National Institute for Health and Care Excellence

Final

Chronic kidney disease

[F] Evidence review for the best combination of measures to identify increased risk of progression in adults, children and young people

NICE guideline NG203

Evidence reviews underpinning recommendations 1.5.1 to 1.5.10 and research recommendations in the NICE guideline

August 2021

Final

These evidence reviews were developed by the Guideline Updates Team

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1.1 Review question

What is the best combination of measures of kidney function and markers of kidney damage to identify increased risk of progression in adults, children and young people with CKD?

Are kidney failure prediction equations good predictors of progression, kidney failure or end-stage renal disease?

1.1.1 Introduction

The NICE guideline on chronic kidney disease in adults: assessment and management (NICE guideline CG182) was reviewed in 2017 as part of NICE's surveillance programme. New evidence was identified which suggested that the use of risk equations in predicting the need for dialysis or a kidney transplant in people with CKD might be useful. As part of the scoping exercise, it was decided to update the review question on identifying the best combination of measures of kidney function and markers of kidney damage to identify increased risk of progression and also expand the question to include children. Additionally, a further question on kidney failure risk equations was included.

The aim of this review is to assess which combination of measures of kidney function and markers of kidney damage is best in identifying risk of progression in adults, children and young people with CKD (part 1 in the summary of protocol table). Additionally, the review aims to identify if kidney failure prediction equations are good predictors of progression, kidney failure or end-stage renal disease (part 2 in the summary of protocol table). See Appendix A for full details of the review protocol.

1.1.2 Summary of the protocol

Table 1: Summary of protocol table

Population	**Inclusion:** Adults, children and young people with chronic kidney disease stages 1 to 5. **Exclusion:** • people receiving renal replacement therapy (RRT) • people with acute kidney injury combined with rapidly progressive glomerulonephritis • pregnant women • people receiving palliative care
Prognostic factor	**For part 1 (combinations of markers for predicting progression):** • MDRD (serum creatinine) plus urinary ACR • CKD-EPI eGFR (serum creatinine) plus urinary ACR • CKD-EPI cystatin C plus urinary ACR • Combined CKD-EPI (serum creatinine + cystatin C eGFR) plus urinary ACR

	• Schwartz + urinary ACR A 'positive' result is determined using an eGFR-creatinine or eGFR-cystatin of less than 60 ml/min/1.73 m2 and/or an ACR greater than 30 mg/g (approximately 3 mg/mmol). **For part 2 (Kidney failure risk equations for predicting progression):** • Kidney failure risk equations (eg. Tangri equation [KFRE])
Covariates	**For part 1:** • Age • Gender • Hypertension • Diabetes • Family origin
Outcomes	**For Part 1:** Hazard ratios, risk ratios and odds ratios for: ○ CKD progression: change in eGFR ○ CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) ○ AKI ○ All-cause mortality ○ Cardiovascular mortality **For Part 2:** Prognostic performance: ○ Calibration (goodness of fit measures.eg. R2; Brier score, Hosmer-Lemeshow test) ○ Discrimination (eg. sn/sp; AUC from ROC, AUROC; c-statistic)

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods section in Appendix B.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Outcomes were assessed using a modified version of GRADE for prognostic accuracy (see Appendix B for methods and Appendix G for GRADE tables). None of the studies identified for combinations of measures of kidney function to predict increased risk of progression were similar enough to be pooled in meta-analysis, however the validation studies for the kidney failure risk equations were suitable for meta-analysis (see Appendix F for forest plots).

Kidney risk failure equations were included if a combination of measures of kidney function were used.

1.1.4 Prognostic evidence

1.1.4.1 Included studies

A systematic search was carried out to identify prognostic observational studies and systematic reviews of prognostic observational studies, which found 4,462 references (see Appendix C for the literature search strategy). Based on title and abstract screening, 4,417 references were excluded, and 45 references were ordered for full text screening. No new observational evidence was found to update the combination of measures of kidney function and markers of kidney damage to identify increased risk of progression. The three studies

included in the 2014 CG182 guideline (Peralta 2011a; Peralta 2011b; Waheed 2013) were included. Six validation studies were included for kidney failure prediction equations. Therefore, 9 studies were included in total.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. This search returned 102 references for this review question, these were screened on title and abstract. One reference was ordered for full text screening and it was excluded based on its relevance to the review protocol (Appendix A). An additional validation study was highlighted during stakeholder consultation (already found by the systematic search) which was included based on their relevance to the review protocol (Appendix A).

See section 1.1.10 References – included studies for a list of references for included studies.

1.1.4.2 Excluded studies

See Appendix K for a list of excluded studies with reasons for exclusion.

1.1.5 Summary of studies included

Table 2: Summary of studies on combination of prognostic measures

Study	Population (N)	Markers	Outcomes (Follow-up)	Covariates
Peralta 2011a	Reasons for Geographic and Racial Differences in Stroke (REGARDS). (N = 26,643)	eGFRcreatinine + eGFRcystatin, eGFRcreatinine + ACR, eGFRcystatin + ACR, eGFRcreatinine + eGFRcystatin + ACR.	All-cause mortality and ESRD. (Max. 7 years 4 months)	Mortality model: age, race, income, educational attainment, hypertension, diabetes, prevalent cardiovascular disease, smoking status and BMI. ESRD: As above plus waist circumference and log albuminto-creatinine ratio.
Peralta 2011b	Multi-Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS). (N = 11.909)	eGFRcreatinine + eGFRcystatin, eGFRcreatinine + ACR, eGFRcystatin + ACR, eGFRcreatinine + eGFRcystatin + ACR.	MESA: All-cause mortality and cardiovascular disease. CHS: All-cause mortality, cardiovascular disease, heart failure and ESRD (MESA: mean 4.7 years CHS: 12.2 years)	Adjusted for age, race, gender, diabetes, hypertension, LDL, HDL, CRP, and prevalent CVD for CHS (persons with baseline CVD were excluded for incident CVD analyses).
Waheed 2013	Atherosclerosis Risk in Communities study (ARIC). (N = up to 476)	eGFRcreatinine + eGFRcystatin, eGFRcreatinine + ACR, eGFRcystatin + ACR, eGFRcreatinine + eGFRcystatin + ACR.	All-cause mortality, coronary heart disease, heart failure, AKI and ESRD. (median 11.2 years)	Adjusted for age, race, sex, and total cholesterol, history of diabetes, hypertension, smoking, BMI, C-reactive protein and eGFR.

Table 3: Summary of studies on kidney failure prediction equations

Study	Population (N)	Prediction equations	Outcomes
Lennartz 2016	Adults, CKD stages 2-4 (N = 403)	KFRE 4 variable at 3 years	C-statistic and R^2 statistic
Major 2019	Adults, CKD stages 2-4 registered at GPs (N = 35,539)	KFRE 4 variable at 2 years, 5 years	C-statistic
Marks 2015	People aged 15 years and older, CKD stages 3a-5 (N = 2274)	KFRE 4 variable and RRT prediction tool at 5 years	C-statistic Sensitivity Specificity
Tangri 2016	Meta-analysis of 30 cohorts to validate equation across different regions (N = 721,357)	KFRE 4 variable at 2 years, 5 years	C-statistic
Wang 2019	Elderly, CKD stages 3 and above, co-morbidities including diabetes, CVD, stroke (N=17,444)	KFRE 4 variable at 2 years, 5 years	Brier score
Whitlock 2017	Adults, CKD stages 3 and 4 (N = 1,512)	KFRE 4 variable at 5 years	C-statistic
Winnicki 2017	Paediatric cohort, CKD stage 3 and 4. (N = 603)	KFRE 4 variable and 8 variable in children, at 1 year, 2 years and 5 years	C-statistic

See Appendix E for full evidence tables.

1.1.6 Summary of the prognostic evidence

Combination of measures to predict outcomes

No of patients		Effect size (95% CI)	Quality	Interpretation of effect
Combination of measures	Reference			
All-cause mortality: REGARDS - CKD by eGFRcreat + eGFRcys (reference: no CKD by eGFRcreat + eGFRcys) Higher HR means combination of measures is predictive of all-cause mortality (1 study)				
799/2055 (38.9%)	1104/22361 (4.9%)	HR 2.1 (1.9 to 2.32)	HIGH	Combined measures to estimate CKD are a better predictor of all-cause mortality compared to combined measures to estimate no CKD
All-cause mortality: REGARDS - CKD by eGFRcreat + eGFRcys (reference: CKD by eGFRcreat alone) Higher HR means combination of measures is predictive of all-cause mortality (1 study)				
223/1172 (19%)	32/701 (4.6%)	HR 3.2 (2.2 to 4.66)	HIGH	Combined measures to estimate CKD are a better predictor of all-cause mortality compared to eGFR creatinine alone to estimate CKD
All-cause mortality: REGARDS - CKD by ACR + eGFRcys (reference: no CKD by ACR or eGFRcys) Higher HR means combination of measures is predictive of all-cause mortality (1 study)				
105/415 (25.3%)	863/19876 (4.3%)	HR 3 (2.4 to 3.75)	HIGH	Combined measures to estimate CKD are a better predictor of all-cause mortality compared to combined measures to estimate no CKD
All-cause mortality: REGARDS - CKD by ACR + eGFRcreat (reference: CKD by eGFRcreat alone) Higher HR means combination of measures is predictive of all-cause mortality (1 study)				
27/148 (18.2%)	32/701 (4.6%)	HR 3.3 (2 to 5.44)	HIGH	Combined measures to estimate CKD are a better predictor of all-cause mortality compared to eGFR creatinine alone to estimate CKD
All-cause mortality: REGARDS - CKD by eGFRcreat + eGFRcys + ACR (reference: CKD by eGFRcreat alone) Higher HR means combination of measures is predictive of all-cause mortality (1 study)				
276/883 (31.3%)	32/701 (4.6%)	HR 5.6 (3.9 to 8.04)	HIGH	Combined measures to estimate CKD are a better predictor of all-cause mortality compared to eGFR creatinine alone to estimate CKD
All-cause mortality: ARIC - CKD by eGFRcreat + eGFRcys (reference: no CKD by any marker) Higher HR means combination of measures is predictive of all-cause mortality (1 study)				

No of patients		Effect size (95% CI)	Quality	Interpretation of effect
Combination of measures	Reference			
IR 32.7 per 1000 person-year	IR 10.5 per 1000 person-year	HR 1.86 (1.42 to 2.44)	HIGH	Combined measures to estimate CKD are a better predictor of all-cause mortality compared to using any measure to estimate no CKD
All-cause mortality: ARIC - CKD by eGFRcreat + ACR (reference: no CKD by any marker) Higher HR means combination of measures is predictive of all-cause mortality (1 study)				
IR 23.3 per 1000 person-year	IR 10.5 per 1000 person-year	HR 1.26 (0.52 to 3.05)	MODERATE	Could not differentiate
All-cause mortality: ARIC - CKD by eGFRcys + ACR (reference: no CKD by any marker) Higher HR means combination of measures is predictive of all-cause mortality (1 study)				
IR 50.4 per 1000 person-year	IR 10.5 per 1000 person-year	HR 2.47 (1.70 to 3.61)	HIGH	Combined measures to estimate CKD are a better predictor of all-cause mortality compared to using any measure to estimate no CKD
All-cause mortality: ARIC - CKD by eGFRcreat + eGFRcys + ACR (reference: no CKD by any marker) Higher HR means combination of measures is predictive of all-cause mortality (1 study)				
IR 70.5 per 1000 person-year	IR 10.5 per 1000 person-year	HR 3.69 (2.79 to 4.87)	HIGH	Combined measures to estimate CKD are a better predictor of all-cause mortality compared to using any measure to estimate no CKD
All-cause mortality: CHS - CKD by eGFRcreat + eGFRcys (reference: no CKD by eGFRcreat + eGFRcys) Higher HR means combination of measures is predictive of all-cause mortality (1 study)				
Total 689	Total 3639	HR 1.74 (1.58 to 1.93)	MODERATE	Combined measures to estimate CKD are a better predictor of all-cause mortality compared to combined measures to estimate no CKD
All-cause mortality: MESA - CKD by eGFRcreat + eGFRcys (reference: no CKD by eGFRcreat + eGFRcys) Higher HR means combination of measures is predictive of all-cause mortality (1 study)				
Total 269	Total 5759	HR 1.93 (1.27 to 2.92)	MODERATE	Combined measures to estimate CKD are a better predictor of all-cause mortality compared to combined measures to estimate no CKD
All-cause mortality: CHS - CKD by eGFRcreat + eGFRcys (reference: CKD by eGFRcreat alone) Higher HR means combination of measures is predictive of all-cause mortality (1 study)				
262/380 (68.9%)	71/170 (41.8%)	HR 1.71 (1.3 to 2.25)	MODERATE	Combined measures to estimate CKD are a better predictor of all-cause mortality compared to eGFR creatinine alone to estimate CKD
All-cause mortality: CHS - CKD by eGFRcreat + ACR (reference: CKD by eGFRcreat alone) Higher HR means combination of measures is predictive of all-cause mortality (1 study)				

