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**STUDY PROTOCOL**

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Development of a Novel Item Bank and Multidimensional Computerised Adaptive Test to Measure Patient-Reported Outcomes and Improve Management of Kidney Diseases: RCAT

Short title: RCAT (renal computerised adaptive test)

**ADMINISTRATIVE INFORMATION**

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**STUDY SUMMARY**

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| **Title** | Development of a novel item bank and multidimensional computerised adaptive test to measure patient-reported outcomes and improve management of kidney diseases: RCAT |
| **Short title/ Acronym** | RCAT (renal computerised adaptive test) |
| **Study design** | Phase 1 – Construction of a renal-specific item bank (Year 1): systematic review and qualitative interviews.Phase 2 – Psychometric evaluation and calibration of the item-bank (Year 2): cognitive interviews and online/postal survey. Phase 3 – CAT development/simulation testing and dissemination (Year 3). |
| **Objectives** | * To develop a new renal-specific item bank and CAT for patients with CKD.
* To develop a paper-based short form for patients without on-line access.
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| **Planned study sites** | **Non-NHS:**Phase 1 (qualitative interviews): invites sent via Help BEAT Kidney disease and advertisement on social media account of Kidney Research UKPhase 2 (online/postal survey): email invites distributed via PatientView.org**NHS:**Phase 2 (cognitive interviews and online/postal survey): University Hospitals Birmingham NHS Foundation Trust, NHS Trusts identified through NIHR ARC WM, general practices identified through NIHR CRN |
| **Total number of participants planned** | Phase 1 – 10-15 adults with CKD and 10-15 healthcare professionalsPhase 2 – 500-1,000 adults with CKD |
| **Main inclusion/exclusion criteria** | Inclusion criteria for adults with CKD:* Aged 18 or over.
* Able to give informed consent.
* CKD: non-dialysis stages 3–5, on dialysis, and post-transplant not requiring dialysis.

Inclusion criteria for HCPs:* Involved in the ongoing management of patients with CKD (non-dialysis stages 3–5, on dialysis, and post-transplant not requiring dialysis).
* Currently practicing in the UK.

Exclusion criteria for adults with CKD:* Inability to speak, read or write English.
* Episode of acute kidney injury in previous 3 months
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**LAY SUMMARY**

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| **Development of a new electronic questionnaire to measure patient outcomes and improve the management of kidney diseases** |
| **Background:**Chronic Kidney Disease (CKD) affects 1 in 7 people in the UK. Those with advanced CKD may need demanding and costly treatments, such as dialysis, for the rest of their lives. These patients often experience a very poor quality of life and can also get worse very quickly. Unfortunately, this can happen between visits to their clinical team, meaning they need to go to hospital as an emergency and have more ill-health as a result. Patients and clinicians believe it would be helpful to ask patients with chronic kidney disease (CKD) to use a computer/smartphone to provide regular information about their quality of life and symptoms in between their hospital appointments. This information can be collected using questionnaires known as ‘electronic Patient-Reported Outcome Measures’ or ePROMs. The use of ePROMs could help clinicians to respond better to patient’s needs.**Aims of study:**This project aims to develop a new ePROM questionnaire which asks targeted questions to patients based on their individual circumstances. This means that the questionnaires are quicker to complete and more tailored to the patient.**What will we do:**The study is split into three phases over three years: **Phase 1:** we will talk to patients with CKD and their health care team, as well as searching through scientific papers, to find out how CKD affects patients. **Phase 2:** we will develop a questionnaire item bank which will allow us to collect information about patients’ quality of life and symptoms. **Phase 3:** we will use the questionnaire to develop a CAT (Computer Adaptive Test). The CAT looks through the full questionnaire and chooses the questions that will be targeted to the patient completing the ePROM. |

1. BACKGROUND AND RATIONALE

1.1 Measuring symptom burden and quality of life in chronic kidney disease

Chronic kidney disease currently affects up to 15% of UK adults, and prevalence rates are rising.(1) It is estimated that prevalence of CKD stage 3-5 in the UK will rise from 6.1% in 2011, to 8.3% by 2036.(2) In 2009/10, the annual estimated cost of CKD to the NHS was £1.45 billion.(1, 3)

Numerous studies have demonstrated that patients with progressive CKD can experience a high symptom burden, associated poor health related quality of life (HRQOL) and increased risk of hospitalisation/mortality.(4) While research has often focused on end-stage renal disease (ESRD), there is emerging evidence highlighting significant symptom burden in earlier CKD stages.(5)

Understanding the burden of symptoms in CKD and impact on HRQOL is especially important given that these constructs are commonly reported by patients as more important than survival.(6) Studies have shown that reduced HRQOL is independently associated with cardiovascular events and death.(7, 8) Accurate and responsive symptom monitoring/management of patients across all stages of disease is therefore a key healthcare priority.

The lack of routine and systematic renal symptom burden/HRQOL assessment has been formally recognized as a concern by the UK parliament, as described during the Kidney Alliance ‘Delivering Excellence’ report in 2013:

“Despite their importance, data on health-related quality of life (HRQOL) or symptom burden scores are not yet systematically collected or measured in UK renal centres, and this should be a focus of future activity for the UK Renal Registry. Patients with poor QOL and symptom scores must be recognised as being likely to have worse outcomes and managed appropriately.”

With increasing use of digital healthcare, there has been much interest in the potential of harnessing electronic Patient-Reported Outcome Measures (ePROMs) to aid the management of symptom burden and optimise use of limited healthcare resources.(9) These measures allow patients to self-report their individual symptoms, overall symptom burden and HRQOL remotely using online platforms, with the opportunity to make the arising data available to health professionals in real-time to help support care.(10)

Evidence in an oncology setting suggests patients are willing to complete ePROM questionnaires on a regular basis, and that the data can be integrated into the electronic patient record (EPR), with beneficial results. Studies in cancer suggest that ePROM symptom monitoring may be associated with enhanced patient-clinician communication and patient activation; earlier detection of adverse events; improved patient quality of life; reduced use of accident and emergency services; fewer inpatient hospital episodes; and improved survival; even for ‘computer-inexperienced’ patients.(11-18)

The feasibility of routine ePROM capture has been demonstrated in patients with end stage kidney disease on home or in-centre dialysis, and in patients with CKD stage 4/5 (pre-dialysis), but without real-time feedback of data.(19, 20) A multi-centre randomised controlled trial (RCT) is required to evaluate ePROM use with real-time feedback and EPR data integration to determine if health professionals, providers and policy-makers should implement systems within routine clinical practice in the NHS. Before a definitive trial is undertaken, the Renal electronic Patient-Reported Outcome (RePROM) pilot trial [ISRCTN12669006] is being conducted to assess feasibility and determine the key design elements for the full-scale RCT.

During the RePROM study, the co-design group were unable to endorse an existing, validated, PROM for use as initially planned. A systematic review demonstrated that renal PROMs frequently lacked validation in English-speaking populations (particularly in the UK) and were missing evidence to support important measurement properties including measurement error, structural validity, responsiveness and patient acceptability.(21) There is therefore a need to develop a renal ePROM that minimises the burden of questionnaire completion, whilst optimising precision, and which demonstrates appropriate validity, reliability, responsiveness and acceptability to be used at an individual patient level in the NHS.

