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## The use of an electronic Patient-Reported Outcome Measure in the Management of Patients with Advanced Chronic Kidney Disease. The RePROM Pilot Trial.

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**TITLE**

The use of an electronic Patient-Reported Outcome Measure in the Management of Patients with Advanced Chronic Kidney Disease. The RePROM Pilot Trial.

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## ABSTRACT

### Introduction

Chronic Kidney Disease (CKD) affects up to 16% of adults in the UK. Patient quality of life is particularly reduced in end stage renal disease and is strongly associated with increased hospitalisation and mortality. Thus, accurate and responsive healthcare is a key priority. Electronic Patient-Reported Outcome Measures (ePROMs) are online questionnaires which ask patients to self-rate their health status. Evidence in oncology suggests the use of ePROM data within routine care, alongside clinical information, may enhance symptom management and improve patient outcomes. However, NHS-based ePROM research in CKD is lacking. This pilot trial will assess the feasibility of undertaking a full-scale randomised controlled trial in patients with CKD within the NHS.

### Methods and analysis

The RePROM pilot trial is an investigator-led single-centre, open-label, two-arm randomised controlled pilot trial of 66 participants  $\geq 18$  years with advanced CKD. Participants will be randomised to receive either usual care, or usual care supplemented with an ePROM intervention. Participants within the intervention arm will be asked to submit monthly self-reports of their health status using the ePROM system. The system will provide tailored information to patients in response to each report and notify the clinical team of patient deterioration. The renal clinical team will monitor for ePROM notifications and will respond with appropriate action, in line with standard clinical practice. Measures of study feasibility, participant quality of life and CKD severity will be completed at 3-monthly intervals. Health economic outcomes will be assessed. Clinicians will record treatment decision-making. Acceptability and feasibility of the protocol will be assessed alongside outcome measure and intervention compliance rates. Qualitative process evaluation will be conducted.

### Ethics and dissemination

The findings will inform the design of a full-scale RCT and the results will be submitted for publication in peer-reviewed journals. The study has ethical approval.

### Trial registration number

ISRCTN12669006

## ARTICLE SUMMARY

### Strengths and limitations of this study

- The study uses a randomised controlled trial design, delivered in an NHS setting.
- The research site, University Hospitals Birmingham NHS Foundation Trust, hosts one of the largest specialist renal research sites in Europe.
- The study protocol and intervention was developed by a multidisciplinary team of experts including: patients, health care professionals and academics.
- As a pilot trial, the study is limited to one clinical centre and is not statistically powered to assess clinical outcomes. Instead, the project will evaluate feasibility of conducting a full-scale RCT in the target population.

## INTRODUCTION

Chronic Kidney Disease (CKD) affects up to 16% of adults in the UK<sup>1</sup>, with an annual estimated cost of £1.45 billion.<sup>2</sup> More than half of these costs were associated with Renal Replacement Therapy (RRT) - haemodialysis, peritoneal dialysis and/or kidney transplantation - for patients with end stage renal disease (ESRD).<sup>2</sup> This is despite the fact that patients requiring RRT comprise less than 1% of the total CKD population.<sup>2</sup> Numerous studies have demonstrated that patients with ESRD experience high symptom burden and a very high prevalence of depression.<sup>3</sup> Moreover, patient quality of life is significantly reduced in ESRD and is strongly associated with increased hospitalisation and mortality.<sup>3</sup> Accurate and responsive healthcare for patients as they progress from advanced CKD to ESRD is therefore a key healthcare priority.

Effective management of advanced CKD relies on the timely detection of clinical deterioration towards ESRD. This can be a major challenge between scheduled clinic visits, when it is often difficult to identify clinical deterioration unless a patient self-refers. Unfortunately, some patients self-refer too late because they have difficulty identifying the point at which they may require assistance. Without prompt recognition of advanced symptoms, such patients are at high risk of severe illness, emergency hospitalisation, and associated worse clinical outcomes.<sup>3</sup>

Patient-Reported Outcome Measures (PROMs) are validated questionnaires which ask patients to self-rate their health status. They can provide important information regarding the patient's perspective on the physical, functional and psychological consequences of treatment and the degree and impact of disease symptoms.<sup>4</sup> Evidence suggests the use of PROM data, alongside regular clinical information, within routine care may:

- Aid patient-provider communication and support shared decision-making.<sup>5</sup>
- Improve patient activation and help patients to feel more involved/empowered in decisions around their care.<sup>6-8</sup>
- Improve the accuracy of symptom assessment and enhance symptom management.<sup>9</sup>
- Enhance patient education and self-management and maximise patient safety.<sup>7 10-15</sup>

With recent advances in technology, there has been considerable interest in the use of electronic PROMs (ePROMs) for the routine monitoring of patients with long-term conditions. ePROMs offer patients an 'electronic' method of data entry – e.g. web-based via PC, smartphone, or using tablet devices – and give clinicians a flexible platform with which they may view PROM data.<sup>14 16 17</sup>

ePROMs offer patients the option of inputting data at a time and place, and via a platform, that is convenient to them. ePROM data can be used to help provide patients with tailored advice on self-management and can provide clinicians with detailed HRQL and symptom data both in-clinic and between scheduled appointments via home/remote data capture.<sup>15</sup>

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3 For patients with advanced CKD, this would allow clinicians to monitor for symptom  
4 deterioration, facilitating the early detection of problems requiring attention and  
5 promoting timely intervention from the clinical team (e.g. advice aimed at aiding  
6 patient self-management or escalation of care). Such intervention may delay disease  
7 progression and the need for costly and invasive RRT, and reduce emergency  
8 hospitalisations and other adverse outcomes.  
9

10 A recent randomised controlled trial (RCT) conducted in an oncology setting in the  
11 US, demonstrated that ePROM use is associated with improved HRQL, reduced  
12 Accident and Emergency visits, reduced hospitalisations, and superior quality-  
13 adjusted survival.<sup>15</sup> Both in Canada and Denmark, ePROM collection has been  
14 shown to be feasible in a renal population.<sup>16 18 19</sup> However, NHS-based ePROM  
15 research in CKD, utilising real-time patient and clinician feedback is lacking. Routine  
16 remote use of ePROM data by patients with advanced CKD may aid self-  
17 management, whilst also helping to improve the flow of information between patients  
18 and their clinicians, potentially improving patient safety, enhancing clinical  
19 interactions, optimising patient outcomes and delivering cost savings to the NHS.  
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22 A RCT is needed to evaluate ePROM efficacy in advanced CKD to determine if  
23 health professionals, providers and policy-makers should implement routine ePROM  
24 collection in renal practice. However, before a definitive trial is undertaken, a pilot  
25 trial is required to assess the feasibility of undertaking such a study and to help  
26 inform the key elements (e.g. appropriate outcome measure, sample size) of the  
27 design for the full-scale RCT.  
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## METHODS

### Design

The RePROM study will span two phases: stage 1 involves development of the ePROM intervention with patient and clinician input; stage 2 is a pilot/feasibility RCT with a qualitative sub-study.

### Setting

Patients under the care of the renal services at Queen Elizabeth Hospital, Birmingham (QEHB) will be recruited for this study.

### Stage 1: Intervention development

Design of the ePROM system will be finalised during a series of operational meetings, held in stage 1 of the study, with regular input from: (1) the QEHB renal clinical and research team; (2) the RePROM Patient Advisory Group; (3) the QEHB IT and Informatics group; (4) the University of Birmingham Clinical Trials Unit; and (5) the Patients Outcomes Group at the University of Leeds.

The ePROM system will be made available to study participants via 'myHealth@QEHB', a secure patient portal linked to the patient's electronic healthcare record (EHR), delivered by the host site. The system will be developed to allow patients to self-report their health status using a variety of electronic platforms, e.g.: PC, smartphone or tablet.

The ePROM system will be designed to: (i) provide appropriate self-management advice to participants whose questionnaire scores suggest mild/moderate symptoms; and (ii) notify the clinical team of patient deterioration via an automated email, where the patient's questionnaire responses indicate severe symptoms/cause for concern.

Patients' longitudinal ePROM scores will be made available to clinicians for use during routine outpatient consultations via the EHR. The RePROM Patient Advisory Group felt this approach would help to focus clinical discussion on patient-centred issues and may enhance symptom management, a view supported by related literature.<sup>7 8 16 17 21-23</sup>

### Stage 2: pilot/feasibility RCT and qualitative sub-study

#### Trial design

The RePROM pilot trial is an investigator led single-centre, open-label, two-arm randomised controlled pilot trial of 66 participants aged 18 years or over with advanced CKD. Participants will be randomised to receive either usual care, or usual care supplemented with an ePROM intervention. The trial is registered with ISRCTN (ISRCTN12669006) and the NIHR Portfolio (CPMS ID: 36497). The study flow is outlined in Figure 1.