No of patients		Effect size (95% CI)	Quality	Interpretation of effect
Combination of measures	Reference			
29/39 (74.4%)	71/170 (41.8%)	HR 1.94 (1.23 to 3.06)	MODERATE	Combined measures to estimate CKD are a better predictor of all-cause mortality compared to eGFR creatinine alone to estimate CKD
All-cause mortality: CHS - CKD by eGFRcreat + eGFRcys + ACR (reference: CKD by eGFRcreat alone) Higher HR means combination of measures is predictive of all-cause mortality (1 study)				
181/200 (90.5%)	71/170 (41.8%)	HR 3.41 (2.54 to 4.58)	MODERATE	Combined measures to estimate CKD are a better predictor of all-cause mortality compared to eGFR creatinine alone to estimate CKD
End stage renal disease: REGARDS - CKD by eGFRcreat + eGFRcys (reference: no CKD by eGFRcreat + eGFRcys) Higher HR means combination of measures is predictive of end stage renal disease (1 study)				
144/2055 (7%)	17/22361 (0.08%)	HR 26.1 (14.9 to 45.72)	HIGH	Combined measures to estimate CKD are a better predictor of end stage renal disease compared to combined measures to estimate no CKD
End stage renal disease: CHS - CKD by eGFRcreat + eGFRcys (reference: no CKD by eGFRcreat + eGFRcys) Higher HR means combination of measures is predictive of end stage renal disease (1 study)				
Total 689	Total 3639	HR 23.82 (12.68 to 44.76)	MODERATE	Combined measures to estimate CKD are a better predictor of end stage renal disease compared to combined measures to estimate no CKD
End stage renal disease: ARIC - CKD by eGFRcreat + eGFRcys (reference: no CKD by any marker) Higher HR means combination of measures is predictive of end stage renal disease (1 study)				
IR 5.5 per 1000 person-year	IR 0.4 per 1000 person-year	HR 14.57 (6.75 to 31.46)	HIGH	Combined measures to estimate CKD are a better predictor of end stage renal disease compared to using any measure to estimate no CKD
End stage renal disease: ARIC - CKD by eGFRcreat + ACR (reference: no CKD by any marker) Higher HR means combination of measures is predictive of end stage renal disease (1 study)				
IR 8.2 per 1000 person-year	IR 0.4 per 1000 person-year	HR 8.91 (2.06 to 38.49)	HIGH	Combined measures to estimate CKD are a better predictor of end stage renal disease compared to using any measure to estimate no CKD
End stage renal disease: ARIC - CKD by eGFRcys + ACR (reference: no CKD by any marker) Higher HR means combination of measures is predictive of end stage renal disease (1 study)				
IR 9.1 per 1000 person-year	IR 0.4 per 1000 person-year	HR 14.55 (5.38 to 39.32)	HIGH	Combined measures to estimate CKD are a better predictor of end stage renal disease compared to using any measure to estimate no CKD
End stage renal disease: ARIC - CKD by eGFRcreat + eGFRcys + ACR (reference: no CKD by any marker) Higher HR means combination of measures is predictive of end stage renal disease (1 study)				

No of patients		Effect size (95% CI)	Quality	Interpretation of effect
Combination of measures	Reference			
IR 60.9 per 1000 person-year	IR 0.4 per 1000 person-year	HR 125.98 (73.06 to 217.22)	HIGH	Combined measures to estimate CKD are a better predictor of end stage renal disease compared to using any measure to estimate no CKD
Acute kidney injury: ARIC - CKD by eGFRcreat + eGFRcys (reference: no CKD by any marker) Higher HR means combination of measures is predictive of acute kidney injury (1 study)				
IR 18.0 per 1000 person-year	IR 3.0 per 1000 person-year	HR 3.90 (2.65 to 5.74)	HIGH	Combined measures to estimate CKD are a better predictor of acute kidney injury compared to using any measure to estimate no CKD
Acute kidney injury: ARIC - CKD by eGFRcreat + ACR (reference: no CKD by any marker) Higher HR means combination of measures is predictive of acute kidney injury (1 study)				
IR 12.2 per 1000 person-year	IR 3.0 per 1000 person-year	HR 2.19 (0.70 to 6.9)	MODERATE	Could not differentiate
Acute kidney injury: ARIC - CKD by eGFRcys + ACR (reference: no CKD by any marker) Higher HR means combination of measures is predictive of acute kidney injury (1 study)				
IR 23.7 per 1000 person-year	IR 3.0 per 1000 person-year	HR 3.96 (2.18 to 7.18)	HIGH	Combined measures to estimate CKD are a better predictor of acute kidney injury compared to using any measure to estimate no CKD
Acute kidney injury: ARIC - CKD by eGFRcreat + eGFRcys + ACR (reference: no CKD by any marker) Higher HR means combination of measures is predictive of acute kidney injury (1 study)				
IR 43.5 per 1000 person-year	IR 3.0 per 1000 person-year	HR 9.78 (6.63 to 14.43)	HIGH	Combined measures to estimate CKD are a better predictor of acute kidney injury compared to using any measure to estimate no CKD

IR: incidence ratio

See Appendix G for full GRADE tables.

Prognostic equations

Table 4: Validity of end-stage renal disease (ESRD) risk prediction – c-statistics

Equation	Outcome	Study(s)	Sample size	Pooled discrimination (C-statistic)	Interpretation[a]	Quality
KFRE 4 variable	2 years follow-up	Major 2019; Tangri 2016	756896	0.92 (0.88, 0.95)	Outstanding discrimination	High
	3 years follow-up	Lennartz 2016	406	0.91 (0.83-0.99)	Outstanding discrimination	High
	5 years follow-up	Major 2019; Marks 2015; Tangri 2016; Whitlock 2017	760682	0.91 (0.89-0.94)	Outstanding discrimination	High
KFRE 4 variable in children	2 years follow-up	Winnicki 2017	603	0.86 (0.81-0.90)	Excellent discrimination	High
	5 years follow-up	Winnicki 2017	603	0.81 (0.77-0.83)	Excellent discrimination	High
KFRE 8 variable in children	1 year follow-up	Winnicki 2017	603	0.91 (0.87-0.94)	Outstanding discrimination	High
	2 years follow-up	Winnicki 2017	603	0.87 (0.82-0.91)	Excellent discrimination	High
	5 years follow-up	Winnicki 2017	603	0.82 (0.78-0.85)	Excellent discrimination	High
RRT prediction tool	5 years follow-up	Marks 2015	2274	0.93 (0.90-0.96)	Outstanding discrimination	High

(a) Outstanding discrimination: 0.9 ≤ c-statistic < 1.0; Excellent discrimination: 0.8 ≤ c-statistic <0.9.

See Appendix G for full GRADE tables.

Table 5: Validity of end-stage renal disease (ESRD) risk prediction – Calibration (Brier score)

Equation	Outcome	Study	Sample size	Calibration (Brier score)[a]	Quality
KFRE 4 variable in elderly	2 years follow-up	Wang 2019	17271	7.9% Bias[b]: 3.4% (-7.8, 11.2%)	High
	5 years follow-up	Wang 2019	17271	6.2% Bias: 4.5% (-1.4, 5.9%)	High

(a) Lower numbers (closer to 0) reflect greater calibration (and therefore predictive accuracy).
(b) the median difference between observed vs predicted ESKD risks)

See Appendix G for full GRADE tables.

Table 6: Validity of end-stage renal disease (ESRD) risk prediction – Calibration (R^2 statistic)

Equation	Outcome	Study(s)	Sample size	Calibration (R2 statistic)[a]	Quality
KFRE 4 variable	3 years follow-up	Lennartz 2016	406	0.29 (SD 37.7%)	High

(a) Higher R^2 (closer to 1.0) means better calibrated (i.e. better model fit).

See Appendix G for full GRADE tables.

Table 7: Validity of end-stage renal disease (ESRD) risk prediction – sensitivity and specificity to start RRT

Equation	Outcome	Study(s)	Sample size	Sensitivity	Specificity	Quality
KFRE 4 variable	5 years follow-up	Marks 2015	2274	0.84	0.89	High
RRT prediction tool	5 years follow-up	Marks 2015	2274	0.56	0.96	High

See Appendix G for full GRADE tables.

1.1.7 Economic evidence

A systematic review was conducted to identify economic evaluations for this review question. The search returned 526 records which were sifted against the review protocol. All records were excluded based on title and abstract. The study selection diagram is presented in Appendix H. For more information on the search strategy please see Appendix C.

No published cost-effectiveness studies were included in this review. An original health economic model was done for this review question A summary of the model results are given in the table below, and full details are available in Appendix J.

Summary of included economic evidence

Study	Applicability	Limitations	Incremental			Uncertainty
			Total cost in study population (£)	Total QALYs in study population	Net monetary benefit (£20,000/ QALY)	
Original model (full details in appendix J)	Directly applicable	Minor limitations	2014 NICE criteria: £1,122,440 KFRE ≥3%: £1,147,831 KFRE ≥5%: £1,080,299 KFRE ≥15%: £886,880	2014 NICE criteria: 190.79 KFRE ≥3%: 189.03 KFRE ≥5%: 187.19 KFRE ≥15%: 171.63	2014 NICE criteria: £2,693,328 KFRE ≥3%: £2,632,856 KFRE ≥5%: £2,663,485 KFRE ≥15%: £2,545,646	A variety of sensitivity analyses were completed, see J.3.4 Sensitivity analysis

Study	Applicability	Limitations	Incremental			Uncertainty
			Total cost in study population (£)	Total QALYs in study population	Net monetary benefit (£20,000/ QALY)	
			KFRE ≥5% or eGFR < 30: £1,117,324 KFRE ≥5% or ACR ≥70: £1,120,944	KFRE ≥5% or eGFR < 30: 187.19 KFRE ≥5% or ACR ≥70: 190.90	KFRE ≥5% or eGFR < 30: £2,626,460 KFRE ≥5% or ACR ≥70: £2.697,108	

1.1.8 The committee's discussion and interpretation of the evidence

1.1.8.1. The outcomes that matter most

The committee agreed that the key outcomes to identify increased risk of progression in adults, children and young people with CKD were all-cause mortality and end stage renal disease using the four and eight variable kidney failure risk equations (KFRE). The committee noted that c-statistics for KFRE were high, especially for the four variable KFRE in adults, which meant that it was a useful tool to predict the risk of progression to end stage renal disease. These studies were also very large, with one cohort being almost three-quarters of a million people. The committee also noted that there was a single large validation study of the KFRE in the UK and that a health economic model would be useful to assess data on the predictive accuracy of the different referral rules for predicting progression to end stage renal disease (need for dialysis or a renal transplant). The committee was aware that using the KFRE would represent a significant change in practice and discussed this in depth, however it agreed that the clinical evidence and economic modelling justified this.

The committee discussed the evidence for combinations of measures that had not changed since publication of the previous guideline. Overall, it agreed the KFRE data were more current and more important and so focussed on these data.

1.1.8.2 The quality of the evidence

The quality of the evidence ranged from moderate to high quality evidence. The committee noted the high heterogeneity identified in the meta-analysis of KFRE c-statistics. It agreed that because the included studies were very large, and therefore the confidence intervals were very narrow, the heterogeneity was not as great as it appeared (all the studies had a calibration estimate of between 88 and 93%). Because the c-statistics were high and confidence intervals narrow, the committee was confident that the tests had high accuracy because even the worst-case estimate was 88%.