To address this, the current project will use questionnaire items from existing PROMs, alongside items identified via qualitative work with patients with CKD and healthcare professionals (HCPs), to develop a new “item bank” and computerised adaptive test (CAT) ePROM and also a paper-based short form for patients without online access.

1.2 Item banks and computerised adaptive testing

The need to reduce patient burden when measuring PROs has led researchers to move away from reliance on classical test theory models, and towards item response theory (IRT) and computer adaptive testing.(22) CATs work by administering questions targeted to each individual’s ability, or trait level, by using an adaptive algorithm to administer questions from an item bank that are of direct relevance, and at an appropriate level. Underlying every CAT is a bank of items ‘calibrated’ to an IRT model. An item bank consists of a large number of pre-calibrated questionnaire items covering all relevant aspects of the construct under study. Responses from individuals who have answered different questions from the same item bank are scored on the same scale, allowing direct comparison.

Benefits of CATs (taken from Bjorner *et al.*)(23):

* By selecting the most appropriate items for each person, test precision is optimised for a given test length and irrelevant items can be avoided.
* Test precision can be adapted to the needs of the application. For example, for a diagnostic purpose test, precision could be high for scores close to diagnostic cut-points.
* By calibrating all items onto a common scale, test scores can be compared, even if different precision levels have been specified.
* Item banks can be expanded gradually by seeding and evaluating new items, without sacrificing backwards comparability.

1.3 Study objectives

1. To develop a new renal-specific item bank and CAT ePROM for patients with CKD.
2. To develop a paper-based short form for patients without on-line access.

1.4 Study overview

The study will be split into three phases over three years:

\*\*Note: Phase 1 activity is covered by ethical approval from the University of Birmingham (Ref: ERN\_19-1868).\*\*

Phase 1 – Construction of a renal-specific item bank (Year 1): systematic review and qualitative interviews.

\*\*Note: HRA ethical approval will be sought for Phase 2 and 3.\*\*

Phase 2 – Psychometric evaluation and calibration of the item-bank (Year 2): cognitive interviews and online/postal survey.

Phase 3 – CAT development/simulation testing and dissemination (Year 3).

1.5 Projected outputs and patient benefit

A validated renal specific item bank, CAT and short-form ready to be implemented for symptom monitoring in routine renal care and research.

This project will develop a tool for patients with CKD that will increase the accuracy and responsiveness of their care, to improve quality of life and clinical outcomes, including reductions in hospitalization and mortality.

The item bank can be expanded over-time to incorporate additional items, for instance dialysis- or transplant-specific items, without the need to develop and validate a whole new ePROM, bringing future efficiency savings.

We intend to apply for additional grants in the future to support such expansion and to produce non-English language translations and culturally validated versions to broaden accessibility.

We will make the tool freely available to the renal academic community, improving clinical research by optimising reliability of assessment, thus increasing the statistical power of studies, and reducing rates of missing PRO data, for the benefit of future patients with kidney diseases.

1.6 Study diagram

**Key:** HRQOL, Health-related quality of life; RCAT, renal computerised adaptive test. Note: Phase 1 ethical approval received from the University of Birmingham (Ref: ERN\_19-1868). HRA ethical approval will be sought for Phase 2 and 3.

1. AIMS AND OBJECTIVES

2.1 Phase 1 – Construction of a renal-specific item bank (Year 1): systematic review and qualitative interviews.

\*\*Note: Phase 1 is covered by ethical approval from the University of Birmingham (Ref: ERN\_19-1868).\*\*

* Objective 1.1 – To identify symptoms and HRQOL domains important in CKD, and where available the prevalence of symptoms, across all stages of the disease.
* Objective 1.2 – To identify common symptom and HRQOL domains/items incorporated within existing validated PROMs used in CKD.
* Objective 1.3 – To group domains/items into a conceptual framework, remove/combine duplicate or overlapping items, and identify gaps where new items may be needed.

\*\*Note: HRA ethical approval will be sought for Phase 2 and 3.\*\*

2.2 Phase 2 – Psychometric evaluation and calibration of the item-bank (Year 2): cognitive interviews and online/postal survey.

* Objective 2.1 – Refinement/development of items using cognitive interviews.
* Objective 2.2 – Psychometric evaluation and calibration of the item bank, in a broad and representative sample of UK patients with CKD, using established IRT methods, thus ensuring that the highest level of measurement precision is achieved.

2.3 Phase 3 – CAT development, simulation testing and dissemination.

* Objective 3.1 – CAT development and simulation testing to assess the number of items administered before specified levels of reliability are met.
* Objective 3.2 – Development of renal CAT paper-based short form for patients without on-line access.
* Objective 3.3 – Dissemination of study findings and future research plans.
1. STUDY DESIGN AND SETTING

3.1 Phase 1 – Construction of a renal-specific item bank (Year 1): systematic review and qualitative interviews.

This component of the project has received ethical approval from the University of Birmingham (Ref: ERN\_19-1868).A summary of Phase 1 activity appears below, further details are available in Appendix 1.

3.1.1 Systematic review

A systematic review will identify symptoms and HRQOL domains reported throughout progression of CKD and, where available, prevalence estimates for symptoms and symptom clusters. The review will also be used to identify existing PROMs that have been validated for use in CKD.

The review will update and expand the findings from the following:

Murtagh *et al* (2007), The prevalence of symptoms in end-stage renal disease: a systematic review.(24)

Almutary *et al* (2013), Symptom burden in chronic kidney disease: a review of recent literature.(25)

Aiyegbusi *et al* (2017), Measurement properties of patient-reported outcome measures (PROMs) used in adult patients with chronic kidney disease: a systematic review.(21)

3.1.2 Qualitative interviews with patients and healthcare professionals

To complement the systematic review, qualitative interviews will be conducted with individuals with CKD (n=10-15) and healthcare professionals (HCPs) (n=10-15), with an aim to explore experiences/perceptions regarding the symptoms and HRQOL domains important in CKD, across all stages of the disease.

3.1.3 Developing conceptual framework and refining items for item bank

To conclude Phase 1 of the study, a conceptual framework will be developed to identify the symptom and HRQOL domain areas and items that should be included in the item bank.

Once the conceptual model has been developed, items relating to those symptoms and HRQOL domains of interest can be systematically grouped together (i.e. have similar content and meaning). The process of grouping items together into a framework is known as ‘binning’ or ‘pile-sorting’. Items will be standardised so that they have a consistent timeframe (i.e. symptoms in past weeks), orientation (first-person), response format (i.e. 5-point Likert-type), and reflect magnitude (i.e., “not at all” to “very much”) or frequency of impact (i.e., “never” to “almost always”).

Following ‘binning’ of similar items, the bank will be reduced to include a less redundant pool of items that is representative of the conceptual model (this process is sometimes known as ‘winnowing’). When evaluating each item, the following criteria will be considered: does the item reflect a symptom or QOL domain in the conceptual model; and is the item redundant with other items?

