# Title of the project

**Point-of-care creatinine tests to assess kidney function before administering intravenous contrast for computed tomography (CT) imaging**

# Name of External Assessment Group (EAG) and project leads

**Centre for Reviews and Dissemination and Centre for Health Economics - York EAG**

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## Plain English Summary

Before hospital CT scans are performed, a contrast agent is usually needed to improve image quality. The improved images help clinicians when making decisions about diagnoses or future treatment decisions, across a range of diseases and illnesses. When contrast agents are given intravenously they may occasionally damage the kidneys, particularly in patients whose kidneys already do not work well. A creatinine blood test is therefore used to identify these patients (as their creatinine levels are usually high) so that steps can be taken to minimise or remove the risk of kidney injury resulting from contrast agents.

Before a contrast-enhanced CT scan takes place some patients already have a recent creatinine blood test result available, as a result of other medical investigations. Their blood samples will have been analysed in a central laboratory but this process usually takes at least an hour. Other patients do not have a recent creatinine measurement which means their CT scan may be delayed or rescheduled. Sometimes, to avoid risking kidney injury, patients may have scans without having received a contrast agent, though this produces less accurate images. “Point-of-care” devices (handheld, table-top or portable) can rapidly measure creatinine, usually from finger-prick samples, to identify patients at high risk of kidney injury. However, their results may not be as accurate as those derived from laboratories so it is unclear whether or not these devices are beneficial.

The purpose of this project is to assess the benefits, harms and the cost-effectiveness of point-of-care creatinine tests used immediately prior to non-emergency, contrast-enhanced CT scans. We will identify relevant studies and analyse the data to see whether the more widespread use of point-of-care creatinine tests can be considered a cost-effective use of NHS resources.

## Decision problem

The purpose of this assessment is to assess the clinical and cost-effectiveness of point-of-care creatinine tests to assess kidney function, for people who need contrast-enhanced computed tomography (CT) imaging in a non-emergency situation and who do not have a recent serum creatinine measurement.

### Interventions

Point-of-care (POC) tests provide rapid measurement of creatinine, a muscle waste product, which is used to evaluate kidney function. When used together with data on age, sex and race, creatinine measurements can also be used to calculate another indicator of kidney function, the estimated glomerular filtration rate (eGFR). Different methods exist to calculate eGFR; in adults the NICE guideline on chronic kidney disease recommends using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation. Another frequently used equation is the MDRD Modification of Diet in Renal Disease (MDRD) study equation. The eGFR result is then used to stratify a patient’s risk before a contrast agent is administered.

Kidney function testing is often done before patients have a diagnostic scan or interventional imaging procedure. This is because the contrast agents used to improve image quality - such as iodine - can sometimes cause acute kidney injury (AKI), particularly in high-risk patients. If patients

do not have a recent creatinine or eGFR measurement, their imaging may be delayed or cancelled. Alternatively, if the patient is thought to be at low risk of kidney injury the planned contrast agent may be given, risking AKI. Sometimes, to avoid the risk of AKI, patients may have unenhanced imaging which are less accurate than contrast-enhanced imaging and therefore could lead to the need for further tests or suboptimal management of the underlying condition for which imaging is required. The imaging procedure may also be performed with a lower dose or volume of contrast agent and/or with prophylactic hydration, to reduce the risk of AKI.

Point of care creatinine testing may minimise the risk of kidney injury, reduce the incidence of delayed or cancelled scans and imaging procedures, and improve patient experience. However, it is important to recognise that AKI after contrast-enhanced imaging is not always caused by the contrast agent. Post-contrast AKI (PC-AKI) is a general term used to describe a sudden deterioration in renal function that occurs soon after intravascular administration of contrast media (within 48 hours). Contrast-induced AKI (CI-AKI) is AKI *caused* by the administration of the contrast media, and should therefore be seen as being a subgroup of PC-AKI.

