a HRQOL instrument is based on the hypothesis being tested. The choice of domains is based on the severity and nature of the illness and the expected benefit and side-effects of treatment. In the case of CKD patients, many of whom are elderly and physically inactive, improvements are likely to be in areas of physical and social functioning and for multinational trials the questionnaire should be available in

several languages. In the CKD population, the two most widely used, validated and reliable self-report instruments are updated versions of the original SF-36® Health Survey and the KDQOL survey, both of which were developed in the early 1990s.[27,28] A less common but potentially useful instrument is the EQ-5D, previously known as the EuroQol instrument, which is a standardized, generic, HRQOL instrument developed around the same period by a group of largely European-based researchers.[29]

Health-related quality of life scores have proven ability to predict morbidity and mortality. A prospective study of 1000 haemodialysis patients at three facilities first established the link between HRQOL scores and hospitalizations, missed treatments, depression and death.[30] The SF-36 consists of eight QOL domains that comprise two summary measures: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). Patients with SF-36 scores below the centre's median were twice as likely to be hospitalized as those above the median. Each 5-point increase in PCS improved the chance of survival by 10% and reduced hospital days by 6%. More recently, the Dialysis Outcomes and Practice Patterns Study established a strong link between HRQOL measures and outcomes. In more than 10 000 patients who completed the KDQOL-36, low scores for the PCS, MCS and Kidney Disease Component Summary predicted a higher risk of death and hospitalization in all participating countries, independent of demographic risk factors. When researchers compared the value of these scores with serum albumin (a known morbidity and mortality predictor), they concluded that low scores were as powerful in independently predicting hospitalization and death as albumin levels.[31] These data suggest that including HRQOL measures in clinical trials may predict meaningful patient effects above and beyond changes in laboratory data. In fact, the importance given to outcome and performance measures in the care of CKD patients is exemplified by the adoption (effective 1 April 2008) by the Centers for Medicare and Medicaid Services, of 26 new clinical performance measures to assess the quality of dialysis care in the United States. They include a new requirement for annual measurement of HRQOL in most patients (Schatell, D, Witten, B. Measuring Dialysis Patients' Health-Related Quality of Life with the KDQOL-36. Medical Education Institute. http://www.kdqol-complete.org/pdfs/kdqol-36.pdf Accessed 4 December 2008).

About the SF-36

The Short Form-36™ Health Survey was constructed to satisfy minimum psychometric standards for group comparisons and has long been regarded as the world standard for patient-reported health outcomes assessment. It measures perceived general health status and the impact of chronic disease on patients' lives with proven validity, reliability, interpretability and ability to detect change. It is used worldwide because it is brief, comprehensive, psychometrically sound and available in over 90 translations and measures health status outcomes in general as well as specific populations. Norms have been developed for the United States and several countries including Australia.[32]

The SF-36v2™ is the next generation of the SF-36.[33,34] It offers significant improvements in instructions, wording, layout, greater comparability with translations and cultural adaptations, response choice, increased scoring precision and more comprehensive norms. Scoring algorithms are available for comparisons to normal populations and world data are available in order to make cross-country comparisons, which may be particularly useful in multicentre trials.[35] The survey can be administered to persons aged 14 years and older and can usually be completed in 5–10 min. It measures eight domains of health (Table 1). The updated SF-12v2 and SF-36v2 surveys are considered the 'tools of choice' for fixed-length, short-form questionnaires that require maximum efficiency and are recommended for use in clinical trials, outcomes and effectiveness research and clinical practice applications.

About the KDQOL

The KDQOL survey was developed in 1994 by the Kidney Disease Quality Life Working Group as a kidney disease-specific measure of HRQOL. The first version contained the Medical Outcomes Study 36 as a generic chronic disease core, and added items relevant to patients with kidney disease, such as symptoms, burden of illness, social interaction, staff encouragement and patient satisfaction.[28] It was originally developed for dialysis patients, but can be modified for use in other stages of CKD.