Binning and winnowing will be carried out with input from clinicians and the patient advisory group, before piloting the final items included in the bank by conducting cognitive interviews and “think aloud” with patients with CKD in Phase 2.

Phase 1 output: candidate item-bank, ready for Phase II psychometric evaluation and calibration.

\*\*\*Note: HRA ethical approval will be sought for Phase 2 and 3 activity.\*\*\*

3.2 Phase 2 – Psychometric evaluation and calibration of the item-bank (Year 2): cognitive interviews and online/postal survey.

3.2.1 Cognitive interviews – piloting items for validity

Cognitive interviewing is a method to identify sources of confusion in assessment items and to assess validity on the basis of content and response processes. Using think-aloud procedures and verbal probes, interviewers ask respondents to describe their thinking either concurrently as they answer each question or retrospectively after they complete the scale. The goal is to identify items where there is a misalignment between participant interpretation and the developer’s intentions and to identify ways to modify those items based on participant response.(30, 31)

Cognitive interviews will be conducted by a member of the research team, an experienced mixed-methods researcher, according to a pre-defined topic guide. Interviewees will be presented with items from the bank and first asked to complete the questions and verbalise their thoughts while doing so. The interviewer will observe and take notes. The second step involves asking participants about their response behaviour after they have completed all items.

All interviews will be digitally recorded, professionally transcribed and the transcripts anonymised. Transcript data will be entered into a specialist software package (e.g. Nvivo, QSR International) to aid organisation and analysis of the data. Data will be analysed on an item level with comments and problems labelled and grouped into categories.

Based on previous published CAT development work it is anticipated that 10-20 interviews will be conducted.(28, 29)

If the participant experiences distress during the interview they will be asked if they wish to delay or discontinue the process. The interviewer is an experienced mixed-methods researcher, supported by a study management group with experience of qualitative methodology. The interviewer will be equipped to provide the participant with the contact details of the senior clinician (a consultant nephrologist) on the research team if they wish for follow up.

Researchers themselves may become upset at the content of an interview. The interviewer will be supported by an academic mentor experienced in qualitative research, who will facilitate a de-brief after any interview that is particularly unsettling. Other members of the trial management team will also be available to discuss any concerns. The interviewer will be offered training and support in handling difficult situations. They will also adhere to the University of Birmingham lone researcher safety protocol.

*Recruitment and consent*

Firstly, participants that were interviewed in Phase 1, and who gave consent to be re-contacted, will be sent an email invite, PIS and ICF (**see Phase 2 cognitive interview email invite template, Phase 2 cognitive interview patient information sheet (PIS) and Phase 2 cognitive interview informed consent form (ICF)**). Purposive recruitment will ensure participants are selected to represent different stages of CKD disease continuum (stage 3/5 pre-dialysis, patients receiving dialysis, patients post renal transplant).

If further targeted recruitment is necessary via the NHS, recruitment of patients via named renal research sites will take place as outlined below, starting with the study host site Queen Elizabeth Hospital Birmingham (QEHB). Members of the renal research team at each renal research site will screen for potentially eligible study participants using the inclusion/exclusion criteria and will send eligible patients a study invite email or letter, PIS and ICF.

The research team will ensure local R&D approval/assurance is in place at each recruitment site activated. Sites will not be permitted to enrol participants until written confirmation of R&D approval/assurance is received by the research team.

Interested individuals will be asked to contact the researchers, either by phone or email if they wish to discuss the study further and/or consent to take part in the research. A time will be arranged for the interview to take place either over the telephone, or in-person at the University of Birmingham or at another location to suit the participant. The research team will ensure that individuals have at least 24 hours to digest the PIS, and responses to any follow-up questions, before making a decision over whether or not to take part. Written or audio recorded verbal consent will be taken prior to the interview taking place, depending on the setting.

3.2.2 Online/postal survey

To allow psychometric evaluation and calibration of the candidate item-bank generated in Phase I and refined in the cognitive interviews, participants in Phase II of the study will be asked to complete a survey including each question in the item bank, along with additional sociodemographic and clinical questions. Depending on the number of items included in the bank in Phase 1, it may be necessary to split the bank into ‘blocks’ so that each participant will only see a subset of the overall bank. This will reduce participant burden. Input from the patient advisory group will be sought at this stage before the item-bank survey is sent out to participants. A subset of participants may be asked to complete a second survey approximately 3 months after the first survey to evaluate responsiveness of the item bank. A member of the research team will liaise with research site-staff to extract baseline clinical data, including dialysis and transplant status, eGFR (patients not on dialysis), comorbid conditions/medical history and CKD clinical status at 3 months to determine better, same, or worse clinical status from baseline.

The survey will include options to complete on-line and on-paper. The on-line version will be piloted for use on smartphones, tablets and personal computers.

Depending on the findings of Phase 1, the survey may contain sensitive questions, such as those around sexual function. Sometimes participants can become uncomfortable when answering these types of questions. We will give participants clear information around why we need to ask these questions and what will be done with the data, but we will also make it clear that participants are free not to answer these questions if they do not want to.

We will ask participants to contact their GP if they have any concerns about their health or care after completing the survey. In addition, we will provide links/contact details for recognised CKD support groups approved by our clinician researchers and PPI group at the beginning and end of the survey.

*Recruitment and consent*

**NIHR Applied Research Collaboration (ARC) West Midlands.** The NIHR ARC is a five-year initiative (2019-2024) funded by the NIHR and with matched funds provided by local health and social services (£135 million). There are currently 15 ARCs in England. **In collaboration with ARC west midlands,** all eligible patients under the care of a renal centre (secondary care) at 1 or more NHS Trusts in the West Midlands will be sent a Phase 2 survey invite. Trusts will be chosen to maximise diversity in patient demographics, catchment size, urban-rural mix.

The research team will ensure local R&D approval/assurance is in place at each recruitment site activated. Sites will not be permitted to enrol participants until written confirmation of R&D approval/assurance is received by the research team.

Renal unit staff who are members of the patient care team at each trust will identify eligible patients from hospital records, and survey packs will be prepared by the university research team. Eligible patients will be sent a letter of invitation from a named renal unit consultant, a PIS and a paper copy of the survey booklet, to be returned directly to the researchers in a pre-paid return envelope (see **Phase 2 survey invite**, **Phase 2 survey PIS**). Participants will also be given the opportunity to complete and submit an online version of the survey instead of the paper copy.Prepaid return envelopes (or online submissions) will be marked with a unique identifier for recording returns, and non-responders will be sent one reminder after 6 weeks.\* The title page of the survey (paper and online versions) will outline to the participant that return of the survey will constitute consent to take part in the research (see **Phase 2 survey title page**).