POC creatinine test devices are either handheld, portable or table-top and require only very small blood samples (usually obtained via finger-prick). Some devices use test cartridges and others test strips. Creatinine may be measured either as one of numerous analytes, or as a single measurement. The following technologies (manufacturer in brackets), which are relevant to this assessment, are CE marked and use an enzymatic method to measure whole blood creatinine, which is used to calculate eGFR: Nova StatSensor (Nova Biomedical), i-STAT Alinity (Abbott), ABL90 FLEX PLUS (Radiometer), ABL800 FLEX (Radiometer), Dri-chem NX500 (Fujifilm), epoc Blood Analysis System (Siemens Healthineers), Piccolo Xpress (Abaxis).

## Comparator technologies

Central laboratory analysers are often used to measure serum creatinine. There is uncertainty about how concordant POC tests results are with the more accurate results obtained from central laboratories. The alkaline picrate (Jaffe) method is a colourimetric assay often used in central laboratories but it can be affected by interfering substances (such as ketones and bilirubin). Alternatively, an enzymatic laboratory method could be used which is less prone to interference, but more expensive. Although both methods take only minutes to give a result, the whole-process turnaround for an urgent sample is around one hour. In order to reduce error and maximise the comparability of creatinine measurements between laboratories, methods should be calibrated against isotope-dilution mass spectrometry (ID-MS).

## Population and relevant subgroups

The relevant population is adults needing a non-emergency outpatient CT scan using an intravenous contrast agent and who do not have a recent serum creatinine measurement.

CT imaging can be performed across a number of clinical indications so the population will include patients with different underlying conditions. These may determine different patient profiles of i) risk of adverse events (particularly AKI), ii) associated comorbidities and iii) outcomes following alternative imaging decisions. The accuracy of POC creatinine tests in identifying people at different levels risk of AKI and optimise subsequent imaging decisions may differ across conditions.

Although many possible clinical risk factors for AKI have been suggested and studied, most relate to chronic kidney disease or AKI rather than specifically to PC-AKI. Impaired renal function appears to be the most important risk factor for PC-AKI. Existing kidney disease will, therefore, be an important predictor of risk for patients undergoing CT imaging. The subgroups relevant to this appraisal can be defined as people at higher (and lower) risk of PC-AKI and those with (and without) known existing kidney disease.

In addition, the type, route of administration and amount of contrast required for imaging will also be considered. Different types of each agent are available and the dose can vary depending on the type of scan and the patient's risk of AKI. Risk factors associated with intravenous contrast media include contrast agent dose and receiving more than one dose across a short time-frame (a few days).

### Place of the intervention in the care pathway

The NICE guideline on acute kidney injury recommends that an eGFR measurement should be taken within three months of administration of iodinated contrast agents to adults. The European Society of Urogenital Radiology guideline on post-contrast acute kidney injury (2018) recommends that for people with an acute disease, an acute deterioration of a chronic disease or who are inpatients, an eGFR measurement should be taken within seven days before contrast medium administration. The eGFR threshold at which there is deemed to be a risk of developing CI-AKI varies across guidelines. The Royal Australian and New Zealand College of Radiologists guideline on iodinated contrast media (2016) states that the risk of CI-AKI is uncertain for people with an eGFR of <45 ml/min/1.73m$^2$, but if there is a risk, it is greatest in those with an eGFR of less than 30 ml/min/1.73m$^2$. The European Society of Urogenital Radiology guideline states that the risk of PC-AKI in patients with an eGFR ≥ 30 ml/min/1.73m$^2$ after intravenous and intra-arterial contrast media administration with second-pass renal exposure is very low, but there is conflicting evidence on the risk for intra-arterial CM administration with first-pass renal exposure.

## Objectives

The aim of the project is to determine the clinical and cost-effectiveness of point-of-care (POC) creatinine tests to assess kidney function, for people who need CT imaging in a non-emergency situation and who do not have a recent serum creatinine measurement. To achieve this, the following objectives are proposed:

### Clinical effectiveness

- To perform a systematic review of studies which compare the results of POC creatinine tests with laboratory-based tests to assess kidney function in a non-emergency setting.
- To perform a systematic review of the clinical impacts and implementation of POC creatinine tests to assess kidney function before CT imaging. This will include assessment of the associated mortality and morbidity, patient-centred outcomes, adverse events, acceptability to clinicians and patients and compliance.