### Figure 1. RePROM trial schema.



## Recruitment and eligibility

Recruitment is scheduled to commence in July 2018. Patients will be invited to participate based on the following eligibility criteria:

### Inclusion Criteria

- Aged  $\geq 18$  years old;
  - Ability to provide fully informed written consent for participation in the study;
  - Patients under the care of the renal services at QEHB;
  - Patients meeting the trial definition of **advanced CKD**:
    - an eGFR  $\geq 6$  and  $\leq 15$  mL/min/1.73m<sup>2</sup> (inclusive)
- OR**
- a projected risk of progression to end-stage renal failure within 2-years  $\geq 20\%$  using the 4-variable Tangri renal risk calculator.<sup>24</sup>

### Exclusion Criteria

- Patients unwilling to use the ePROM intervention;
  - Patients who, in the opinion of the consenting professional, cannot speak, read or write English sufficiently well to complete the ePROM unaided;
  - An episode of **acute kidney injury** (defined in accordance with national guidelines) within the last 3 months<sup>25</sup>;
  - Patients meeting the trial definition of **End Stage Renal Disease**:
    - Currently receiving dialysis or scheduled to start in the next 2 weeks
- OR**
- Has received (or has a scheduled date to receive) a kidney transplant
- OR**
- eGFR  $\leq 5$  mL/min/1.73m<sup>2</sup>;
- A terminal illness that, in the opinion of the consultant assessing eligibility, is likely to lead to the death of the patient within 6 months of starting participation in the study.

Patients fulfilling the entry criteria will have their eligibility assessed by qualified personnel at the host research site with access to/full understanding of their medical history. All patients approached will be given a copy of the participant information sheet (PIS). Usually, this will be sent to the patient in the post, along with an invitation letter, normally in advance of their next clinic assessment. The renal research team may also contact the patient by phone at the time of sending out the PIS. Staff will allow time for potential participants to consider the information provided, discuss the trial with their family and friends, and decide whether to take part. Alternatively, if deemed appropriate by the recruiting renal research team member, the PIS and invitation letter may be provided directly in clinic. Provided the patient feels they have had sufficient time to consider their potential involvement, consent may be sought at this same appointment.

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3 Investigators/delegate(s) will ensure that they adequately explain the aim, trial  
4 intervention, anticipated benefits and potential hazards of taking part in the trial to  
5 the participant. They will also stress that participation is voluntary and that the  
6 participant is free to refuse to take part and may withdraw from the trial at any time.  
7 The participant will be given the opportunity to ask questions. If the participant  
8 expresses an interest in participating in the trial, they will be asked to sign and date  
9 the latest version of the Informed Consent Form.  
10

### 11 **Trial intervention**

12 Participants in the control arm will continue to receive usual care. Participants  
13 randomised to the intervention arm will be asked to commence monthly self-  
14 reporting of their health status using the ePROM system, after receiving a face-to-  
15 face training session.  
16

17  
18 Participants will receive automated reminders prior to each scheduled self-report and  
19 24 hours after a failure to report if necessary, these will be delivered via a secure  
20 myHealth QEHB patient portal email or text message, according to participants'  
21 preferences. Participants may also upload additional ad-hoc reports to the system, if  
22 they feel this is necessary (e.g.: if they wish to communicate a sudden change in  
23 symptoms).  
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26 The ePROM system will provide tailored information to patients in response to each  
27 report (both scheduled and ad-hoc) and alert the clinical team of patient deterioration  
28 according to a *priori* determined alert threshold criteria established in the intervention  
29 development stage. After receiving training during the study setup period, the renal  
30 clinical team will monitor for ePROM alerts and will respond with appropriate clinical  
31 action, in line with standard clinical practice.  
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### 34 **Randomisation**

35 Participants will be randomised at the level of the individual in a 1:1 ratio to either  
36 usual care (control arm) or usual care supplemented with an electronic Patient-  
37 Reported Outcome Measure (ePROM) system (experimental arm). A minimisation  
38 algorithm will be used within the online randomisation system to ensure balance in  
39 the treatment allocation over the following variables:  
40

- 41 • Risk progression (<40%, versus ≥40%, using the 4-variable Tangri renal  
42 risk calculator<sup>24</sup>);
- 43 • Self-reported computer experience (defined as: regular use of a computer  
44 or tablet or smartphone at least weekly versus less than weekly);
- 45 • Ethnicity ('white' versus 'non-white')
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48 A 'random element' will be included in the minimisation algorithm, so that each  
49 patient has a probability (unspecified here), of being randomised to the opposite  
50 treatment that they would have otherwise received.  
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### 53 **Outcome measures and study procedures**

#### 54 *Primary outcome*

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3 The primary aims of the study are to pilot the trial protocol and assess the feasibility  
4 of undertaking a full-scale RCT on the use of ePROMs in the management of  
5 advanced CKD. This will include assessment of both quantitative and qualitative  
6 data. The pilot study will:

- 7 • Test and pilot the trial protocol (including recruitment and retention rates, data  
8 collection processes, data completeness and adherence to the ePROM  
9 intervention);
- 10 • Assess the willingness of clinicians to randomise participants into the trial;
- 11 • Assess the willingness of people with advanced CKD to be randomised into  
12 the trial;
- 13 • Assess the acceptability of the ePROM intervention;
- 14 • Explore the need for a non-web-based intervention platform for participants  
15 who are unable to use the ePROM;
- 16 • Inform selection of the most appropriate primary outcome measure for the full-  
17 scale RCT;
- 18 • Provide data to help estimate the sample size for the full-scale RCT;
- 19 • Provide a platform to develop and pilot the processes to capture costs and  
20 outcomes to inform the health economic evaluation for the full-scale RCT;
- 21 • Determine key participation criteria for centre involvement in the full-scale  
22 RCT.

#### 23 24 25 26 27 *Outcome data*

28 This pilot trial is not powered to detect differences in outcome measures, but it  
29 provides the opportunity to ensure that there are no issues with completion of the  
30 outcome data and proposed outcome measures for the main RCT. The following  
31 outcome data will be collected:

- 32 • HRQL data, using the paper version of the EQ-5D-5L. The EQ-5D-5L is a  
33 reliable/validated generic measure of health status/utility commonly used  
34 internationally in cost-effectiveness research.<sup>26</sup>
- 35 • Clinical data, including: Serum Creatinine, Calcium, Phosphate,  
36 Bicarbonate, Albumin, eGFR, ACR, blood pressure, and for participants  
37 with diabetes: glucose and HbA1c.
- 38 • The following event data: progression to end stage renal disease, contact  
39 with health care professionals in secondary care (outpatient clinics and  
40 Accident and Emergency); inpatient hospitalisation; death.
- 41 • Healthcare resource use data will be collected at each study visit.

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46 All study staff/participants will be invited to complete a trial process questionnaire at  
47 the end of the study, which will evaluate aspects surrounding: data collection  
48 forms/questionnaires; randomisation procedure; acceptability of the intervention;  
49 appropriateness of the frequency of ePROM reporting; alert thresholds and  
50 management.

### *Study procedures*

During the baseline visit, patients will have demographic details recorded including age, self-assigned ethnicity, educational status, residential postcode (to derive Index of Multiple Deprivation), self-reported computer experience and medical history.

Patient quality of life will be assessed using a paper version of the EQ-5D-5L questionnaire (not a routine test). This will be completed by the participant at baseline, and at 3, 6, 9 and 12 months post randomisation (assessment window +/- 3 weeks). This questionnaire may be posted out to participants prior to their scheduled clinic/research visit, but research staff will be on hand in clinic to assist with completion where required. The EQ-5D-5L instrument is a reliable/validated generic measure of health status commonly used in CKD trials research.<sup>26</sup>

Clinical data will be collected at baseline, and at 3, 6, 9 and 12 months (assessment window +/- 3 weeks), including: Serum Creatinine, Calcium, Phosphate, Bicarbonate, Albumin, eGFR, ACR, blood pressure, and for participants with diabetes: glucose and HbA1c. Since these measures are routinely collected for clinical monitoring, the results closest to the calculated visit due date will be used for trial data, rather than repeating tests which have already been performed. If a result is not available within the visit window, the test should be performed at the trial visit. Healthcare resource use will be collected at 3, 6, 9 and 12 months (assessment window +/- 3 weeks).

All data will be extracted from the source records and entered onto a secure database maintained by the Birmingham Clinical Trials Unit (BCTU) after each scheduled follow-up visit. The database will automatically capture ePROM notification data. Between clinic visits, patients will be managed in accordance with local practice.

### **Sample size and justification**

As this is a pilot trial, no formal sample size calculation has been performed. Following recommendations for pilot studies, 30 patients or more are typically required to obtain estimates of the parameters needed for sample size estimation.<sup>27 28</sup> To allow for a 10% drop-out and lost to follow-up rate, this pilot trial will aim to recruit at least 33 participants in each group, a total of 66 participants. This will also allow the recruitment and retention rates to be estimated with 95% confidence interval maximum widths of 20% and 25% respectively.

### **Analysis of Outcome Measures**

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below.