**Step by step outline of recruitment:**

1. Renal unit staff who are members of the patient care team at each trust will search through clinic lists and identify potential participants.
2. Renal staff will inform the RCAT research team of the number of potentially eligible patients, allowing the team to produce the required number of questionnaire packs, which would include an invite letter, PIS, questionnaire and pre-paid return envelope. Each questionnaire/return envelope would have a unique ID number.
3. The RCAT team will provide the renal unit staff with sufficient questionnaire packs.
4. Where required, RCAT staff will also provide a label printer for Renal unit staff to print address labels and attach to the packs.
5. Renal staff would make a note of the unique ID number for each participant's questionnaire.
6. Questionnaire packs would be mailed out by the renal unit staff.
7. The RCAT team will receive anonymised questionnaires directly from patients and forward the ID numbers to the Renal unit staff. The PIS and title page of the questionnaire will clearly state that return of the questionnaire (or electronic submission for the online questionnaire option) would constitute consent to take part in the study.
8. Using the unique ID numbers to identify responder groups, Renal unit staff will: (a) post out reminders to non-responders after a set time period; and (b) post out a second questionnaire pack to a sub-set of responders after approximately 3 months.
9. RCAT staff will never know the identities of those approached or completed.
10. Renal unit staff will not have access to questionnaire responses.
11. Identifiable information and questionnaire responses will never be linked in any way.

One initial site will be used to optimise processes for identifying eligible individuals and mailing out questionnaires, and to pilot data extraction and analysis, before roll-out to additional sites. Of particular interest will be response rates, and coverage of important demographics, in order to tailor/target recruitment at the remaining Trusts.

If required, additional research sites may be added in other geographical areas, with the collaboration of additional ARC’s. Recruitment/consent will be conducted as outlined above in each case.

\*Note: as with any survey study involving patients with end stage kidney disease, there is a risk of upsetting family members where questionnaires/reminders are posted out to patients who may have died. The research fellow will work closely with site staff to ensure they are extra vigilant around this issue.

**NIHR Clinical Research Network West Midlands (CRN).** Patients with CKD not yet requiring specialist care in renal units, will be recruited from general practice. An application for NIHR CRN support will be made at the time of HRA approval through IRAS. We will approach the CRN for support with identifying interested practices for participation in the study. General practices maintain a record of this patients aged 18 or over who have CKD Stage 3a to 5 as part of the NICE Quality and Outcomes Framework (QOF). A similar approach to that used in secondary care through NIHR ARC (above) will be used to invite all eligible patients at each practice using the Phase 2 survey invite (from a named GP), Phase 2 survey PIS and paper/online survey. Again, one initial site will be used to pilot study procedures.

For recruitment of participants in primary care, the research fellow will liaise with practice staff who will identify eligible individuals, utilising practice data to highlight patients diagnosed with CKD (nondialysis stages 3–5, on dialysis, and post-transplant not requiring dialysis). There is a risk that some patients with milder CKD (i.e. stage 3A) who receive a study invite may not have been made aware by their GP that they have the disease. We will attempt to mitigate this risk by recruiting via practices who have a policy of contacting all patients who have been diagnosed with CKD stage 3A and above to discuss the diagnosis. We will also provide appropriate information and contact details in the study invite and ask patients to contact their GP/practice nurse if they have any concerns about their health or care after receiving the invite or completing the survey.

**UK renal patient portal (patientview.org)**. PatientView.org is an online patient portal provided by a not-for-profit organisation based at the University of Edinburgh which provides patients with secure access to their blood tests, clinic letters and medicines. PatientView is managed through the UK Renal Registry (www.renalreg.org), which is part of the UK Renal Association (https://renal.org). PatientView offers live access to test results, with information about these and about users’ diagnosis and treatment. It has approximately 60,000 registered users across the UK, in renal units covering over 90% of UK renal patients. PatientView is accessed via the Internet and an App for Android and Apple devices. News items (e.g. to seek recruitment) can be posted within the application, targeted by the patients’ home Unit or to all. There is also a very active Facebook page. A **Phase 2 electronic survey invite** will be distributed to all PatientView members (no screening will be undertaken) by patientview.org containing links to the PIS and survey and offering interested patients the opportunity to discuss their potential involvement in the study with the research fellow via a method of the patient’s choosing (e.g. email, telephone call). Patients who wish to take part will access the online survey using the link provided in the invite, or if they prefer, will be sent a paper questionnaire in the post with a prepaid return envelope. Return of the survey using either mode will constitute consent to take part in the research.

*Data analysis plan – psychometric evaluation*

The goal of psychometric testing at this stage is to help distil the item bank (through removal of overlapping items, removal of poorly functioning items, and identification of any gaps), and to calibrate the item bank.

Exploratory factor analysis will be used initially to identify and define the number of domains in the item bank, and how these compare with the conceptual framework developed in Phase 1.

Items will be evaluated using item response theory (IRT). IRT provides a robust framework and toolbox for psychometric evaluation, encompassing a family of measurement models that focuses on explaining the dependencies between item responses within a person and between persons. IRT models are especially suitable for dichotomous or polytomous (e.g., Likert scale) item response data, where the items are expected to measure a common latent trait.

Traditionally, the reliability of a measurement instrument is represented by a single fixed number such as Cronbach’s alpha; yet, this in conflict with the fact that a test cannot be expected to measure each person equally efficiently along the latent trait dimension. In IRT, this problem is solved by using (Fisher) information as an estimate of measurement precision/reliability conditional on the latent trait value. This function, showing information for different latent trait values, is known as the test information function (TIF). The TIF will be used to evaluate whether the item bank can support precise measurement for all latent trait values of interest. If gaps are found, new items will be developed to fill these gaps. All items will be tested against a number of tests-of-fit, along with assessments of local response dependence and differential item functioning (DIF), which is a form of item bias. DIF occurs when, at an equivalent level of the underlying construct, different demographic or diagnostic groups (eg. gender, age, CKD stage) respond in systematically different ways to certain items. A computer adaptive testing process can deliver a tailored item set, with options to select certain items for certain patients, accounting for the fact that the item may operate differently among other groups. The calibration process allows for this separation through common-item linking, and therefore items can be retained and presented to the specific targeted patients for whom the item is relevant and meaningful.

Several IRT models will be compared, and the final model will be selected based on both substantive and statistical criteria. Candidate models include the (generalized) partial credit model and the graded response model.

As a first step, unidimensional models will be fit to each separate domain in the multidimensional item bank. When it has been established that each domain is adequately measured, a multidimensional model will be fit to the data. The item parameters and variance-covariance matrix estimated using this model will be used as a basis for the CAT. All statistical analyses and IRT models will be performed using a recognized software package, e.g. R, RUM2020.

Sample size

For the majority of reasonably sized item sets, a sample size of 400 would estimate the item parameters within a scale, with α of 0.01, to within ± 0.3 logits. This is the minimum practical level of stability expected for most variables. However, in accordance with recent best-practice CAT development guidance, we will aim to achieve a minimum sample size of 500.

*Feasibility*

The research team are collaborating with Dr Sarah Damery at the University of Birmingham, who recently led a successful ARC-supported survey exploring the prevalence of mild-to-moderate distress in patients with end-stage renal disease across four hospital Trusts in the West Midlands.(32) In total, 1040/3730 surveys were returned using the recruitment methods outlined above, demonstrating the feasibility of this approach.