The evidence for combinations of measures was moderate to high, but the committee noted that all of the outcomes relied on one study each and none of them were poolable in a meta-analysis. It additionally noted that the 3 studies included in the combination of measures analysis were the same studies that had been included at the last update, and that even

though they demonstrated that combinations of measures are better than single measures at predicting progression of disease, this was no surprise.

1.1.8.3 Benefits and harms

Since no new evidence was identified and included which examined combinations of measures to predict progression of chronic kidney disease, the committee discussed the previous evidence on combined measures (different combinations of eGFRcreatinine, eGFRcystatin C, and albumin:creatinine ratio). It showed that these combinations predicted a higher risk of all-cause mortality, end stage renal disease and acute kidney injury, but not all evidence reported on the same combinations of measures and the reference groups also varied. The committee agreed that the evidence was not as conclusive as the evidence on the KFRE.

New evidence was found on the 4 variable and 8 variable KFRE. Most evidence was found for the 4 variable KFRE in adults, though there was also evidence for older people. This evidence had not been considered by the previous committee because it was newer evidence. The committee discussed the KFRE equations together with the evidence from the health economic model and amended the criteria for referral from using GFR less than 30 ml/min/1.73 m^2 to using the KFRE with 5-year risk of end-stage renal disease greater than 5% or an ACR >70. Given the size and quality of the included studies, the economic modelling and the high discrimination of the equation, the committee were able to make a strong recommendation. This recommendation was based on the 2014 NICE guideline which had the same list of referral rule criteria apart from the referral rule of the KFRE ≥5%.

The committee agreed that the 4 variable KFRE could provide helpful information about adults risk of disease progression over time. Having this information might help people to be more proactive in terms of managing their own risk and be used as part of the management plan with the nephrologist.

The committee highlighted that it is important to discuss risk with people. The committee agreed that education to explain what risk means and how to manage risk is essential when discussing the risk of severe kidney disease with people. Therefore, the committee made additional recommendations about allowing enough time for the provision of information, using jargon free language and documenting the discussion to allow people to make an informed decision with their health practitioner.

The committee discussed the practicalities of using the 4 variable KFRE in daily practice (see section 1.1.8.4 Cost effectiveness and resource use which includes a discussion about implementation issues).

The use of the 4 variable KFRE might identify people at risk of progression to end stage renal disease (ESRD) earlier, which could help to optimise their care before referring to secondary care.

The 4 variable KFRE has not been validated in the UK for children and young people with CKD. The committee noted a US validation study, but agreed that since the validation of the equation in UK adults involved a different mathematical multiplier than in the US it was not possible to extrapolate from US children and young people to those in the UK. Therefore, the committee agreed that children and young people should not be added to the recommendation including the KFRE. Instead, the committee recommended to have an agreement between primary, secondary and tertiary care services for the referral of children and young people being followed-up in primary care and made a research recommendation to validate the equation in the UK for children and young people.

The committee highlighted that black, some Asian and other minority ethnic groups were underrepresented in the UK study validating the KFRE. Therefore, it was agreed to make a research recommendation to validate the risk equation in this population.

1.1.8.4 Cost effectiveness and resource use

The committee noted that there was evidence from the clinical review to suggest the kidney failure risk equations (KFRE) may be a useful tool to predict the need for dialysis or a kidney transplant, and therefore may have value as a tool to guide decisions on referral to secondary care. They felt that a health economic model would be useful for this review question as a UK validation study for the KFRE had recently been published, with data available to model different referral rules. The committee noted that paper only looked at the predictive accuracy of the referral rules, and that there is a trade-off between the sensitivity and specificity of different referral rules. High specificity is important as it prevents referral of patients who will not go into ESRD, where referral would increase the cost of monitoring, without providing clear benefits to the patient. Conversely, high sensitivity is important as it is also crucial not to miss patients who will go into ESRD, as they need to be identified early enough to provide sufficient time to be prepared before starting renal replacement therapy. The NICE guideline on renal replacement therapy suggests that assessment should take place at least 1 year before therapy is likely to be needed.

There has been a single validation study of the KFRE in the UK (Major 2019). This found that the equations had high predictive accuracy within the UK population, once the baseline risk was adjusted to account for the lower baseline risks of kidney disease in the UK compared to the US, where the equations were originally derived. The committee noted as a limitation that these new baseline risks had not been externally validated in a separate study, but agreed that as the equation itself was not changed from the US version, they were still confident in the results of this validation. This study supplied data from which the cost-effectiveness of different referral rules could be assessed; specifically, data on the predictive accuracy of the different referral rules for predicting progression to end stage renal disease.

The committee agreed that the model should be restricted to the use of the four-variable KFRE equations in adults, as there was no evidence from the clinical review that the eight-variable equation performed better, and also that version had not been validated in the UK. Similarly, they agreed that since there was no UK validation for the KFRE equations in children, they should be excluded from the analysis. The committee agreed that children should usually be referred to secondary care much earlier, due to chronic kidney disease being rarer and therefore there being less experience of how to manage the condition in primary care. They agreed that children with CKD would almost always be under secondary care management, and that for the small number discharged back to primary care, rules for re-referral would need to be agreed for the individual.

The KFRE equations are designed to identify the need for dialysis or a kidney transplant, and therefore the committee agreed it was appropriate to design a model based around the costs and benefits of identifying people and referring them to secondary care earlier. Thus, the model should estimate the additional secondary care monitoring costs for people referred earlier, and the benefits of better outcomes for renal replacement therapy (RRT) when people are identified sufficiently in advance. The key clinical data parameters used to populate the model was an update of a Cochrane review looking at the impact of early referral on post-dialysis outcomes. This found that people referred at least 6 months in advance had considerably lower hospitalisation costs and post-dialysis mortality than those only referred within 6 months of needing to start dialysis.

The cost-effectiveness model found that the two best referral rules were the “KFRE ≥5% or ACR ≥70” and the existing 2014 NICE referral rule (eGFR <30 or ACR ≥70). More specific referral rules, such as using the KFRE at a threshold of 15%, saved money on monitoring costs, but at the expense of considerably worse outcomes for people who were missed and therefore not appropriately prepared for needing dialysis. Similarly, more sensitive referral rules, such as those using the KFRE at a threshold of 3%, did identify more people who will enter ESRD earlier, but at the expense of too high an increase in monitoring costs as to be cost-effective.

In the base-case analysis, the “KFRE ≥5% or ACR ≥70” referral rule came out as the most cost-effective option, though the magnitude of the benefit over the current NICE criteria was small. Most of the sensitivity and scenario analyses agreed that “KFRE ≥5% or ACR ≥70” was the preferred rule, as did the results of the probabilistic sensitivity analysis, and therefore the committee were confident in this ordering, despite the small magnitude of the differences. They also noted this finding was consistent with the results of the Major study, which found this rule had both higher sensitivity and specificity than the current NICE criteria. They also noted this rule tends to, on average, refer younger people than the current criteria. The committee recognised that kidney function naturally reduces with age, meaning that a referral rule based on a simple eGFR cut-off will identify people who have normal age-related kidney function decline but are unlikely to reach ESRD within their lifetime. Referral to secondary care is only expected to improve outcomes for people who progress to ESRD and require RRT or conservative management. Because of this, the committee considered that identifying younger people who are more likely to require RRT is a benefit of the ‘KFRE>5% or ACR 70’ referral rule.’

The committee noted there was more uncertainty in the part of the model relating to pre-emptive transplants than the part on dialysis. For example, one scenario where the current NICE criteria came out as better than the “KFRE ≥5% or ACR ≥70” rule was when the hazard ratio for mortality from living pre-emptive kidney donors versus deceased pre-emptive kidney donors was set to the upper limit of the 95% confidence interval. However, the upper limit of the confidence interval implied that clinical outcomes for transplants from deceased donors are better than transplants from living donors, which the committee did not believe to be true, therefore the committee were not concerned about this result. They also noted that when the outcomes for people with a pre-emptive transplant were excluded from the analysis (so benefits were measures solely in people who go on to dialysis) the model once again showed the “KFRE ≥5% or ACR ≥70” rule to be the most cost-effective.

The committee discussed the probabilistic sensitivity analysis and noted that the “KFRE ≥5% or ACR ≥70” rule had the highest probability of being cost-effective. However, in some cases other referral rules may be preferred. The committee felt that the “KFRE ≥5% or ACR ≥70” rule was still a better referral rule than the 2014 NICE criteria and therefore should be adopted into practice. The committee also felt that the sensitivity analysis around the costs did not change the preferred referral rule. Specifically, they noted that the two referral rules involving the KFRE≥5% had a combined probability of over 60% of being the optimal choice, compared to around 20%for the current NICE criteria, and therefore it was three times more likely that a change in practice would be optimal, rather than remaining with the current criteria.

The committee discussed whether the small benefits identified for the alternative referral rule were sufficient to justify changing the referral recommendations and agreed that they were. In particular, they noted that the model only captured clinical benefits for people based on whether they were referred more or less than 6 months before needing dialysis, as this is what the source of the key clinical data. They noted the finding that at the start of the Major study considerably (close to 10%) more people who will progress to ESRD were correctly identified using the “KFRE ≥5% or ACR ≥70” rule, but by 6 months before dialysis both rules were predicted to be picking up approximately the same number. Therefore, the alternative rule, whilst not being much better at identifying people 6 months in advance, was meaningfully better at identifying people at earlier time points (such as 1 year in advance). The committee agreed that, whilst there was no data to capture this in the model, they were confident there would be additional benefits from identifying people 1 year in advance compared to 6 months in advance, and therefore the real world benefits of switching from the current criteria would be larger than those estimated in the model. Additional benefits include more time to test family members to find a suitable match for a kidney transplant, and more time for the patient to choose and prepare for the right type of dialysis for them (there was evidence that a higher proportion of people referred earlier will choose peritoneal rather than haemodialysis). They also noted the model currently only captures the post-dialysis benefits

of early referral, not the benefits that may result if early referral either enables progression to ESRD to be delayed, or enables someone to obtain a pre-emptive transplant rather than needing to go on to dialysis at all. Once again therefore, they agreed that the earlier identification of people using the "KFRE ≥5% or ACR ≥70" rule was likely to provide additional clinical benefits to those captured in the model.

The committee also felt that the analysis was not able to capture the full benefits of using the KFRE equations in other ways. They agreed many patients would find it useful to be given information on their risk of going into ESRD in the next 5 years. The committee felt that this is a large gain for the patient as sometimes they do not understand eGFR and ACR, and what changes in these measurements may mean for their condition, but are likely to understand the meaning of risk over the next 5 years. They agreed it may also be a useful way of motivating patients into making healthier choices i.e. giving up smoking or losing weight. However, they also noted that if explained poorly, being given a risk may be worrisome for some patients. The committee felt that this worry could be mitigated by supporting the patient, ensuring the information is delivered in a clear way and providing opportunities for discussion. To capture this, the committee adapted recommendations from other NICE guidelines where risk scores are used, and noted the upcoming guideline on shared decision making, which is also expected to contain recommendations on this topic.

The committee noted that the model had used a hard cut-off of an ACR of 70 for referral decisions, as this was the data available, whilst in reality the criteria is more complex - "ACR ≥70, unless known to be caused by diabetes and already appropriately treated." The committee noted this as a limitation but agreed that, since this modification applied to both the 2014 NICE criteria and the new KFRE based criteria, this change was unlikely to lead to changes in differential effectiveness between the two different referral rules.

The committee noted there will be implementation difficulties in moving to the new referral rule. Changing to the new referral rule requires the entire country to adopt the new practice as the combination of some areas using the "KFRE ≥5% or ACR ≥70" referral rule and for some the current NICE guidance may cause confusion and so be worse than either rule on its own. The committee acknowledged this difficulty but felt that there should be ways these implementation difficulties could be managed. They noted there were two ways the KFRE could be implemented in practice – either the calculations could be performed by laboratories and returned to primary care alongside eGFR and ACR results (and then stored as a separate field in GP computed systems), or the individual results could be returned to primary care and automated calculations built into GP computer systems. They felt that either one of these methods would in principle be appropriate and were confident if one of these methods were available GPs would adopt the KFRE quickly. They also noted that no other measurements need to be taken to use the KFRE, as it is based on the same variables already measured for monitoring CKD. The committee also noted that other risks associated with using the equation, for example that the US numbers could be used by accident instead of the UK numbers, would also be mitigated by the KFRE being routinely built into IT systems. It was also felt that some GPs would be unwilling to input data into a website, or use some other method to manually calculate the results. In practice, the committee agreed that laboratories performing calculations was likely to be an easier system to introduce, due to the smaller number of laboratories that would need to introduce these calculations, compared to the number of primary care providers.