The primary comparison groups will be composed of those randomised to usual care (control group) versus those randomised to usual care supplemented with the ePROM intervention (experimental group). In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of compliance with the allocated treatment or other protocol deviation. The data analysis for this pilot trial

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3 will be descriptive and mainly focus on confidence interval estimation, with no  
4 hypothesis testing performed.  
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6 Data will be explored to assess the key feasibility aspects of undertaking a full-scale  
7 RCT on the use of ePROMs in the management of advanced CKD. Dichotomous  
8 feasibility measures, such as the recruitment and retention rates, as well as data  
9 completeness will be reported as numbers and percentages. Where appropriate,  
10 these values will be summarised across treatment groups.  
11

12 Adherence with the ePROM intervention will be assessed by calculating the number  
13 and percentage of participants who complete the ePROM reports as scheduled. To  
14 be considered adherent, participants will need to have submitted their report within  
15 72 hours of the scheduled time-point. Incomplete submissions (i.e. with some  
16 questions not answered) will be accepted for the purpose of measuring adherence.  
17 Ad-hoc ePROM reports (i.e. those completed outside the scheduled reporting  
18 periods) will not contribute to the assessment of adherence, although we will assess  
19 the number of ePROM reports completed by each participant.  
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22 The pilot data will also help inform the selection of the most appropriate primary  
23 outcome measure for the main RCT and provide data to facilitate estimation of the  
24 sample size required for the main RCT. Outcome data on HRQL and clinical data are  
25 collected at 3, 6, 9 and 12 months post-randomisation. Analysis methods will be  
26 chosen according to the data type of the outcome under investigation, in brief:  
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- 29 • *Continuous endpoints (e.g. quality of life)*: These data will be summarised  
30 using means and standard deviations, with differences in means with 95%  
31 confidence intervals reported. Longitudinal plots of the data over time will also  
32 be constructed for visual presentation of the data.
- 33 • *Categorical (dichotomous) endpoints (e.g. hospitalisation rates)*: The number  
34 of participants and percentages experiencing the event will be summarised  
35 between groups.
- 36 • *Time to Event endpoints (e.g. time to ESRD, mortality)*: The numbers of  
37 participants and percentages experiencing the event will be summarised over  
38 time between groups. Kaplan-Meier survival curves will be constructed for  
39 visual presentation of time-to-event data.  
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#### 42 *Subgroup Analyses*

43 Descriptive reports of subgroup variables will be limited to the same variables used  
44 in the minimisation algorithm. The availability and completeness of data for the  
45 subgroup variables will be summarised to assess their appropriateness as  
46 minimisation variables for the main trial, but no formal analysis will be undertaken.  
47

#### 48 *Missing data and sensitivity analyses*

49 Every attempt will be made to collect full follow-up data on all study participants; it is  
50 thus anticipated that missing data will be minimal. The assessment of missing data is  
51 an outcome measure of this pilot trial. If a suitable primary outcome is identified  
52 during the pilot trial, the level of missing data will form one component of the  
53 assessment of feasibility for a future trial. As this is a pilot trial, no formal sensitivity  
54 analysis will be conducted.  
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### *Planned interim analysis*

As this is a pilot trial, there are no plans for undertaking any interim analyses. However, the Trial Steering Committee (TSC) will have access to recruitment, retention and data collection information.

### *Planned final analyses*

The primary analysis for the trial will occur once all participants have completed the 12 month assessment and corresponding outcome data has been entered onto the trial database, validated as being ready for analysis, and the database locked. This analysis will include data items up to and including the 12 month assessment.

### **Health economics**

In this study, we will develop and pilot methods to capture the costs and outcomes to inform an economic evaluation in the main RCT. This will examine healthcare resource use and outcomes across the two arms of the study.

The primary perspective adopted will be NHS/personal social care; which will focus on healthcare resource use and costs including: renal staff activity in response to ePROM notifications; GP and hospital consultations; in-patient hospitalisation; medications; referrals; and NHS costs associated with maintenance of the ePROM system.

Where possible, data on NHS resource utilisation will be collected from the electronic patient records. Other data will be collected via CRFs, either completed in study follow-up visits or on event-triggered forms (e.g. generated in response to an ePROM alert). Resource use will be valued using appropriate unit costs such as the British National Formulary and the most recent version of Unit Costs of Health and Social Care and NHS Reference Costs.<sup>29</sup>



## Monitoring

### *Management and oversight*

The Trial Management Group will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

A single Trial Steering Committee (TSC) will be convened and will meet at least yearly and as required depending on the needs of the TSC/trial office. The TSC will provide overall oversight of the trial, including the practical aspects of the study, as well as ensuring that the study is run in a way which is both safe for the patients and provides appropriate feasibility data to the sponsor and investigators. The TSC will also undertake the final assessment of feasibility. Given this is a pilot study, a data monitoring committee is not required.

### **Adverse events**

The collection and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research and the requirements of the Health Research Authority (HRA). The Investigator will assess the seriousness and causality (relatedness) of all AEs experienced by the trial participants and this assessment will be documented in the source data, with reference to the protocol.

### **Audit**

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent data clarification forms requesting missing data or clarification of inconsistencies or discrepancies. Sites will be requested to send in copies of signed ICFs and other documentation for in-house review for all participants providing explicit consent.

## Qualitative Sub-study

### *Objective*

To explore patient and study personnel/clinician thoughts/experiences regarding the RePROM trial processes.

### *Methods*

Participants and study personnel/clinicians involved in the pilot trial will be invited to take part in the qualitative sub-study. Up to 40 participants (20 patients and 20 study personnel/clinicians) will be recruited, purposively selected to capture those participants who experienced a range of outcomes and experiences during the trial where possible. However, recruitment will continue until data saturation is reached.

Semi-structured interviews will be conducted by a member of the Centre for Patient Reported Outcome Research (CPROR) research team at the University of Birmingham according to a pre-defined topic guide, but there will be sufficient scope

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3 to explore novel themes where appropriate. All interviews will be digitally recorded,  
4 professionally transcribed and the transcripts anonymised. Transcript data will be  
5 entered into a specialist software package (e.g. Nvivo, QSR International) to aid  
6 organisation and analysis of the data. All data will be analysed by the CI using  
7 conventional content analysis. Formal triangulation of coding and member checking  
8 will be employed to enhance the credibility of the analysis. Only anonymised quotes  
9 will be used in any arising publications or reports.  
10

### 11 12 **ETHICS, CONFIDENTIALITY AND DISSEMINATION**

13 The study has received a favourable opinion from the West Midlands - Edgbaston  
14 Research Ethics Committee (Reference: 18/WM/0013). Personal data recorded on  
15 all documents will be regarded as strictly confidential and will be handled and stored  
16 in accordance with the Data Protection Act 1998. Data transferred from the host site  
17 to the researchers (University of Birmingham) will be securely stored and only used  
18 for analysis or study monitoring relevant to the participant taking part in the research.  
19 The findings from the trial will be used to inform the design of a future, full-scale,  
20 RCT. Results will be submitted for publication in a peer reviewed journal, presented  
21 at scientific conferences and disseminated to the public via lay  
22 summaries/newsletters in partnership with our patient advisory group. Study  
23 manuscripts will be prepared by the Chief Investigator (CI) and authorship will be  
24 determined by the trial publication policy. Intellectual property rights will be  
25 addressed in the Clinical Study Site Agreement between Sponsor and site. The full  
26 protocol is available on request to the corresponding author.  
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30

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32 This study is sponsored by the University of Birmingham (reference: RG\_16-141)  
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34 09-009). Protocol version 1.1, 07/02/2018.  
35

### 36 **PATIENT AND PUBLIC INVOLVEMENT**

37 Development of the research question, outcome measures and study design was informed  
38 by a series of meetings held with the RePROM patient advisory group (PAG), which  
39 included people with lived experience of CKD. The PAG reviewed all patient-facing study  
40 documentation and considered the overall burden of study participation during the design  
41 process.  
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## FOOTNOTES

### Author Contributions

DK is the chief investigator and takes final responsibility for study design, conduct and decision to submit for publication. DK prepared the first draft of the protocol with approval from all authors. PC, HE, MD, GH and SS provided clinical expertise. EB, NI and MV provided trials expertise. JB (statistician) designed and wrote the statistical analysis section. LJ (health economist) advised on the health economic data collection and analysis. All investigators provided advice and critical input on the study design. All authors critically revised the manuscript for its important intellectual content. All authors read and approved the final manuscript.

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### Disclaimer

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The study sponsor and funders have no role in study design, including collection, management, analysis and interpretation of data; writing of the report and the decision to submit the report for publication.

**Competing interests** EB and MV report grants from NIHR. MC receives personal fees from Astellas Pharma and Ferring.

**Patient consent** Not applicable.

**Ethics approval** This protocol (V.1.1) was approved by West Midlands - Edgbaston Research Ethics Committee (Ref: 18/WM/0013) on 23rd February 2018.

### Acknowledgements

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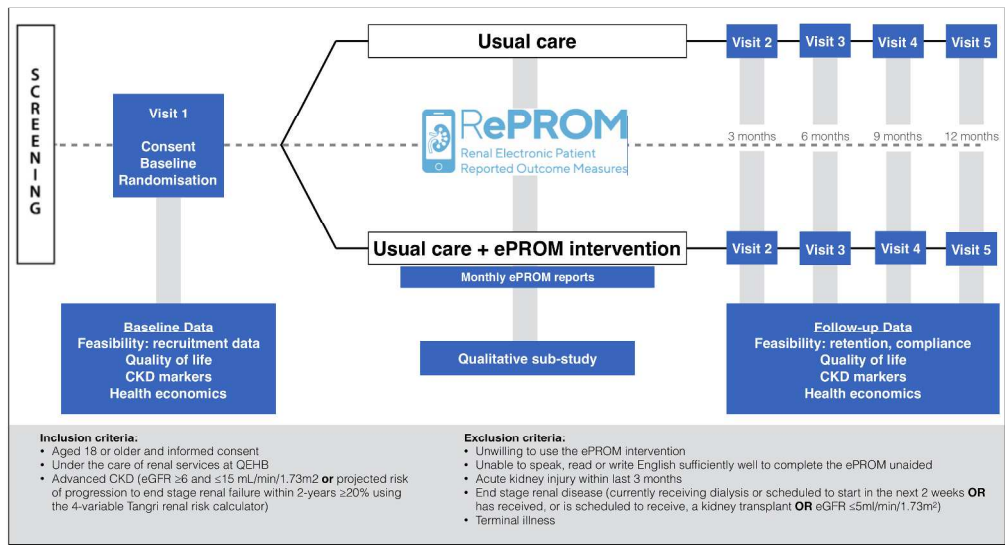


Figure 1. RePROM trial schema.