3.3 Phase 3 – CAT development, simulation testing and dissemination.

Phase 3 will focus on CAT development and simulation testing, however, data arising from phase 2 (psychometric evaluation and calibration) will be used to develop and validate a paper-based short-form for patients without online access. CAT simulations will be run in R with the package mirtCAT. We will conduct 1000 iterations of the CAT with data simulated using distribution of person location (theta) values based on multidimensional estimations from the current dataset.

We will implement the most commonly used algorithm for a multidimensional CAT as proposed by Segall (1996): item selection and latent trait estimation are based on a Maximum A Posteriori (MAP) procedure using a multivariate normal prior with mean vector equal to zero and covariance matrix equal to the estimated matrix using the available empirical data. Following Paap, Born and Braeken, item selection will be based on the value of the determinant of the posterior information matrix (this value is computed and evaluated for each of the remaining items in the item bank, and the item for which the value is largest is selected).

To initialize the CAT, the most informative item in the (multi)dimensional bank for an "average person" in the population will be used as the starting item. Subsequent item selection is based on the same information criterion, while taking into account the responses to previously administered items. We will define two marginal stopping rules for the CAT simulations based on standard errors equivalent to reliability values of .70 and .90 (SE=.55 and .32, respectively). These values represent the minimum value for group measurement (.70) and the minimum value for individual-level measurement (.90).15 If, for a certain iteration, the fixed-precision threshold has been reached for a particular domain, the remaining items pertaining to that dimension will no longer be selected for the following iteration.

The following CAT evaluation criteria will be inspected: 1) The percentage of simulees for whom the CAT reached SE termination on all domains included in the multidimensional bank; 2) maximum obtained SE of the latent trait estimates across the domains; 3) average absolute bias across the dimensions; 4) total test length across the domains.

1. ELIGIBILITY

Inclusion criteria for adults with CKD:

* Aged 18 or over.
* Able to give informed consent.
* CKD: nondialysis stages 3–5, on dialysis, and post-transplant not requiring dialysis.

Inclusion criteria for HCPs:

* Involved in the ongoing management of patients with CKD (nondialysis stages 3–5, on dialysis, and post-transplant not requiring dialysis).
* Currently practicing in the UK.

Exclusion criteria for adults with CKD:

* Inability to speak, read or write English.
* Episode of acute kidney injury in previous 3 months
1. PARTICIPANT WITHDRAWAL

Participants can withdraw at any time from the study without giving any reason and no further data would be collected. However, data collected up to the point of withdrawal will be retained.

1. DATA SECURITY

The security of study data is governed by the policies of the University of Birmingham. The University’s Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the University of Birmingham have to be registered with the Data Protection Officer and data held in accordance with the Data Protection Act (2018). The Study Centre has arrangements in place for the secure storage and processing of the study data which comply with the University of Birmingham policies.

The System incorporates the following security countermeasures:

* Physical security measures: restricted access to the building, offices and filing cabinets, password protected university computers and servers, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
* Logical measures for access control and privilege management: including restricted accessibility, access-controlled servers, separate controls used for non-identifiable data etc.
* Network security measures: including site firewalls, antivirus software, separate secure network protected hosting etc.
* Operational Processes: the data will be processed and stored within the Study Centre (University of Birmingham).
* Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University’s Data Protection Registration number is Z6195856.
1. ARCHIVING

All study information will be archived in the BEAR (Birmingham Environment for Academic Research) Archive for 10 years after the end of the study, unless otherwise indicated. In accordance with UK data archive best practice for researchers recommendations, data will be stored in open-standard formats for long-term preservation of data.

1. AUDIT AND INSPECTION

The CI will permit study-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The investigator will comply with these visits and any required follow up.

1. INSURANCE AND INDEMNITY

The University of Birmingham has in place indemnity coverage for this study which provides cover to the University for harm which comes about through the University’s, or its staff’s, negligence in relation to the design or management of the study and may alternatively, and at the University’s discretion provide cover for non-negligent harm to participants.

1. FINANCE

Kidney Research UK (KRUK) is funding this study. Clinical Research Network (CRN) support will be sought. No individual per patient payments will be made to NHS Trusts, Investigators or participants.

1. ETHICAL CONSIDERATIONS

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996 (website: <http://www.wma.net/en/30publications/10policies/b3/index.html>*).*

The study will be conducted in accordance with the UK Policy Framework for Health and Social Care Research, the applicable UK Statutory Instruments, (which include the Data Protection Act 2018) and the Principles of GCP. The protocol will be submitted to and approved by the main REC prior to the study commencing.

Before any participants are enrolled into the trial, the PI at each site will obtain local R&D approval/assurance. Sites will not be permitted to enrol participants until written confirmation of R&D approval/assurance is received by the BCTU trials team.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians’ responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

1. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act (2018). Prior participant consent will be sought to obtain the following study data:

* Medical history (e.g. dialysis and transplant status, eGFR (patients not on dialysis), comorbid conditions/medical history and CKD clinical status).
* Demographic data (e.g. age, gender, ethnicity, highest level of education).
* Interview recordings/transcripts: from the qualitative aspects of the study.

Note: Only a member of the patient's existing clinical care team will have access to patient records without explicit consent in order to identify potential participants.

The research team will maintain the confidentiality of all participant’s data and will not disclose information by which participants may be identified to any third party*.* Representatives of the research team and sponsor may be required to have access to participant’s notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times. The study will do its utmost to preserve participant’s anonymity and keep comments unidentifiable, therefore their name will not be mentioned in any report of this research.

Data transferred from research sites to the researchers (University of Birmingham) will be securely stored and only used for analysis or study monitoring relevant to the participant taking part in the research.

Participants will give their explicit consent for the transfer of study data to the University of Birmingham and University of Leeds for analysis. Participants will always be identified using their unique study identification number in correspondence between the research sites and the University of Birmingham, and between the University of Birmingham and University of Leeds.

For participants involved in the qualitative aspects of the study, we will ask their permission to audio record the study interview using an encrypted digital recording device. We will then ask a reputable company to produce a written version of the recording called a transcript. The transcript company will need to sign a confidentiality agreement before they do so. We will then anonymise the transcript, removing all identifying information. After this, we will delete the original recording. We will only use anonymised quotes from the transcript in any arising publications or reports.

For participants involved in the online/postal survey, the survey data will be pseudoanonymised. Prepaid survey return envelopes (or online submissions) will be marked with a unique identifier for recording returns. The host research sites will hold the key and will send out follow-up reminders where appropriate. The RCAT study team will notify host research sites at the end of the study (date of last data capture) who will then destroy the key.

The research team will hold personal contact data for participants wishing to receive a summary of the results of the study - we anticipate this will be made available within 12 months of completion of the study. After we share the results, we will delete participants’ contact details, meaning no personal identifiable data, other than study consent forms, will be retained.

1. PATIENT AND PUBLIC INVOLVEMENT

This project is supported by the kidney patient advisory group (KPAG), who provided early input regarding the generation of the research idea and study design.

