**Review protocol for the accuracy of cystatin C-based equations to estimate GFR as a measurement of kidney function in adults, children and young people?**

| ID | Field | Content |
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| 0. | PROSPERO registration number | 153331 |
| 1. | Review title | What is the accuracy of cystatin C-based equations to estimate GFR as a measurement of kidney function in adults, children and young people? |
| 2. | Review question | What is the accuracy of cystatin C-based equations to estimate GFR as a measurement of kidney function in adults, children and young people? |
| 3. | Objective | To determine the accuracy of cystatin C-based equations to estimate GFR as a measurement of kidney function. |
| 4. | Searches | The following databases will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br><br>Searches will be restricted by: |

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| | | • From 25 November 2013 for adults<br>• No limit for children and young people<br>• English language<br>• Human studies<br><br>The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion.<br><br>The full search strategies for MEDLINE database will be published in the final review. |
| 5. | Condition or domain being studied | The risk of progression and adverse outcomes in a person with, or at risk of, CKD is currently determined through monitoring creatinine-based estimates of GFR (eGFRcreatinine) and urine albumin:creatinine ratio. Estimates of GFR based on serum cystatin C (eGFRcystatinC) have a higher specificity for significant disease outcomes than those based on serum creatinine. For people with a borderline diagnosis, eGFRcystatinC is an additional diagnostic tool that may reduce over diagnosis. New evidence suggests the use of risk equations in predicting end stage renal disease in CKD patients. |
| 6. | Population | Inclusion: Adults, children and young people with suspected or diagnosed chronic kidney disease (GFR categories G1-G5).<br><br>Exclusion:<br>• people receiving renal replacement therapy (RRT) |

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| | | • people with acute kidney injury combined with rapidly progressive glomerulonephritis<br>• pregnant women<br>• people receiving palliative care |
| 7. | Test | Different Cystatin-C equations to estimate GFR |
| 8. | Reference standard | Measured GFR<br>(urinary or plasma clearance of inulin, iohexol, iothalamate, para aminohippurate [PAH], diethylenetriaminepentaacetic acid [DTPA] or ethylenediaminetetraacetic acid [EDTA]). |
| 9. | Types of study to be included | • Diagnostic cross-sectional studies<br>• Systematic reviews of diagnostic cross-sectional studies[1] |
| 10. | Other exclusion criteria | • Abstracts and conference proceedings<br>• Theses<br>• Non-human studies<br>• Studies that do not use international standardisation for cystatin C tests (CE marked or FDA approved) |
| 11. | Context | NICE guideline CG182 chronic kidney disease in adults: assessment and management will be updated by this question. This guideline will be combined with guidelines CG157 chronic kidney disease (stage 4 or 5): management of hyperphosphataemia and NG 8 |

[1] Cohort studies were also included as a protocol deviation

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| | | chronic kidney disease: managing anaemia. The guideline will be extended to cover the assessment and management of chronic kidney disease in children and young people. |
| 12. | Primary outcomes (critical outcomes) | • Likelihood ratios[2] |
| 13. | Secondary outcomes (important outcomes) | • Area Under Curve calculations<br><br>If necessary we will calculate likelihood ratios from:<br>o Specificity<br>o Sensitivity<br>o PPV<br>o NPV |
| 14. | Data extraction (selection and coding) | All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. |

[2] P measures were also used as primary outcomes as a protocol deviation

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| | | The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the test and reference standard used; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.<br>Study investigators may be contacted for missing data where time and resources allow. |
| 15. | Risk of bias (quality) assessment | Risk of bias will be assessed using the QUADAS 2 checklist as described in Developing NICE guidelines: the manual. |
| 16. | Strategy for data synthesis | Meta-analysis of diagnostic test accuracy data will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).<br><br>Where five or more studies are available for all included strata, a bivariate model will be fitted using the mada package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data are not available (2-4 studies), separate independent pooling was performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using Microsoft Excel. |

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| | | Random-effects models (der Simonian and Laird) will be fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010). |
| 17. | Analysis of sub-groups | If there is heterogeneity within pooled data for an outcome, and if the data can be disambiguated, specific consideration will be given to the following subgroups:<br>• Age band (older people [>70] and children and young people [<18]).<br>• Family background (ethnic group).<br>• Risk (people at high risk of developing progressive CKD (for example, people with diabetes, hypertension or cardiovascular disease, or people recovering from acute kidney injury, HIV)).<br>• Family history of renal disease<br>• BMI (low/normal/high as defined by author)<br>• Gender. |
| 18. | Type and method of review | ☐ Intervention<br>☒ Diagnostic<br>☐ Prognostic<br>☐ Qualitative<br>☐ Epidemiologic<br>☐ Service Delivery<br>☐ Other (please specify) |

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| 19. | Language | English | | |
| 20. | Country | England | | |
| 21. | Anticipated or actual start date | 7th October 2019 | | |
| 22. | Anticipated completion date | December 2020 | | |
| 23. | Stage of review at time of this submission | **Review stage** | **Started** | **Completed** |
| | | Preliminary searches | ☐ | ☐ |
| | | Piloting of the study selection process | ☐ | ☐ |
| | | Formal screening of search results | ☐ | ☐ |

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| | | against eligibility criteria | | |
| | | Data extraction | ☐ | ☐ |
| | | Risk of bias (quality) assessment | ☐ | ☐ |
| | | Data analysis | ☐ | ☐ |
| 24. | Named contact | **5a. Named contact**<br>Guideline Updates Team<br><br>**5b Named contact e-mail**<br>TBA@nice.org.uk<br><br>**5e Organisational affiliation of the review**<br>National Institute for Health and Care Excellence (NICE) | | |
| 25. | Review team members | From the Guideline Updates Team:<br>• Mr Chris Carmona | | |

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| | | • Mr Thomas Jarratt<br>• Dr Yolanda Martinez<br>• Mr Gabriel Rogers<br>• Ms Hannah Nicholas<br>• Ms Lynda Ayiku |
| 26. | Funding sources/sponsor | This systematic review is being completed by the Guideline Updates Team which is part of NICE. |
| 27. | Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. |
| 28. | Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage]. |

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| 29. | Other registration details | |
| 30. | Reference/URL for published protocol | |
| 31. | Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. |
| 32. | Keywords | Chronic Kidney Disease, eGFR measures, Cystatin C-based equations |
| 33. | Details of existing review of same topic by same authors | None |
| 34. | Current review status | ☒ Ongoing<br>☒ Completed but not published |

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| | | ☐ Completed and published<br>☐ Completed, published and being updated<br>☐ Discontinued |
| 35.. | Additional information | None |
| 36. | Details of final publication | www.nice.org.uk |