### Cost-effectiveness

- To perform a systematic review of published cost-effectiveness studies of the use of POC creatinine tests in a secondary care setting to assess kidney function before contrast-enhanced imaging.

- To develop a decision model to estimate the cost-effectiveness of the use of POC creatinine tests to assess kidney function before contrast-enhanced imaging. The relevant population is people who need contrast-enhanced imaging in a non-emergency situation and who do not have a recent serum creatinine measurement.

- The objective of the decision model will link the diagnostic accuracy of POC creatinine tests to short-term costs and consequences (e.g. the impact on cancelled or delayed appointments, use and volume of contrast media and associated risks such as PC- AKI). We will link the short-term risks of PC- AKI to potential longer-term costs and consequences (e.g. chronic kidney disease, end stage renal disease and death) using the best available evidence. Depending on the robustness of the evidence, we may also undertake additional exploratory analyses using assumptions and expert opinion.

- We will also assess the feasibility of extending the decision model to include other clinical outcomes that could be affected by any changes in the imaging decision based on the POC tests. These outcomes could include: (i) any anxiety associated with having a delayed or cancelled CT scan and (ii) morbidity and mortality implications of performing unenhanced scans, or using lower doses of contrast agent. However, given that these outcomes will differ depending on the specific population and the underlying reason for imaging, we envisage that any extension of this nature will need to be constrained to a specific population/reason for the scan. The practicalities and value of developing a specific 'exemplar' application (with potentially limited generalisability) will be considered versus using a simpler and more generic approach (e.g. using threshold analysis to determine the magnitude of any impact necessary to result in a different decision based on conventional cost-effectiveness decision rules).

- The cost-effectiveness of the alternative POC tests will be expressed in terms of incremental cost per quality-adjusted life year and/or net health (or monetary) benefits.

## Methodology

### Systematic review of diagnostic accuracy and clinical effectiveness

The systematic review will be conducted following the general principles recommended in CRD's guidance and reported in accordance with the PRISMA statement.

**Literature searching**

Comprehensive searches of the literature will be conducted to identify studies relating to POC tests for measuring creatinine levels in the blood.

The following databases will be searched: MEDLINE, PubMed, EMBASE, CINAHL, Health Management Information Consortium (HMIC), Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), CENTRAL, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) Database, NHS Economic Evaluation Database (NHS EED) and EconLit.

Ongoing and unpublished studies will be identified by searches of ClinicalTrials.gov, Conference Proceedings Citation Index: Science, EU Clinical Trials Register, Open Access Theses and Dissertations, Proquest Dissertaions & Theses A&I, PROSPERO, WHO International Clinical Trials Registry Platform portal and manufacturer websites. Abstracts from any recent conferences which are thought to be relevant to the review will also be consulted.

A search strategy for Ovid MEDLINE is included in Appendix 1. The MEDLINE strategy will be translated to run appropriately on the other databases and resources. No language or date restrictions will be applied to the searches. A study design search filter will not be used.

Reference lists of relevant reviews will be scanned in order to identify additional potentially relevant reports.

Searches for studies for cost and quality of life data will also be undertaken, as determined by the economic model. Appropriate searches will also be made to identify evidence to inform estimation of the probability of an acute kidney injury following a CT scan.

Pragmatic supplementary searches for primary and secondary data (including existing systematic reviews) will be carried out as necessary, depending on the gaps and limitations identified during the review of clinical and economic evidence and during the development of the model. For example, studies will need identifying which report data on important clinical outcomes following acute kidney injury.

### *Contact with study authors and manufacturers*

It is anticipated that many studies may not report sufficient data in publications to perform full syntheses or fully populate the economic model. Therefore, study authors and manufacturers may be contacted to seek detailed diagnostic and other clinical data as appropriate.

## Study selection

Two reviewers will independently screen all titles and abstracts. Full papers of any titles and abstracts that may be relevant will be obtained where possible, and the relevance of each study assessed independently by two reviewers according to the criteria below. Any disagreements will be resolved by consensus or, where necessary, by consulting a third reviewer. Conference abstracts will be eligible and attempts will be made to contact authors for further data.

