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The Oxford Renal (OxRen) Cross-Sectional Study of Chronic Kidney Disease in the UK - A Protocol.

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Abstract

Introduction

Chronic Kidney Disease(CKD) diagnosed with objective measures of kidney damage and function has been recognised as a major public health burden. Independent of age, sex, ethnicity, and comorbidity, strong associations exist between cardiovascular disease, mortality, morbidity and CKD, defined by reduced glomerular filtration rate and increased urinary albumin excretion. Detection of CKD within the population is therefore a priority for health systems.

Methods and Analysis

Fifteen thousand patients aged 60 years or over meeting the inclusion criteria will be invited to the study. Recruitment will be stratified to represent the distribution of socio-economic position in the UK general population. Patients will be excluded if terminally ill (expected survival <1 year), or if they have received a solid organ transplant.

Patients will attend up to two screening visits, to determine if they have CKD, followed by an assessment visit where demographic and physiological parameters will be recorded alongside questionnaires on exercise, diet, cognitive assessment and quality of life. Blood and urine specimens will be taken for immediate routine assays as well as for freezing pending peptide and genetic studies. Patients will have office and home BP measurements as well as pulse wave velocity assessment. Healthcare costs of screening and subsequent monitoring will be calculated.

Ethics and Dissemination

The protocol and related documents have been approved NRES Committee South Central - Oxford B – Reference 13/SC/0020.

Findings will be presented to a primary care audience (at scientific meetings of the Society for Academic Primary Care) and a renal audience (at the Renal Association). Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. The findings of the study will be submitted for publication in an appropriate peer-review medical journal. We would seek to publish in open access journals to encourage the dissemination of the information.

INTRODUCTION

Chronic Kidney Disease (CKD) is a worldwide health problem associated with high morbidity and mortality [1 2] and its prevalence is increasing [3]. Decreased renal function is a well known predictor of hospitalisation [4], cognitive dysfunction [5] and reduced quality of life [6 7]. Cardiovascular disease (CVD) is the primary cause of morbidity and mortality in this population where CKD is regarded as both an accelerator of CVD risk and an independent risk factor for CVD events [4]. Even the earliest stages of CKD are known to be associated with significantly increased risks of cardiovascular morbidity, premature mortality, and decreased quality of life [1 4 8]. While the CVD risk in end stage renal failure is high, the healthcare burden resides in early stages of disease as it is more prevalent, affecting around 35% of those over 70 years [9].

Interventions for patients with CKD can delay progression, decrease morbidity [10] and decrease mortality rates [11]. Antihypertensive medications blocking the renin-angiotensin-aldosterone system (RAAS) - such as angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers - have been systematically proven to be of benefit to patients with proteinuric CKD [12]. A recent systematic review by Sharma reported a statistically significant reduction in the risk of doubling of creatinine levels (in people with stage 3 CKD stratified by baseline 24-hour urinary protein) in those with ≥ 3 g/L of proteinuria (66%, 95% CI 34 to 82). Numerous other studies examining the role of interventions have also been shown to be effective in CKD to delay progression and/or improve mortality rates, including statin therapy [13], blood pressure lowering [14 15], control of metabolic bone disease [16] and lifestyle changes in diet [17] and physical activity [18].

Early stages of CKD are defined on the combination of kidney damage (quantified with evidence of renal damage - imaging or proteinuria) and decreased kidney function (defined as glomerular filtration rate [GFR] estimated from serum creatinine concentration). The National Institute for Clinical Excellence (NICE) [19] recommends using urine creatinine concentration for estimation of GFR using the Modification of Diet in Renal Disease study (MDRD) four variable equation [20]. NICE highlight the need for strategies aimed at earlier identification and (where possible) prevention of progression to established renal failure [19]. Since CKD is usually asymptomatic until later stages of the disease (Stage 4+), it may be beneficial to establish efficient detection mechanisms for patients with early-stage CKD [21].

Screening enables early detection, but mass screening of all age groups for kidney disease is expensive, low yield, and not cost-effective [22]. There is an age related decline in renal function, and it has been shown in contemporary UK data sources [9 23] - including retrospective laboratory data, audit studies and GP record systems - that from age 60 years, CKD prevalence increases rapidly. It may, therefore, be reasonable to screen systematically in this age group.

