



## TRIAL PROTOCOL

# RePROM

*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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## PROTOCOL DEVELOPMENT

Protocol Amendments				
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Trial website	<a href="http://www.birmingham.ac.uk/RePROM">www.birmingham.ac.uk/RePROM</a>
Trial social media	<TBC>

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## ABBREVIATIONS

Abbreviation	Term
A&E	Accident and Emergency
ACR	Albumin:creatinine ratio
AE	Adverse Event
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
BCTU	Birmingham Clinical Trials Unit
CI	Chief Investigator
CKD	Chronic Kidney Disease
CPROR	Centre for Patient Reported Outcome Research
CRF	Case Report Form
CRN	Clinical Research Network
eGFR	Estimated Glomerular Filtration Rate
ePROM	Electronic Patient Reported Outcome Measure
EQ-5D-5L	EuroQoL-5 Domain-5 level
ERA-EDTA	European Renal Association - European Dialysis and Transplant Association
ESRD	End Stage Renal Disease
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HbA1c	A1c form of haemoglobin
HRQL	Health Related Quality of Life
ICF	Informed Consent Form
IPOS-R	Integrated Palliative care Outcome Scale - Renal
ISF	Investigator Site File
NIHR	National Institute for Health Research
KDQOL-36	Kidney Disease Quality of Life - 36 questionnaire
NHS	National Health Service
PI	Principal Investigator
PIS	Participant Information Sheet
POL	Policy



<b>POS</b>	Palliative care Outcome Scale
<b>PPI</b>	Public and Patient Involvement
<b>PROM</b>	Patient Reported Outcome Measure
<b>QCD</b>	Quality Control Documents
<b>AMS</b>	Quality Management System
<b>QEHB</b>	Queen Elizabeth Hospital Birmingham
<b>RCT</b>	Randomised Controlled Trial
<b>REC</b>	Research Ethics Committee
<b>RGT</b>	Research Governance Team
<b>RRT</b>	Renal Replacement Therapy
<b>SAE</b>	Serious Adverse Event
<b>sCr</b>	Serum Creatinine
<b>SF-12</b>	Short form-12 questionnaire
<b>SOP</b>	Standard Operating Procedure
<b>UoB</b>	University of Birmingham

## DEFINITIONS

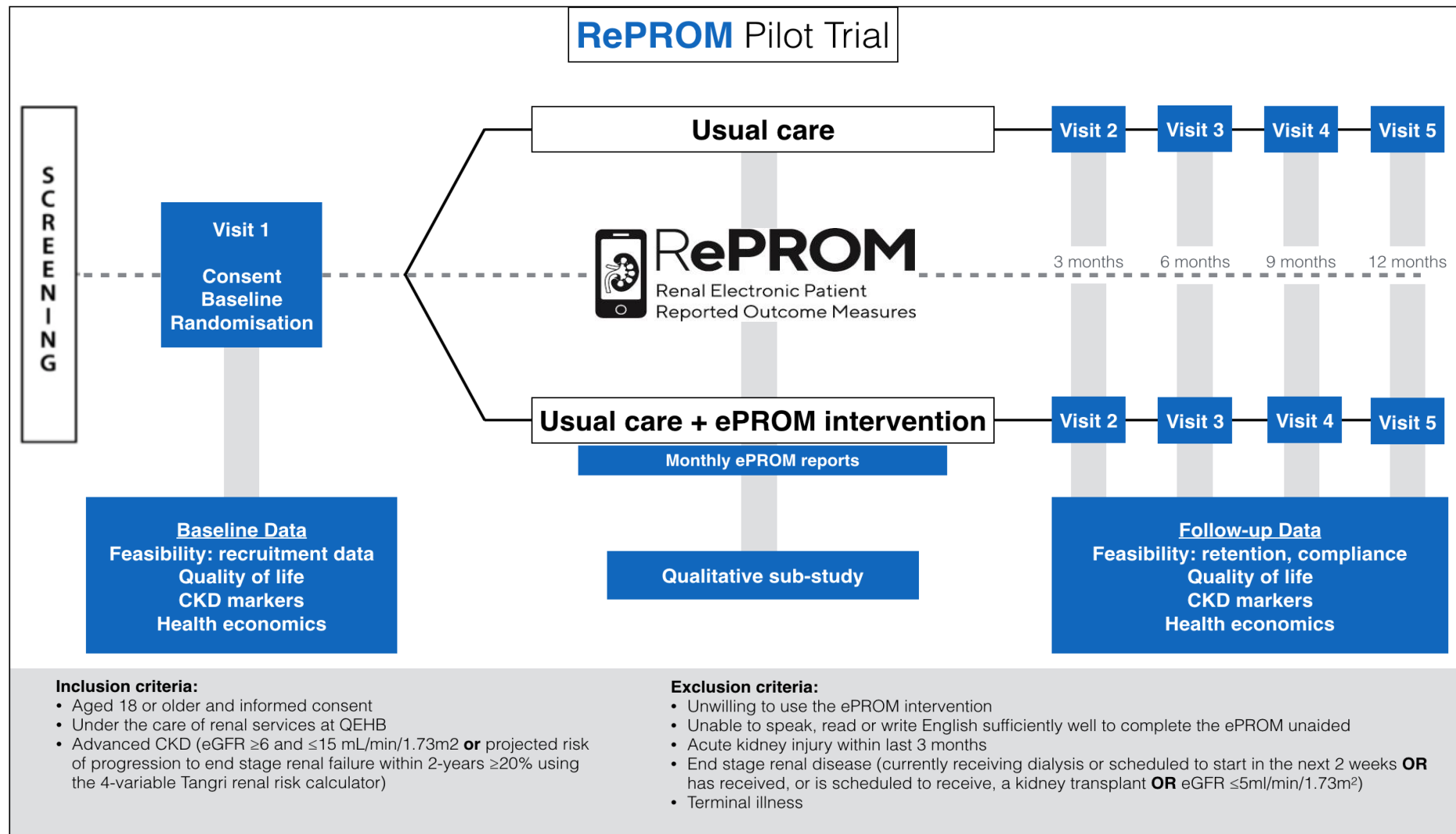
Term	Abbreviation	Description
<b>Policies</b>	POL	Policies are developed to describe the approach of the University of Birmingham (UoB) on areas that are heavily regulated. Policies may also be developed when there is ambiguity in how regulatory requirements should be implemented in the QMS or when procedures to be captured in the QMS address areas controversial within the UoB at the time of implementation. Policies explain why the UoB has its procedures, especially when they seem to deviate from the regulatory requirements. Policies should be read in conjunction with the relevant SOP. Policies that are not part of a Quality Manual are coded up as 'POL'.
<b>Quality Control Documents</b>	QCD	Quality Control Documents can be instructions, forms, templates or checklists. They are developed to share best practices, promote standardisation to guarantee quality standards are maintained and reduce resources otherwise needed to develop similar documents. Unless indicated otherwise in the relevant SOP, QCDs are not mandatory and are designed to be an optional aid to UoB staff.
<b>Quality Management System</b>	QMS	A Quality Management System (QMS) is a system that includes procedures and policies to describe how certain tasks should be performed and that encapsulate any standards and/or regulatory requirements that may apply to those tasks. By adhering to the

		Quality Management System, the user and the UoB will be assured that applicable regulations are adhered to.
<b>Standard Operating Procedures</b>	SOP	Standard Operating Procedures are detailed written instructions to achieve uniformity in the performance of a specific function. They define tasks, allocate responsibilities, detail processes, indicate documents and templates to be used and cross-reference to other work instructions and guidance or policy documents. They are standards to which the UoB may be audited or inspected.
<b>Adverse Event</b>	AE	Any untoward medical occurrence in a participant or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the intervention received. See section 9.2.
<b>Related Event</b>		An event which resulted from the administration of any of the research procedures.
<b>Serious Adverse Event</b>	SAE	<p>An untoward occurrence that:</p> <ul style="list-style-type: none"> <li>• Results in death</li> <li>• Is life-threatening</li> <li>• Requires hospitalisation or prolongation of existing hospitalisation</li> <li>• Results in persistent or significant disability or incapacity</li> <li>• Consists of a congenital anomaly/ birth defect</li> <li>• Or is otherwise considered medically significant by the Investigator</li> </ul> <p>See section 9.3.</p>
<b>Unexpected and Related Event</b>		An event which meets the definition of both an Unexpected Event and a Related Event
<b>Unexpected Event</b>		The type of event that is not listed in the protocol as an expected occurrence.
<b>Source data</b>		All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial
<b>Birmingham Clinical Trials Unit</b>	BCTU	The co-ordinating centre for the trial.