The committee were aware there was likely to be an implementation period before KFRE results were available to all GPs, and therefore for a time some GPs were likely to have to continue to base referral decisions on eGFR and ACR values independently, as is currently done, and would be unable to provide patients with a quantitative assessment of their risk of needing renal replacement therapy.

The committee noted the potential for the KFRE (or other similar equations) to be improved in the future; noting that equations can be improved, but exact limits such as the current

NICE criteria cannot. For example, there is also an eight-parameter equation which includes co-morbidities. Whilst this has not been shown to have any benefit over the four-parameter equation at present, the committee agreed there was potential for comorbidities or other factors to be built into the equations in the future.

There are other sections to the recommendations that have not been changed by the committee. The four parameter KFRE does not consider comorbidities and therefore the committee felt that the other criteria for referring patients (such as those with haematuria or hypertension) were important to keep. Referral back to the GP was included as a recommendation as not all patients require secondary monitoring, and this re-referral was included in the economic model. The committee agreed that a discussion with secondary care on whether the patient needs to be referred or can still be monitored in primary care could be considered as the equivalent to a referral.

Downstream costs of dialysis were excluded from the analysis, in keeping with other NICE guidelines that contain dialysis. This is because dialysis is not a cost-effective treatment by standard NICE criteria, and therefore including the costs of it can lead to nonsensical results (such as an intervention with high mortality coming out as better, since it saves costs of later dialysis). The committee noted this and agreed it was appropriate, since society has indicated that it is willing to pay for dialysis even though it is not a cost-effective treatment by the standard criteria, and therefore the analysis should reflect this choice. One sensitivity analysis was done including downstream dialysis costs which showed that the preferred option was KFRE ≥15%. KFRE ≥15% has the highest specificity; it does not refer many patients unnecessarily; however, it also does not find many patients who will need RRT. This is why when the committee looked at the information, they disregarded this option as patients 'crash landing' onto dialysis is very detrimental to patient costs and quality of life.

1.1.8.5 Other factors the committee took into account

An issue within the data from the Major study was that the black population was under-represented, both compared to the UK population overall and compared to the population in the UK Renal Registry. The committee noted this was an issue that had run throughout the guideline, with many studies not containing sufficient representation of the black population to enable good recommendation to be made for that group, or to be confident the same recommendations were appropriate. In the long-term the committee agreed this could only be addressed by further research studies appropriately sampling from this population. However, the committee noted that in this case, these limitations applied to both the current NICE criteria and the KFRE based criteria, and therefore there was no reason to suspect that changing would have a detrimental effect on any given population. They also noted again that an advantage of moving to an equation-based method was the potential for those equations to be improved with the inclusion of extra factors, be those ethnicity itself or other factors (such as muscle mass) that may be correlated with ethnicity at a population level, but be better predictors of individual outcomes than ethnicity itself.

COVID-19 has changed the way healthcare has been provided and it is unknown how much of this change will persist. Monitoring appointments have been moved to telephone consultation; this is less expensive than in person appointments. This change was caught in the sensitivity analyses with reducing monitoring costs, this showed that the KFRE ≥5% or ACR ≥70 referral rule was still the most cost-effective rule, and therefore the committee were confident their recommendations were robust to any potential future changes in the configuration of CKD services.

The rules on organ donation changed on 20 May 2020 to an opt out system, which means that there are likely to be more available kidneys for transplantations. Therefore, more patients are likely to be able to receive a kidney transplant, rather than need to go on to dialysis. However, early referral is then even more important in making sure the necessary

tests are completed, otherwise the patient may have to go on dialysis before the transplant, which leads to worse outcomes.

1.1.9 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1 to 1.5.10 and the research recommendation on the accuracy of the kidney failure risk equation in adults, children and young people with CKD from black, Asian and minority ethnic groups living on the UK.

1.1.10 References – included studies

1.1.10.1 Prognostic

Lennartz, C.S., Pickering, J.W., Seiler-Mussler, S. et al. (2016) External validation of the kidney failure risk equation and re-calibration with addition of ultrasound parameters. Clinical Journal of the American Society of Nephrology 11(4): 609-615

Major, R.W., Shepherd, D., Medcalf, J.F. et al. (2019) The kidney failure risk equation for prediction of end stage renal disease in UK primary care: An external validation and clinical impact projection cohort study. PLoS Medicine 16(11): e1002955

Marks, Angharad, Fluck, Nicholas, Prescott, Gordon J et al. (2015) Looking to the future: predicting renal replacement outcomes in a large community cohort with chronic kidney disease. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 30(9): 1507-17

Peralta CA, Katz R, Sarnak MJ et al. (2011) Cystatin C identifies chronic kidney disease patients at higher risk for complications. Journal of the American Society of Nephrology : JASN 22(1): 147-155

Peralta CA, Shlipak MG, Judd S et al. (2011) Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. JAMA 305(15): 1545-1552

Tangri, N., Grams, M.E., Levey, A.S. et al. (2016) Multinational assessment of accuracy of equations for predicting risk of kidney failure ameta-analysis. JAMA - Journal of the American Medical Association 315(2): 164-174

Waheed S, Matsushita K, Astor BC et al. (2013) Combined association of creatinine, albuminuria, and cystatin C with all-cause mortality and cardiovascular and kidney outcomes. Clinical journal of the American Society of Nephrology : CJASN 8(3): 434-442

Wang, Y., Nguyen, F.N.H.L., Allen, J.C. et al. (2019) Validation of the kidney failure risk equation for end-stage kidney disease in Southeast Asia. BMC Nephrology 20(1): 451

Whitlock, R.H., Chartier, M., Komenda, P. et al. (2017) Validation of the kidney failure risk equation in Manitoba. Canadian Journal of Kidney Health and Disease 4: 5372

Winnicki, Erica, McCulloch, Charles E, Mitsnefes, Mark M et al. (2018) Use of the Kidney Failure Risk Equation to Determine the Risk of Progression to End-stage Renal Disease in Children With Chronic Kidney Disease. JAMA pediatrics 172(2): 174-180

Appendices

Appendix A – Review protocols

Review protocol for predicting disease progression

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Measures of kidney function and markers of kidney damage to identify increased risk of progression in adults, children and young people with CKD?
2.	Review questions	What is the best combination of measures of kidney function and markers of kidney damage to identify increased risk of progression in adults, children and young people with CKD? Are kidney failure prediction equations good predictors of progression, kidney failure or end-stage renal disease.
3.	Objective	To determine the best combination of measures of kidney function and markers of kidney damage to identify increased risk of progression, and to determine whether kidney risk equations are good predictors of progression in adults, children and young people with CKD?
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase Searches will be restricted by: From 25 November 2013 for adults No limit for children and young people English language Human studies The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion.

ID	Field	Content
		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 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 chronic kidney disease stages 1 to 5. Exclusion: people receiving renal replacement therapy (RRT) people with acute kidney injury combined with rapidly progressive glomerulonephritis pregnant women people receiving palliative care
7.	Prognostic factor	For part 1: MDRD (serum creatinine) plus urinary ACR CKD-EPI eGFR (serum creatinine) plus urinary ACR CKD-EPI cystatin C plus urinary ACR Combined CKD-EPI (serum creatinine + cystatin C eGFR) plus urinary ACR Schwartz + urinary ACR A 'positive' result is determined using an eGFR-creatinine or eGFR-cystatin of less than 60 ml/min/1.73 m2 and/or an ACR greater than 30 mg/g (approximately 3 mg/mmol). For part 2: Kidney failure risk equations (eg. Tangri equation [KFRE])
8.	Co- variates	For part 1: Age

ID	Field	Content
		Gender Hypertension Diabetes Family origin
9.	Types of study to be included	Prospective cohort studies (retrospective cohorts will be included if no prospective studies are found) Systematic reviews of prospective cohort studies For part 2, we will only consider validation cohorts for kidney risk equations and not derivation cohorts.
10.	Other exclusion criteria	Abstracts and conference proceedings Theses Non-human studies 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 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)	For Part 1. Hazard ratios, risk ratios and odds ratios for: CKD progression: change in eGFR CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) AKI All-cause mortality Cardiovascular mortality For Part 2 Prognostic performance:

ID	Field	Content	
		Calibration (goodness of measures.eg. R2; Brier score, Hosmer-Lemeshow test) Discrimination (eg. sn/sp; AUC from ROC, AUROC; c-statistic)	
13.	Secondary outcomes (important outcomes)	None.	
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. 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. 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 PROBAST checklist as described in Developing NICE guidelines: the manual.	
16.	Strategy for data synthesis	Where appropriate, risk ratios, odds ratios and hazard ratios will pooled using the inverse-variance method. Outcomes will only be pooled if the same set of predictor variables are used across multiple studies and are on the same scale.	
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: Older people. People from black, Asian and other minority ethnic groups. People at high risk of developing progressive CKD (for example, people with diabetes, hypertension or cardiovascular disease, or people recovering from acute kidney injury). People with a family history of renal disease..	
18.	Type and method of review	☐	Intervention
		☐	Diagnostic

ID	Field	Content		
		☒	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	Feb 2020		
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 against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact Guideline Updates Team 5b Named contact e-mail GUTprospero@nice.org.uk		

ID	Field	Content
		5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)
25.	Review team members	From the Guideline Updates Team: Mr Chris Carmona Dr Yolanda Martinez Ms Omnia Abdulrazeg Dr Joshua Pink Mr Rui Martins 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].
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: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts

ID	Field	Content	
		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, MDRD, CKD-EI, Schwartz.	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

Appendix B – Methods

Evidence synthesis and meta-analyses of pair-wise data

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. For continuous outcomes analysed as mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately. For continuous outcomes analysed as standardised mean differences, where only baseline and final time point values were available, change from baseline standard deviations were estimated, assuming a correlation coefficient of 0.5. In cases where SMDs were used they were back converted to a single scale to aid interpretation by the committee where possible.

Predictive accuracy evidence

In this guideline, predictive accuracy data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in some people who go on to develop the condition of interest and some people who do not. Such data either explicitly provide, or can be manipulated to generate, a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly develop the condition) and false positives and true negatives (in people who, according to the reference standard, do not). This category would include studies classed as prediction models under the TRIPOD statement, provided the data were reported a 2x2 classification data.

The 'raw' 2x2 data can be summarised in a variety of ways. Those that were used for decision making in this guideline are as follows:

- **Positive likelihood ratios** describe how many times more likely positive features are in people who develop the condition compared to people who do not. Values greater than 1 indicate that a positive result makes the condition more likely.
  - LR^+ = (TP/[TP+FN])/(FP/[FP+TN])
- **Negative likelihood ratios** describe how many times less likely negative features are in people who develop the condition compared to people who do not. Values less than 1 indicate that a negative result makes the condition less likely.
  - LR^- = (FN/[TP+FN])/(TN/[FP+TN])
- **Sensitivity** is the probability that the feature will be positive in a person who goes on to develop the condition.
  - sensitivity = TP/(TP+FN)
- **Specificity** is the probability that the feature will be negative in a person who does not go on to develop the condition.
  - specificity = TN/(FP+TN)

The following schema, adapted from the suggestions of Jaeschke et al. (1994), was used to interpret the findings from prognostic test accuracy reviews.

Table 8: Interpretation of likelihood ratios

Value of likelihood ratio	Interpretation
LR ≤ 0.1	**Very large** decrease in probability of disease
0.1 < LR ≤ 0.2	**Large** decrease in probability of disease
0.2 < LR ≤ 0.5	**Moderate** decrease in probability of disease
0.5 < LR ≤ 1.0	**Slight** decrease in probability of disease
1.0 < LR < 2.0	**Slight** increase in probability of disease
2.0 ≤ LR < 5.0	**Moderate** increase in probability of disease
5.0 ≤ LR < 10.0	**Large** increase in probability of disease
LR ≥ 10.0	**Very large** increase in probability of disease

The schema above has the effect of setting a minimal important difference for positive likelihoods ratio at 2, and a corresponding minimal important difference for negative likelihood ratios at 0.5. Likelihood ratios (whether positive or negative) falling between these thresholds were judged to indicate no meaningful change to probability of disease.