Aims: The primary aim is to establish the number of previously undetected cases of CKD. They will be detected by screening of a blood test for the estimation of glomerular filtration rate (eGFR) and a quantification of urinary protein.
The secondary aims are to 1) determine the cost-effectiveness of screening for CKD; 2) determine the prevalence of selected risk factors and levels of distribution of estimated kidney function in screen-detected patients.

METHODS AND ANALYSIS

Study design

This cross-sectional screening study is part of the Oxford Renal Study (OxRen), recruiting from a population of patients aged 60 years and older who are registered at GP surgeries within the Thames Valley region. OxRen consists of a further study that will longitudinally follow up patients who are diagnosed with CKD through this screening study and elsewhere.

The Thames Valley has 278 practices and supports a population of approximately 2.3 million. OxRen consists of a co-ordinating centre, the NIHR School for Primary Care Research (SPCR) Oxford and a minimum of eleven GP surgeries (covering a population of approximately 60,000 patients) from which patients are recruited. There will be up to three additional practices that will serve as a control group for the cost-effectiveness analysis.

Inclusion criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female, aged 60 years or above.
- No blood test within last 12 months.

Exclusion criteria

In order to be as inclusive as possible there are a minimal number of exclusion criteria:

- Not previously diagnosed with CKD (either coded by their GP or someone else and any recorded eGFR > 90 mL/min/1.73m^2 within the last 12 months or other renal disease
- Terminally ill (expected survival <1 year)
- Previous solid organ transplant
- Patients whom the GP feel are inappropriate for the study

Recruitment Process

Patients will be identified by staff, at GP surgeries, who will review electronic patient records and select patients who fulfil the study criteria.

A spread of practices representative of the UK general population will be achieved by stratifying practices into national quartiles of deprivation, taking into account practice size and, selecting practices that agree to take part sequentially until each quartile practice target is reached. Over the course of recruitment the sequential practice selection strategy will be examined to ensure practices serving high proportions of ethnic minorities are included in the final places if this has not already occurred in earlier recruitment.

Study Patients

Fifteen thousand patients (15,000) aged over 60 years old from primary care will be invited by letter to be part of the study. The letter will include the study patient information sheet. Patients will be given a contact number and email address of the study team who will be able to answer any questions they might have.

The patients' first visits will depend on any previous record of impaired renal function as defined by an abnormal eGFR (eGFR ≥ 60 mL/min/1.73m^2 and albumin to creatinine ratio (ACR) ≥30 mg/g or eGFR <59 mL/min/1.73m^2 regardless of ACR):

No prior record of abnormal eGFR: Patients with no prior record of impaired renal function will attend the first screening visit (Visit 1) for a blood test to determine eGFR. If at this visit they are deemed to have impaired renal function they will then proceed to a second screening visit (Visit 2) after a 3-month interval to have their

CKD diagnosis confirmed. The results must be at least 3 months apart and within the last 12 months to be in line with NICE guidance.

Participants within 5 mL/min/1.73m^2 of the upper limit eGFR range of Stage 3a CKD (i.e. between 60 and 65 mL/min/1.73m^2) will be invited to the second screening visit (Visit 2). This is to ensure the intra-individual variation in eGFR does not lead to a false negative classification of disease. Patients will also undergo a urinary ACR.

One positive result for CKD: Patients with a previously recorded single result for impaired renal function (within the last 12 months), defined by an abnormal eGFR and/or urinary protein will have CKD status determined with a confirmatory blood test for calculation of eGFR as well as urinary ACR. If CKD is diagnosed then they will then attend the baseline assessment (Visit 3).

All patients diagnosed with CKD through at least two abnormal eGFRs and/or ACRs will attend the baseline assessment visit (visit 3). If a patient's eGFR and/or ACR tests are abnormal at visit 1 and normal at visit 2 they will be defined as having transient CKD and will proceed to the baseline assessment visit (visit 3). All other patients will not attend the baseline assessment visit.

CKD Definition

CKD diagnoses will be established through eGFR and evidence of renal damage (proteinuria - ACR) to define the early stages. The eGFR will be estimated using the MDRD equation using an IDMS compatible creatinine assay as recommended by NICE. The CKD-EPI equation for estimation of eGFR will also be used as a method to determine if there is any difference in CKD categorisation as the MDRD may underestimate the actual GFR in healthy patients by up to 29% [24]. Albuminuria is defined using ACR with micro-albuminuria being an ACR of 3.4 mg/mmol (30 mg/g) to 33.9 mg/mmol (299 mg/g). Sex specific cut offs for ACR will also be used [25]: micro-albuminuria (1.9 mg/mmol (≥17 µg/mg) in men and 2.8 mg/mmol (≥25 µg/mg) in women). Macro-albuminuria will be defined as an ACR ≥34 mg/ mmol (300 mg/g). Stages of CKD will be defined in line with NICE guidelines as shown in Table 1.