## TRIAL SUMMARY

<b>Title</b>	<b>The use of an electronic Patient-Reported Outcome Measure in the Management of Patients with Advanced Chronic Kidney Disease – The RePROM Pilot Trial</b>
<b>Short title/ Acronym</b>	<b>RePROM</b>
<b>Type of trial</b>	Randomised pilot trial
<b>Trial design</b>	An investigator led single-centre open-label, two-arm randomised controlled pilot trial of 66 participants with advanced progressive Chronic Kidney Disease (CKD).
<b>Trial Treatments</b>	Control arm: usual care Experimental arm: usual care supplemented with an electronic Patient-Reported Outcome Measure (ePROM) system
<b>Objectives</b>	<p>To assess the feasibility of undertaking a randomised controlled trial (RCT) of the use of ePROMs in the management of advanced CKD. The pilot study will:</p> <ul style="list-style-type: none"> <li>• Test and pilot the trial protocol (including recruitment and retention rates, data collection processes, data completeness and adherence to the ePROM intervention);</li> <li>• Assess the willingness of clinicians to randomise participants into the trial;</li> <li>• Assess the willingness of people with advanced CKD to be randomised into the trial;</li> <li>• Assess the acceptability of the ePROM intervention;</li> <li>• Explore the need for a non-web-based intervention platform for participants who are unable to use the ePROM;</li> <li>• Inform selection of the most appropriate primary outcome measure for the full-scale RCT;</li> <li>• Provide data to help estimate the sample size for the full-scale RCT;</li> <li>• Provide a platform to develop and pilot the processes to capture costs and outcomes to inform the health economic evaluation for the full-scale RCT;</li> <li>• Determine key participation criteria for centre involvement in the full-scale RCT.</li> </ul>
<b>Trial duration per participant</b>	12 months
<b>Estimated total trial duration</b>	30 months (12 months recruitment, 12 months follow-up, 6 months analysis and write-up)
<b>Planned trial sites</b>	UK single-site
<b>Total number of participants planned</b>	66

<b>Main inclusion/exclusion criteria</b>	<p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Aged <math>\geq 18</math> years old;</li> <li>• Ability to provide fully informed consent for participation in the study;</li> <li>• Patients under the care of the renal services at Queen Elizabeth Hospital Birmingham (QEHB);</li> <li>• Patients meeting the trial definition of <b>advanced CKD</b>: <ul style="list-style-type: none"> <li>◦ an eGFR <math>\geq 6</math> and <math>\leq 15</math> mL/min/1.73m<sup>2</sup> (inclusive)</li> </ul> <p><b>OR</b></p> <li>◦ a projected risk of progression to end-stage renal failure within 2-years <math>\geq 20\%</math> using the 4-variable Tangri renal risk calculator.<sup>1</sup></li> </li></ul> <p><b>Exclusion Criteria</b></p> <ul style="list-style-type: none"> <li>• Patients unwilling to use the ePROM intervention;</li> <li>• Patients who, in the opinion of the consenting professional, cannot speak, read or write English sufficiently well to complete the ePROM unaided;</li> <li>• An episode of <b>acute kidney injury</b> (defined in accordance with <a href="#">national guidelines</a>) within the last 3 months;</li> <li>• Patients meeting the trial definition of <b>End Stage Renal Disease</b>: <ul style="list-style-type: none"> <li>◦ Currently receiving dialysis or scheduled to start in the next 2 weeks</li> </ul> <p><b>OR</b></p> <li>◦ Has received (or has a scheduled date to receive) a kidney transplant</li> <p><b>OR</b></p> <li>◦ eGFR <math>\leq 5</math> mL/min/1.73m<sup>2</sup>;</li> </li></ul> <li>• 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.</li>
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**Figure 1. RePROM trial schema. Follow-up ends if participant progresses to End Stage Renal Disease. Note: myHealth registration process should commence by visit 1 for all participants.**

## LAY SUMMARY

**Background:** Chronic Kidney Disease (CKD) affects around 1 in 7 people in the UK. Those with advanced CKD may go on to need demanding and costly treatments, such as dialysis, for the rest of their lives. These patients often experience a very poor quality of life and live less long than people without CKD.

Patients with advanced CKD can also get worse very quickly. Unfortunately, this can happen between visits to their clinical team, meaning they need to go to hospital as an emergency and have more ill-health as a result.

Some researchers and clinicians believe it would be helpful to ask patients to use a computer or smartphone to provide regular information about their quality of life and symptoms, in between their hospital appointments. This information can be collected using questionnaires known as 'electronic Patient-Reported Outcome Measures' or ePROMs.

Kidney clinicians believe they could use ePROMs to find out if a patient needs urgent care, so that they can take action straight away. This could help patients with advanced CKD by responding to their health needs before emergency care is needed.

International research in cancer has shown that ePROMs can:

- Improve communication between patients and doctors
- Help shared decision-making
- Improve patient quality of life
- Reduce the risk of hospital admission and prolong patient survival

The value of ePROMs has not, however, been tested in CKD. Therefore, a randomised controlled trial (RCT) is needed to assess whether ePROM use can improve patient outcomes and safety when compared to standard treatment alone in the NHS. Before this can happen, a pilot trial is needed to determine if a RCT can be done.

### Aims of study:

- Develop a kidney ePROM system through patient and clinician input.
- Conduct a pilot trial of ePROMs in advanced CKD to determine if a full-scale RCT is possible, and to gather information to help plan the full-scale trial.

**Design & Methods:** This study will take place across two stages.

**Stage 1** will involve the development of the kidney ePROM system, which will allow: (i) patients to input their data in multiple ways (e.g. via computer or smartphone or tablet) and (ii) clinicians to view the patient's data in real time.

**Stage 2** is a pilot study in which 66 consenting patients with advanced CKD will be randomly allocated to receive either standard treatment alone or standard treatment plus the ePROM. The study will assess: (a) the willingness of clinicians and people with advanced CKD to be involved in the study; (b) acceptability of the ePROMs; and (c) the best way to measure the impact of the ePROM on patients' health status in the full-scale RCT.

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## 1. BACKGROUND AND RATIONALE

### 1.1. Background

#### 1.1.1. The burden of chronic kidney disease

Chronic Kidney Disease (CKD) affects up to 16% of adults in the UK<sup>2</sup> and prevalence rates are increasing. The annual cost of CKD in the UK was estimated at £1.45 billion in 2009/10.<sup>3</sup> More than half of these costs (£780 million) were associated with Renal Replacement Therapy (RRT) - haemodialysis, peritoneal dialysis and/or kidney transplantation - for patients with end stage renal disease (ESRD).<sup>3</sup> This is despite the fact that patients requiring RRT comprise less than 2% of the total CKD population.<sup>3</sup>

Numerous studies have demonstrated that patients with ESRD experience high symptom burden and a very high prevalence of depression.<sup>4</sup> Moreover, patient quality of life and utility is significantly reduced in ESRD and is strongly associated with increased hospitalisation and mortality.<sup>4</sup> Accurate and responsive healthcare for patients as they move from advanced CKD to ESRD is therefore a key healthcare priority.