The KDQOL-36, available since 2002,[36] is a 36-item HRQOL survey with subscales listed in Table 1. The SF-12 subscale measures physical (PCS) and mental (MCS) functioning, with items about general health, activity limits, ability to accomplish desired tasks, depression and anxiety, energy level and social activities. Burden of Kidney Disease includes items about how much kidney disease interferes with daily life, takes up time, causes frustration or makes the respondent feel like a burden. Symptoms and Problems includes items about how bothered a respondent feels by sore muscles, chest pain, cramps, itchy or dry skin, shortness of breath, faintness/dizziness, lack of appetite, feeling washed out or drained, numbness in the hands or feet, nausea, or problems with dialysis access. Effects of Kidney Disease on Daily Life includes items about how bothered the respondent feels by fluid limits, diet restrictions, ability to work around the house or travel, feeling dependent on doctors and other medical staff, stress or worries, sex life and personal appearance. The KDQOL is a non-proprietary measure, assessed by the Institutes of Medicine in 1994 as reliable, valid, easy-to-use, patient friendly and economical.[37]

About the EQ-5D

The EQ-5D is applicable to a wide range of health conditions and treatments. It provides a simple descriptive profile and a single index value for health status (Table 1). The EQ-5D was originally designed to complement other

Table 1 Features of some readily available quality of life (QOL) instruments

QOL instrument	Domains/dimensions	Benefits	Disadvantages	Access	Website
SF-36v2®	• Physical functioning • Role limitation (physical) • Bodily pain • General health perceptions • Vitality (energy/fatigue) • Social functioning • Role limitations (emotional) • Mental health (psychological distress or well-being)	• Comprehensive • Psychometrically sound • Useful in general and specific populations • Population norms • World data for multicentre trial use • Multiple translations • Suitable for clinical practice and trials • 5–10 min completion	• Complex scoring • Self-administration limited by poor literacy	• Commercial licence or permission for use in scholarly research	http://www.qualitymetric.com http://kdqol-complete.org
KDQOL-36®	• The SF-12 measure of physical (PCS) and mental (MCS) functioning • Symptoms/problems • Effects of kidney disease on daily life • Burden of kidney disease	• Psychometrically sound • CKD specific • Population norms • Multiple translations • 10–15 min completion	• Self-administration limited by poor literacy	• Free for non-commercial purposes	http://gim.med.ucla.edu/kdqol
EQ-5D®	• Mobility • Self-care • Usual activities • Pain/discomfort • Anxiety/depression	• Brief • Cognitively simple • Useful in telephone and postal surveys • Valid for CKD • Translations • Population norms in development	• Simple profile • Single index	• Free for non-commercial purposes	http://www.euroqol.org

CKD, chronic kidney disease; MCS, Mental Component Summary; PCS, Physical Component Summary.

instruments but is now increasingly used as a 'stand alone' measure, and international population norms are being developed. It has been assessed as a valid instrument for renal transplant and end-stage kidney disease patients.[38] It is ideally suited for use in postal and telephone surveys, in clinics and face-to-face interviews. It is cognitively simple, taking about 8 min to complete and instructions to respondents are included in the questionnaire.

FUNCTIONAL ASSESSMENT

In its simplest form, functional assessment evaluates the patient's ability to carry out the basic activities of daily living. These are key functions, especially in the elderly or those with chronic illness, when mortality is an insufficient measure of outcome. Examples of tests of functional performance include using a combination of muscle strength dynamometers, functional capacity tests and via self-report 'falls' or 'near miss' diaries. In some cases, other outcomes such as rates of hospitalization and adverse events can be accessed from medical records. Functional assessment over the course of a study can be an important patient-level outcome measure.