CKD Stage	eGFR (mL/min/1.73m^2)	ACR (mg/g)
Stage 1	≥ 90	≥30
Stage 2	60-89	≥30
Stage 3a	45–59	-
Stage 3b	30-44	-
Stage 4	15-29	-
Stage 5	<15	-

Table 1 – CKD stages defined by estimated Glomerular Filtration Rate(eGFR) and Albumin Creatinine Ratio(ACR)

Outcome Measures

Primary outcome: The proportion of patients diagnosed with CKD from a primary care population of patients aged 60 years+ demographically representative of the UK general population.

Secondary outcome: 1) The cost and cost effectiveness of screening for CKD in the 60+ age group 2) The prevalence of selected risk factors and the distribution of eGFRs within that group.

Study Procedures

Patient visits are at their own GP practice. Practices will be trained in study procedures including obtaining informed consent. The study will be carried out in accordance with the Declaration of Helsinki and OxRen has been approved by Ethics Committee South Central Oxford REC B - 13/SC/0020. An algorithm, that specifies what nephrology advice is given should a patient be diagnosed with CKD, will be provided to GPs. Patients who are identified for the first time as having advanced CKD (eGFR <30 mL /1.73 m^2, Stage 4+) will be referred to a specialist renal clinic.

Screening Visit (Visit 1)

The study will be explained to potential participants and they have the opportunity to ask questions about the study. Consent will be sought and potential participants have as much time as required to decide if they wish to participate. If they consent,

patients will then have a blood test for calculation of kidney function using the MDRD eGFR and urinary assessment for ACR.

Patients who test positive will proceed to Visit 2 - as will patients within 5 mL/min/1.73m^2 of the upper limit eGFR range of Stage 3a CKD (i.e. between 60 and 65 mL/min/1.73m^2). Patients who test negative will not proceed.

Screening Visit (Visit 2)

Patients with a single eGFR and/or ACR in the range for a CKD diagnosis will have a second confirmatory blood test for kidney function performed at this visit. If after this visit the patient has two abnormal results for impaired renal function they will be classified as being diagnosed with CKD and invited to attend the baseline assessment (Visit 3). Patients with an eGFR >60 ml/min/1.73m^2 but persistent proteinuria as evidenced by a raised ACR at Visit 2 will also be diagnosed and invited to attend baseline assessment.

If on the second occasion the patient's blood results do not fall within the criteria for CKD diagnosis then the patients will still be invited to the assessment baseline visit (visit 3) but classified as having "transient CKD" and will proceed to the next visit (Visit 3 – Baseline Assessment).

Baseline Assessment visit (Visit 3)

The baseline assessment visit will occur after the screening visits (Visits 1 and 2). Patients have full demographic details recorded including age, self-assigned ethnicity, educational status, residential postcode, clinical history, past medical history, family history, smoking and alcohol use, major co-morbidities, current medication, physical examination (weight, height, and waist circumference using a validated method) and BP measurement using a validated automated device. Patients will have a 12 lead electrocardiograph (ECG).

Blood specimens will be obtained for creatinine and electrolytes, blood glucose, hepatic and bone profiles, HbA1c, lipids (total cholesterol, LDL, HDL), urate, B type natriuretic peptide (BNP), Cystatin C, full blood count and a random spot urine sample for the calculation of the albumin to creatinine ratio (ACR). Serum creatinine will be measured by automatic analyser (using the Jaffe method calibrated to IDMS values). Five sample bottles (20 ml/s in total) will be required to collect the blood

specimens for analysis by the biochemistry laboratory. One 20 ml sample bottle will be required for the collection of urine. All samples will be sent to the laboratory from the GP practices in the routine way.

Additional samples (5 bottles, 25 mls) will be collected and stored at -80°C for future genetic and protein testing. One additional 20 ml sample bottle for the collection of urine will be collected. All samples will be sent to the lab with the blood specimens for the routine haematology and biochemistry. Once at the laboratory they will be prepared and sent on to the bio-bank.