#### 1.1.2. Care of patients with advanced CKD

Patients with advanced CKD (study definition: pre-ESRD/RTT with an estimated Glomerular Filtration Rate (eGFR) between 6 and 15ml/min/1.73m<sup>2</sup>) are primarily managed in secondary care in the UK. Evidence suggests that prompt therapeutic intervention in advanced CKD can delay the progression of the disease and the subsequent need for RRT, reduce the risk of associated cardiovascular disease and prevent complications including myocardial infarction and stroke.<sup>5</sup> High quality treatment, consistently delivered to patients with advanced CKD at the point of need, should reduce premature death, enhance short and long-term quality of life and ensure patients have a positive experience of care.<sup>5</sup>

Effective management of advanced CKD relies on the timely detection of deterioration. 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>4</sup>

#### 1.1.3. Current problems with outcomes measurement in advanced CKD

Treatment success of advanced CKD in secondary care has been historically evaluated using objective laboratory measures (e.g. renal function estimating equations (eGFR), urinary albumin creatinine ratio (ACR), serum phosphate, serum bicarbonate) collected during routine clinic appointments, supplemented by brief subjective information from the patient. This model does not support the identification of patient deterioration *between* appointments. Neither does it provide clinicians with detailed information regarding the impact of the disease on patient health-related quality of life (HRQL), symptom burden and psychological function: all identified by patients, clinicians and researchers as important factors in advanced CKD.<sup>4</sup>

#### 1.1.4. Benefits of electronic patient-reported outcome measurement

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>6</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>7</sup>
- Improve patient activation and help patients to feel more involved/empowered in decisions around their care.<sup>8-10</sup>
- Improve the accuracy of symptom assessment and enhance symptom management.<sup>11</sup>
- Enhance patient education and self-management and maximise patient safety.<sup>9,12-17</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>16,18,19</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>17</sup>

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

A recent randomised controlled trial (RCT) conducted in an oncology setting in the US, demonstrated that ePROM use is associated with improved HRQL, reduced Accident and Emergency (A&E) visits, reduced hospitalisations, and superior quality-adjusted survival.<sup>17</sup> However, NHS-based ePROM research in CKD, utilising real-time patient and clinician feedback is lacking.

### 1.2. Study Rationale

CKD, and in particular ESRD, is a costly condition, which results in significant patient burden (physical and psychological), reduced quality of life and increased risk of morbidity and mortality. Routine remote use of ePROM data by patients with advanced CKD may aid self-management, whilst also helping to improve the flow of information between patients and their clinicians, potentially improving patient safety, enhancing clinical interactions, optimising patient outcomes and delivering cost savings to the NHS.

A RCT is needed to evaluate ePROM efficacy in advanced CKD to determine if health professionals/healthcare providers/policy-makers should implement routine ePROM collection in renal practice. However, before a definitive trial is undertaken, a pilot trial is required to assess the feasibility of undertaking such a study and to help inform the key elements (e.g. appropriate outcome measure, sample size) of the design for the full-scale RCT.

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## 2. AIMS AND OBJECTIVES

### 2.1. Aims and Objectives

#### 2.1.1. Stage 1 - Intervention development

**Objectives:**

- Development of the ePROM intervention with patient and clinician input – see section 3.1.1.

#### 2.1.2. Stage 2 – Pilot trial

The pilot trial will address the following research questions:

- *Is it feasible to conduct a RCT investigating the use of ePROMs in the management of advanced CKD?*
- *What are the key elements of the optimal design for such a trial?*

**Objectives:**

The pilot trial will:

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

#### 2.1.3. Qualitative sub-study

**Objective:**

- To explore patient and study personnel/clinician thoughts/experiences regarding the RePROM trial processes – see section 8.1.

### 3. TRIAL DESIGN AND SETTING

#### 3.1.1. Stage 1 - Intervention development

##### *Objective*

Development of the ePROM intervention with patient and clinician input.

##### *Eligibility*

See section 4.

##### *Methods*

Development of the ePROM system will be informed by the content of two renal-specific PROMs drawn from our systematic review of the literature<sup>21</sup> and selected by our Patient Advisory Group: the Kidney Disease Quality of Life-36 (KDQOL-36) questionnaire and Integrated Palliative care Outcome Scale – Renal (IPOS-R) (see below). The ePROM system will be made available to study participants via the award winning ‘myHealth’ secure patient portal delivered by the host site QEHB, University Hospitals NHS Foundation Trust. 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 KDQOL-36 is a valid and reliable tool<sup>20,21</sup> which incorporates the SF-12 (which measures general HRQL), and condition-specific questions surrounding: (i) the patient's perceived burden of kidney disease; (ii) the symptoms commonly associated with kidney disease; (iii) the impact of kidney disease on patient quality of life. This measure has been advocated for use in CKD in two recent systematic reviews produced by the Oxford PROMs group<sup>20</sup> and the Centre for Patient Reported Outcomes Research (CPROR) at the University of Birmingham<sup>21</sup>, and in 2015 was supported by the ERA-EDTA (The European Renal Association – European Dialysis and Transplant Association).<sup>22</sup> The IPOS-R is predominantly a symptom questionnaire that is currently being used within the measurement work stream of the UK Renal Registry. Its validation by the Palliative care Outcome Scale (POS) team, and within our team at the CPROR at the University of Birmingham, is on-going.<sup>21</sup>

The ePROM system will be designed to: (i) provide tailored feedback and self-management advice to patients; and (ii) to notify the clinical team of patient deterioration, according to a *priori* determined threshold criteria, providing, for example:

- automated messages of reassurance, and appropriate self-management advice, to participants whose ePROM scores suggest mild/moderate symptoms;
- alert messages to the patient and clinical team where the patient's ePROM score crosses the pre-agreed (absolute and change-score) threshold, indicating severe symptoms/cause for concern.

Patients' longitudinal ePROM scores will be made available to clinicians for use during routine outpatient consultations. The RePROM Patient Advisory Group felt this approach would help to focus discussion on patient-centred issues and may enhance symptom management, a view supported by related literature.<sup>9,10,18,19,23-25</sup>

Design of the ePROM system will be finalized during a series of operational meetings, held in stage I 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, led by ePROM expert Prof Galina Velikova.

In addition, usability testing of the ePROM system will be conducted with a small group of patients with CKD (n=6-10). Individuals will be identified as outlined in section 3.3. (see section 4 for eligibility details, and the following recruitment documentation: Patient Information Sheet (PIS) 1: usability testing; Informed Consent Form (ICF) 1:usability testing). Either the Principal Investigator (PI) or a member of QEHB renal research team will take consent. Written patient information will be provided to potential participants (see PIS-1:usability testing). Investigators/delegate(s) will ensure that they adequately explain the study to the participant. They will also stress that participation is voluntary and that the participant is free to refuse to take part or may withdraw from the study at any time. The participant will be given the opportunity to ask questions. If the participant expresses an interest in participating they will be asked to sign and date the latest version of ICF (ICF-1:user testing).

Consenting participants will each be asked to complete an ePROM report in the presence of a member of the research team, who will take notes. During the task, the participant will be encouraged to think aloud and vocalise his/her thoughts throughout the process of completing the electronic questionnaire ('Concurrent Think Aloud' technique). Following the task, the researcher will use the 'Retrospective Probing' technique to further explore the observations made during the test session.

All user testing session dialogue will be digitally recorded, professionally transcribed and the transcripts anonymised. Transcript data will be entered into a specialist software package (e.g. Nvivo, QSR International) to aid organisation and analysis of the data. All data will be analysed by a member of the research team at the CPROR at the University of Birmingham, using conventional content analysis. Only anonymised quotes will be used in any arising publications or reports.