361x270mm (300 x 300 DPI)

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	See note 1
Protocol version	#3	Date and version identifier	14
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	14

1	sponsor contact			
2	information			
3				
4	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	17
5	responsibilities:		collection, management, analysis, and interpretation of	
6	sponsor and funder		data; writing of the report; and the decision to submit the	
7			report for publication, including whether they will have	
8			ultimate authority over any of these activities	
9				
10				
11				
12	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	12
13	responsibilities:		centre, steering committee, endpoint adjudication	
14	committees		committee, data management team, and other individuals or	
15			groups overseeing the trial, if applicable (see Item 21a for	
16			data monitoring committee)	
17				
18				
19				
20	Background and	#6a	Description of research question and justification for	4
21	rationale		undertaking the trial, including summary of relevant studies	
22			(published and unpublished) examining benefits and harms	
23			for each intervention	
24				
25				
26				
27	Background and	#6b	Explanation for choice of comparators	5
28	rationale: choice of			
29	comparators			
30				
31				
32	Objectives	#7	Specific objectives or hypotheses	9
33				
34				
35	Trial design	#8	Description of trial design including type of trial (eg, parallel	8
36			group, crossover, factorial, single group), allocation ratio,	
37			and framework (eg, superiority, equivalence, non-inferiority,	
38			exploratory)	
39				
40				
41				
42	Study setting	#9	Description of study settings (eg, community clinic,	6
43			academic hospital) and list of countries where data will be	
44			collected. Reference to where list of study sites can be	
45			obtained	
46				
47				
48	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	7
49			eligibility criteria for study centres and individuals who will	
50			perform the interventions (eg, surgeons, psychotherapists)	
51				
52				
53				
54	Interventions:	#11a	Interventions for each group with sufficient detail to allow	8
55	description		replication, including how and when they will be	
56			administered	
57				
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1	Interventions:	#11b	Criteria for discontinuing or modifying allocated	8
2	modifications		interventions for a given trial participant (eg, drug dose	
3			change in response to harms, participant request, or	
4			improving / worsening disease)	
5				
6				
7				
8	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	11
9	adherence		and any procedures for monitoring adherence (eg, drug	
10			tablet return; laboratory tests)	
11				
12				
13	Interventions:	#11d	Relevant concomitant care and interventions that are	n/a
14	concomitant care		permitted or prohibited during the trial	
15				
16				
17	Outcomes	#12	Primary, secondary, and other outcomes, including the	9
18			specific measurement variable (eg, systolic blood pressure),	
19			analysis metric (eg, change from baseline, final value, time	
20			to event), method of aggregation (eg, median, proportion),	
21			and time point for each outcome. Explanation of the clinical	
22			relevance of chosen efficacy and harm outcomes is strongly	
23			recommended	
24				
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27				
28	Participant timeline	#13	Time schedule of enrolment, interventions (including any	6
29			run-ins and washouts), assessments, and visits for	
30			participants. A schematic diagram is highly recommended	
31			(see Figure)	
32				
33				
34				
35	Sample size	#14	Estimated number of participants needed to achieve study	10
36			objectives and how it was determined, including clinical and	
37			statistical assumptions supporting any sample size	
38			calculations	
39				
40				
41				
42	Recruitment	#15	Strategies for achieving adequate participant enrolment to	10
43			reach target sample size	
44				
45				
46	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	8
47	generation		computer-generated random numbers), and list of any	
48			factors for stratification. To reduce predictability of a random	
49			sequence, details of any planned restriction (eg, blocking)	
50			should be provided in a separate document that is	
51			unavailable to those who enrol participants or assign	
52			interventions	
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57	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	8
58	concealment		central telephone; sequentially numbered, opaque, sealed	
59				
60				

1	mechanism		envelopes), describing any steps to conceal the sequence	
2			until interventions are assigned	
3				
4	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	8
5	implementation		participants, and who will assign participants to	
6			interventions	
7				
8				
9	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	6
10			trial participants, care providers, outcome assessors, data	
11			analysts), and how	
12				
13				
14	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	n/a
15	emergency		permissible, and procedure for revealing a participant's	
16	unblinding		allocated intervention during the trial	
17				
18				
19				
20	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	10
21			and other trial data, including any related processes to	
22			promote data quality (eg, duplicate measurements, training	
23			of assessors) and a description of study instruments (eg,	
24			questionnaires, laboratory tests) along with their reliability	
25			and validity, if known. Reference to where data collection	
26			forms can be found, if not in the protocol	
27				
28				
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31	Data collection plan:	#18b	Plans to promote participant retention and complete follow-	10
32	retention		up, including list of any outcome data to be collected for	
33			participants who discontinue or deviate from intervention	
34			protocols	
35				
36				
37				
38	Data management	#19	Plans for data entry, coding, security, and storage, including	10
39			any related processes to promote data quality (eg, double	
40			data entry; range checks for data values). Reference to	
41			where details of data management procedures can be	
42			found, if not in the protocol	
43				
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46	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	10
47			outcomes. Reference to where other details of the statistical	
48			analysis plan can be found, if not in the protocol	
49				
50				
51	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	11
52	analyses		adjusted analyses)	
53				
54				
55	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	11
56	population and		adherence (eg, as randomised analysis), and any statistical	
57	missing data		methods to handle missing data (eg, multiple imputation)	
58				
59				
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1	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	12
2	formal committee		of its role and reporting structure; statement of whether it is	
3			independent from the sponsor and competing interests; and	
4			reference to where further details about its charter can be	
5			found, if not in the protocol. Alternatively, an explanation of	
6			why a DMC is not needed	
7				
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11	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	12
12	interim analysis		including who will have access to these interim results and	
13			make the final decision to terminate the trial	
14				
15				
16	Harms	#22	Plans for collecting, assessing, reporting, and managing	13
17			solicited and spontaneously reported adverse events and	
18			other unintended effects of trial interventions or trial conduct	
19				
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21	Auditing	#23	Frequency and procedures for auditing trial conduct, if any,	13
22			and whether the process will be independent from	
23			investigators and the sponsor	
24				
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27	Research ethics	#24	Plans for seeking research ethics committee / institutional	14
28	approval		review board (REC / IRB) approval	
29				
30				
31	Protocol	#25	Plans for communicating important protocol modifications	14
32	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
33			relevant parties (eg, investigators, REC / IRBs, trial	
34			participants, trial registries, journals, regulators)	
35				
36				
37	Consent or assent	#26a	Who will obtain informed consent or assent from potential	7
38			trial participants or authorised surrogates, and how (see	
39			Item 32)	
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43	Consent or assent:	#26b	Additional consent provisions for collection and use of	n/a
44	ancillary studies		participant data and biological specimens in ancillary	
45			studies, if applicable	
46				
47				
48	Confidentiality	#27	How personal information about potential and enrolled	14
49			participants will be collected, shared, and maintained in	
50			order to protect confidentiality before, during, and after the	
51			trial	
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55	Declaration of	#28	Financial and other competing interests for principal	18
56	interests		investigators for the overall trial and each study site	
57				
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59	Data access	#29	Statement of who will have access to the final trial dataset,	See
60				

		and disclosure of contractual agreements that limit such access for investigators	note 2
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

## Author notes

- <https://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/renal/RePROM/index.aspx>
- Journal System

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# BMJ Open

## The use of an electronic Patient-Reported Outcome Measure in the Management of Patients with Advanced Chronic Kidney Disease. The RePROM Pilot Trial Protocol.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026080.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Sep-2018
Complete List of Authors:	Kyte, Derek; University of Birmingham, Centre for Patient-Reported Outcomes Research, Institute of Applied Health Research Bishop, Jon; NIHR Surgical Reconstruction and Microbiology Research Centre, Medical Statistician Brettell, Elizabeth; 1. Birmingham Clinical Trials Unit (BCTU), Institute of Applied Health Research University of Birmingham, Birmingham, UK Calvert, Melanie; The University of Birmingham, Centre for Patient-Reported Outcomes Research, Institute of Applied Health Research Cockwell, Paul; University Hospitals Birmingham NHS Foundation Trust, Renal Medicine Dutton, Mary; University Hospitals Birmingham NHS Foundation Trust, Renal Medicine Eddington, Helen; University Hospitals Birmingham NHS Foundation Trust, Renal Medicine Hadley, Gabby; University Hospitals Birmingham NHS Foundation Trust, Renal Medicine Ives, Natalie; 1. Birmingham Clinical Trials Unit (BCTU), Institute of Applied Health Research University of Birmingham, Birmingham, UK Jackson, Louise; University of Birmingham, Health Economics Unit Stringer, Stephanie; University Hospitals Birmingham NHS Foundation Trust, Renal Medicine Valente, Marie; 1. Birmingham Clinical Trials Unit (BCTU), Institute of Applied Health Research University of Birmingham, Birmingham, UK
<b>Primary Subject Heading</b>:	Renal medicine
Secondary Subject Heading:	Patient-centred medicine
Keywords:	End stage renal failure < NEPHROLOGY, Chronic renal failure < NEPHROLOGY, patient-reported outcomes, symptom monitoring

SCHOLARONE™  
Manuscripts

**TITLE**

The use of an electronic Patient-Reported Outcome Measure in the Management of Patients with Advanced Chronic Kidney Disease. The RePROM Pilot Trial Protocol.