The following eligibility criteria will be used to identify relevant studies:

### *Participants*

To maximise the amount of data on test accuracy the eligible population for test accuracy studies will be any adult patient group receiving POC creatinine testing compared with laboratory testing in a non-emergency setting.

For studies reporting clinical or implementation outcomes only studies of adult patients receiving POC tests before CT imaging in a non-emergency, outpatient setting will be included.

### *Interventions*

For studies of test accuracy eligible interventions will be CE marked POC devices which can analyse whole blood samples for creatinine. These include:

- Nova StatSensor (Nova Biomedical)
- i-STAT Alinity (Abbott)
- ABL90 FLEX PLUS (Radiometer)
- ABL800 FLEX (Radiometer)
- Dri-chem NX500 (Fujifilm)
- epoc Blood Analysis System (Siemens Healthineers)
- Piccolo Xpress (Abaxis)

For studies reporting clinical or implementation outcomes any POC creatinine device used in a radiology or imaging department setting will be eligible.

### *Comparators*

- Non-urgent (results available after an hour) laboratory-based serum creatinine measurement: (a) Jaffe method; (b) enzymatic method
- Urgent (results available within an hour) laboratory-based serum creatinine measurement: (a) Jaffe method; (b) enzymatic method
- No testing, clinical judgement alone

### *Reference standard*

The reference standard is also laboratory-based measurement of serum creatinine (i.e. the same as the comparator).

### *Outcomes*

The eligible intermediate outcome measures are:

- Diagnostic accuracy of POC creatinine devices compared with laboratory-based creatinine devices
- Correlation between POC creatinine devices and laboratory-based creatinine devices
- Test failure rates
- Number of delayed, or cancelled and rescheduled scans
- Volume of intravenous contrast material used
- Number of unenhanced scans
- Number of hospital admissions
- Hospital length of stay

Studies are likely to report accuracy and correlation outcomes using different definitions (e.g. eGFR, serum creatinine), different cut-offs (e.g. eGFR <30 mL/min vs. <60 mL/min) and different adjustments. Furthermore, some studies will also report accuracy between the POC devices and the reference standard in terms of clinical concordance or risk classification. All relevant outcome

definitions and cut-offs will be extracted and their applicability to the decision problem will be accounted for when presenting the results.

In addition, the following clinical outcomes will be eligible:

- Acute kidney injury (either PC-AKI or CI-AKI)
- Fall in baseline eGFR or rise of baseline creatinine
- Temporary renal replacement therapy
- New onset chronic kidney disease (stage 3 or worse)
- End stage renal disease with the need for permanent renal replacement therapy
- Health related quality of life
- Mortality

Eligible outcomes related to the implementation of the interventions of interest and related practical issues include:

- Acceptability of POC devices (to clinicians and patients)
- Patient satisfaction
- Training requirements
- Uptake and compliance

### *Study designs*

#### Diagnostic accuracy and correlation studies

Eligible study designs will be studies in which the POC test and laboratory test are done independently in the same patients.

#### Clinical effectiveness/implementation

Eligible study designs will be any experimental or observational study which compares POC tests with laboratory testing and which report relevant clinical outcomes as listed above. Studies with a single group design will also be eligible. We will also include relevant publications reporting issues related to implementation of, or practical advice relating to POC creatinine test technologies (experimental or observational studies or reviews).

The following types of publication will be excluded: case reports and studies focusing only on technical aspects of POC creatinine test technologies (such as technical descriptions of the testing process or specifications of machinery).

## Data extraction

Data on study characteristics and results will be extracted by one reviewer using a standardised data extraction form and independently checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer where necessary. If time constraints allow, attempts will be made where possible to contact authors and/or manufacturers for missing data. Data from relevant studies with multiple publications will be extracted and reported as a single study. The most

recent or most complete publication will be used in situations where we cannot exclude the possibility of overlapping populations.