Quality assessment

Individual studies were quality assessed using the PROBAST tool, which contains five domains: participant selection, predictors, outcome, sample size and participant flow, analysis (Wolff et al. 2018). Each individual study was classified into one of the following three groups based on an assessment of the overall risk of bias:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, predictive features and/or reference standard in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, predictive feature and/or reference standard.
- Partially indirect – Important deviations from the protocol in one of the population, predictive feature and/or reference standard.
- Indirect – Important deviations from the protocol in at least two of the population, predictive feature and/or reference standard.

Modified GRADE for prognostic test accuracy evidence

GRADE has not been developed for use with prognostic test accuracy studies; therefore a modified approach was applied using the GRADE framework. GRADE assessments were only undertaken for positive and negative likelihood ratios, as the MIDs used to assess imprecision were based on these outcomes.

Cross-sectional and cohort studies were initially rated as high-quality evidence if well conducted, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table 9 below.

Table 9: Rationale for downgrading quality of evidence for prognostic questions

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If the 95% confidence interval for sensitivity crossed one of the clinical decision thresholds, the outcome was downgraded one level, as the data were deemed to be imprecise.. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if either of the following conditions were met:

- Data showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts or protocols without

accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Other prognostic evidence

Other prognostic studies were also included if they reported outcomes of c-statistics, hazard ratios or model fit statistics. These studies were also quality assessed using the PROBAST checklist, as in the prognostic test accuracy section above.

Methods for combining prognostic association data

Where appropriate, hazard ratios were pooled using the inverse-variance method. Adjusted hazard ratios from multivariate models were only pooled if the same set of predictor variables were used across multiple studies and they were on the same scale

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

For hazard ratios, the line of no effect (HR=1) was used to assess imprecision in the absence of a more clinically meaningful MID.

Where meta-analysis was possible a modified GRADE rating was generated for each outcome.

In the absence of hazard ratio data that could be meta-analysed, data was pooled to obtain single GRADE ratings per index using the following decision rules:

1. Risk of bias and indirectness were assessed as detailed in Table 9 for other prognostic evidence, but % of study population was used instead of the weight in a meta-analysis.
2. Imprecision:
    a. In cases where a single or multiple per point increase hazard ratios are presented, the level of imprecision was calculated for each study using the line of no effect HR=1. If >33% of the studies by population weight had 95% CI that spanned one side of the MID then the index was rated as serious, if >33% had 95% CI that spanned both MID values then the overall index was rated as at very serious risk of imprecision.
3. Inconsistency:
    a. For a single study this is judged to be not applicable (N/A).
    b. For multiple studies with single HRs this is judged using I^2 calculated using Review Manager v5.3 and assessed following the rules in Table 9.
    c. In cases with multiple studies each presenting several hazard ratios compared to the same reference category, the HR data for the most severe category was pooled in RevMan and inconsistency was assessed using the I^2 value following the rules in Table 8.
    d. If hazard ratio data for a single index was reported in several ways (per point increase, with reference to high and/or low categories) then inconsistency for this outcome was determined to be serious as the results were not comparable

Methods for combining c-statistics for prediction models

C-statistics are a measure oof calibration for prediction models with a score ranging from 0 to 1.0 with higher scores representing better calibration (classification accuracy). C-statistics were assessed in a similar manner to likelihood ratios using the categories in Table 10 below.

Table 10 Interpretation of c-statistics

Value of c-statistic	Interpretation
c-statistic <0.6	**Poor classification accuracy**
0.6 ≤ c-statistic <0.7	**Adequate classification accuracy**
0.7 ≤ c-statistic <0.8	**Good classification accuracy**
0.8 ≤ c-statistic <0.9	**Excellent classification accuracy**
0.9 ≤ c-statistic < 1.0	**Outstanding classification accuracy**

Meta-analyses were carried out using the metamisc package in R v3.4.0, which confines the analysis results to between 0 and 1 matching the limited range of values that c-statistics can take. Random effects meta-analysis was used when the I^2 was 50% or greater.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

A modified version of GRADE was carried out to assess the quality of the meta-analysed c-statistics as follows:

- Imprecision - the 95% CI boundaries were examined and if they crossed 2 categories of test classification accuracy then the study was downgraded once (imprecision rated as serious); if the boundaries crossed 3 categories then the study was downgraded twice (very serious imprecision).
- Inconsistency, indirectness and risk of bias were determined using the methods in the section on GRADE for prognostic test accuracy evidence.

In cases where meta-analyses could not be carried out due to the large numbers of studies without 95% CI, the following decision rules were used to assess risk of bias, indirectness, imprecision and inconsistency for each outcome:

1. Risk of bias and indirectness were assessed as detailed in Table 9 but using the study weight by population, rather than weight in the meta-analysis.
2. Imprecision
    a. Single study with 95% CI: the 95% CI boundaries were examined and if they crossed 2 categories of test classification accuracy then the study was downgraded once (imprecision rated as serious); if the boundaries crossed 3 categories then the study was downgraded twice (very serious imprecision).
    b. Multiple studies with 95% CI: the individual studies were rated as in a. and then if >33.3% of the studies by population weight were rated serious then the analysis was downgraded once; if > 33.33% were rated very serious the analysis was downgraded twice.
    c. Single study or multiple studies without 95% CI: the mean sample size was calculated and if this was < 250 then the analysis was downgraded twice (very serious); if it was >250, but > 500 the analysis was downgraded once (serious); if

the mean was > 500 people/study then the analysis was not downgraded (not serious).

d. Multiple studies with and without 95% CI: the studies without 95% CI were analysed as in 2c; those with 95% CI were analysed as in 2b. The results were averaged, but the number of studies in each group were also taken into account with the result that if there were a lot more studies in one group compared to the other then that group rating would be used. In general, not serious and serious or not serious and very serious were averaged to serious; serious and very serious resulted in a very serious rating.

3. Inconsistency
    a. Single study with or without 95% CI: N/A
    b. Multiple studies with or without 95% CI: the highest and lowest point estimates were examined. If they spanned < 2 categories of c-statistic classification accuracy the analysis was rated as not serious for inconsistency; if they spanned 2 categories this was rated as serious and ≥ 3 categories was rated as very serious.

Methods for assessing discrimination in prediction models

Models included in this review assessed model discrimination using Brier scores and R^2 statistics. These data were not combined or pooled.

The committee interpreted these figures based on its best judgment since in isolation measures of discrimination are difficult to interpret. They are most useful to allow models to be compared.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 11.

Table 11 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness

Level	Explanation
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 12.

Table 12 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

RQ2.1 What is the best combination of measures of kidney function and markers of kidney damage to identify increased risk of progression in adults, children and young people with CKD?

A NICE information specialist conducted the literature searches for the evidence review. The searches were originally run on the 24th of January 2020 and updated on the 7th of September 2020. This search report is compliant with the requirements of PRISMA-S.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

The MEDLINE strategy below was quality assured (QA) by trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

English language limits were applied in adherence to standard NICE practice and the review protocol.

To retrieve evidence on adults that had been published since the search strategies were last run for the former guideline, the search was limited from 2013. No date restrictions were applied to the section of the search strategies on children and young people because this population had not been included in the former guideline.

Limits to exclude conferences, notes, letters and books in Embase were applied in adherence to standard NICE practice.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286

Clinical searches

Databases	Date searched	Version/files	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	24th Jan 2020	Issue 1 of 12, January 2020	486
Cochrane Database of Systematic Reviews (CDSR)	24th Jan 2020	Issue 1 of 12, January 2020	10
Database of Abstracts of Reviews of Effect (DARE)	24th Jan 2020	Up to 2015	30

Embase (Ovid)	24th Jan 2020	Embase <1974 to 2020 Week 03>	3686
MEDLINE (Ovid)	24th Jan 2020	Ovid MEDLINE(R) <1946 to January 24, 2020>	2336
MEDLINE In-Process (Ovid)	24th Jan 2020	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to January 22, 2020>	336
MEDLINE Epub Ahead of Print[a]	24th Jan 2020	Ovid MEDLINE(R) Epub Ahead of Print <January 22, 2020>	60

Search strategies

Database: Ovid MEDLINE(R) <1946 to January 24, 2020>

Search Strategy:

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1 exp Renal Insufficiency, Chronic/ (112011)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (72064)

3 ((kidney* or renal*) adj1 insufficien*).tw. (21205)

4 ckd*.tw. (22662)

5 ((kidney* or renal*) adj1 fail*).tw. (86132)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (35010)

7 (esrd* or eskd*).tw. (14106)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3440)

9 or/1-8 (211762)

10 Glomerular Filtration Rate/ (43077)

11 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (156870)

12 or/10-11 (170198)

13 9 and 12 (35418)

14 Cystatin C/ (3909)

15 cystatin*.tw. (7022)

16 Creatinine/ (55613)

[a] Please search for both development and re-run searches

17 (creatinine or acr or pcr).tw. (540316)

18 or/14-17 (566247)

19 (formula* or equation* or calculat* or reclassif* or re classif*).tw. (948302)

20 (modif* of diet in renal disease* or MDRD*).ti,ab. (3371)

21 (ckdepi or epi or epidemiology collaboration).tw. (16916)

22 (multimark* or multi-mark* or mark*).tw. (1315317)

23 or/19-22 (2215237)

24 schwartz*.tw. (2255)

25 13 and 24 (161)

26 (13 and 18 and 23) or 25 (4540)

27 limit 26 to ed=20131101-20200123 (1957)

28 exp Infant/ or Infant Health/ or Infant Welfare/ (1120991)

29 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (834681)

30 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1881776)

31 Minors/ (2552)

32 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2297216)

33 exp pediatrics/ (56888)

34 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (806306)

35 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (1987328)

36 Puberty/ (13150)

37 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (410763)

38 Schools/ (36770)

39 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (8700)

40 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (456740)

41 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (3824)

42 or/28-41 (5082128)

43 26 and 42 (1120)

44 27 or 43 (2585)

45 limit 44 to english language (2432)

46 animals/ not humans/ (4634055)

47 45 not 46 (2336)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to January 22, 2020>

Search Strategy:

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1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (9167)

3 ((kidney* or renal*) adj1 insufficien*).tw. (1077)

4 ckd*.tw. (4334)

5 ((kidney* or renal*) adj1 fail*).tw. (6210)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (4674)

7 (esrd* or eskd*).tw. (1928)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (17944)

10 Glomerular Filtration Rate/ (0)

11 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (15782)

12 or/10-11 (15782)

13 9 and 12 (3539)

14 Cystatin C/ (0)

15 cystatin*.tw. (786)

16 Creatinine/ (0)

17 (creatinine or acr or pcr).tw. (57276)

18 or/14-17 (57658)

19 (formula* or equation* or calculat* or reclassif* or re classif*).tw. (283775)

20 (modif* of diet in renal disease* or MDRD*).ti,ab. (305)

21 (ckdepi or epi or epidemiology collaboration).tw. (2436)

22 (multimark* or multi-mark* or mark*).tw. (144955)

23 or/19-22 (420160)

24 schwartz*.tw. (357)

25 13 and 24 (24)

26 (13 and 18 and 23) or 25 (481)

27 limit 26 to dt=20131101-20200123 (428)

28 exp Infant/ or Infant Health/ or Infant Welfare/ (0)

29 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (75075)

30 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)

31 Minors/ (0)

32 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (298174)

33 exp pediatrics/ (0)

34 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (111307)

35 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)

36 Puberty/ (0)

37 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (55805)

38 Schools/ (0)

39 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)

40 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (64481)

41 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (565)

42 or/28-41 (432383)

43 26 and 42 (114)

44 27 or 43 (440)

45 limit 44 to english language (436)

46 animals/ not humans/ (0)

47 45 not 46 (436)

Database: Ovid MEDLINE(R) Epub Ahead of Print <January 22, 2020>

Search Strategy:

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1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (1374)