**AUTHORSHIP**

Derek Kyte<sup>1</sup>, Jon Bishop<sup>2</sup>, Elizabeth Brettell<sup>2</sup>, Melanie Calvert<sup>1</sup>, Paul Cockwell<sup>3</sup>, Mary Dutton<sup>3</sup>, Helen Eddington<sup>3</sup>, Gabby Hadley<sup>3</sup>, Natalie Ives<sup>2</sup>, Louise Jackson<sup>4</sup>, Stephanie Stringer<sup>3</sup>, Marie Valente<sup>2</sup>.

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**WORD COUNT**

3994

**KEYWORDS**

Chronic Kidney Diseases, Patient-reported outcomes, symptom monitoring

## ABSTRACT

### Introduction

Chronic Kidney Disease (CKD) affects up to 16% of adults in the UK. Patient quality of life is particularly reduced in end stage renal disease and is strongly associated with increased hospitalisation and mortality. Thus, accurate and responsive healthcare is a key priority. Electronic Patient-Reported Outcome Measures (ePROMs) are online questionnaires which ask patients to self-rate their health status. Evidence in oncology suggests the use of ePROM data within routine care, alongside clinical information, may enhance symptom management and improve patient outcomes. However, NHS-based ePROM research in CKD is lacking. This pilot trial will assess the feasibility of undertaking a full-scale randomised controlled trial in patients with CKD within the NHS.

### Methods and analysis

The RePROM pilot trial is an investigator-led single-centre, open-label, two-arm randomised controlled pilot trial of 66 participants  $\geq 18$  years with advanced CKD. Participants will be randomised to receive either usual care, or usual care supplemented with an ePROM intervention. Participants within the intervention arm will be asked to submit monthly self-reports of their health status using the ePROM system. The system will provide tailored information to patients in response to each report and notify the clinical team of patient deterioration. The renal clinical team will monitor for ePROM notifications and will respond with appropriate action, in line with standard clinical practice. Measures of study feasibility, participant quality of life and CKD severity will be completed at 3-monthly intervals. Health economic outcomes will be assessed. Clinicians will record treatment decision-making. Acceptability and feasibility of the protocol will be assessed alongside outcome measure and intervention compliance rates. Qualitative process evaluation will be conducted.

### Ethics and dissemination

The findings will inform the design of a full-scale RCT and the results will be submitted for publication in peer-reviewed journals. The study has ethical approval.

### Trial registration number

ISRCTN12669006

## ARTICLE SUMMARY

### Strengths and limitations of this study

- The study uses a randomised controlled trial design, delivered in an NHS setting.
- The research site, University Hospitals Birmingham NHS Foundation Trust, hosts one of the largest specialist renal research sites in Europe.
- The study protocol and intervention was developed by a multidisciplinary team of experts including: patients, health care professionals and academics.
- As a pilot trial, the study is limited to one clinical centre and is not statistically powered to assess clinical outcomes. Instead, the project will evaluate feasibility of conducting a full-scale RCT in the target population.

## INTRODUCTION

Chronic Kidney Disease (CKD) affects up to 16% of adults in the UK<sup>1</sup>, with an annual estimated cost of £1.45 billion.<sup>2</sup> More than half of these costs were associated with Renal Replacement Therapy (RRT) - haemodialysis, peritoneal dialysis and/or kidney transplantation - for patients with end stage renal disease (ESRD).<sup>2</sup> This is despite the fact that patients requiring RRT comprise less than 1% of the total CKD population.<sup>2</sup> Numerous studies have demonstrated that patients with ESRD experience high symptom burden and a very high prevalence of depression.<sup>3</sup> Moreover, patient quality of life is significantly reduced in ESRD and is strongly associated with increased hospitalisation and mortality.<sup>3</sup> Accurate and responsive healthcare for patients as they progress from advanced CKD to ESRD is therefore a key healthcare priority.

Effective management of advanced CKD relies on the timely detection of clinical deterioration towards ESRD. This can be a major challenge between scheduled clinic visits, when it is often difficult to identify clinical deterioration unless a patient self-refers. Unfortunately, some patients self-refer too late because they have difficulty identifying the point at which they may require assistance. Without prompt recognition of advanced symptoms, such patients are at high risk of severe illness, emergency hospitalisation, and associated worse clinical outcomes.<sup>3</sup>

Patient-Reported Outcome Measures (PROMs) are validated questionnaires which ask patients to self-rate their health status. They can provide important information regarding the patient's perspective on the physical, functional and psychological consequences of treatment and the degree and impact of disease symptoms.<sup>4</sup> Evidence suggests the use of PROM data, alongside regular clinical information, within routine care may:

- Aid patient-provider communication and support shared decision-making.<sup>5</sup>
- Improve patient activation and help patients to feel more involved/empowered in decisions around their care.<sup>6-8</sup>
- Improve the accuracy of symptom assessment and enhance symptom management.<sup>9</sup>
- Enhance patient education and self-management and maximise patient safety.<sup>7 10-15</sup>

With recent advances in technology, there has been considerable interest in the use of electronic PROMs (ePROMs) for the routine monitoring of patients with long-term conditions. ePROMs offer patients an 'electronic' method of data entry – e.g. web-based via PC, smartphone, or using tablet devices – and give clinicians a flexible platform with which they may view PROM data.<sup>14 16 17</sup>

ePROMs offer patients the option of inputting data at a time and place, and via a platform, that is convenient to them. ePROM data can be used to help provide patients with tailored advice on self-management and can provide clinicians with detailed HRQL and symptom data both in-clinic and between scheduled appointments via home/remote data capture.<sup>15</sup>

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3 For patients with advanced CKD, this would allow clinicians to monitor for symptom  
4 deterioration, facilitating the early detection of problems requiring attention and  
5 promoting timely intervention from the clinical team (e.g. advice aimed at aiding  
6 patient self-management or escalation of care). Such intervention may delay disease  
7 progression and the need for costly and invasive RRT, and reduce emergency  
8 hospitalisations and other adverse outcomes.  
9

10 A recent randomised controlled trial (RCT) conducted in an oncology setting in the  
11 US, demonstrated that ePROM use is associated with improved HRQL, reduced  
12 Accident and Emergency visits, reduced hospitalisations, and superior quality-  
13 adjusted survival.<sup>15</sup> Both in Canada and Denmark, ePROM collection has been  
14 shown to be feasible in a renal population.<sup>16 18 19</sup> However, NHS-based ePROM  
15 research in CKD, utilising real-time patient and clinician feedback is lacking. Routine  
16 remote use of ePROM data by patients with advanced CKD may aid self-  
17 management, whilst also helping to improve the flow of information between patients  
18 and their clinicians, potentially improving patient safety, enhancing clinical  
19 interactions, optimising patient outcomes and delivering cost savings to the NHS.  
20  
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22 A RCT is needed to evaluate ePROM efficacy in advanced CKD to determine if  
23 health professionals, providers and policy-makers should implement routine ePROM  
24 collection in renal practice. However, before a definitive trial is undertaken, a pilot  
25 trial is required to assess the feasibility of undertaking such a study and to help  
26 inform the key elements (e.g. appropriate outcome measure, sample size) of the  
27 design for the full-scale RCT.  
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## METHODS

### Design

The RePROM study will span two phases: stage 1 involves development of the ePROM intervention with patient and clinician input; stage 2 is a pilot/feasibility RCT with a qualitative sub-study.

### Setting

Patients under the care of the renal services at Queen Elizabeth Hospital, Birmingham (QEHB) will be recruited for this study.

### Stage 1: Intervention development

Design of the ePROM system will be finalised during a series of operational meetings, held in stage 1 of the study, with regular input from: (1) the QEHB renal clinical and research team; (2) the RePROM Patient Advisory Group; (3) the QEHB IT and Informatics group; (4) the University of Birmingham Clinical Trials Unit; and (5) the Patients Outcomes Group at the University of Leeds.

The ePROM system will be made available to study participants via 'myHealth@QEHB', a secure patient portal linked to the patient's electronic healthcare record (EHR), delivered by the host site. The system will be developed to allow patients to self-report their health status using a variety of electronic platforms, e.g.: PC, smartphone or tablet.

The ePROM system will be designed to: (i) provide appropriate self-management advice to participants whose questionnaire scores suggest mild/moderate symptoms; and (ii) notify the clinical team of patient deterioration via an automated email, where the patient's questionnaire responses indicate severe symptoms/cause for concern.