### Quality assessment strategy

The quality of the diagnostic accuracy studies will be assessed using the QUADAS-2 tool (Quality Assessment tool of Diagnostic Accuracy Studies), modified as necessary to incorporate review-specific issues. QUADAS-2 evaluates both risk of bias and study applicability to the review question. The Cochrane risk of bias tool for randomised studies and the ROBINS-I tool for published non-randomised studies will be used (and adapted as appropriate) for comparative studies which report other eligible clinical outcomes.

The quality assessments will be performed by one reviewer and independently checked by a second reviewer. Disagreements will be resolved through consensus, and where necessary, by consulting a third reviewer.

### Synthesis

In the initial synthesis, the results of data extraction will be presented in structured tables and as a narrative summary, grouped by population and device characteristics. Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques.

Where data permit, the following subgroups may be considered:

- People with known existing kidney disease
- People at different levels of risk of PC-AKI

In addition, the amount of contrast required for imaging will also be considered.

## Systematic review of cost-effectiveness evidence and development of decision model

Relevant cost-effectiveness evidence of the use of POC creatinine tests before contrast-enhanced imaging will be systematically identified, appraised for quality and summarised. The review will examine existing decision-analytic models in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. The findings of the clinical and cost-effectiveness reviews will inform the development of a new decision model.

### Systematic review of cost-effectiveness studies

The results of the searches carried out for the systematic review of clinical effectiveness will be used to identify any relevant studies of the cost-effectiveness of POC creatinine tests.

A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both

costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature.

The main findings of existing economic evaluations will be narratively summarised and tabulated for comparison. In particular, information will be extracted on the comparators, study population, main analytic approaches (e.g. patient-level analysis/decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality-of life, direct costs and indirect costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic/probabilistic sensitivity analysis).

Our initial scoping searches indicate that the existing cost-effectiveness literature addressing the relevant decision problem is likely to be limited. However, we are aware of one unpublished, economic study that is close to completion that may be relevant (Prof. Beverley Snaith, personal communication). Hence, we anticipate that additional targeted reviews may be necessary.

A key conceptual issue concerns the nature of the linked evidence modelling required to estimate the occurrence of PC-AKI and their associated consequences (e.g. chronic kidney disease, end stage renal disease and death). Given the potential limitations of the existing cost-effectiveness literature, we will undertake targeted literature searches to identify UK cost-effectiveness studies evaluating the treatment and management of AKI. The model structures, inputs and assumptions in these studies may be important to consider as part of the conceptualisation and development of the new decision model. These studies will not be subject to a formal assessment but will be used, if necessary, to assist in the overall development of a new analytical model with the aim of identifying important structural assumptions, parameter estimates and highlighting key areas of uncertainty.

We also anticipate that it may also be necessary to consider the relevance of existing UK decision models for the treatment and management of chronic kidney disease. In this situation, we propose to restrict our consideration to decision models used to inform recent NICE clinical guidelines and/or Technology appraisals guidance.

We will assess the feasibility and appropriateness of adapting previously developed models for the treatment and management of AKI (and possible chronic kidney disease) for the purposes of the current study assessed based on:

i) Appropriateness for the decision problem being considered in this assessment.
ii) Relevance of outputs for decision making (i.e. to estimate long-term NHS costs and QALYs based on morbidity and mortality).
iii) Ability to reproduce the model or to collaborate with model developers.

### Evaluation of costs and cost effectiveness

Following the review of existing cost-effectiveness evidence, we will develop a decision model to estimate the cost-effectiveness of POC creatinine tests in a secondary care setting before contrast-enhanced imaging. The relevant population includes adult patients who need to have a non-

emergency contrast-enhanced in an outpatient setting imaging and who do not have a recent serum creatinine measurement. Where data permits, the following subgroups may also be considered:

- People with (and without) known existing kidney disease
- People at different levels of risk of PC-AKI

In addition amount of contrast required for imaging will also be considered.

The model will be populated using results from the systematic clinical effectiveness review, other focused reviews to inform key parameters, routine sources of cost data, and if necessary additional study specific cost estimates provided by experts and/or relevant investigators.