Patients will be given questionnaires to be completed at visit 3. taking approximately 50 minutes to complete:

- Quality of life – Assessed using the EQ-5D-5L questionnaire - 6 items taking approximately 5 minutes to complete.
- Dietary assessment – Assessed using the Million Woman Study Diet (MWS-D) Questionnaire – 9 items taking approximately 15 minutes to complete.
- Physical activity – Assessed using the International Physical Activity Questionnaire: Short version (iPAQ-Short) - 7 items taking approximately 10 minutes to complete.
- Cognitive function – Assessed using the Montreal Cognitive Assessment questionnaire (MoCA) - 8 tasks requiring approximately 20 minutes to complete.

Patients are provided with a BP monitor suitable for home use and asked to document their blood pressure 3 times daily over a typical week and to return it. We also seek to provide patients with a 24h blood pressure monitor. The device will be provided following the baseline visit for use on one day in a typical week and will then be returned. Further BP information will be collected using a Pulse Wave Analysis (PWA) machine that will be used on patients at their clinic visits.

Hypertension will be defined as a clinic measurement of systolic BP of 140 mmHg or greater, diastolic BP of 90 mmHg or greater confirmed with ambulatory blood pressure monitoring [26] or use of antihypertensive medications irrespective of BP. Diabetes mellitus will be defined as an HbA1c of 48 mmol/mol (6.5%) or greater or use of hypoglycemic agents [27]. A history of cardiovascular disease is defined as a history of coronary arterial disease, cerebrovascular disease or peripheral arterial

disease. Body mass index (BMI) will be calculated based on weight and height (weight [kg]/height [m^2]). Any new diagnosis of disease will be followed up with the patients GP informing them of the NICE guidelines in the relevant area.

Procedures

Oxford University Hospitals NHS Trust Clinical Biochemistry laboratories will perform all the tests using standardised methods that are periodically recalibrated against reference samples.

Number of Patients

Fifteen thousand patients will be invited to the study. We estimate a recruitment rate of 40% per practice giving a cohort of 6000 patients. We require a total practice population of 82,500 (or about 11 GP surgeries) determined from an average practice size with a patient list of 7500. This is based on data from the Oxford Vascular Study of 4627 people (Jan 2012) within Oxfordshire, that detailed the percentage of an average practice list that is over 60 is 21% [28].

Analyses

To estimate the benefits of screening for the diagnosis of CKD using a blood test for the estimation of glomerular filtration rate (eGFR), we have based the calculation on the cohort of 6000 patients. Prevalence estimates for CKD vary between 20% [23] and 28% [9] for patients who are ≥ 60 years old. Using a sample size of 6000 and a 20% and 28%, as lower and upper limits for the estimated prevalence, then this number of patients with CKD will yield a precision (defined as the total length of the 95%CI) of between 1% and 1.1% around the prevalence estimate.

Descriptive analyses will be used to characterise the participant population by sociodemographic data, health status, and lifestyle factors. Prevalence and mean values of CKD stages and selected conditions (diabetes, hypertension, etc.) by sex, age, and race/ethnicity will be examined using chi-square statistics for categorical variables and Wilcoxon's rank sum for continuous values. We will carry out univariate analyses to explore associations between different patient characteristics and eGFR levels as a continuous variable at baseline and we will explore multivariate models that will include these characteristics such as: age, gender, and the other factors we measure during the baseline assessment.

Economic Analysis

The health economic analysis will consider three questions:

- What is the cost to the NHS of screening for CKD, in terms of the cost of the screen and subsequent health care costs related to treating and managing the disease?
- How cost-effective is systematic screen-detection compared with current detection of CKD via the provision of routine care, in terms of cost per additional case detected?
- What is the long-term cost-effectiveness of screen detection/active case finding in terms of cost per additional quality adjusted life (QALY) year gained?

For the purpose of the economic analysis, the cohort of individuals invited to be screened will need to be compared with a control cohort with no screening. It is proposed that up to 3 practices will be recruited to act as a control group. The economic evaluation will be split into two components. The cost per case detected will be estimated using data collected from individuals in the cohort. The long-term cost-effectiveness of screening/case-finding will be determined by developing a life-time disease model for CKD.

Data collection

Resource use and costs: The cost analysis will adopt an NHS perspective.