It is anticipated that iterative refinements will be made to the ePROM system, based on the usability test findings, with input from the QEHB renal clinical and research team; the RePROM Patient Advisory Group; the QEHB IT and Informatics group and the University of Birmingham Clinical Trials Unit. Sign-off for the final version implemented in the RePROM pilot trial will require approval from the RePROM TMG (which includes QEHB Renal research team members) and patient Advisory Group, and the QEHB IT and Informatics department.

### 3.2. Stage 2: Pilot Trial

The **RePROM** trial is an investigator led single-centre, open-label, 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 the ePROM intervention.

### 3.3. Trial Setting

Patients under the care of the renal services at Queen Elizabeth Hospital, Birmingham (QEHB) will be recruited for this study. Participants randomised to the experimental arm of the trial will use the ePROM intervention at home and in the community.

### 3.4. Identification of participants

Currently, patients with CKD under the care of a nephrologist are reviewed regularly in a hospital out-patient clinic. The frequency of follow-up appointments varies depending on the particular patient's needs and patient/clinician preferences, but averages at around one appointment every 3 months.

Members of the renal research team at QEHB will screen for potential eligible study participants using the inclusion/exclusion criteria. Patients who fulfil the entry criteria will have their eligibility assessed by qualified personnel (research nurse in consultation with a nephrologist) with access to, and a full understanding of, their medical history. Eligible patients will be approached to participate in the trial. 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.

After having received the PIS and invitation letter, patients will be approached by an appropriately trained member of the renal research team (listed on the delegation log) at a routine clinic appointment regarding entering the **RePROM** study. This may be a research nurse, nephrologist or clinical trials practitioner. This individual will discuss the study with the patient in detail and give a comprehensive verbal explanation (explaining both the investigational and standard treatment options, and highlighting any possible benefits or risks relating to participation in the trial). Time for questions throughout the discussion will be given and any questions adequately addressed. Informed consent will then be sought from the participants who agree to enter the trial. Details of all patients approached about the trial will be recorded on the **RePROM Screening and Approach Log**.

Identification of patients for user testing of the ePROM during the intervention development stage (see section 3.1.1.) will be conducted as outlined above, but a screening and approach log will not be required.

## 4. ELIGIBILITY

The entry criteria for participants in stage 1 and 2 of the project are the same and are outlined below.

### 4.1. 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>1</sup>

### 4.2. 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;
- 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.



## 5. CONSENT

It will be the responsibility of the Investigator to ensure written informed consent has been obtained for each participant prior to performing any trial related procedures. Either the Principal Investigator (PI) or a member of QEHB renal research team will take consent (this responsibility will be delegated to appropriate individuals (e.g. where permitted by the NHS Trust, consent may be taken by a nurse or clinical trials practitioner) by the PI as captured on the **Site Signature and Delegation Log**).

Written patient information will be provided to potential participants as described in section 3.4. Within clinic, investigators/delegate(s) will ensure that they adequately explain the aim, trial intervention, anticipated benefits and potential hazards of taking part in the trial to the participant. They will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time. The participant will be given the opportunity to ask questions. If the participant expresses an interest in participating in the trial they will be asked to sign and date the latest version of the Informed Consent Form (ICF). The participant must give explicit consent for the regulatory authorities, members of the research team and or representatives of the sponsor to be given direct access to their medical records. Pilot trial participants must consent to register on the secure QEHB 'myHealth' patient portal, which will deliver the ePROM.

The investigator/delegate(s) will then sign and date the ICF. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the ISF. In addition, if the participant has given explicit consent, a copy of the signed ICF will be sent to the **RePROM** Trial Office at Birmingham Clinical Trials Unit (BCTU) trials team for review/audit purposes.

Details of the informed consent discussions will be recorded in the participant's medical notes/electronic patient record. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant and version number of ICF signed, and date consent received.

At each visit, the participant's willingness to continue in the trial will be ascertained and documented in the medical notes/electronic patient record where appropriate. Throughout the trial, the participant will have the opportunity to ask further questions. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available, which may affect the participants' decision to continue, participants will be given time to consider, and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the Trials Office and will be printed or photocopied onto the headed paper of the local institution. Details of all patients approached about the trial will be recorded on the **RePROM Screening and Approach Log**. For the pilot trial, with the participant's prior consent, their General Practitioner (GP) will be informed that they are taking part in the trial.

The participant's GP will not be notified for those taking part in user-testing, or the qualitative sub-study, however, it will be made clear that participants are free to discuss the study with their GP if they would like.

## 6. ENROLMENT AND RANDOMISATION

### 6.1. Enrolment and Screening

Sixty-six patients meeting the eligibility criteria set out in section 4 will be enrolled.

Before randomising the patient, e.g. at the baseline assessment, a member of the research team will fully complete the **Randomisation Case Report Form (CRF)** which includes an eligibility checklist. The person assessing eligibility must have this responsibility delegated (as detailed on the **RePROM Site Signature and Delegation Log**) and will sign the **Randomisation CRF** to document the eligibility assessment. The signed Randomisation CRF should be filed in the ISF, and a copy sent to BCTU for central monitoring purposes. All information on the Randomisation CRF is required to randomise the patient.

Details of the study enrolment will be recorded in the participant's medical notes/electronic patient record. This will include confirmation of eligibility and the date of enrolment into the study.

### 6.2. Randomisation

Randomisation will be provided by a secure online randomisation system at the Birmingham Clinical Trials Unit (BCTU) (available at [www.trials.bham.ac.uk/RePROM](http://www.trials.bham.ac.uk/RePROM)). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the study, as detailed on the **RePROM Site Signature and Delegation Log**. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. A telephone toll-free randomisation service ((0044) 0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days.

After participant eligibility has been confirmed and informed consent has been received, the participant can be randomised into the trial. A **Randomisation CRF** will be provided to investigators and should be used to collate the necessary information prior to randomisation. Only when all eligibility criteria and items on the Randomisation CRF have been provided, will a Trial Number be allocated.

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

- Risk progression (<40%, versus ≥40%, using the 4-variable Tangri renal risk calculator<sup>1</sup>);
- Self-reported computer experience (defined as: regular use of a computer or tablet or smartphone at least weekly versus less than weekly);
- Ethnicity ('white' versus 'non-white')

A 'random element' will be included in the minimisation algorithm, so that each patient has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received. Full details of the randomisation specification will be stored in a confidential document at BCTU.

Following randomisation, a confirmatory e-mail will be sent to the CI, PI and renal research member initiating randomisation.

Investigators will keep their own log which links patients with their allocated trial number in the **RePROM Patient Recruitment and Identification Log**. The Investigator must maintain this document, which is not for submission to the Trials Office. The Investigator will also keep and maintain the **RePROM Screening/Enrolment Log** which will be kept in the ISF, and should be available to be sent to the Trials Office upon request.

### 6.3. Informing the participant's GP

If the participant has agreed, the participant's GP should be notified that they are in **RePROM** pilot trial, using the **RePROM GP Letter**. The GP need not be contacted for patients taking part in the usability testing or qualitative phases of the study, but patient will be free to discuss any aspect of the **RePROM** study with their GP if they so wish.

### 6.4. Masking

Due to the nature of the intervention, it is not possible to mask participants or clinicians involved in the study to the intervention group each participant is randomised to.

## 7. TRIAL INTERVENTION

### 7.1. Intervention

Participants randomised to the intervention arm will commence monthly self-reporting of their health status using the ePROM system, after receiving a face-to-face training session.

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

The ePROM system will provide tailored information to patients in response to each report (both scheduled and ad-hoc) and alert the clinical team of patient deterioration according to *a priori* determined alert threshold criteria established in the intervention development study (see section **Error! Reference source not found.**). After receiving training during the study setup period, the renal clinical team will monitor for ePROM alerts and will respond with appropriate clinical action, in line with standard clinical practice.