Costs will be considered from an NHS and Personal Social Services perspective and depending on data availability will include:

- Costs of the POC creatinine tests including the cost of the devices, consumables, maintenance (and/or insurance), staff costs and associated training.
- Costs of existing urgent and non-urgent laboratory based serum creatinine measurement based on: (a) Jaffe method and (b) enzymatic method.
- Costs of imaging, including contrast material and prophylactic hydration.
- Cost of follow-up imaging or other testing, including contrast material and prophylactic hydration.
- Cost of cancelled or delayed imaging procedures.
- Any additional costs arising from POC testing including repeat testing (e.g. due to test failure) or impact on other aspects of patient management.
- Costs arising from adverse events.
- Costs associated with the treatment of kidney disease, including short and longer terms costs arising from AKI.
- Cost associated with the treatment of the underlying clinical condition.

It will be important to consider patient throughput and its impact on the cost per patient for the POC creatinine tests. Although the population of interest is people who are scheduled to have contrast-enhanced imaging and who do not have a recent serum creatinine measurement, it will be necessary to estimate the proportion of patients who do, and do not, have recent creatinine measurements in order to appropriately estimate throughput. It will also be important to consider whether the provision of POC creatinine tests might also influence referral behaviour and any possible implications for the throughput assumptions. Finally, it will also be important to consider any implications for throughput in the context of any subgroup analyses.

Data for the cost-analysis will be obtained from routine NHS sources, published studies and information provided by the manufacturers of the devices.

The model will attempt to establish a link between diagnostic test accuracy and final health outcomes. The purpose of the POC and existing urgent and non-urgent laboratory based serum creatinine measurement tests is to inform subsequent scanning decisions, specifically concerning the

use and volume of contrast material. It is envisaged that the model will characterise the impact of the alternative tests (POC versus laboratory based) based on the person's estimated eGFR and the subsequent use and volume of contrast material according to specific eGFR thresholds. We recognise that the specific eGFR thresholds and guidance concerning the appropriate use of contrast material may vary depending on other factors (e.g. patient characteristics, purpose of scan). However, a necessary pre-requisite of the model will be the need to translate measures of creatine into eGFR measures and ultimately to categorise the resulting (continuous) measure of eGFR into specific threshold values. This means it will be necessary for each individual test to be able to determine diagnostic accuracy for alternative eGFR thresholds either directly, based on evidence from relevant diagnostic accuracy studies, or indirectly by translating correlation measures into diagnostic accuracy measures.

It will also be necessary to model the alternative imaging decisions that might be considered when (i) the result of laboratory based serum creatinine tests is known; (ii) the result of the POC creatinine test is known and (iii) when the result from either a POC or laboratory estimate is not known (i.e. the decision is based on clinical judgement only). The different imaging decisions will affect the volume of contrast material used. For example, the volume of contrast will depend upon whether a decision is made to proceed with imaging using either full, reduced dose or no use of contrast material (based on knowledge of the eGFR measurement). Similarly in the absence of a recent eGFR measurement, the volume of contrast will be affected by whether a decision is made to delay/reschedule a scan or to proceed based on clinical judgement alone (using either full, reduced dose or no use of contrast media). The model will also need to consider how specific patient characteristics and/or the purpose of the imaging approach (as well as knowledge of a person's eGFR), may also affect the use and volume of contrast material.

The alternative decisions and subsequent use and volume of contrast material will also have to be linked to any possible impact on the risks of PC-AKI. The risks of PC-AKI, will need to be estimated for each possible decision. This will require careful consideration of existing epidemiological evidence. Specifically whether these risks depend solely on a person's eGFR and the volume of contrast material, or whether other factors (e.g. patient characteristics, comorbidity and the purpose of the contrast-enhanced image) might independently affect these risks.

Depending on the findings from the clinical and cost-effectiveness review, it may be necessary to undertake additional targeted searches to inform the risks of PC-AKI. If this is considered necessary, we will initially restrict the review to published systematic reviews and meta-analyses. If data gaps are still evident, it may be necessary to take a more pragmatic approach to supplement our findings with highly targeted searches for long-term, RCTs and/or prospective cohort studies.

Another key aspect of the model will be the estimation of both the short-term costs and consequences of AKI. As previously stated, we will inform this using targeted literature searches to identify UK cost-effectiveness studies evaluating the treatment and management of AKI (and possibly chronic kidney disease).