Patients' longitudinal ePROM scores will be made available to clinicians for use during routine outpatient consultations via the EHR. The RePROM Patient Advisory Group felt this approach would help to focus clinical discussion on patient-centred issues and may enhance symptom management, a view supported by related literature.<sup>7 8 16 17 20-22</sup>

### Stage 2: pilot/feasibility RCT and qualitative sub-study

#### Trial design

The RePROM pilot trial is an investigator led single-centre, open-label, two-arm randomised controlled pilot trial of 66 participants aged 18 years or over with advanced CKD. Participants will be randomised to receive either usual care, or usual care supplemented with an ePROM intervention. The trial is registered with ISRCTN (ISRCTN12669006) and the NIHR Portfolio (CPMS ID: 36497). The study flow is outlined in Figure 1.

### Figure 1. RePROM trial schema.

## Recruitment and eligibility

Recruitment is scheduled to commence in July 2018. Patients will be invited to participate based on the following eligibility criteria:

### Inclusion Criteria

- Aged  $\geq 18$  years old;
  - Ability to provide fully informed written consent for participation in the study;
  - Patients under the care of the renal services at QEHB;
  - Patients meeting the trial definition of **advanced CKD**:
    - an eGFR  $\geq 6$  and  $\leq 15$  mL/min/1.73m<sup>2</sup> (inclusive)
- OR**
- a projected risk of progression to end-stage renal failure within 2-years  $\geq 20\%$  using the 4-variable Tangri renal risk calculator.<sup>23</sup>

### Exclusion Criteria

- Patients unwilling to use the ePROM intervention;
  - Patients who, in the opinion of the consenting professional, cannot speak, read or write English sufficiently well to complete the ePROM unaided;
  - An episode of **acute kidney injury** (defined in accordance with national guidelines) within the last 3 months<sup>24</sup>;
  - Patients meeting the trial definition of **End Stage Renal Disease**:
    - Currently receiving dialysis or scheduled to start in the next 2 weeks
- OR**
- Has received (or has a scheduled date to receive) a kidney transplant
- OR**
- eGFR  $\leq 5$  mL/min/1.73m<sup>2</sup>;
- A terminal illness that, in the opinion of the consultant assessing eligibility, is likely to lead to the death of the patient within 6 months of starting participation in the study.

Patients fulfilling the entry criteria will have their eligibility assessed by qualified personnel at the host research site with access to/full understanding of their medical history. All patients approached will be given a copy of the participant information sheet (PIS). Usually, this will be sent to the patient in the post, along with an invitation letter, normally in advance of their next clinic assessment. The renal research team may also contact the patient by phone at the time of sending out the PIS. Staff will allow time for potential participants to consider the information provided, discuss the trial with their family and friends, and decide whether to take part. Alternatively, if deemed appropriate by the recruiting renal research team member, the PIS and invitation letter may be provided directly in clinic. Provided the patient feels they have had sufficient time to consider their potential involvement, consent may be sought at this same appointment.

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3 Investigators/delegate(s) will ensure that they adequately explain the aim, trial  
4 intervention, anticipated benefits and potential hazards of taking part in the trial to  
5 the participant. They will also stress that participation is voluntary and that the  
6 participant is free to refuse to take part and may withdraw from the trial at any time.  
7 The participant will be given the opportunity to ask questions. If the participant  
8 expresses an interest in participating in the trial, they will be asked to sign and date  
9 the latest version of the Informed Consent Form.  
10

### 11 **Trial intervention**

12 Participants in the control arm will continue to receive usual care. Participants  
13 randomised to the intervention arm will be asked to commence monthly self-  
14 reporting of their health status using the ePROM system, after receiving a face-to-  
15 face training session.  
16

17  
18 Participants will receive automated reminders prior to each scheduled self-report and  
19 24 hours after a failure to report if necessary, these will be delivered via a secure  
20 myHealth QEHB patient portal email or text message, according to participants'  
21 preferences. Participants may also upload additional ad-hoc reports to the system, if  
22 they feel this is necessary (e.g.: if they wish to communicate a sudden change in  
23 symptoms).  
24

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26 The ePROM system will provide tailored information to patients in response to each  
27 report (both scheduled and ad-hoc) and alert the clinical team of patient deterioration  
28 according to a *priori* determined alert threshold criteria established in the intervention  
29 development stage. After receiving training during the study setup period, the renal  
30 clinical team will monitor for ePROM alerts and will respond with appropriate clinical  
31 action, in line with standard clinical practice.  
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### 34 **Randomisation**

35 Participants will be randomised at the level of the individual in a 1:1 ratio to either  
36 usual care (control arm) or usual care supplemented with an electronic Patient-  
37 Reported Outcome Measure (ePROM) system (experimental arm). A minimisation  
38 algorithm will be used within the online randomisation system to ensure balance in  
39 the treatment allocation over the following variables:  
40

- 41 • Risk progression (<40%, versus ≥40%, using the 4-variable Tangri renal  
42 risk calculator<sup>23</sup>);
- 43 • Self-reported computer experience (defined as: regular use of a computer  
44 or tablet or smartphone at least weekly versus less than weekly);
- 45 • Ethnicity ('white' versus 'non-white')
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48 A 'random element' will be included in the minimisation algorithm, so that each  
49 patient has a probability (unspecified here), of being randomised to the opposite  
50 treatment that they would have otherwise received.  
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### 53 **Outcome measures and study procedures**

#### 54 *Primary outcome*

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3 The primary aims of the study are to pilot the trial protocol and assess the feasibility  
4 of undertaking a full-scale RCT on the use of ePROMs in the management of  
5 advanced CKD. This will include assessment of both quantitative and qualitative  
6 data. The pilot study will:

- 7 • Test and pilot the trial protocol (including recruitment and retention rates, data  
8 collection processes, data completeness and adherence to the ePROM  
9 intervention);
- 10 • Assess the willingness of clinicians to randomise participants into the trial;
- 11 • Assess the willingness of people with advanced CKD to be randomised into  
12 the trial;
- 13 • Assess the acceptability of the ePROM intervention;
- 14 • Explore the need for a non-web-based intervention platform for participants  
15 who are unable to use the ePROM;
- 16 • Inform selection of the most appropriate primary outcome measure for the full-  
17 scale RCT;
- 18 • Provide data to help estimate the sample size for the full-scale RCT;
- 19 • Provide a platform to develop and pilot the processes to capture costs and  
20 outcomes to inform the health economic evaluation for the full-scale RCT;
- 21 • Determine key participation criteria for centre involvement in the full-scale  
22 RCT.

#### 23 24 25 26 27 *Outcome data*

28 This pilot trial is not powered to detect differences in outcome measures, but it  
29 provides the opportunity to ensure that there are no issues with completion of the  
30 outcome data and proposed outcome measures for the main RCT. The following  
31 outcome data will be collected:

- 32 • HRQL data, using the paper version of the EQ-5D-5L. The EQ-5D-5L is a  
33 reliable/validated generic measure of health status/utility commonly used  
34 internationally in cost-effectiveness research.<sup>25</sup>
- 35 • Clinical data, including: Serum Creatinine, Calcium, Phosphate,  
36 Bicarbonate, Albumin, eGFR, ACR, blood pressure, and for participants  
37 with diabetes: glucose and HbA1c.
- 38 • The following event data: progression to end stage renal disease, contact  
39 with health care professionals in secondary care (outpatient clinics and  
40 Accident and Emergency); inpatient hospitalisation; death.
- 41 • Healthcare resource use data will be collected at each study visit.

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46 All study staff/participants will be invited to complete a trial process questionnaire at  
47 the end of the study, which will evaluate aspects surrounding: data collection  
48 forms/questionnaires; randomisation procedure; acceptability of the intervention;  
49 appropriateness of the frequency of ePROM reporting; alert thresholds and  
50 management.

### *Study procedures*

During the baseline visit, patients will have demographic details recorded including age, self-assigned ethnicity, educational status, residential postcode (to derive Index of Multiple Deprivation), self-reported computer experience and medical history.

Patient quality of life will be assessed using a paper version of the EQ-5D-5L questionnaire (not a routine test). This will be completed by the participant at baseline, and at 3, 6, 9 and 12 months post randomisation (assessment window +/- 3 weeks). This questionnaire may be posted out to participants prior to their scheduled clinic/research visit, but research staff will be on hand in clinic to assist with completion where required. The EQ-5D-5L instrument is a reliable/validated generic measure of health status commonly used in CKD trials research.<sup>25</sup>

Clinical data will be collected at baseline, and at 3, 6, 9 and 12 months (assessment window +/- 3 weeks), including: Serum Creatinine, Calcium, Phosphate, Bicarbonate, Albumin, eGFR, ACR, blood pressure, and for participants with diabetes: glucose and HbA1c. Since these measures are routinely collected for clinical monitoring, the results closest to the calculated visit due date will be used for trial data, rather than repeating tests which have already been performed. If a result is not available within the visit window, the test should be performed at the trial visit. Healthcare resource use will be collected at 3, 6, 9 and 12 months (assessment window +/- 3 weeks).

All data will be extracted from the source records and entered onto a secure database maintained by the Birmingham Clinical Trials Unit (BCTU) after each scheduled follow-up visit. The database will automatically capture ePROM notification data. Between clinic visits, patients will be managed in accordance with local practice.

### **Sample size and justification**

As this is a pilot trial, no formal sample size calculation has been performed. Following recommendations for pilot studies, 30 patients or more are typically required to obtain estimates of the parameters needed for sample size estimation.<sup>26 27</sup> To allow for a 10% drop-out and lost to follow-up rate, this pilot trial will aim to recruit at least 33 participants in each group, a total of 66 participants. This will also allow the recruitment and retention rates to be estimated with 95% confidence interval maximum widths of 20% and 25% respectively.