Musculoskeletal strength dynamometers

Musculoskeletal strength testing can be easily, accurately and inexpensively performed using medical isometric dynamometers and hand grip strength dynamometers. Isometric muscle assessment is reliable and reproducible and involves a maximal voluntary contraction performed at specified joint position against unyielding resistance. Muscle dynamometers are generally designed for hand held use and can measure muscle strength in flexion/extension, internal/external rotation, plantar flexion/dorsiflexion and abduction/adduction. For improved accuracy, fixed mounting can improve the consistency and reproducibility of results, with the gauge wall mounted or incorporated into a portable but stable frame. Table 2 provides examples of protocols for proximal muscle dynamometer testing.

Hand grip strength can be measured using a hand gauge, one example being the Jamar® hand gauge, which has been used since the 1970s.[39–41] This gauge is a sealed hydraulic instrument that measures grip strength in kilograms or pounds and caters for variable hand spans. The instrument has five positions for measurement, and maximal grip strength and is usually tested at the second position (3.8 cm). While single testing is accurate, clinical physiotherapy practices generally use the best of three tests, with rest periods of 15–60 s between measurements. Grip strength varies with a number of factors: gender, age, height and weight and dominant *versus* non-dominant hand – with the exception of left-handed individuals, whose grip strength is approximately equal. Most normative data apply to the Jamar® dynamometer, but few data are available for people with disabilities. Table 3 provides a general guide to grip strength assessment.

Table 2 Dynamometer testing of upper and lower limb proximal muscle groups

Gauge	General guidelines	Test instructions	Shoulder abduction	Elbow extension/flexion	Knee extension/flexion	Hip flexion
Chatillon MSC® (example only)	Position subject to minimize influence of gravity Gauge perpendicular to segment tested, in line with effort Position gauge as far form pivot joint as possible Contact point of gauge on limb changes amount of force generated	Take a second or two to come to full effort Wait 2 s. Instruct 'Push as hard as you can. Push, push, push.' Perform test for count of 4–5 s Rest for 30 s. Best of 3	Seat subject with arm hanging at side, flexed to 90° at elbow with thumb pointing upward Support forearm with hand to eliminate gravity Apply force bar to lateral surface of arm proximal to epicondyle	Seat subject with shoulder adducted Support the arm beneath the elbow, parallel to ground, palms facing upwards Flex forearm – thumb pointed outwards Extension: Apply force plate proximal to ulnar styloid process Flexion: Repeat with gauge on other side of wrist	Seat subject across chair so leg clears chair Hip and knee flexed at 90°, foot resting lightly on floor Extension: Apply force plate to extensor surface of leg proximal to malleoli Flexion: Repeat with gauge on opposite side of leg	Seat subject with hip and knee flexed at 90° Apply force plate to anterior surface of thigh, proximal to femoral condyles

These simple instructions have been used by the authors and are included only as a guide. The aim is to eliminate effects of gravity when testing muscle strength.

Table 3 A general guide to grip strength testing

Gauge	Testing position[42]	Instructions	Protocol
Jamar® Grip Strength Dynamometer (example only)	Sit in straight backed chair Feet flat on floor, shoulders adducted to neutral, arms unsupported Elbows flexed at 90°, forearm rotation neutral, wrist 0–30° dorsiflexion; 0–15° ulnar deviated	Face subject and squeeze gauge so he/she sees dial rotate Subject holds gauge in dominant hand Say '1, 2, 3, squeeze, squeeze, squeeze as hard as you can. OK you can stop now.' Rest 15 s. Then test non-dominant hand	Single or best of 3 at Jamar® position 2 (3.8 cm) Repeat on alternate hand after 15 s rest

Table 4 Examples of functional tests; standing balance

Test	Instructions	Side by side	Semi tandem	Tandem
Standing balance Subjects are asked to maintain feet in 3 positions: • side by side • semi tandem • tandem Stand for 10 s each	Stand next to subject and support until ready Ask 'Are you ready?' Say 'Ready, begin.' Say 'stop' after 10 s. If participant is unable to hold the position for 10 s, record result	Subject stands with feet side by side for 10 s. Use arms, bend knees, move body to maintain balance but try not to move feet	Subject stand with the side of the heel of one foot touching the big toe of the other foot for about 10 s Either foot may be put in front, whichever is more comfortable	Subject stands with the heel of one foot in front of and touching the toes of the other foot for about 10 s Either foot may be put in front, whichever is more comfortable.