We will also assess the feasibility of extending the decision model to include other clinical outcomes that could affected by any changes in the imaging decision based on the POC tests. These outcomes

may include: (i) any anxiety associated with having a delayed or cancelled scan and (ii) morbidity and mortality implications of performing unenhanced scans, or using lower doses of contrast agent. However, given that these outcomes will differ depending on the specific population and the underlying reason for imaging, we envisage that any extension of this nature will need to be constrained to a specific population/reason for the scan. The practicalities and value of developing a specific 'exemplar' application (with potentially limited generalisability) will be considered versus a simpler and more generic approach (e.g. using threshold analysis to determine the magnitude of any impact necessary to result in a different decision based on conventional cost-effectiveness decision rules).

Further details of the model structure and data to populate it will have to await the findings of the systematic searches of the literature. However, it is expected that particular consideration will be given to the following key variables:

- Diagnostic accuracy in terms of creatinine measurements and eGFR estimates (and linking correlation measures to diagnostic accuracy) of the different devices.
- Compliance to POC tests.
- Resource utilisation and costs for the different devices, including the acquisition cost of the devices (and anticipated lifespan of each device), consumables, maintenance (and/or insurance), staff costs and associated training.
- Size of the relevant population and anticipated throughput for each device.
- The 'true' underling distribution of eGFR in the population and relevant subgroups.
- The volume of contrast medium associated with different decisions.
- The risks of AKI (CI-AKI and PC-AKI).
- The short-term and longer term costs and consequences of AKI (including new onset chronic kidney disease, end stage renal disease and death).
- HRQoL impact of a delayed or cancelled CT scan
- HRQoL and (possibly) mortality implications arising from performing unenhanced scans, or using lower doses of contrast agent.

The specific objectives of the cost-effectiveness analysis are:

- To structure an appropriate decision model to characterise existing care pathways and the subsequent impact of POC creatinine tests compared to laboratory based serum creatinine measurement and no testing (i.e. clinical judgement alone), for people presenting for contrast-enhanced imaging and who do not have a recent serum creatinine measurement.
- To incorporate sufficient flexibility within the model structure (or to develop separate structures) to reflect different subgroups to be considered (e.g. people with known existing kidney disease, people at higher risk of PC-AKI).
- To populate this model using the most appropriate data. This is likely to be identified systematically from published literature, routine data sources and potentially using data elicited from relevant clinical experts and manufacturers.

- To relate intermediate outcome measures, such as diagnostic accuracy and the correlation between POC creatinine tests and laboratory-based creatinine tests, to subsequent CT scanning decisions and to final health outcomes including: morbidity and mortality associated with changes in the volume of contrast material used. Final health outcomes will be evaluated in terms of QALYs. This is necessary in order to provide decision makers with an indication of the health gain achieved by POC creatinine tests, relative to their additional cost, in units which permit comparison with other uses of health service resources.
- To estimate the incremental cost-effectiveness of alternative POC devices, compared to laboratory based serum creatinine measurement and no testing, based on an assessment of long-term NHS and Personal Social Service costs and quality-adjusted survival. The time horizon of the model will be sufficient to capture both the short-term and longer-term outcomes. The final specification of the model will be determined during the review and model conceptualisation stage.
- To characterise the uncertainty in the data used to populate the model and present the resulting uncertainty in the results to decision makers. A probabilistic model will be developed which requires that, where possible, uncertainty in inputs are reflected through the use of appropriate distributions. Using Monte Carlo simulation, this parameter uncertainty will be translated into uncertainty in the overall results. This will be presented graphically using cost-effectiveness acceptability curves which show the probability that an intervention is cost-effective for a given cost-effectiveness threshold (cost per QALY).
- Sensitivity and scenario analyses will be undertaken explore the robustness of the cost-effectiveness results to changes in the parameter inputs (e.g. impact of increasing/decreasing sensitivity and specificity) structural assumptions of the model and the time horizon.
- Heterogeneity in the cost-effectiveness estimates will be assessed based on the findings of the clinical effectiveness review.