### **Analysis of Outcome Measures**

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below.

The primary comparison groups will be composed of those randomised to usual care (control group) versus those randomised to usual care supplemented with the ePROM intervention (experimental group). In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of compliance with the allocated treatment or other protocol deviation. The data analysis for this pilot trial

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3 will be descriptive and mainly focus on confidence interval estimation, with no  
4 hypothesis testing performed.  
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6 Data will be explored to assess the key feasibility aspects of undertaking a full-scale  
7 RCT on the use of ePROMs in the management of advanced CKD. Dichotomous  
8 feasibility measures, such as the recruitment and retention rates, as well as data  
9 completeness will be reported as numbers and percentages. Where appropriate,  
10 these values will be summarised across treatment groups.  
11

12 Adherence with the ePROM intervention will be assessed by calculating the number  
13 and percentage of participants who complete the ePROM reports as scheduled. To  
14 be considered adherent, participants will need to have submitted their report within  
15 72 hours of the scheduled time-point. Incomplete submissions (i.e. with some  
16 questions not answered) will be accepted for the purpose of measuring adherence.  
17 Ad-hoc ePROM reports (i.e. those completed outside the scheduled reporting  
18 periods) will not contribute to the assessment of adherence, although we will assess  
19 the number of ePROM reports completed by each participant.  
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22 The pilot data will also help inform the selection of the most appropriate primary  
23 outcome measure for the main RCT and provide data to facilitate estimation of the  
24 sample size required for the main RCT. Outcome data on HRQL and clinical data are  
25 collected at 3, 6, 9 and 12 months post-randomisation. Analysis methods will be  
26 chosen according to the data type of the outcome under investigation, in brief:  
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- 29 • *Continuous endpoints (e.g. quality of life)*: These data will be summarised  
30 using means and standard deviations, with differences in means with 95%  
31 confidence intervals reported. Longitudinal plots of the data over time will also  
32 be constructed for visual presentation of the data.
- 33 • *Categorical (dichotomous) endpoints (e.g. hospitalisation rates)*: The number  
34 of participants and percentages experiencing the event will be summarised  
35 between groups.
- 36 • *Time to Event endpoints (e.g. time to ESRD, mortality)*: The numbers of  
37 participants and percentages experiencing the event will be summarised over  
38 time between groups. Kaplan-Meier survival curves will be constructed for  
39 visual presentation of time-to-event data.  
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#### 42 *Subgroup Analyses*

43 Descriptive reports of subgroup variables will be limited to the same variables used  
44 in the minimisation algorithm. The availability and completeness of data for the  
45 subgroup variables will be summarised to assess their appropriateness as  
46 minimisation variables for the main trial, but no formal analysis will be undertaken.  
47

#### 48 *Missing data and sensitivity analyses*

49 Every attempt will be made to collect full follow-up data on all study participants; it is  
50 thus anticipated that missing data will be minimal. The assessment of missing data is  
51 an outcome measure of this pilot trial. If a suitable primary outcome is identified  
52 during the pilot trial, the level of missing data will form one component of the  
53 assessment of feasibility for a future trial. As this is a pilot trial, no formal sensitivity  
54 analysis will be conducted.  
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### *Planned interim analysis*

As this is a pilot trial, there are no plans for undertaking any interim analyses. However, the Trial Steering Committee (TSC) will have access to recruitment, retention and data collection information.

### *Planned final analyses*

The primary analysis for the trial will occur once all participants have completed the 12 month assessment and corresponding outcome data has been entered onto the trial database, validated as being ready for analysis, and the database locked. This analysis will include data items up to and including the 12 month assessment.

### **Health economics**

In this study, we will develop and pilot methods to capture the costs and outcomes to inform an economic evaluation in the main RCT. This will examine healthcare resource use and outcomes across the two arms of the study.

The primary perspective adopted will be NHS/personal social care; which will focus on healthcare resource use and costs including: renal staff activity in response to ePROM notifications; GP and hospital consultations; in-patient hospitalisation; medications; referrals; and NHS costs associated with maintenance of the ePROM system.

Where possible, data on NHS resource utilisation will be collected from the electronic patient records. Other data will be collected via CRFs, either completed in study follow-up visits or on event-triggered forms (e.g. generated in response to an ePROM alert). Resource use will be valued using appropriate unit costs such as the British National Formulary and the most recent version of Unit Costs of Health and Social Care and NHS Reference Costs.<sup>28</sup>

## Monitoring

### *Management and oversight*

The Trial Management Group will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

A single Trial Steering Committee (TSC) will be convened and will meet at least yearly and as required depending on the needs of the TSC/trial office. The TSC will provide overall oversight of the trial, including the practical aspects of the study, as well as ensuring that the study is run in a way which is both safe for the patients and provides appropriate feasibility data to the sponsor and investigators. The TSC will also undertake the final assessment of feasibility. Given this is a pilot study, a data monitoring committee is not required.

### **Adverse events**

The collection and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research and the requirements of the Health Research Authority (HRA). The Investigator will assess the seriousness and causality (relatedness) of all AEs experienced by the trial participants and this assessment will be documented in the source data, with reference to the protocol.

### **Audit**

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent data clarification forms requesting missing data or clarification of inconsistencies or discrepancies. Sites will be requested to send in copies of signed ICFs and other documentation for in-house review for all participants providing explicit consent.

## Qualitative Sub-study

### *Objective*

To explore patient and study personnel/clinician thoughts/experiences regarding the RePROM trial processes.

### *Methods*

Participants and study personnel/clinicians involved in the pilot trial will be invited to take part in the qualitative sub-study. Up to 40 participants (20 patients and 20 study personnel/clinicians) will be recruited, purposively selected to capture those participants who experienced a range of outcomes and experiences during the trial where possible. However, recruitment will continue until data saturation is reached.

Semi-structured interviews will be conducted by a member of the Centre for Patient Reported Outcome Research (CPROR) research team at the University of Birmingham according to a pre-defined topic guide, but there will be sufficient scope



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3 to explore novel themes where appropriate. All interviews will be digitally recorded,  
4 professionally transcribed and the transcripts anonymised. Transcript data will be  
5 entered into a specialist software package (e.g. Nvivo, QSR International) to aid  
6 organisation and analysis of the data. All data will be analysed by the CI using  
7 conventional content analysis. Formal triangulation of coding and member checking  
8 will be employed to enhance the credibility of the analysis. Only anonymised quotes  
9 will be used in any arising publications or reports.  
10

### 11 12 **ETHICS, CONFIDENTIALITY AND DISSEMINATION**

13 The study has received a favourable opinion from the West Midlands - Edgbaston  
14 Research Ethics Committee (Reference: 18/WM/0013). Personal data recorded on  
15 all documents will be regarded as strictly confidential and will be handled and stored  
16 in accordance with the Data Protection Act 1998. Data transferred from the host site  
17 to the researchers (University of Birmingham) will be securely stored and only used  
18 for analysis or study monitoring relevant to the participant taking part in the research.  
19 The findings from the trial will be used to inform the design of a future, full-scale,  
20 RCT. Results will be submitted for publication in a peer reviewed journal, presented  
21 at scientific conferences and disseminated to the public via lay  
22 summaries/newsletters in partnership with our patient advisory group. Study  
23 manuscripts will be prepared by the Chief Investigator (CI) and authorship will be  
24 determined by the trial publication policy. Intellectual property rights will be  
25 addressed in the Clinical Study Site Agreement between Sponsor and site. The full  
26 protocol is available on request to the corresponding author.  
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32 This study is sponsored by the University of Birmingham (reference: RG\_16-141)  
33 and funded by the UK National Institute for Health Research (reference: PDF-2016-  
34 09-009). Protocol version 1.1, 07/02/2018.  
35

### 36 **PATIENT AND PUBLIC INVOLVEMENT**

37 Development of the research question, outcome measures and study design was informed  
38 by a series of meetings held with the RePROM patient advisory group (PAG), which  
39 included people with lived experience of CKD. The PAG reviewed all patient-facing study  
40 documentation and considered the overall burden of study participation during the design  
41 process.  
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## FOOTNOTES

### Author Contributions

DK is the chief investigator and takes final responsibility for study design, conduct and decision to submit for publication. DK prepared the first draft of the protocol with approval from all authors. PC, HE, MD, GH and SS provided clinical expertise. EB, NI and MV provided trials expertise. MC provided expertise surrounding PROM trial methodology. JB (statistician) designed and wrote the statistical analysis section. LJ (health economist) advised on the health economic data collection and analysis. All investigators provided advice and critical input on the study design. All authors critically revised the manuscript for its important intellectual content. All authors read and approved the final manuscript.

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### Disclaimer

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The study sponsor and funders have no role in study design, including collection, management, analysis and interpretation of data; writing of the report and the decision to submit the report for publication.

**Competing interests** EB and MV report grants from NIHR. MC receives personal fees from Astellas Pharma and Ferring.

**Patient consent** Not applicable.

**Ethics approval** This protocol (V.1.1) was approved by West Midlands - Edgbaston Research Ethics Committee (Ref: 18/WM/0013) on 23rd February 2018.