Screening/case finding cost: The cost of screening/case finding will be determined using data from the invited cohort of individuals. Resource use and unit costs will be collected in relation to the identification of the cohort through routine clinical records, the invitation and diagnostic tests performed.

Cost related to follow-up health care: Data on health care resource use will be collected from all individuals in the 'invited to-screen' and 'no screen' cohorts, including all relevant hospital and GP consultations, medications, referrals, tests and equipment. Where possible, data on resource utilisation will be collected from electronic patient records. One–third of the records for this cohort will be amenable to this form of data collection. For the remainder of the cohort we will set up an electronic data-capture for a number of pre-determined health-care resource-use events which are likely to represent key cost-drivers, such as medications and hospitalisations.

Where possible, we will value our items of health care resource utilisation using appropriate unit costs (staff costs, equipment, drug costs etc.) obtained from published sources, including the most recent version of Unit Costs of Health and Social Care and NHS Reference Costs. We will estimate unit costs that are not available from secondary sources using the approach used in the most recent version of Unit Costs of Health and Social Care.

Outcomes/utility data: The outcome of interest for the purpose of the economic evaluation will be number of CKD cases detected/diagnosed. This will be obtained directly from the screen-detected cohort and compared with the numbers arising in the 'no-screen' control group.

NICE recommends the use of preference-based health-related quality of life (HRQL) measures for the purpose of determining Quality Adjusted Life Years (QALYs) for economic evaluation. The use of quality-adjusted life years aims to capture the impact of disease progression and non-fatal events on quality of life in addition to any impact on survival. The EQ-5D (Available in Appendix C) will be used to measure patient health-related QoL across 5-dimensions, mobility, self-care, usual activities, pain/discomfort, anxiety and depression. It will be collected from the cohort at baseline and at their annual follow-up contact. EQ-5D scores at each time point will be converted into a utility score on a 0 to 1 scale where 0 is equivalent to dead, and 1, to perfect health. This conversion will be made using the new algorithm based on the UK value set currently being conducted by the EuroQol Group, if available at the time of analysis. If not available, the current crosswalk algorithm provided by the EuroQol group and algorithm estimated by Dolan et al. derived from a survey of the UK population (n=3337), will be used. Utility values in the tariff set range from no problems on any of the five dimensions in the EQ-5D descriptive system (value=1.0) to severe or extreme problems across all five dimensions (value=−0.594) [29 30]. The utility scores will be combined with survival data to estimate the quality adjusted life-years (QALY's) required for the cost-utility analysis. This utility data will be used for the purpose of modelling the cost per QALY of screening for CKD.

Analysis

Missing data: The resource-use/cost and EQ-5D data will be investigated to ascertain the extent of missing data and whether this is due to random missingness

and/or censoring. Standard methods will be used to handle any relevant missing data [31 32].

Cost Analysis: The focus of studying the healthcare resource use is to investigate how screening for CKD affects the health care costs of treating and managing the disease. With the aim of the economic analysis to estimate how the costs of the 'screen/case-finding' minus the difference in health care costs between the screen-detected and routinely diagnosed group of patients balances against the health care benefits. A three-stage analysis of the healthcare resource use and their costs will be conducted. First, the cost associated with the case-finding/screen will be estimated using the resource-use related to the identification of the cohort through routine clinical records, the invitation and diagnostic tests performed (including staff time, equipment, tests and consumables). Second, the impact of the screen-detection on (1) all healthcare resource use/costs, (2) kidney disease specific healthcare resource use/costs, and (3) CVD related healthcare resources costs will be evaluated over the duration of the study (3 years). Third, a regression framework that relates healthcare costs to baseline characteristics age, gender, kidney disease stage, progression, other co-morbidities and CVD will be developed. The objective being to provide estimates of healthcare costs for different kidney disease stages and CVD events to inform the extrapolation model (see below). A similar regression framework approach will be used for the EQ-5D tariff data at the different data collection time-points, again to inform the extrapolation model.

Cost per-CKD case detected: The incremental cost-effectiveness of screening compared to routine diagnosis of CKD will be determined using the cost analysis data (described above); cost of screening plus its cost impact on treating and managing CKD in the 'screen-detected' cohort will be compared with health care costs related to CKD in the routine diagnosis cohort. This incremental cost will be weighed up against the incremental benefit in terms of the incremental CKD cases detected by screening compared to routine diagnosis over the initial two-year period that the entire screened cohort will run. Discounting at a rate of 3.5% will be applied. By using data from the cohort that uses Thames Valley practices only, there may be limits to the generalisability of the results of the study. This will be explored within the economic evaluation using extensive sensitivity analysis. Key parameters will be varied to determine the impact of changes on results. Case finding in different patient sub-groups will also be considered. Non-parametric bootstrapping and probabilistic

sensitivity analysis will be undertaken to explore uncertainty in the confidence to be placed on the results of the economic analysis and cost effectiveness acceptability curves will be presented.