It is anticipated that the model will be developed in Microsoft Excel.

## Handling information from the companies

Any 'commercial in confidence' data provided by the manufacturers and specified as such will be highlighted in blue and underlined in the assessment report. Any 'academic in confidence' data provided by the manufacturers will be highlighted in yellow and underlined in the assessment report.

If confidential information is included in economic models then a version using dummy data or publically available data in place of confidential data will be provided.

## Competing interests of authors

None of the authors have any conflicts of interest.

## Timetable/milestones

| Milestone | Date to be completed |
|---|---|
| Submission of final protocol | 26/10/2019 |
| Submission of progress report | 28/01/2019 |
| Submission of draft Diagnostic Assessment Report | 27/03/2019 |
| Submission of final Diagnostic Assessment Report | 24/04/2019 |

**Appendix 1**

**Search strategy for MEDLINE**

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to October 19, 2018>

22nd October 2018

1 Point-of-Care Systems/ (11035)

2 Point-of-Care Testing/ (980)

3 point-of-care.ti,ab,kf. (15729)

4 (POC or POCT).ti,ab,kf. (4557)

5 (rapid$ adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).ti,ab. (72079)

6 ((bedside or bed-side) adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).ti,ab. (3631)

7 ((on-site or onsite) adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).ti,ab. (2456)

8 (near adj4 patient adj4 test$).ti,ab. (378)

9 (near adj4 patient adj4 determin$).ti,ab. (10)

10 (near adj4 patient adj4 assess$).ti,ab. (24)

11 (near adj4 patient adj4 analys$).ti,ab. (29)

12 (near adj4 patient adj4 analyz$).ti,ab. (8)

13 (near adj4 patient adj4 identif$).ti,ab. (4)

14 (near adj4 patient adj4 measur$).ti,ab. (33)

15 (near adj4 patient adj4 screen$).ti,ab. (8)

16 or/1-15 (98342)

17 Creatinine/ (53514)

18 creatinine.ti,ab,kf. (102251)

19 serumcreatinine.ti,ab,kf. (3)

20 SCr.ti,ab,kf. (6092)

21 or/17-20 (126250)

22 16 and 21 (575)

23 Kidney Function Tests/ (24277)

24 Glomerular Filtration Rate/ (40313)

25 ((kidney$ or renal) adj3 (function$ or dysfunction$)).ti,ab. (122033)

26 glomerul$ filtration rate$.ti,ab. (38889)

27 glomerulofiltration rate$.ti,ab. (6)

28 GFR.ti,ab,kf. (17876)

29 eGFR.ti,ab,kf. (49536)

30 or/23-29 (207288)

31 16 and 30 (518)

32 22 or 31 (913)

33 Computers, Handheld/ (3262)

34 ((handheld or hand held) adj2 (device$ or analyser$ or analyzer$)).ti,ab. (1593)

35 ((desktop or desk top) adj2 (device$ or analyser$ or analyzer$)).ti,ab. (74)

36 ((table top or tabletop or bench top or benchtop) adj2 (device$ or analyser$ or analyzer$)).ti,ab. (145)

37 ((portable or transportab$) adj2 (device$ or analyser$ or analyzer$)).ti,ab. (3181)

38 (near patient adj2 (device$ or analyser$ or analyzer$)).ti,ab. (28)

39 or/33-38 (7983)

40 21 or 30 (288646)

41 39 and 40 (49)

42 32 or 41 (945)

43 (i-STAT or iSTAT).ti,ab,kf. (484)

44 40 and 43 (23)

45 (StatSensor or Stat Sensor).ti,ab,kf. (16)

46 ABL90 FLEX PLUS.ti,ab,kf. (0)

47 (ABL800 FLEX or ABL800FLEX or ABL 800 FLEX).ti,ab,kf. (25)

48 Dri-chem NX500.ti,ab,kf. (0)

49 epoc Blood Analysis.ti,ab,kf. (3)

50 Piccolo Xpress.ti,ab,kf. (7)

51 or/44-50 (69)

52 42 or 51 (982)

53 exp animals/ not humans/ (4506554)

54 52 not 53 (915)