Table 5 Examples of functional tests; 6 min walk

Test	Set-up	Instructions	Protocol
6 min walk	Set up unobstructed walkway with known distance, e.g. 33 m with chair at each end Assess the patient's fitness to walk on a level corridor by asking them as if they have any musculoskeletal pain or if they are feeling unwell.	'The object of this test is to see how far you can walk in 6 min. You will walk back and forth in the hallway. You will be exerting yourself so you may get out of breath, experience pain or get exhausted. You can slow down or stop as necessary but resume walking as soon as you are able. If you cannot continue, we will stop the test.'	Walk slightly behind and not beside the patient to avoid influencing the patient's self- selected walking pace Encourage every 30 s with standard set of encouraging statements: 'You're doing well.' 'Keep up the good work.' 'Keep going, only X minutes to go.' Mark the floor with tape where the patient stops Measure distance walked in 6 min

FUNCTIONAL CAPACITY TESTS

Reliable, validated and reproducible functional capacity tests such as standing balance,[43,44] sway and stance tests,[45] 6 min or timed walks[46,47] and sit-to-stand chair rises[48] can be used as predictive tools and to assess exercise capacity, postural performance, lower extremity function and muscle strength. These tests require little equipment apart from a chair, a tape measure and a stop watch, and minimal expertise. Testing is standardized by using a script card with instructions delivered by the tester to the subject. Specialist physiotherapists are not required, but staff involved in trials should be proficient in conducting the tests to reduce negative influences or confusion. Tables 4–6 provide some examples of functional performance assessment.

CONCLUSION

Health has been defined by the World Health Organisation as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity'. In caring for patients with CKD, professionals spend a great deal of time educating, encouraging and counselling in order to maximize the benefits of treatment. It is noteworthy that despite their availability and relative ease of use, quality of life instruments and functional tests are rarely used in clinical practice to evaluate clinical status and guide treatments that improve overall health. We should keep in mind recent lessons that normalizing or improving laboratory values may not necessarily translate to improved patient outcomes and should be cautious about surrogates that are valid in the

Table 6 Examples of functional tests; chair stands

Test	Protocol	Instructions single stand	Instructions repeated stands
Chair stands	Subjects are asked to fold their arms across their chests and to stand up from a sitting position once If they successfully rise from the chair, they are asked to stand up and sit down five times as quickly as possible STOP: If participant uses his/her arms After 1 min, if participant has not completed rises If concerned for participant's safety	'First, fold your arms across your chest and sit so that your feet are on the floor; then stand up keeping your arms folded across your chest.' 'Please stand up keeping your arms folded across your chest.' (Record result) If participant cannot rise without using arms, say 'Ok – Try to stand up using your arms.'	'Please stand up straight as QUICKLY as you can 5 times, without stopping in between. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. I'll be timing you with a stopwatch.' When the participant is properly seated, say: 'Ready? Stand.' and begin timing Count out loud as the participants rises each time, up to 5 times Stop when he/she has straightened up completely for the fifth time OR if the participant becomes tired or short of breath during repeated chair stands If the participant sits down after the fifth stand-up, stop timing as he/she begins to sit down

general population and extrapolating from association studies. While some patient-level outcomes require long studies and large patient numbers, others can be readily measured using the accurate, validated, reproducible and inexpensive instruments that have been discussed here and consideration should also be given to their use in regular clinical care. The extra effort required to measure what we are all working to improve should not be overlooked.

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