3 ((kidney* or renal*) adj1 insufficien*).tw. (157)

4 ckd*.tw. (708)

5 ((kidney* or renal*) adj1 fail*).tw. (747)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (687)

7 (esrd* or eskd*).tw. (299)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (2557)

10 Glomerular Filtration Rate/ (0)

11 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (2296)

12 or/10-11 (2296)

13 9 and 12 (514)

14 Cystatin C/ (0)

15 cystatin*.tw. (108)

16 Creatinine/ (0)

17 (creatinine or acr or pcr).tw. (7229)

18 or/14-17 (7277)

19 (formula* or equation* or calculat* or reclassif* or re classif*).tw. (24760)

20 (modif* of diet in renal disease* or MDRD*).ti,ab. (31)

21 (ckdepi or epi or epidemiology collaboration).tw. (306)

22 (multimark* or multi-mark* or mark*).tw. (19540)

23 or/19-22 (43172)

24 schwartz*.tw. (55)

25 13 and 24 (2)

26 (13 and 18 and 23) or 25 (60)

27 limit 26 to english language (60)

Database: Embase <1974 to 2020 Week 03>

Search Strategy:

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1 exp kidney failure/ (347216)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (121146)

3 ((kidney* or renal*) adj1 insufficien*).tw. (29885)

4 ckd*.tw. (48485)

5 ((kidney* or renal*) adj1 fail*).tw. (131226)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (57356)

7 (esrd* or eskd*).tw. (26828)

8 or/1-7 (438663)

9 exp glomerulus filtration rate/ (96469)

10 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (261066)

11 9 or 10 (289333)

12 8 and 11 (76380)

13 cystatin C/ (11312)

14 cystatin*.tw. (11625)

15 creatinine/ (174036)

16 creatinine blood level/ (106947)

17 (creatinine or acr or pcr).tw. (897118)

18 or/13-17 (984014)

19 (formula* or equation* or calculat* or reclassif* or re classif*).tw. (1629852)

20 (modif* of diet in renal disease* or MDRD*).tw. (9138)

21 (ckdepi or epi or epidemiology collaboration).tw. (30624)

22 (multimark* or multi-mark* or mark*).tw. (1987159)

23 or/19-22 (3521404)

24 schwartz*.tw. (3705)

25 12 and 24 (479)

26 (12 and 18 and 23) or 25 (11478)

27 limit 26 to dc=20131101-20200123 (6766)

28 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ (3345714)

29 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,ad,jw. (1177692)

30 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,ad,jw. (3539015)

31 exp pediatrics/ (103178)

32 (pediatric* or paediatric* or peadiatric*).ti,ab,in,ad,jw. (1589924)

33 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (101324)

34 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,ad,jw. (638586)

35 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (101138)

36 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jw. (679543)

37 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (7156)

38 or/28-37 (6267562)

39 26 and 38 (2296)

40 27 or 39 (7712)

41 limit 40 to english language (7510)

42 limit 41 to (books or chapter or conference abstract or conference paper or "conference review" or letter or note or tombstone) (3625)

43 41 not 42 (3885)

44 nonhuman/ not human/ (4540772)

45 43 not 44 (3686)

Cochrane Library

#1 MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees 6190

#2 (((chronic* or progressi*) near/1 (renal* or kidney*))):ti,ab,kw 10095

#3 (((kidney* or renal*) near/1 insufficien*)):ti,ab,kw 4869

#4 (ckd*):ti,ab,kw 4708

#5 (((kidney* or renal*) near/1 fail*)):ti,ab,kw 16190

#6 (((endstage* or end-stage* or "end stage*") near/1 (renal* or kidney*))):ti,ab,kw 4428

#7 ((esrd* or eskd*)):ti,ab,kw 2009

#8 MeSH descriptor: [Chronic Kidney Disease-Mineral and Bone Disorder] this term only 83

#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 25439

#10 MeSH descriptor: [Glomerular Filtration Rate] this term only 2638

#11 (glomerul* or GFR* or eGFR* or e-GFR*):ti,ab,kw 17927

#12 #10 or #11 17927

#13 #9 and #12 5434

#14 MeSH descriptor: [Cystatin C] this term only 169

#15 (cystatin*):ti,ab,kw 1048

#16 MeSH descriptor: [Creatinine] this term only 3880

#17 (creatinine or acr or pcr):ti,ab,kw 39595

#18 #14 or #15 or #16 or #17 39938

#19 (formula* or equation* or calculat* or reclassif* or re classif*):ti,ab,kw 103556

#20 (modif* of diet in renal disease* or MDRD*):ti,ab,kw 1298

#21 (ckdepi or epi or epidemiology collaboration):ti,ab,kw 2319

#22 (multimark* or multi-mark* or mark*):ti,ab,kw 86820

#23 #19 or #20 or #21 or #22 183958

#24 (schwartz*):ti,ab,kw 153

#25 #13 and #24 19

#26 (#13 and #18 and #23) or #25 968

#27 "conference":pt or (clinicaltrials or trialsearch):so 446662

#28 #26 not #27 496 (10 CDSR, 486 CENTRAL)

CRD databases

1 (MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES) 538 Delete

2 (((chronic* or progressi*) near1 (renal* or kidney*))) 489 Delete

3 ((ckd*)) 93 Delete

4 (((kidney* or renal*) near1 fail*)) 836 Delete

5 (((endstage* or end-stage* or "end stage*") near1 (renal* or kidney))) 354 Delete

6 ((esrd* or eskd*)) 150 Delete

7 (((kidney* or renal*) near1 insufficien*)) 320 Delete

8 ((MeSH DESCRIPTOR Chronic Kidney Disease-Mineral and Bone Disorder)) 0 Delete

9 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8) 1407 Delete

10 (MeSH DESCRIPTOR Glomerular Filtration Rate) 92 Delete

11	(glomerul* or GFR* or eGFR* or e-GFR*)			416	Delete
12	(#10 or #11)	416	Delete		
13	#9 AND #12	151	Delete		
14	MeSH DESCRIPTOR Cystatin C	8	Delete		
15	(cystatin*)	12	Delete		
16	MeSH DESCRIPTOR Creatinine	114	Delete		
17	(creatinine or acr or pcr)	913	Delete		
18	(#14 or #15 or #16 or #17)	919	Delete		
19	(formula* or equation* or calculat* or reclassif* or re classif*)			17684	Delete
20	(modif* of diet in renal disease* or MDRD*)			6	Delete
21	(ckdepi or epi or epidemiology collaboration)			52	Delete
22	(multimark* or multi-mark* or mark*)			5764	Delete
23	(#19 or #20 or #21 or #22)	21088	Delete		
24	(schwartz*)	149	Delete		
25	#13 AND #24	1	Delete		
26	#13 AND #18 AND #23	40	Delete		
27	#25 OR #26	40	Delete		
28	(#25 OR #26) IN DARE	30	Delete		
29	(#25 OR #26) IN NHSEED	8	Delete		
30	(#25 OR #26) IN HTA	2	Delete		

Cost-effectiveness searches

Databases	Date searched	Version/files	No. retrieved
MEDLINE (Ovid)	23rd Jan 2020	Ovid MEDLINE(R) <1946 to January 22, 2020>	250
MEDLINE in Process (Ovid)	23rd Jan 2020	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to January 22, 2020>	35

MEDLINE epub (Ovid)	23rd Jan 2020	Ovid MEDLINE(R) Epub Ahead of Print <January 22, 2020>	7
Embase (Ovid)	23rd Jan 2020	Embase <1974 to 2020 Week 03>	438
EconLit (Ovid)	23rd Jan 2020	Econlit <1886 to January 09, 2020>	0
NHS Economic Evaluation Database (NHS EED) (legacy database)	24th Jan 2020	Up to 2015	8
CRD HTA	24th Jan 2020	Up to 2018	2

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

  Several modifications have been made to these filters over the years that are standard NICE practice.

Search strategies

Database: Ovid MEDLINE(R) <1946 to January 22, 2020>

Search Strategy:

---

1 exp Renal Insufficiency, Chronic/ (111986)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (72036)

3 ((kidney* or renal*) adj1 insufficien*).tw. (21202)

4 ckd*.tw. (22655)

5 ((kidney* or renal*) adj1 fail*).tw. (86121)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (35001)

7 (esrd* or eskd*).tw. (14102)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3439)

9 or/1-8 (211713)

10 Glomerular Filtration Rate/ (43068)

11 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (156834)

12 or/10-11 (170159)

13 9 and 12 (35406)

14 Cystatin C/ (3908)

15 cystatin*.tw. (7020)

16 Creatinine/ (55603)

17 (creatinine or acr or pcr).tw. (540180)

18 or/14-17 (566107)

19 (formula* or equation* or calculat* or reclassif* or re classif*).tw. (947950)

20 (modif* of diet in renal disease* or MDRD*).ti,ab. (3371)

21 (ckdepi or epi or epidemiology collaboration).tw. (16911)

22 (multimark* or multi-mark* or mark*).tw. (1315016)

23 or/19-22 (2214604)

24 schwartz*.tw. (2255)

25 13 and 24 (161)

26 (13 and 18 and 23) or 25 (4538)

27 Economics/ (27119)

28 exp "Costs and Cost Analysis"/ (231914)

29 Economics, Dental/ (1910)

30 exp Economics, Hospital/ (24169)

31 exp Economics, Medical/ (14160)

32 Economics, Nursing/ (3996)

33 Economics, Pharmaceutical/ (2911)

34 Budgets/ (11216)

35 exp Models, Economic/ (14660)

36 Markov Chains/ (13934)

37 Monte Carlo Method/ (27671)

38 Decision Trees/ (10874)

39 econom$.tw. (229866)

40 cba.tw. (9693)

41 cea.tw. (20139)

42 cua.tw. (972)

43 markov$.tw. (17404)

44 (monte adj carlo).tw. (29147)

45 (decision adj3 (tree$ or analys$)).tw. (12810)

46 (cost or costs or costing$ or costly or costed).tw. (445350)

47 (price$ or pricing$).tw. (32460)

48 budget$.tw. (23091)

49 expenditure$.tw. (47924)

50 (value adj3 (money or monetary)).tw. (2022)

51 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3432)

52 or/27-51 (899176)

53 "Quality of Life"/ (187171)

54 quality of life.tw. (220622)

55 "Value of Life"/ (5682)

56 Quality-Adjusted Life Years/ (11769)

57 quality adjusted life.tw. (10339)

58 (qaly$ or qald$ or qale$ or qtime$).tw. (8488)

59 disability adjusted life.tw. (2552)

60 daly$.tw. (2330)

61 Health Status Indicators/ (23173)

62 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (21846)

63 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1290)

64 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4686)

65 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (28)

66 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (376)

67 (euroqol or euro qol or eq5d or eq 5d).tw. (8416)

68 (qol or hql or hqol or hrqol).tw. (42095)

69 (hye or hyes).tw. (60)

70 health$ year$ equivalent$.tw. (38)

71 utilit$.tw. (165491)

72 (hui or hui1 or hui2 or hui3).tw. (1254)

73 disutili$.tw. (369)

74 rosser.tw. (92)

75 quality of wellbeing.tw. (13)

76 quality of well-being.tw. (377)

77 qwb.tw. (187)

78 willingness to pay.tw. (4217)

79 standard gamble$.tw. (773)

80 time trade off.tw. (1009)

81 time tradeoff.tw. (227)

82 tto.tw. (875)

83 or/53-82 (475669)

84 52 or 83 (1308898)

85 26 and 84 (270)

86 limit 85 to english language (250)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to January 22, 2020>

Search Strategy:

---

1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (9167)

3 ((kidney* or renal*) adj1 insufficien*).tw. (1077)

4 ckd*.tw. (4334)

5 ((kidney* or renal*) adj1 fail*).tw. (6210)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (4674)

7 (esrd* or eskd*).tw. (1928)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (17944)

10 Glomerular Filtration Rate/ (0)

11 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (15782)

12 or/10-11 (15782)

13 9 and 12 (3539)

14 Cystatin C/ (0)

15 cystatin*.tw. (786)

16 Creatinine/ (0)

17 (creatinine or acr or pcr).tw. (57276)

18 or/14-17 (57658)

19 (formula* or equation* or calculat* or reclassif* or re classif*).tw. (283775)