Cost per QALY of screen-detection in CKD: Building on the results of the cohort-based economic evaluation (incremental cost-per-case detected), a model-based analysis will be conducted to estimate the cost per QALY of screening for CKD. The methods used will depend on the available cohort data, but will either use parametric methods as set out by the NICE Decision Support Unit [33] or use a lifetime decision-model (developing a Markov model similar to that used by Manns and colleagues [33] or adapting available CKD models. This will be based on the individual patient data (using the results from the regression analyses outlined above) from the study and external data (where required). It will be carried out from an NHS and Personal Social Services perspective, to take into account health care costs and longer term social care costs of cardiovascular events and the impact on life expectancy, quality adjusted life expectancy. The model will be run over remaining patient lifetime, with costs and benefits discounted at a rate of 3.5%. The lifetime cost-effectiveness analysis will be driven by the decision analytic model and the way treatment effects are propagated in the model. Extensive deterministic sensitivity analysis will be undertaken to assess the impact of changing the values of key parameters and will be used to explore the importance of modelling assumptions. Probabilistic sensitivity analyses will be conducted to deal with uncertainty in model parameters and cost-acceptability curves will be presented.

ETHICS AND DISSEMINATION

Ethics

The Chief Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki and ensure this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996. Site staff will be fully trained in Good Clinical Practice (GCP) as appropriate to their study role.

The protocol and related documents have been approved by an appropriate Research Ethics Committee (NRES Committee South Central - Oxford B – Reference 13/SC/0020). The Chief Investigator will submit and, where necessary, obtain approval for all substantial amendments to the original approved documents.

Ensuring patient confidentiality is an established and robust process within the Primary Care Clinical Trials Unit (PC-CTU) where the study data will be run. All staff adhere to the principles of GCP and the Data Protection Act, 1998. It is the PC-CTU's preferred procedure that patients will only be identified on study documents by use of a unique screening id and, if diagnosed with CKD, a unique participant ID, which cannot be used to identify individual participants. All study documents such as case report forms holding patient information are held securely with restricted access either electronically or in paper format.

The holding of patient identifiable information will be kept separate from the information collected on the patient and will be used only to follow-up the patient. For example if a member of the research team needs to make a follow up phone call to a patient or recall them for their annual follow-up visit. Case report forms and all other documents holding identifiers are anonymised as soon as possible with the process of management being outlined in detail within the ethics application and in study specific procedures.

Dissemination

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the National Institute for Health Research Biomedical Research Centre (NIHR BRC) and the NIHR School of Primary Care Research funded the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

The results of this study will be of relevance to the renal research community and the primary care research community. We would present our findings to both a primary care audience (e.g. at scientific meetings of the Society for Academic Primary Care and the Confederation of Primary Care Research Organisations) and a renal audience (e.g. at the Renal Association and American Society of Nephrology).

It is expected that this study will generate a high impact manuscript. The findings of the study will be submitted for publication in an appropriate peer-review medical journal. Where possible we would seek to publish in open access journals to encourage the dissemination of the information.

AUTHORS CONTRIBUTIONS

RH, RM, DL, CO'C & NH conceived and designed the study. NH, BT, SF, DL are supervising all recruitment and enrolment. JW is providing support and interpretation for the health economics, RP is supervising the statistical analysis, BS is providing laboratory/pathology supervision & analysis, CP & CO'C are providing nephrology expertise and oversight. All authors contributed substantially to the manuscript's revision. RH takes responsibility for the paper as a whole.

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COMPETING INTERESTS

The authors declare that they have no competing interests

FIGURE LEGENDS

Figure 1 – Patient Flow Diagram. * NICE criteria for diagnosis of CKD – 2 or more results at least 3 months apart in the last 12 months. ** (eGFR < 60 mL/min/1.73m^2) or (eGFR > 60 mL/min/1.73m^2 AND ACR > 30) at least one result must be from V1 or V2

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