Please note: the ePROM questionnaire **will not** be used to derive trial-level Quality of Life (QoL) outcome data; these data will be collected using a paper version of the EuroQoL-5 Domain-5 Level (EQ-5D-5L) PROM at baseline and follow-up visits (see section 8.2).

### 7.2. Accountability Procedures

Participants will receive automated reminders 24 hours prior to each scheduled self-report and 24 hours after a failure to report if necessary. Upon a patient ePROM report, the system will generate tailored patient advice aimed at supporting self-management for mild/moderate symptoms. Resource usage data will give an indication of patient use of the self-management advice generated by the ePROM system for accountability purposes. Severe symptoms will trigger an email alert to the renal clinical team at QEHB (dedicated monitored email inbox) and a simultaneous patient notification advising them to make contact with the renal team during office hours (or to use standard NHS support mechanism outside of these hours). Actions taken in response to an alert will be logged in the patient's electronic healthcare record by a member of the renal team.

### 7.3. Cessation of Treatment / Continuation after the Trial

Participants who, during the course of the study, progress to meet the trial definition of End Stage Renal Disease (e.g. are receiving dialysis **OR** have received a kidney transplant **OR** have a GFR  $\leq 5\text{ml/min/1.73m}^2$ ) will be withdrawn from trial intervention and follow-up schedule.

The ePROM intervention will not be available after the end of trial follow-up. The clinical team should discuss ongoing management and monitoring of the participant's clinical status with the participant at the end of trial participation. Provision should be made for ongoing clinical management in accordance with normal local clinical practice.

## 8. OUTCOME MEASURES AND STUDY PROCEDURES

**SCREENING:** Please note, details of the screening assessment have been described earlier in section 6.1.

### 8.1. Primary Outcome

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

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

### 8.2. Outcome Data

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

- HRQL data, using the paper version of the EQ-5D-5L. The EQ-5D-5L is a reliable/validated generic measure of health status commonly used internationally in cost-effectiveness research.<sup>26</sup>
- Clinical data, including: Serum Creatinine, Calcium, Phosphate, Bicarbonate, Albumin, eGFR, ACR, blood pressure, and for participants with diabetes: glucose and HbA1c.
- The following event data: progression to end stage renal disease, contact with health care professionals in secondary care (outpatient clinics and A&E); inpatient hospitalisation; death.

Healthcare resource use data will be collected at each study visit (see section 8.3).

All study staff/participants will be invited to complete a trial process questionnaire at the end of the study, which will evaluate aspects surrounding:

- Data collection forms/questionnaires
- Randomisation procedure
- Acceptability of the intervention
- Appropriateness of the frequency of ePROM reporting, alert thresholds and management.

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### 8.3. Study Procedures

Please see Table 1 for the schedule of assessments.

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 BCTU database after each scheduled follow-up visit. The database will use event-triggered forms, generated via input from the QEHB myHealth system, to capture ePROM alert data.

Between clinic visits, patients should be managed in accordance with local practice.

## 8.4. Schedule of Assessments

Visit	Screening/approach	Consent	Baseline/Randomisation (+ or – 3 weeks)	Month 3 (+ or – 3 weeks)	Month 6 (+ or – 3 weeks)	Month 9 (+ or – 3 weeks)	Month 12 (+ or – 3 weeks)
Database search to identify potential participants	x*						
Eligibility check	x*	x*	x*				
Completion of screening log	x						
Mail out PIS/ICF	x						
Approach potential participant to discuss study (phone/clinic)***	x						
MyHealth Registration***	x						
Completion of approach log	x						
Informed consent		x	x				
Completion of randomisation CRF (including participant details and randomisation minimisation criteria)			x				
Randomisation and trial number allocation			x				
Participant ePROM training**			x				
Completion of baseline/follow-up CRF			x	x	x	x	x
Medical history			x				
Quality of life questionnaire (EQ-5D)			x††	x	x	x	x
Collection of clinical data from patient's medical record <sup>§</sup> , including: <ul style="list-style-type: none"> <li>eGFR, 4-variable Tangri renal risk calculator</li> <li>ACR, Serum Creatinine, Calcium, Phosphate, Bicarbonate, Albumin</li> <li>Blood Pressure</li> <li>Glucose†</li> <li>HbA1c†</li> </ul>			x*††	x	x	x	x
Review/report progression to ESRD				x	x	x	x
Clinical contacts				x	x	x	x
Review/reporting of patient AEs/SAEs				x	x	x	x
Participant exit questionnaire							x

**Table 1. Schedule of Assessments.** \*Data from existing medical records. \*\*Intervention group only. \*\*\*may continue into initial study visit, but must be completed prior to randomisation. †Glucose and HbA1c will only be recorded in participants with diabetes. ††complete before randomisation. § If a result is not available from within the visit window, the test should be performed at the trial visit.



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## 8.5. 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.

All patients consenting to take part in the RePROM pilot/feasibility trial will be asked if they would be willing to also take part in the qualitative sub-study (see PIS-2:pilot/feasibility trial and ICF-2:pilot/feasibility trial). In addition, a member of the renal research team will email/post a qualitative sub-study invite and associated PIS/ICF to QEHB renal clinicians and staff involved in delivery of the RePROM pilot/feasibility study (see qualitative sub-study invite, PIS-3: qualitative sub-study and ICF-3: 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 research team at the CPROR at the University of Birmingham according to a pre-defined topic guide, but there will be sufficient scope to explore novel themes where appropriate. All interviews will be digitally recorded, professionally transcribed and the transcripts anonymised. Transcript data will be entered into a specialist software package (e.g. Nvivo, QSR International) to aid organisation and analysis of the data. All data will be analysed by the CI using conventional content analysis. Formal triangulation of coding and member checking will be employed to enhance the credibility of the analysis. Only anonymised quotes will be used in any arising publications or reports.

It is not anticipated that the topics discussed will be sensitive, embarrassing or upsetting. However, if the participant experiences distress during the interview they will be asked if they wish to delay or discontinue the process. The interviewer will be an experienced mixed-methods researcher, supported by a study management group with experience of qualitative methodology. The interviewer will be equipped to provide the participant with the contact details of the senior clinician (a consultant nephrologist) on the research team if they wish for follow up.

If the participant divulges criminal or other disclosures requiring action, the researcher will discuss the matter with the senior clinician on the research team, after first informing the participant, and agree on the most appropriate course of action.

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



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## 8.6. Participant Withdrawal

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation; this should be confirmed at each assessment visit and recorded in the CRF and in the patient's medical notes.

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the feasibility/pilot trial (or part of) at any time. Participants may also be withdrawn from the trial by the investigator if considered in the participant's best interest.

Types of trial withdrawal as defined are:

- The participant would like to withdraw from the trial intervention (i.e. will stop reporting ePROMs), but is willing to be followed up in accordance with the schedule of assessments and, if applicable, using any central UK NHS bodies for long term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis).
- The participant would like to withdraw from the trial intervention **and** trial specific follow-up visits but is willing to be followed-up according to standard practice (i.e. has agreed that follow-up data can be collected at standard clinic visits and used in the trial final analysis)
- The participant would like to withdraw from trial intervention and is **not** willing to be followed up in any way for the purposes of the trial and for no further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis)

**or**

- The participant wishes to withdraw completely (i.e. from trial intervention and all follow up) and is **not** willing to have any of their data, including that already collected, to be used in any future trial analysis

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source data and the CRF.

**Note:** participants involved in the user testing or qualitative sub-study may only withdraw from this aspect up to the point of data analysis (5 working days following the interview). After this point, it will not be possible to extract an individuals' interview data from the analyses.