20 (modif* of diet in renal disease* or MDRD*).ti,ab. (305)

21 (ckdepi or epi or epidemiology collaboration).tw. (2436)

22 (multimark* or multi-mark* or mark*).tw. (144955)

23 or/19-22 (420160)

24 schwartz*.tw. (357)

25 13 and 24 (24)

26 (13 and 18 and 23) or 25 (481)

27 Economics/ (0)

28 exp "Costs and Cost Analysis"/ (0)

29 Economics, Dental/ (0)

30 exp Economics, Hospital/ (0)

31 exp Economics, Medical/ (0)

32 Economics, Nursing/ (0)

33 Economics, Pharmaceutical/ (0)

34 Budgets/ (0)

35 exp Models, Economic/ (0)

36 Markov Chains/ (0)

37 Monte Carlo Method/ (0)

38 Decision Trees/ (0)

39 econom$.tw. (42754)

40 cba.tw. (403)

41 cea.tw. (1822)

42 cua.tw. (194)

43 markov$.tw. (5424)

44 (monte adj carlo).tw. (16488)

45 (decision adj3 (tree$ or analys$)).tw. (2266)

46 (cost or costs or costing$ or costly or costed).tw. (91635)

47 (price$ or pricing$).tw. (5590)

48 budget$.tw. (4794)

49 expenditure$.tw. (6129)

50 (value adj3 (money or monetary)).tw. (346)

51 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (514)

52 or/27-51 (158872)

53 "Quality of Life"/ (0)

54 quality of life.tw. (36526)

55 "Value of Life"/ (0)

56 Quality-Adjusted Life Years/ (0)

57 quality adjusted life.tw. (1590)

58 (qaly$ or qald$ or qale$ or qtime$).tw. (1359)

59 disability adjusted life.tw. (482)

60 daly$.tw. (443)

61 Health Status Indicators/ (0)

62 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (2545)

63 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (744)

64 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (710)

65 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (5)

66 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (19)

67 (euroqol or euro qol or eq5d or eq 5d).tw. (1578)

68 (qol or hql or hqol or hrqol).tw. (6989)

69 (hye or hyes).tw. (8)

70 health$ year$ equivalent$.tw. (2)

71 utilit$.tw. (29623)

72 (hui or hui1 or hui2 or hui3).tw. (173)

73 disutili$.tw. (69)

74 rosser.tw. (4)

75 quality of wellbeing.tw. (7)

76 quality of well-being.tw. (25)

77 qwb.tw. (12)

78 willingness to pay.tw. (897)

79 standard gamble$.tw. (59)

80 time trade off.tw. (119)

81 time tradeoff.tw. (18)

82 tto.tw. (119)

83 or/53-82 (68410)

84 52 or 83 (218256)

85 26 and 84 (36)

86 limit 85 to english language (35)

Database: Ovid MEDLINE(R) Epub Ahead of Print <January 22, 2020>

Search Strategy:

---

1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (1374)

3 ((kidney* or renal*) adj1 insufficien*).tw. (157)

4 ckd*.tw. (708)

5 ((kidney* or renal*) adj1 fail*).tw. (747)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (687)

7 (esrd* or eskd*).tw. (299)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (2557)

10 Glomerular Filtration Rate/ (0)

11 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (2296)

12 or/10-11 (2296)

13 9 and 12 (514)

14 Cystatin C/ (0)

15 cystatin*.tw. (108)

16 Creatinine/ (0)

17 (creatinine or acr or pcr).tw. (7229)

18 or/14-17 (7277)

19 (formula* or equation* or calculat* or reclassif* or re classif*).tw. (24760)

20 (modif* of diet in renal disease* or MDRD*).ti,ab. (31)

21 (ckdepi or epi or epidemiology collaboration).tw. (306)

22 (multimark* or multi-mark* or mark*).tw. (19540)

23 or/19-22 (43172)

24 schwartz*.tw. (55)

25 13 and 24 (2)

26 (13 and 18 and 23) or 25 (60)

27 Economics/ (0)

28 exp "Costs and Cost Analysis"/ (0)

29 Economics, Dental/ (0)

30 exp Economics, Hospital/ (0)

31 exp Economics, Medical/ (0)

32 Economics, Nursing/ (0)

33 Economics, Pharmaceutical/ (0)

34 Budgets/ (0)

35 exp Models, Economic/ (0)

36 Markov Chains/ (0)

37 Monte Carlo Method/ (0)

38 Decision Trees/ (0)

39 econom$.tw. (5892)

40 cba.tw. (64)

41 cea.tw. (323)

42 cua.tw. (17)

43 markov$.tw. (723)

44 (monte adj carlo).tw. (1183)

45 (decision adj3 (tree$ or analys$)).tw. (401)

46 (cost or costs or costing$ or costly or costed).tw. (12184)

47 (price$ or pricing$).tw. (853)

48 budget$.tw. (529)

49 expenditure$.tw. (1147)

50 (value adj3 (money or monetary)).tw. (67)

51 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (46)

52 or/27-51 (20041)

53 "Quality of Life"/ (0)

54 quality of life.tw. (6848)

55 "Value of Life"/ (0)

56 Quality-Adjusted Life Years/ (0)

57 quality adjusted life.tw. (397)

58 (qaly$ or qald$ or qale$ or qtime$).tw. (331)

59 disability adjusted life.tw. (105)

60 daly$.tw. (95)

61 Health Status Indicators/ (0)

62 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (460)

63 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (41)

64 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (160)

65 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)

66 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (3)

67 (euroqol or euro qol or eq5d or eq 5d).tw. (337)

68 (qol or hql or hqol or hrqol).tw. (1347)

69 (hye or hyes).tw. (1)

70 health$ year$ equivalent$.tw. (0)

71 utilit$.tw. (4621)

72 (hui or hui1 or hui2 or hui3).tw. (23)

73 disutili$.tw. (14)

74 rosser.tw. (0)

75 quality of wellbeing.tw. (1)

76 quality of well-being.tw. (8)

77 qwb.tw. (5)

78 willingness to pay.tw. (163)

79 standard gamble$.tw. (6)

80 time trade off.tw. (18)

81 time tradeoff.tw. (3)

82 tto.tw. (17)

83 or/53-82 (11730)

84 52 or 83 (30008)

85 26 and 84 (7)

86 limit 85 to english language (7)

Database: Econlit <1886 to January 09, 2020>

Search Strategy:

---

1 [exp Renal Insufficiency, Chronic/] (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (21)

3 ((kidney* or renal*) adj1 insufficien*).tw. (3)

4 ckd*.tw. (5)

5 ((kidney* or renal*) adj1 fail*).tw. (32)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (54)

7 (esrd* or eskd*).tw. (31)

8 ["Chronic Kidney Disease-Mineral and Bone Disorder"/] (0)

9 or/1-8 (100)

10 [Glomerular Filtration Rate/] (0)

11 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (12)

12 or/10-11 (12)

13 9 and 12 (0)

14 [Cystatin C/] (0)

15 cystatin*.tw. (0)

16 [Creatinine/] (0)

17 (creatinine or acr or pcr).tw. (83)

18 or/14-17 (83)

19 (formula* or equation* or calculat* or reclassif* or re classif*).tw. (64079)

20 (modif* of diet in renal disease* or MDRD*).ti,ab. (0)

21 (ckdepi or epi or epidemiology collaboration).tw. (68)

22 (multimark* or multi-mark* or mark*).tw. (307044)

23 or/19-22 (356184)

24 schwartz*.tw. (659)

25 13 and 24 (0)

26 (13 and 18 and 23) or 25 (0)

Database: Embase <1974 to 2020 Week 03>

Search Strategy:

---

1 exp kidney failure/ (347216)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (121146)

3 ((kidney* or renal*) adj1 insufficien*).tw. (29885)

4 ckd*.tw. (48485)

5 ((kidney* or renal*) adj1 fail*).tw. (131226)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (57356)

7 (esrd* or eskd*).tw. (26828)

8 or/1-7 (438663)

9 exp glomerulus filtration rate/ (96469)

10 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (261066)

11 9 or 10 (289333)

12 8 and 11 (76380)

13 cystatin C/ (11312)

14 cystatin*.tw. (11625)

15 creatinine/ (174036)

16 creatinine blood level/ (106947)

17 (creatinine or acr or pcr).tw. (897118)

18 or/13-17 (984014)

19 (formula* or equation* or calculat* or reclassif* or re classif*).tw. (1629852)

20 (modif* of diet in renal disease* or MDRD*).tw. (9138)

21 (ckdepi or epi or epidemiology collaboration).tw. (30624)

22 (multimark* or multi-mark* or mark*).tw. (1987159)

23 or/19-22 (3521404)

24 schwartz*.tw. (3705)

25 12 and 24 (479)

26 (12 and 18 and 23) or 25 (11478)

27 exp Health Economics/ (831580)

28 exp "Health Care Cost"/ (287475)

29 exp Pharmacoeconomics/ (201536)

30 Monte Carlo Method/ (39041)

31 Decision Tree/ (12128)

32 econom$.tw. (353480)

33 cba.tw. (12569)

34 cea.tw. (33764)

35 cua.tw. (1447)

36 markov$.tw. (29219)

37 (monte adj carlo).tw. (46872)

38 (decision adj3 (tree$ or analys$)).tw. (22206)

39 (cost or costs or costing$ or costly or costed).tw. (742602)

40 (price$ or pricing$).tw. (55488)

41 budget$.tw. (37485)

42 expenditure$.tw. (72311)

43 (value adj3 (money or monetary)).tw. (3349)

44 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (8568)

45 or/27-44 (1707094)

46 "Quality of Life"/ (451049)

47 Quality Adjusted Life Year/ (25585)

48 Quality of Life Index/ (2710)

49 Short Form 36/ (27577)

50 Health Status/ (124220)

51 quality of life.tw. (419442)

52 quality adjusted life.tw. (18858)

53 (qaly$ or qald$ or qale$ or qtime$).tw. (19331)

54 disability adjusted life.tw. (3821)

55 daly$.tw. (3769)

56 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (40209)

57 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2333)

58 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (9050)

59 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (57)

60 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (441)

61 (euroqol or euro qol or eq5d or eq 5d).tw. (19375)

62 (qol or hql or hqol or hrqol).tw. (92389)

63 (hye or hyes).tw. (131)

64 health$ year$ equivalent$.tw. (41)

65 utilit$.tw. (278117)

66 (hui or hui1 or hui2 or hui3).tw. (2198)

67 disutili$.tw. (891)

68 rosser.tw. (118)

69 quality of wellbeing.tw. (42)

70 quality of well-being.tw. (470)

71 qwb.tw. (244)

72 willingness to pay.tw. (8327)

73 standard gamble$.tw. (1088)

74 time trade off.tw. (1671)

75 time tradeoff.tw. (288)

76 tto.tw. (1611)

77 or/46-76 (950356)

78 45 or 77 (2506212)

79 26 and 78 (814)

80 limit 79 to english language (782)

81 limit 80 to (books or chapter or conference abstract or conference paper or "conference review" or letter or note or tombstone) (344)

82 80 not 81 (438)

CRD databases

1 (MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES) 538 Delete

2 (((chronic* or progressi*) near1 (renal* or kidney*))) 489 Delete

3 ((ckd*)) 93 Delete

4 (((kidney* or renal*) near1 fail*)) 836 Delete

5 (((endstage* or end-stage* or "end stage*") near1 (renal* or kidney))) 354 Delete