### Acknowledgements

The authors acknowledge Anita Walker for her administrative support and the RePROM patient advisory group for their input into the design of the study.

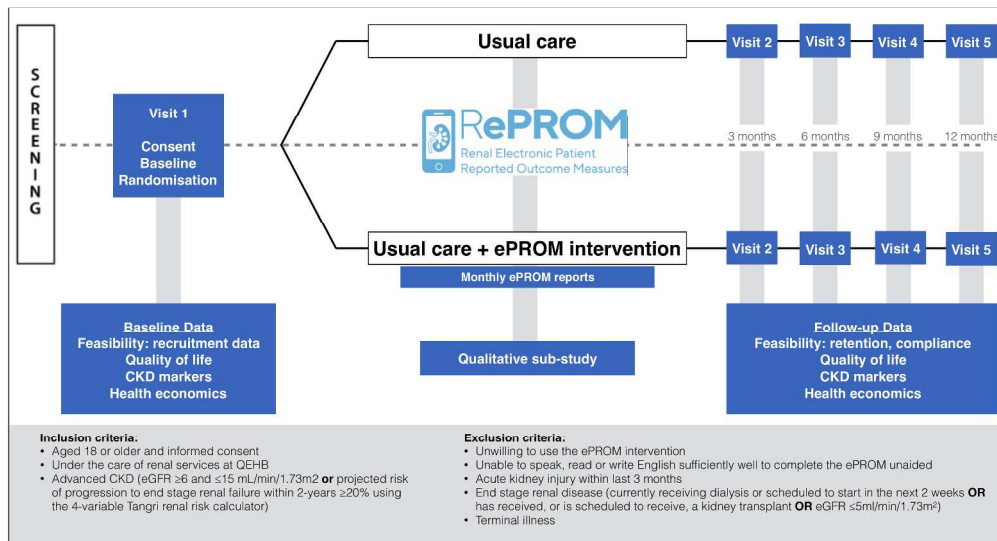


Figure 1. RePROM trial schema.

361x270mm (300 x 300 DPI)

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	See note 1
Protocol version	#3	Date and version identifier	14
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	14



1	sponsor contact			
2	information			
3				
4	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	17
5	responsibilities:		collection, management, analysis, and interpretation of	
6	sponsor and funder		data; writing of the report; and the decision to submit the	
7			report for publication, including whether they will have	
8			ultimate authority over any of these activities	
9				
10				
11				
12	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	12
13	responsibilities:		centre, steering committee, endpoint adjudication	
14	committees		committee, data management team, and other individuals or	
15			groups overseeing the trial, if applicable (see Item 21a for	
16			data monitoring committee)	
17				
18				
19				
20	Background and	#6a	Description of research question and justification for	4
21	rationale		undertaking the trial, including summary of relevant studies	
22			(published and unpublished) examining benefits and harms	
23			for each intervention	
24				
25				
26				
27	Background and	#6b	Explanation for choice of comparators	5
28	rationale: choice of			
29	comparators			
30				
31				
32	Objectives	#7	Specific objectives or hypotheses	9
33				
34				
35	Trial design	#8	Description of trial design including type of trial (eg, parallel	8
36			group, crossover, factorial, single group), allocation ratio,	
37			and framework (eg, superiority, equivalence, non-inferiority,	
38			exploratory)	
39				
40				
41				
42	Study setting	#9	Description of study settings (eg, community clinic,	6
43			academic hospital) and list of countries where data will be	
44			collected. Reference to where list of study sites can be	
45			obtained	
46				
47				
48	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	7
49			eligibility criteria for study centres and individuals who will	
50			perform the interventions (eg, surgeons, psychotherapists)	
51				
52				
53				
54	Interventions:	#11a	Interventions for each group with sufficient detail to allow	8
55	description		replication, including how and when they will be	
56			administered	
57				
58				
59				
60				



1	Interventions:	#11b	Criteria for discontinuing or modifying allocated	8
2	modifications		interventions for a given trial participant (eg, drug dose	
3			change in response to harms, participant request, or	
4			improving / worsening disease)	
5				
6				
7				
8	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	11
9	adherence		and any procedures for monitoring adherence (eg, drug	
10			tablet return; laboratory tests)	
11				
12				
13	Interventions:	#11d	Relevant concomitant care and interventions that are	n/a
14	concomitant care		permitted or prohibited during the trial	
15				
16				
17	Outcomes	#12	Primary, secondary, and other outcomes, including the	9
18			specific measurement variable (eg, systolic blood pressure),	
19			analysis metric (eg, change from baseline, final value, time	
20			to event), method of aggregation (eg, median, proportion),	
21			and time point for each outcome. Explanation of the clinical	
22			relevance of chosen efficacy and harm outcomes is strongly	
23			recommended	
24				
25				
26				
27				
28	Participant timeline	#13	Time schedule of enrolment, interventions (including any	6
29			run-ins and washouts), assessments, and visits for	
30			participants. A schematic diagram is highly recommended	
31			(see Figure)	
32				
33				
34				
35	Sample size	#14	Estimated number of participants needed to achieve study	10
36			objectives and how it was determined, including clinical and	
37			statistical assumptions supporting any sample size	
38			calculations	
39				
40				
41				
42	Recruitment	#15	Strategies for achieving adequate participant enrolment to	10
43			reach target sample size	
44				
45				
46	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	8
47	generation		computer-generated random numbers), and list of any	
48			factors for stratification. To reduce predictability of a random	
49			sequence, details of any planned restriction (eg, blocking)	
50			should be provided in a separate document that is	
51			unavailable to those who enrol participants or assign	
52			interventions	
53				
54				
55				
56				
57	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	8
58	concealment		central telephone; sequentially numbered, opaque, sealed	
59				
60				

1	mechanism		envelopes), describing any steps to conceal the sequence	
2			until interventions are assigned	
3				
4	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	8
5	implementation		participants, and who will assign participants to	
6			interventions	
7				
8				
9	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	6
10			trial participants, care providers, outcome assessors, data	
11			analysts), and how	
12				
13				
14	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	n/a
15	emergency		permissible, and procedure for revealing a participant's	
16	unblinding		allocated intervention during the trial	
17				
18				
19				
20	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	10
21			and other trial data, including any related processes to	
22			promote data quality (eg, duplicate measurements, training	
23			of assessors) and a description of study instruments (eg,	
24			questionnaires, laboratory tests) along with their reliability	
25			and validity, if known. Reference to where data collection	
26			forms can be found, if not in the protocol	
27				
28				
29				
30				
31	Data collection plan:	#18b	Plans to promote participant retention and complete follow-	10
32	retention		up, including list of any outcome data to be collected for	
33			participants who discontinue or deviate from intervention	
34			protocols	
35				
36				
37				
38	Data management	#19	Plans for data entry, coding, security, and storage, including	10
39			any related processes to promote data quality (eg, double	
40			data entry; range checks for data values). Reference to	
41			where details of data management procedures can be	
42			found, if not in the protocol	
43				
44				
45				
46	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	10
47			outcomes. Reference to where other details of the statistical	
48			analysis plan can be found, if not in the protocol	
49				
50				
51	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	11
52	analyses		adjusted analyses)	
53				
54				
55	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	11
56	population and		adherence (eg, as randomised analysis), and any statistical	
57	missing data		methods to handle missing data (eg, multiple imputation)	
58				
59				
60				

1	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	12
2	formal committee		of its role and reporting structure; statement of whether it is	
3			independent from the sponsor and competing interests; and	
4			reference to where further details about its charter can be	
5			found, if not in the protocol. Alternatively, an explanation of	
6			why a DMC is not needed	
7				
8				
9				
10				
11	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	12
12	interim analysis		including who will have access to these interim results and	
13			make the final decision to terminate the trial	
14				
15				
16	Harms	#22	Plans for collecting, assessing, reporting, and managing	13
17			solicited and spontaneously reported adverse events and	
18			other unintended effects of trial interventions or trial conduct	
19				
20				
21	Auditing	#23	Frequency and procedures for auditing trial conduct, if any,	13
22			and whether the process will be independent from	
23			investigators and the sponsor	
24				
25				
26				
27	Research ethics	#24	Plans for seeking research ethics committee / institutional	14
28	approval		review board (REC / IRB) approval	
29				
30				
31	Protocol	#25	Plans for communicating important protocol modifications	14
32	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
33			relevant parties (eg, investigators, REC / IRBs, trial	
34			participants, trial registries, journals, regulators)	
35				
36				
37	Consent or assent	#26a	Who will obtain informed consent or assent from potential	7
38			trial participants or authorised surrogates, and how (see	
39			Item 32)	
40				
41				
42				
43	Consent or assent:	#26b	Additional consent provisions for collection and use of	n/a
44	ancillary studies		participant data and biological specimens in ancillary	
45			studies, if applicable	
46				
47				
48	Confidentiality	#27	How personal information about potential and enrolled	14
49			participants will be collected, shared, and maintained in	
50			order to protect confidentiality before, during, and after the	
51			trial	
52				
53				
54				
55	Declaration of	#28	Financial and other competing interests for principal	18
56	interests		investigators for the overall trial and each study site	
57				
58				
59	Data access	#29	Statement of who will have access to the final trial dataset,	See
60				

		and disclosure of contractual agreements that limit such access for investigators	note 2
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

## Author notes

- <https://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/renal/RePROM/index.aspx>
- Journal System

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