## 9. ADVERSE EVENT REPORTING

### 9.1. Reporting Requirements

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). Definitions of different types of AEs are listed in the table of abbreviations and definitions. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the trial participant and this assessment should be documented in the source data, with reference to the protocol.

### 9.2. Adverse Events (AE)

Patients with advanced CKD can have high disease burden. It is expected that the trial population will be older, with co-morbidities such as diabetes, hypertension, gout, thyroid dysfunction, cardiovascular disease or raised cardiovascular risk, along with associated complications and symptoms including abnormal lab results. A relatively high number of adverse events are anticipated as a result of the patients' existing disease history. However, there are no foreseeable risks of mortality or significant morbidity associated with the study ePROM intervention. AE reporting will therefore be limited to those events identified on the CRF, which are required for trial monitoring or outcome assessment. This does not negate the need for the research team at site to record any reported or observed adverse events in the participant's medical records, in line with routine medical practice.

### 9.3. Serious Adverse Adverts (SAE)

All events which meet the definition of serious will be collected and recorded in the participant notes and the CRF. SAEs that are expected for the patient population, but that are not likely to be related to the trial intervention, are not subject to expedited reporting and will not require completion of an SAE form. Instead, they will be reported on the CRF in line with the normal CRF reporting timelines. These SAEs comprise hospitalisations, prolongation of hospitalisation or deaths caused by the events listed below in Table 2.

SAE Category	Event
1 - Allergy/Immunology	Reaction to medication/s
10 - Endocrine	Symptoms, exacerbations or complications of thyroid dysfunction
10 - Endocrine	Symptoms, exacerbations or complications of diabetes
11 - Gastrointestinal	Gastritis
11 - Gastrointestinal	Bowel obstruction including symptoms or complications thereof
11 - Gastrointestinal	Abdominal pain/vomiting/diarrhoea/constipation/nausea including symptoms or complications thereof
11 - Gastrointestinal	GI bleed
11 - Gastrointestinal	Hernia including symptoms or complications thereof
15 - Infection	Pneumonia or chest infection, including symptoms or complications thereof
15 - Infection	Sepsis
15 - Infection	Abscess including symptoms or complications thereof
15 - Infection	Cellulitis including symptoms or complications thereof
15 - Infection	Viral or bacterial infection, including symptoms or complications thereof
17 - Metabolic/Laboratory	Anaemia

17 - Metabolic/Laboratory	Hyponatraemia
17 - Metabolic/Laboratory	Hyperkalaemia
17 - Metabolic/Laboratory	Hypocalcaemia
17 - Metabolic/Laboratory	Hypomagnesemia
17 - Metabolic/Laboratory	Acidosis
17 - Metabolic/Laboratory	Uraemia
17 - Metabolic/Laboratory	Deranged blood results
18 - Musculoskeletal/Soft Tissue	Pain or injury following a fall or accident
18 - Musculoskeletal/Soft Tissue	Symptoms, exacerbations or complications of arthritis
18 - Musculoskeletal/Soft Tissue	Symptoms, exacerbations or complications of gout
19 - Neurology	Stroke or TIA including symptoms or complications thereof.
21 - Pain	Chest pain/angina
22 - Pulmonary/Upper Respiratory	Symptoms, exacerbations or complications of respiratory tract infection
22 - Pulmonary/Upper Respiratory	Shortness of breath
22 - Pulmonary/Upper Respiratory	Pulmonary embolism, including symptoms or complications thereof
23 - Renal/Genitourinary	UTI or urosepsis, including symptoms or complications thereof
23 - Renal/Genitourinary	Symptoms, exacerbations or complications of Chronic Kidney Disease, including the underlying aetiology
23 - Renal/Genitourinary	Complications of dialysis, including dialysis fistula, catheter or bag.
23 - Renal/Genitourinary	AKI including symptoms or complications thereof
23 - Renal/Genitourinary	Fluid overload/oedema including symptoms or complications thereof
24 - Secondary Malignancy	Primary cancer or malignancy, including symptoms or complications thereof
26 - Surgery/Intra-Operative Injury	Planned surgical procedure including symptoms or complications thereof
28 - Vascular	Thrombosis including symptoms or complications thereof
4 - Cardiac Arrhythmia	Symptoms, exacerbations or complications of arrhythmia or atrial fibrillation
5 - Cardiac General	Myocardial infarction including symptoms or complications thereof
5 - Cardiac General	Hypertension including symptoms or complications thereof
5 - Cardiac General	Hypotension including symptoms or complications thereof
5 - Cardiac General	Systolic dysfunction/heart failure including symptoms or complications thereof
8 - Death	Death from pre-existing medical condition

**Table 2. Example of SAEs expected in the study population, but unlikely to be related to the trial intervention.**

**Any SAEs not listed above that are thought to be related to the trial intervention will be reported to the trials office on an SAE form immediately, and within 24 hours of being made aware of the event.**

In particular, staff will monitor for serious anxiety/depression or psychological distress related to ePROM completion.

## 9.4. Reporting period

The reporting period will commence when the participant has been consented into the trial and ends 2 weeks after the participant completes their last EQ-5D-5L or ePROM. Trial outcome and end point data, which includes some safety end points, should be reported for the full duration of the participant's trial participation.

## 9.5. Reporting period – At Site

### 9.5.1. Adverse Events

AEs should be recorded in the participant's medical notes or electronic health records in accordance with routine clinical practice. Targeted AEs, as outlined on the CRF, should be reported on the CRF. Records of AEs should be returned to the BCTU trials team in the same way and with the same timeframes as other CRF data. AEs will be identified by review of the participant's medical records and discussion with the participant at the study visits.

### 9.5.2. Serious Adverse Events

AEs defined as serious and which require reporting as an SAE as per Protocol section 9.3 should be reported on a SAE Form. When completing the form, the PI will be asked to define the causality and the severity of the AE, where the suspected causal relationship is indicated using a scale containing the following options: definitely related; probably related; possibly related; unlikely to be related or unrelated.

On becoming aware that a participant has experienced an SAE, the PI should report the SAE to their own Trust in accordance with local practice and to the BCTU trials office.

To report an SAE to the BCTU trials office, the PI must complete, date and sign the trial specific BCTU SAE form. The form should be completed as soon as possible and no later than 24 hours after first becoming aware of the event:

**The SAE form should be sent via fax to:**

**0121 415 9135**

**Alternatively, SAE forms can be submitted by e-mail to the following address. E-mail submissions must be accompanied by a telephone notification (0121 415 9133):**

**[RePROM@trials.bham.ac.uk](mailto:RePROM@trials.bham.ac.uk)**

**When submitting SAE forms via e-mail, care should be taken to anonymise the information. SAE reports and supporting information should not contain: patient name, patient address, discharge address, GP name, GP address, hospital number, patient initials, NHS number.**

On receipt of an SAE form, the BCTU trials team will allocate each SAE a unique reference number and return this via email to the site as proof of receipt. If the site has not received confirmation of receipt of the SAE from the BCTU or if the SAE has not been assigned a unique SAE identification number, the site should contact the BCTU trials team within 1 working day. The site and the BCTU trials team should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Site File.

Where an SAE Form has been completed by someone other than the Investigator, the original SAE form must be countersigned by the Investigator to confirm agreement with the causality and severity assessments.

### **9.5.3. Provision of follow-up information**

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should ideally be provided on a new SAE Form, using the SAE reference number provided by the BCTU trials team. Once the SAE has been resolved, all follow-up information has been received and the paperwork is complete, the original SAE form that was completed at site must be returned to the BCTU trials office and a copy kept in the Site File.

## **9.6. Reporting Procedure – BCTU Trials Team**

On receipt of an SAE form from the site, the BCTU trials team will allocate each SAE form with a unique reference number and enter this onto the SAE form in the section for office use only. The SAE form (containing the unique reference number completed) will be forwarded to the site as proof of receipt within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Trial Master File (TMF).