Members of the KPAG will be asked to provide input on study materials: participant information sheets, participant invitations, and consent forms. In Phase 1 of the study, they will be involved in developing the conceptual framework for the item bank, ensuring patient centricity. In Phase 2 they will be instrumental in ensuring the questionnaire is acceptable and non-burdensome. In the final phase, PPI will be used to think about how the developed CAT can best be implemented from a patient perspective in future studies.

1. PUBLICATION POLICY

Results of this study will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Research Fellow/CI who will be listed as first/last authors. Theremaining authorship will be agreed by the study management group.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the study management group. Manuscripts must be submitted to the groupin a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the study was performed with the support of sponsor (University of Birmingham).

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**APPENDIX I**

**Phase 1 protocol**

**Developing a renal-specific item bank: a systematic review.**

**Background and aims**

We will develop a new “item bank” and computerised adaptive test (CAT) electronic patient reported outcome measure (ePROM) and paper-based short form to measure symptom burden and impact on quality of life in chronic kidney disease (CKD). This will address the lack of a valid, reliable, responsive and brief patient reported outcome measure (PROM) for use by the UK renal community.

The need to reduce patient burden when measuring PROMs has led researchers to move away from reliance on classical test theory models, and towards item response theory (IRT) and computer adaptive testing. CATs work by administering questions targeted to each individual’s ability or trait level, by using an adaptive algorithm to administer questions from an item bank that are of direct relevance, and at an appropriate level. Responses from individuals who have answered different questions from the same item bank are scored on the same scale, allowing direct comparison.

Underlying every CAT is a bank of items ‘calibrated’ to an IRT model. An item bank consists of a large number of pre-calibrated questionnaire items covering all relevant aspects of the construct under study.

The aim of this review is to contribute towards the development of the item bank by:

Identifying symptoms and Health-Related Quality of Life (HRQOL) domains important in CKD, and where available the prevalence of those symptoms, across all stages of the disease.

Identifying common symptom and HRQOL domains/items incorporated within existing validated PROMs used in CKD.

**Anticipated or actual start date.**

 February 2020.

**Review team members and their organisational affiliations.**

Ben Fletcher

Nicola Anderson

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Centre for Patient Reported Outcomes Research (CPROR), Institute for Applied Health Research (IAHR), University of Birmingham, UK

**Funding**

The review is funded by Kidney Research UK.

**Review questions**

1. What symptoms and Health-Related Quality of Life (HRQOL) domains are important in CKD, and how do these differ across the different stages of CKD?
2. What is the prevalence of those symptoms?
3. What common symptom and HRQL domains/items are incorporated within existing validated PROMs used in CKD.

**Searches**

The following databases will be searched from January 2000 until present:

Ovid MEDLINE, Ovid PsycINFO and EBSCO CINAHL

Three strategies will be employed to identify:

1. Quantitative studies assessing symptom burden, HRQOL or adverse events in CKD (longitudinal or cross-sectional studies) – update of systematic review investigating symptoms in end-stage renal disease by Murtagh *et al* (2007)(24) and Almutary *et al* (2013)(25). The search will be expanded to include any CKD stage, HRQOL and adverse events.
2. Qualitative studies assessing symptom burden/severity, HRQOL or adverse events in CKD.
3. Studies reporting either the development of a PROM measuring HRQOL and/or CKD symptoms in any CKD population, or evaluation of one or more psychometric properties. We will update the searches conducted in a systematic review of measurement properties of PROMs used in CKD by Aiyegbusi *et al.* (2016)(21)

Forward citation searches and a hand search of the reference lists of included articles will be carried out.

Search strategies for each of the three objectives in OVID Medline are available in the Appendices.

**Types of study to be included.**

All studies must be:

1. Original research articles published in English
2. Involve adults with chronic kidney disease, including: stage 1-5, on dialysis or in receipt of a renal transplant

Studies from search strategy 1 must:

1. Assess quality of life, symptom burden or adverse events as the primary aim of research (report prevalence data on symptoms/impacts on HRQOL)

Studies from search strategy 2 must:

1. Assess patient and healthcare professional perspectives on CKD symptoms, HRQOL or adverse events (data from interviews or focus groups)

Studies from search strategy 3 must:

1. Report either the development, or evaluation of one or more psychometric properties, of a PROM measuring HRQOL and/or CKD symptoms in any CKD population.

Studies will be screened for inclusion independently by two researchers (BF all records, and either DK or NA).

**Exclusions**

1. Editorials, conference abstracts, case reports, systematic reviews
2. Full text not available
3. Articles not in English

**Main outcome(s).**

Symptoms, symptom clusters, HRQOL and adverse events reported in CKD.

Validated PROMs used to monitor symptoms and/or HRQOL in CKD.

**Data extraction (selection and coding).**

Data will be extracted in duplicate all included studies using a pre-piloted data extraction form.

Data will be extracted on:

Study information: year conducted, country of origin, study design, sample size, study design

Study population: inclusion/exclusion criteria, CKD stage, demographic information, treatments

Study outcomes: symptoms/symptom clusters definition (and prevalence if available), QOL domain definitions, experiences/perceptions around CKD HRQOL/symptoms/symptom clusters (from qualitative studies)

PROMs: generic/CKD specific/utility based, mode of administration (self- or interviewer-administered), method of capture (paper-based, telephone, electronic), recall period, number of items, scoring, permissions for use

**Strategy for data synthesis.**

Symptoms/QOL domains/items from PROMs used in CKD research will be extracted and combined into similar categories. Initial categories will be based on those reported in Lockwood (2019)(26) and van der Willik (2019)(27) Categories will be refined and new categories introduced when necessary during data extraction.

Initial symptom/impact categories:

* Neuromuscular (e.g., sore muscles, cramps, joint pain, numbness in hands/feet, muscle spasms, poor mobility, etc)
* Cardiopulmonary (e.g., chest pain, heart palpitation, shortness of breath, feeling faint, etc)
* Gastrointestinal (e.g., constipation, diarrhoea, nauseas, decreased appetite, heartburn, etc)
* Psychological/emotional (e.g., depression, anxiety, nervousness, worry, anger, low motivation, intrusive thoughts, etc)
* Energy/fatigue (e.g., tiredness, difficulty sleeping, feeling weak, waking in the night, etc)
* Skin problems (e.g., dry skin, itchiness, loss of hair, sweating, etc)
* Sexual function (e.g., decreased interest in sex, inability to enjoy sex, difficulty becoming aroused, etc)

Prevalence figures will be combined using meta-analysis, if the heterogeneity is acceptable. Data will be pooled using either the random- or the fixed-effects model depending on the heterogeneity of the included studies. Heterogeneity will be determined using Cochran's Q-test at a significance level of 0.10. I² will be calculated to quantify the heterogeneity; acceptable heterogeneity will be defined as I² <70%. In studies with a high heterogeneity (I² >70%), a random-effects model was used.

Logit transformation of the prevalence figures will be applied as logits are more likely to have a normal distribution, essential for pooling data. The final pooled logit will be back transformed, resulting in pooled prevalence and 95% CIs.

Subgroup analyses will be performed based on the stage of CKD, but only if there are at least three studies in a subgroup.

OVID Medline search strategy for objective 1 (update of Almutary 2013)

1. (Symptom AND CKD).ti.