On receipt of an SAE Form, a TMG nephrologist will independently determine the seriousness and causality of the SAE. An SAE judged by the PI or TMG nephrologist to have a reasonable causal relationship with the intervention will be regarded as a related SAE. The causality assessment given by the PI will not be downgraded by the TMG nephrologist. If the TMG nephrologist disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

The CI (or delegate) will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

## **9.7. Reporting to the Research Ethics Committee**

### **9.7.1. Unexpected and Related Serious Adverse Events**

BCTU will report all events categorised as Unexpected and Related SAEs to the main Research Ethics Committee (REC) and Research Governance Team (RGT) at the University of Birmingham within 15 days.

### **9.7.2. Other safety issues identified during the course of the trial**

The main REC and RGT will be notified immediately if a significant safety issue is identified during the course of the trial.

## **9.8. Investigators**

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to PI. A copy of any such correspondence should be filed in the site file and TMF.

### 9.9. Data Monitoring Committee

A Data Monitoring Committee will not be required for this pilot study.

## 10. DATA HANDLING AND RECORD KEEPING

### 10.1. Source Data

Source data is defined as: all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

Source data is kept as part of the participants' medical notes generated and maintained at site.

The source data for key study outcomes and end points are clearly identified and detailed below.

Data	Source
HRQL from the ED-5D-5L	The original participant-completed paper form is the source and will be kept with the participant's trial record at site.
Lab results	The original lab report, which may be electronic, is the source data and will be kept and maintained, in line with normal local practice.
Blood pressure	The last routine clinic blood pressure available from the QEHB electronic patient record system, which will be kept and maintained in line with normal local practice.
Clinical event data	The original clinical annotation is the source data. This may be found on clinical correspondence, or electronic or paper patient records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source data.
Recruitment	The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.
Drop out	Where a participant expressed a wish to withdraw, a source record must be made of the conversation, e.g. in the medical records.
ePROM completion	The original electronic record of the patient-completed ePROM is the source and will be held and maintained at QEHB.

**Table 3. Source data.**

## 10.2. Case Report Form Completion

A CRF is required and should be completed for each individual subject. The completed original CRFs should not be made available in any form to third parties, except for authorised representatives or appropriate regulatory authorities, without written permission from the sponsor.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The **RePROM Site Signature & Delegation Log** will identify all those personnel with responsibilities for data collection.

The CRFs will comprise of (but will NOT be limited to) the following Forms:

Form Name	Schedule for submission
Randomisation CRF	At the point of randomisation
Baseline and follow-up CRFs	As soon as possible after each follow-up assessment time point
Serious Adverse Event Form	Submitted within 24 hours of research staff at site becoming aware of event
Exit CRF	At the point of withdrawal or death

**Table 4. CRFs**

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried in accordance with the trial specific Data Validation Plan. Staff delegated to complete CRFs will be trained to adhere to the **RePROM Guide for CRF Completion**.

CRFs will be completed online at [www.trials.bham.ac.uk/RePROM](http://www.trials.bham.ac.uk/RePROM) from the source data. Authorised staff at sites (as delegated on the **RePROM Site Signature & Delegation Log**) will require an individual secure login username and password to access this online data entry system.

If information is not known, this must be clearly indicated on the CRF. All sections are to be completed. Missing and ambiguous data will be queried in line with the **RePROM Data Management Plan**.

Investigators will keep their own study file logs which link patients with anonymised CRFs. The Investigator must maintain documents not for submission to the Trials Office (e.g. **RePROM Patient Recruitment and Identification Logs**) in strict confidence.

In all cases, it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate. The investigator has ultimate responsibility for the collection and reporting of all clinical safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely, enduring and available when required. Since data entry on the electronic CRFs are attributable by virtue of the user log-in, submission of data on the electronic form will be taken as 'sign-off' to attest the data entered is accurate. Any changes made on the electronic CRF are automatically tracked. A reason will be provided for changes.



CRFs may be amended by the **RePROM** Trial Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the CRFs must be implemented by participating sites immediately on receipt.

Note: The QEHB informatics department may securely transfer some anonymised trial data (e.g. routine clinical data such as lab results, hospital outpatient appointments and in-patient hospitalisation) to BCTU for incorporation into the trial database. Data transfer will be underpinned by a QEHB/University of Birmingham data sharing agreement. All data will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998.

### 10.3. Participant completed Questionnaires

Participants will complete a paper version of the Euroqol (EQ-5D-5L) questionnaire (in clinic where possible or via post) at baseline, and at 3, 6, 9 and 12 months post randomisation. This questionnaire will be used to provide quality of life outcome data to: (i) aid selection of the primary outcome for the main RCT, and (ii) to inform the future economic evaluation.

Where possible, the questionnaire will be posted out to the participant in advance of their trial visit. For those participants who have not already completed the form by the time of their trial visit, the research nurse will be on hand in clinic to assist completion if necessary. However, it must be made clear that the questionnaire responses should come directly from the participant, with no external influence from individuals present during completion.

Proxy reporting should not be required during the study, however, if for some reason the research nurse determines there is no alternative but to accept a proxy report, details should be recorded in the source data.

Large font versions of the questionnaire will be made available for those with visual impairments.

Entries on the questionnaire should be made in ballpoint pen, in black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Following questionnaire completion, the research nurse should review the form in clinic for missing data or scoring errors (e.g. two answers given instead of one), while the participant is still in clinic where possible. The research nurse should discuss any instances with the participant, asking them to address accidental omissions or errors where appropriate. If a participant has purposefully omitted data, the research nurse should record the reason on the questionnaire, where provided.

If a questionnaire with missing data has been received through the post (or a postal questionnaire has not been received by the expected date), the research nurse will contact the participant within the appropriate time window and questionnaire recall period to discuss, using the participant's preferred contact method, in order to correct any accidental omissions or errors where appropriate, or record reasons for purposefully omitted data.

**Important – please note:**

If, when reviewing the completed EQ-5D-5L questionnaire, the research nurse becomes concerned for the wellbeing of the participant, they should discuss their concerns with the participant directly, working in partnership to determine the best course of action. With the participant's permission, the research nurse may need to consult with the PI and/or treating clinician to address these concerns. In exceptional circumstances, the research nurse may consult with the PI and/or treating clinician without the permission of the participant if they are concerned for the participant's safety.

#### 10.4. Data Management

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the trial specific data management plan. Coding and validation will be agreed between the trial's coordinator, statistician and programmer and the trial database will be signed off once the implementation of these has been assured.

Missing and ambiguous data will be queried in line with the **RePROM Data Management Plan**, and will focus on data required for trial analysis and safety reporting. Single data entry with central monitoring will be employed. Staff at site (as delegated on the **RePROM Site Signature & Delegation Log**) will enter and submit data on an electronic CRF online at [www.trials.bham.ac.uk/RePROM](http://www.trials.bham.ac.uk/RePROM). The system will include data validations to improve data quality (e.g. to prevent nonsensical dates or numerical values). Changes to the data on the system will be documented and attributable, with a reason for the change documented. Changes to the CRF will be made by site staff. Staff at the Trials Office will not have access to alter CRF data, though will have access to administrative aspects of the system.

#### 10.5. Data Security

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

The System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls used for non-identifiable data etc.
- Network security measures: including site firewalls, antivirus software, separate secure network protected hosting etc.
- System Management: The System shall be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.
- System Design: the system shall comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational Processes: the data will be processed and stored within the Study Centre (University of Birmingham).

- System Audit: The System shall benefit from the following internal/external audit arrangements:
  - Internal audit of the system
  - Periodic IT risk assessment
- Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

#### 10.6. **Archiving**

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years.