2. (Symptom AND chronic kidney disease).ti.

3. (Symptom AND end-stage renal failure).ti.

4. (Symptom AND end-stage kidney disease OR kidney disease).ti.

5. ((Symptom\* AND (haemodialysis or peritoneal dialysis)).ti.

6. (Symptom burden AND renal failure).ti.

7. (Symptom burden instrument AND kidney failure).ti.

8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7

9. ((Quality of life OR QOL) AND CKD).ti.

10. ((Quality of life OR QOL) AND chronic kidney disease).ti.

11. ((Quality of life OR QOL) AND end-stage renal failure).ti.

12. ((Quality of life OR QOL) AND (end-stage kidney disease OR kidney disease)).ti.

13. ((Quality of life OR QOL) AND (haemodialysis or peritoneal dialysis)).ti.

14. ((Quality of life OR QOL) AND renal failure).ti.

15. ((Quality of life OR QOL) AND kidney failure).ti.

16. 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15

17. (Adverse event\* AND CKD).ti.

18. (Adverse event\* AND chronic kidney disease).ti.

19. (Adverse event\* AND end-stage renal failure).ti.

20. (Adverse event\* AND (end-stage kidney disease OR kidney disease)).ti.

21. (Adverse event\* AND (haemodialysis or peritoneal dialysis)).ti.

22. (Adverse event\* AND renal failure).ti.

23. (Adverse event\* AND kidney failure).ti.

24. 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23

25. 8 OR 16 OR 24

OVID Medline search strategy for objective 2.

1. Kidney diseases/

2. Kidney disease.ti,ab.

3. CKD.ti,ab.

4. End stage renal disease.ti,ab.

5. End stage renal failure.ti,ab

6. End stage kidney disease.ti,ab

7. End stage kidney failure.ti,ab.

8. \*dialysis.ti,ab

9. haemodialysis.ti,ab

10. peritoneal dialysis.ti,ab.

11. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10

12. Symptom\*.ti,ab.

13. Symptom burden.ti,ab.

14. Quality of life.ti,ab.

15. QOL.ti,ab.

16. Health related quality of life.ti,ab.

17. HRQOL.ti,ab.

18. (Adverse event\* or AE\*).ti,ab.

19. 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18

20. Qualitative research/

21. Observation.ti,ab.

22. Interview.ti,ab.

23. ((qualitative or semi-structured or semistructured or unstructured or informal or in-depth or indepth or "face-to-face" or structured or guide\*) adj3 (interview\* or discussion\* or questionnaire\*)).ti,ab.

24. (qualitative or focus group or story or stories or narration or narrative\* or discourse or discursive or grounded theory or ethnogra\* or phenomenolog\* or fieldwork or field work or key informant\*).ti,ab.

25. 20 OR 21 OR 22 OR 23 OR 24

26. 11 AND 19 AND 25

OVID Medline search strategy for objective 3 (update of Aiyegbusi 2017)

1. (HR-PRO or HRPRO or HRQL or HRQoL or QL or QoL).ti,ab.

2. quality of life.mp.

3. (health index\* or health indices or health profile\*).ti,ab.

4. health status.mp.

5. ((patient or self or child or parent or carer or proxy) adj (appraisal\* or appraised or report or reported or reporting or rated or rating or based or assessed or assessment\*)).ti,ab.

6. ((disability or function or functional or functions or subjective or utility or utilities or wellbeing or well being) adj2 (index or indices or instrument or instruments or measure or measures or questionnaire\* or profile or profiles or scale or scales or score or scores or status or survey or surveys)).ti,ab.

7. ((((patient adj reported adj outcome adj measure\*) or patient) adj reported adj outcome\*) or capability or capabilities).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. (Renal replacement therapy or APD or Automated Peritoneal Dialysis or CAPD, Continuous Ambulatory Peritoneal Dialysis or CCPD or Continuous cyclic peritoneal dialysis or dialysis or h\*emofiltration or h\*emodiafiltration or h\*emodialysis or kidney transplant\* or predialysis or renal replacement or renal transplant\*).mp.

10. (CRF or chronic renal failure or CKF or chronic kidney failure or kidney disease\* or renal disease or kidney failure or renal failure or CKD or chronic kidney disease or ESKD or end stage kidney disease or ESKF or end stage kidney failure or ESRF or end stage renal failure or ESRD or end stage renal disease or kidney insufficiency).mp.

11. Renal Insufficiency, Chronic/

12. 9 or 10 or 11

13. (((((((((((((((((((((((((((((Instrumentation or method\* or Validation Studies or Comparative Study).mp. or psychometrics/ or psychometr\*.mp. or clinimetr\*.mp. or clinometr\*.mp. or outcome assessment health care/ or outcome assessment\*.ti,ab. or outcome measure\*.mp. or observer variation/ or observer variation\*.ti,ab. or Health Status Indicators/ or reproducibility of results/ or reproducib\*.ti,ab. or discriminant analysis/ or reliab\*.ti,ab. or unreliab\*.ti,ab. or valid\*.ti,ab. or coefficient of variation.ti,ab. or coefficient\*.ti,ab. or homogeneity.ti,ab. or homogeneous.ti,ab. or internal consistency.ti,ab. or cronbach\*.ti,ab.) and alpha\*.ti,ab.) or item\*.ti,ab.) and correlation\*.ti,ab.) or selection\*.ti,ab. or reduction\*.ti,ab. or agreement.mp. or precision.mp. or imprecision.mp. or precise value\*.mp. or test-retest.ti,ab. or test.ti,ab.) and retest.ti,ab.) or reliab\*.ti,ab.) and test.ti,ab.) or retest.ti,ab. or stability.ti,ab. or interrater.ti,ab. or inter-rater.ti,ab. or intrarater.ti,ab. or intra- rater.ti,ab. or intertester.ti,ab. or inter-tester.ti,ab. or intratester.ti,ab. or intra- tester.ti,ab. or interobserver.ti,ab. or inter-observer.ti,ab. or intraobserver.ti,ab. or intra-observer.ti,ab. or intertechnician.ti,ab. or inter-technician.ti,ab. or intratechnician.ti,ab. or intra-technician.ti,ab. or interexaminer.ti,ab. or inter- examiner.ti,ab. or intraexaminer.ti,ab. or intra-examiner.ti,ab. or interassay.ti,ab. or inter-assay.ti,ab. or intraassay.ti,ab. or intra-assay.ti,ab. or interindividual.ti,ab. or inter-individual.ti,ab. or intraindividual.ti,ab. or intra-individual.ti,ab. or interparticipant.ti,ab. or inter-participant.ti,ab. or intraparticipant.ti,ab. or intra- participant.ti,ab. or kappa\*.ti,ab. or kappa's.ti,ab. or repeatab\*.mp. or replicab\*.mp. or repeated.mp.) and measure\*.mp.) or finding\*.mp. or result\*.mp. or test\*.mp. or generaliza\*.ti,ab. or generalisa\*.ti,ab. or concordance.ti,ab. or intraclass.ti,ab.) and correlation\*.ti,ab.) or discriminative.ti,ab. or known group.ti,ab. or factor analysis.ti,ab. or factor analyses.ti,ab. or factor structure.ti,ab. or factor structure.ti,ab. or dimension\*.ti,ab. or subscale\*.ti,ab. or multitrait.ti,ab.) and scaling.ti,ab. and analysis.ti,ab.) or analyses.ti,ab. or item discriminant.ti,ab. or interscale correlation\*.ti,ab. or error.ti,ab. or errors.ti,ab. or individual variability.ti,ab. or interval variability.ti,ab. or rate variability.ti,ab. or variability.ti,ab.) and analysis.ti,ab.) or value\*.ti,ab. or uncertainty.ti,ab.) and measurement.ti,ab.) or measuring.ti,ab. or standard error of measurement.ti,ab. or sensitiv\*.ti,ab. or responsive\*.ti,ab. or limit\*.ti,ab.) and detection.ti,ab.) or minimal detectable concentration.ti,ab. or interpretab\*.ti,ab. or minimal.ti,ab. or minimally.ti,ab. or clinical.ti,ab. or clinically.ti,ab.) and important.ti,ab.) or significant.ti,ab. or detectable.ti,ab.) and change.ti,ab.) or difference.ti,ab. or small\*.ti,ab.) and real.ti,ab.) or detectable.ti,ab.) and change.ti,ab.) or difference.ti,ab. or meaningful change.ti,ab. or ceiling effect.ti,ab. or floor effect.ti,ab. or Item response model.ti,ab. or IRT.ti,ab. or Rasch.ti,ab. or Differential item functioning.ti,ab. or DIF.ti,ab. or computer adaptive testing.ti,ab. or item bank.ti,ab. or cross-cultural equivalence.ti,ab.

14. (PRO integration or Clinical PRO application\* or telePRO or automated PRO algorithm\* or screening purpose\* or PRO questionnaire\* or Patient-reported outcome questionnaire\* or Patient-reported symptom\* or Patient-centred care or Patient self- report\* or Self-report health or Self-rated health or Self-reported measure\* of health or Health outcome\* or Health communication\* or Hospital performance evaluation\* or Automated telephone survey system\* or paper-based survey\* or web-based survey\* or web-based PRO platform\* or web-based system\* or PRO collection\* or PRO measure\* or PRO intervention\* or PRO assessment intervention\* or PRO data or PRO assessment\* or Routine PRO assessment\* or Routine PRO collection or Symptom assessment\* or Symptom monitoring or Symptom data or Functional status or Electronic PRO assessment\* or Electronic PRO system\* or ePRO or ePRO\* or ePRO system\* or PRO system\* or Generic PRO system\* or PRO-based clinical alert system\* or PROM or eRPOM or electronic PROM).mp.

15. 13 or 14

16. 8 and 12 and 15

Qualitative interviews with patients and healthcare professionals

To complement the systematic review, qualitative interviews will be conducted with individuals with CKD (n=10-15) and healthcare professionals (HCPs) (n=10-15), with an aim to explore experiences/perceptions regarding the symptoms and HRQOL domains important in CKD, across all stages of the disease. **This component of the project has received ethical approval from the University of Birmingham (Ref: ERN\_19-1868).**

Participants will be recruited as outlined in below and interviewed either by telephone, or in-person at the University of Birmingham, or another location to suit the participant.

Semi-structured interviews will be conducted by a member of the research team, an experienced mixed-methods researcher, according to a pre-defined topic guide, but there will be sufficient scope to explore novel themes where appropriate. All interviews will be digitally recorded, professionally transcribed and the transcripts anonymised. Transcript data will be entered into a specialist software package (e.g. Nvivo, QSR International) to aid organisation and analysis of the data. All data will be analysed thematically, with reported symptoms mapped onto the same categories developed for data extraction in the systematic review. Formal triangulation of coding and member checking will be employed to enhance the credibility of the analysis. Only anonymised quotes will be used in any arising publications or reports.

If the participant experiences distress during the interview they will be asked if they wish to delay or discontinue the process. The interviewer is an experienced mixed-methods researcher, supported by a study management group with experience of qualitative methodology. The interviewer will also be supported by a senior clinician (a consultant nephrologist).

Based on previous published CAT development work it is anticipated that 20-30 interviews will be conducted, with individuals purposively selected to capture a range of experiences.(28, 29) However, recruitment will continue until data saturation is reached.

*Recruitment and consent*

The following approaches will be used to identify and recruit adults with CKD:

* An email invite will be sent to people registered with HelpBeatKidneyDisease (a NIHR initiative whereby people have signed up in advance and given their consent to be contacted about opportunities to participate in research targeted at their condition).
* Advertising on social media of Kidney Research UK (charity that has funded the research).

HCPs will be recruited using convenience and snowball sampling:

* An email invite will be sent through the professional network of nephrologists and renal nurses involved in the research project (University Hospitals Birmingham NHS Foundation Trust).
* Snowballing - Interviewees will also be asked to pass on the study invite to other interested individuals.

Individuals will be provided with information about the study either via the host organisation (e.g. HelpBeatKidneyDisease and Kidney Research UK) or via the professional network of nephrologists and renal nurses involved in the research project (see Phase 1 email invite/advert, Phase 1 patient information sheets (PIS) and Phase 1 informed consent forms (ICF).

If interested, potential participants will be asked to contact the researchers, either by phone or email if they wish to discuss the study further and/or consent to take part in the research. A time will be arranged for the interview to take place either over the telephone, or in-person at the University of Birmingham or at another location to suit the participant. The research team will ensure that individuals have at least 24 hours to digest the PIS, and responses to any follow-up questions, before making a decision over whether or not to take part. Written or audio recorded verbal consent will be taken prior to the interview taking place, depending on the setting. Within the ICF, individuals will be asked if they would be willing to be contacted about potentially taking part in the Phase 2 cognitive interviews [OPTIONAL] (see section 3.2.1).

**Developing conceptual framework and refining items for item bank**

To conclude Phase 1 of the study, a conceptual framework will be developed to identify the symptom and HRQOL domain areas and items that should be included in the item bank.

Once the conceptual model has been developed, items relating to those symptoms and HRQOL domains of interest can be systematically grouped together (i.e. have similar content and meaning). The process of grouping items together into a framework is known as ‘binning’ or ‘pile-sorting’. Items will be standardised so that they have a consistent timeframe (i.e. symptoms in past weeks), orientation (first-person), response format (i.e. 5-point Likert-type), and reflect magnitude (i.e., “not at all” to “very much”) or frequency of impact (i.e., “never” to “almost always”).

Following ‘binning’ of similar items, the bank will be reduced to include a less redundant pool of items that is representative of the conceptual model (this process is sometimes known as ‘winnowing’). When evaluating each item, the following criteria will be considered: does the item reflect a symptom or QOL domain in the conceptual model; and is the item redundant with other items?

Binning and winnowing will be carried out with input from clinicians and the patient advisory group, before piloting the final items included in the bank by conducting cognitive interviews and “think aloud” with patients with CKD in Phase 2.

**References**

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