Patient ePROM reports will be stored within the secure QEHB myHealth patient portal system and patient electronic healthcare record in accordance with local trust policy.

## 11. QUALITY CONTROL AND QUALITY ASSURANCE

### 11.1. Site Set-up and Initiation

The CI is required to sign a University of Birmingham (UoB) CI agreement to document the expectations of both parties. The **UoB CI agreement document** must be completed prior to participation. The CI is required to sign a **Clinical Trials Task Delegation Log** which documents the agreements between the CI and BCTU. In addition, all local PIs will be asked to sign the necessary agreements including a **Site Signature and Delegation log** between the PI and the CTU, and supply a current CV and GCP certificate to BCTU. All members of the site research team are required to sign the **Site Signature and Delegation Log**, which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The BCTU trials team must be informed immediately of any change in the site research team.

### 11.2. Monitoring

#### 11.2.1. Onsite Monitoring

Monitoring is carried out as required following trial specific risk assessment and as documented in the **monitoring plan**. For this trial, no onsite monitoring is planned due to the low risk of the intervention and nature of the outcome data. Any monitoring activities will be reported to the trials team and any issues noted will be followed up to resolution. If a monitoring visit is required, the Trials team will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the **RePROM** trial staff access to source documents as requested.

#### 11.2.2. Central Monitoring

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 DCFs 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. This will be detailed in the monitoring plan

#### 11.2.3. Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The investigator will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections.

### 11.3. **Notification of Serious Breaches**

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of Good Clinical Practice (GCP) in connection with that trial or the protocol relating to that trial. Sites are therefore requested to notify the Trials Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group, and the REC. This includes reporting serious breaches of GCP and/or the trial protocol to the REC. A copy will be sent to the University of Birmingham Clinical Research Compliance Team at the time of reporting to the REC.

## 12. END OF TRIAL DEFINITION

The end of trial will be the date of the last data capture. The BCTU trial team will notify the main REC and RGT that the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial. A copy of the end of trial notification as well as the summary report is also sent to the University of Birmingham RGT at the time of sending these are sent to the REC.

The ePROM intervention will not be available after the end of trial follow-up. The clinical team should discuss ongoing management and monitoring of the participant's clinical status with the participant at the end of trial participation. Provision should be made for ongoing clinical management in accordance with normal local clinical practice.

## 13. STATISTICAL CONSIDERATIONS

### 13.1. Sample Size

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>28,29</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.

### 13.2. 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 will be descriptive and mainly focus on confidence interval estimation, with no hypothesis testing performed.

Data will be explored to assess the key feasibility aspects of undertaking a full-scale RCT on the use of ePROMs in the management of advanced CKD, for example:

- willingness of clinicians to randomise participants into the trial;
- willingness of people with advanced CKD to be randomised into the trial;
- recruitment and retention rates;
- data completeness;
- adherence with the ePROM intervention.

Dichotomous feasibility measures, such as the recruitment and retention rates, as well as data completeness will be reported as numbers and percentages. Where appropriate, these values will be summarised across treatment groups.

Adherence with the ePROM intervention will be assessed by calculating the number and percentage of participants who complete the ePROM reports as scheduled. To be

considered adherent, participants will need to have submitted their report within 72 hours of the scheduled time-point. Incomplete submissions (i.e. with some questions not answered) will be accepted for the purpose of measuring adherence. Ad-hoc ePROM reports (i.e. those completed outside the scheduled reporting periods) will not contribute to the assessment of adherence, although we will assess the number of ePROM reports completed by each participant.

The pilot data will also help inform the selection of the most appropriate primary outcome measure for the main RCT and provide data to facilitate estimation of the sample size required for the main RCT. Outcome data on HRQL and clinical data are collected at 3, 6, 9 and 12 months post-randomisation. Analysis methods will be chosen according to the data type of the outcome under investigation, in brief:

- *Continuous endpoints (e.g. quality of life)*: These data will be summarised using means and standard deviations, with differences in means with 95% confidence intervals reported. Longitudinal plots of the data over time will also be constructed for visual presentation of the data.
- *Categorical (dichotomous) endpoints (e.g. hospitalisation rates)*: The number of participants and percentages experiencing the event will be summarised between groups.
- *Time to Event endpoints (e.g. time to ESRD, mortality)*: The numbers of participants and percentages experiencing the event will be summarised over time between groups. Kaplan-Meier survival curves will be constructed for visual presentation of time-to-event data.

### 13.2.1. Subgroup Analyses

Descriptive reports of subgroup variables will be limited to the same variables used in the minimisation algorithm (see section 6.2). The availability and completeness of data for the subgroup variables will be summarised to assess their appropriateness as minimisation variables for the main trial, but no formal analysis will be undertaken.

### 13.2.2. Missing Data and Sensitivity Analyses

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

## 13.3. 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.

## 13.4. 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.



## 14. 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/PSC (personal social care); which will focus on healthcare resource use and costs including:

- Renal staff activity in response to ePROM alerts; GP and hospital consultations; in-patient hospitalisation; medications; referrals.
- NHS costs associated with maintenance of the ePROM system.

We will also develop mechanisms to capture data from a societal perspective, such as CKD-related loss of work time and patient costs associated with receiving treatment, where appropriate.

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>27</sup>

As part of the study, we will develop processes to capture quality of life information to inform the future economic evaluation. This will primarily be the EQ-5D-5L instrument, but other outcome measures that could potentially be used to inform the economic evaluation, will also be examined.

## 15. TRIAL ORGANISATIONAL STRUCTURE

### 15.1. Sponsor

The University of Birmingham is the study Sponsor.

### 15.2. Coordinating Centre

BCTU is the Coordinating Centre. Delegation of tasks to BCTU from the Sponsor are documented in the Clinical Trials Task Delegation Log.

### 15.3. Trial Management Group

The Trial Management Group (membership detailed in the Administrative Information section above) 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.

### 15.4. Trial Steering Committee

A single TSC (membership detailed in the Administrative Information section above) will be created for the RePROM trial and meet (face-to-face or via teleconference) at least yearly and as required depending on the needs of the TSC/trial office.



Membership and duties/responsibilities are outlined in the TSC Charter. In summary, 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.

#### 15.5. **Data Monitoring Committee**

There will be no Data Monitoring Committee. There are no plans to perform any interim analyses for this pilot study.

#### 15.6. **Finance**

The National Institute for Health Research (NIHR) is funding this trial. Clinical Research Network (CRN) support will be sought. No individual per patient payments will be made to NHS Trusts, Investigators or participants. Excess cost for the study remains part of NHS costs while study resources outside routine care and not covered by the CRN will be funded by the study.

## 16. ETHICAL CONSIDERATIONS

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

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research, the applicable UK Statutory Instruments, (which include the Data Protection Act 1998) and the Principles of GCP. The protocol will be submitted to and approved by the main REC prior to the study commencing.

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

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

## 17. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998. Study data will include:

- Medical history: to determine eligibility\* and for baseline comparison of groups.
- Demographic data (date of birth, gender, ethnicity and postcode (needed for deprivation indices)): for minimisation variables as part of the randomisation process and baseline comparison of groups.
- Lab results, health care utilisation data, self-reported quality of life data: pre-specified trial outcomes.
- Patient ePROM reports: arising from the intervention.
- Interview recordings/transcripts: from the qualitative aspects of the study.

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

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

Participants will give their explicit consent for the transfer of study data to the University of Birmingham (BCTU) for analysis. Participants will always be identified using their unique trial identification number and partial date of birth in correspondence with the BCTU. Participants will give their explicit consent for the movement of their consent form, giving permission for BCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to BCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

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

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

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

## 18. INSURANCE AND INDEMNITY

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

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

## 19. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the CI and authorship will be determined by the trial publication policy.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of sponsor (University of Birmingham). Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

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