6 ((esrd* or eskd*)) 150 Delete

7 (((kidney* or renal*) near1 insufficien*)) 320 Delete

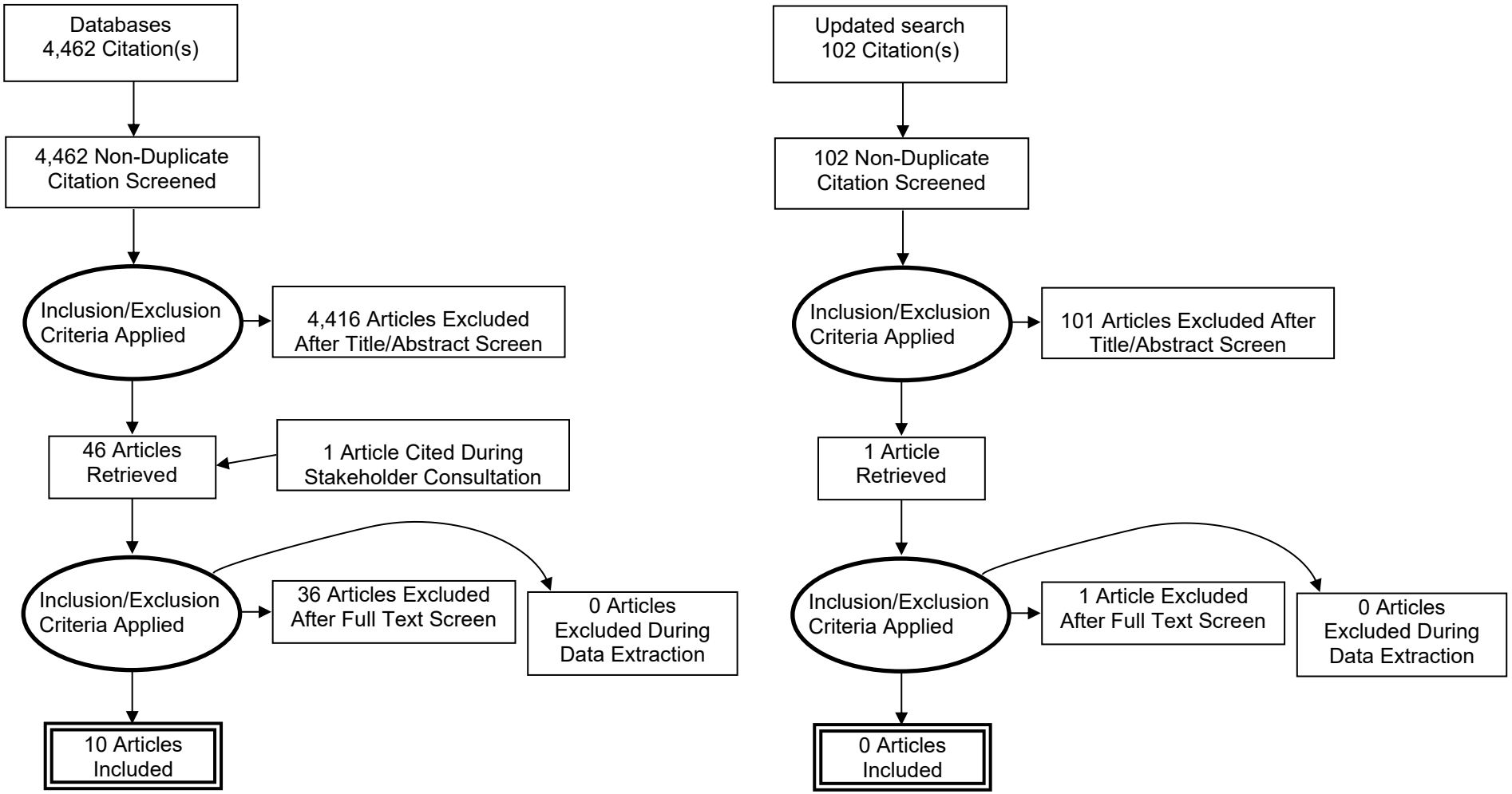
8 ((MeSH DESCRIPTOR Chronic Kidney Disease-Mineral and Bone Disorder)) 0 Delete

9 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8) 1407 Delete

10 (MeSH DESCRIPTOR Glomerular Filtration Rate) 92 Delete

11	(glomerul* or GFR* or eGFR* or e-GFR*)	416	Delete
12	(#10 or #11)	416	Delete
13	#9 AND #12	151	Delete
14	MeSH DESCRIPTOR Cystatin C	8	Delete
15	(cystatin*)	12	Delete
16	MeSH DESCRIPTOR Creatinine	114	Delete
17	(creatinine or acr or pcr)	913	Delete
18	(#14 or #15 or #16 or #17)	919	Delete
19	(formula* or equation* or calculat* or reclassif* or re classif*)	17684	Delete
20	(modif* of diet in renal disease* or MDRD*)	6	Delete
21	(ckdepi or epi or epidemiology collaboration)	52	Delete
22	(multimark* or multi-mark* or mark*)	5764	Delete
23	(#19 or #20 or #21 or #22)	21088	Delete
24	(schwartz*)	149	Delete
25	#13 AND #24	1	Delete
26	#13 AND #18 AND #23	40	Delete
27	#25 OR #26	40	Delete
28	(#25 OR #26) IN DARE	30	Delete
29	(#25 OR #26) IN NHSEED	8	Delete
30	(#25 OR #26) IN HTA	2	Delete

Appendix D – Prognostic evidence study selection



Appendix E – Prognostic evidence tables

Lennartz, 2016

Bibliographic Reference	Lennartz, C.S.; Pickering, J.W.; Seiler-Mussler, S.; Bauer, L.; Untersteller, K.; Emrich, I.E.; Zawada, A.M.; Radermacher, J.; Tangri, N.; Fliser, D.; Heine, G.H.; External validation of the kidney failure risk equation and re-calibration with addition of ultrasound parameters; Clinical Journal of the American Society of Nephrology; 2016; vol. 11 (no. 4); 609-615

Study Characteristics

Study design	Prospective cohort study CARE FOR HOMe study
Study details	Study location Germany Study setting Saarland University Medical Centre outpatient department Study dates Sept 2008 - Nov 2012 Duration of follow-up 3 years
Inclusion criteria	CKD criteria Stage 2 - 4 Creatinine clearance <75% of their normal value for age and sex Proteinuria 150 mg/d or more and/or hypertension
Exclusion criteria	Pregnant women Age < 18 years HIV positive Active malignancy Acute kidney injury Clinically apparent infections Renal artery stenosis
Sample characteristics	Sample size N=403 Female 42% Mean age (SD) 60.3 (15.3)
Prognostic factors	KFRE 4 variable ESRD at 3 years
Outcome	R squared statistic

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes

Section	Question	Answer
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	No information
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Probably yes
	3.2 Was a pre-specified or standard outcome definition used?	Probably yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	Yes
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Yes
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	Yes
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	Yes
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Major, 2019

Bibliographic Reference	Major, R.W.; Shepherd, D.; Medcalf, J.F.; Xu, G.; Gray, L.J.; Brunskill, N.J.; The kidney failure risk equation for prediction of end stage renal disease in UK primary care: An external validation and clinical impact projection cohort study; PLoS Medicine; 2019; vol. 16 (no. 11); e1002955

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location UK Study setting Primary care (4 clinical commissioning groups). Study dates CKD patients between 2004 - 2016. Duration of follow-up 2 and 5 year follow-up. Sources of funding National Institute for Health Research (NIHR).
Inclusion criteria	CKD criteria MDRD eGFR < 60-65 ml/min Proteinuria Recorded quantifiable urine proteinuria measurement.
Exclusion criteria	None
Sample characteristics	Sample size 35539 Female 57.5% Mean age (SD) 75.9 (10.6) Diabetes 31.5%
Prognostic factors	KFRE 4 variable At 2 and 5 years
Outcome	C-statistic

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	No information
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low

Section	Question	Answer
Outcome or its determination	3.1 Was the outcome determined appropriately?	Probably yes
	3.2 Was a pre-specified or standard outcome definition used?	No information
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Probably yes
	3.5 Was the outcome determined without knowledge of predictor information?	No information
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Yes
	Overall risk of bias for outcome or its determination domain	Unclear
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	Yes
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	Probably yes
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Marks, 2015

Bibliographic Reference	Marks, Angharad, Fluck, Nicholas, Prescott, Gordon J et al. (2015) Looking to the future: predicting renal replacement outcomes in a large community cohort with chronic kidney disease. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 30(9): 1507-17

Study Characteristics

Study design	Prospective cohort study The second Grampian Laboratory Outcomes Mortality and Morbidity Study (GLOMMS-II) cohort
Study details	Study location UK Study setting Validation cohort based on the second Grampian Laboratory Outcomes Mortality and Morbidity Study (GLOMMS-II) cohort. Study dates

	2003-2009. Duration of follow-up 5 years follow-up. Sources of funding Supported by the Chief Scientists Office for Scotland [CZH/4/656], NHS Grampian Endowment Research Fund and NHS Grampian Renal Endowment.
Inclusion criteria	Age Aged over 15 years. CKD criteria Sustained (for at least 3 months) stage 3a – 5.
Exclusion criteria	None
Sample characteristics	Sample size 2274 Female 64.8% of the total population included in GLOMMS-II (N=18687) Age Age was reported for the total population included in GLOMMS-II (N=18687) 15 to 44 years (n=305) 45 to 54 years (n=660) 55 to 64 years (n=2201) 65 to 74 years (n=5630) 75 to 84 years (n=7119) 85 or more years (n=2772)
Prognostic factors	KFRE 4 variable RRT at 5 years RRT prediction tool RRT at 5 years
Outcome	C-statistic Sensitivity Specificity

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	No information
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Yes

Section	Question	Answer
	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	No information
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Yes
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	Yes
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	Probably yes
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Peralta, 2011b

Bibliographic Reference	Peralta CA; Katz R; Sarnak MJ; Ix J; Fried LF; De Boer I; Palmas W; Siscovick D; Levey AS; Shlipak MG; Cystatin C identifies chronic kidney disease patients at higher risk for complications.; Journal of the American Society of Nephrology : JASN; 2011; vol. 22 (no. 1)

Study Characteristics

Study design	Prospective cohort study Participants from the Multi - Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS).
Study details	Study location USA Study setting
Inclusion criteria	Age MESA – mean 62 years CHS – mean 72 years (+/- 5 years) Race and ethnicity MESA: 39% white, 28% black, 12% Chinese, and 22% Hispanic CHS: 84% white and 16% black.

Exclusion criteria	MESA: If they had physician diagnosed heart attack, angina, heart failure, stroke, transient ischemic attack, or atrial fibrillation; had undergone coronary artery bypass grafting, angioplasty, valve replacement, or pacemaker; or weighed >300 lbs. CHS: Excluded if they were not expected to remain in the current community for 3 yrs or longer, were receiving treatment for cancer, or were unable to provide informed consent.
Sample characteristics	Sample size N = 11909 (6749 from MESA and 5160 from CHS)
Prognostic factors	GFR
Reference Factor (s)	No CKD GFR
Co-variates	Adjusted for age, gender, race, diabetes, smoking, total cholesterol, body mass index, prevalent CVD, and C -reactive protein

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	Probably yes
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Yes
	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	Probably yes
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Yes
	Overall risk of bias for outcome or its determination domain	Low

Section	Question	Answer
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	Yes
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	No information
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	Overall risk of bias for analysis domain	High *(ACR not adjusted for in multi-variable model.)*
Overall Risk of bias and Applicability	Risk of bias	Some *(ACR not adjusted for in multi-variable model.)*
	Concerns for applicability	Low

Peralta, 2011a

Bibliographic Reference Peralta CA; Shlipak MG; Judd S; Cushman M; McClellan W; Zakai NA; Safford MM; Zhang X; Muntner P; Warnock D; Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality.; JAMA; 2011; vol. 305 (no. 15)

Study Characteristics

Study design	Prospective cohort study Reasons for Geographic and Racial Differences in Stroke (REGARDS)
Study details	Study location Study setting Population based Study dates 2003 - 2010 Duration of follow-up Maximum: 7 years 4 months Sources of funding National Institute of Neurological disorders and Stroke, National Institute of Health, Dept of Health and Human Services. Amgen Corp
Inclusion criteria	Age 45 years and over Race and ethnicity black and white participants Cancer status Free of cancer Other At the time of the initial telephone call were able to answer the questions and were not living in an assisted living home.

Exclusion criteria	Participants with missing baseline data for serum creatinine, cystatin C, or urine albumin and creatinine. Dialysis Renal transplant
Sample characteristics	Sample size 26643 Mean age (SD)
Prognostic factors	urinary ACR and cystatin c Creatinine and urinary ACR Creatinine and cystatin C Creatinine and cystatin c and urinary ACR
Reference Factor (s)	No CKD eGFR < 60

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	No information
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Yes
	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	No information
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Yes
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	Yes

Section	Question	Answer
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	No *(Missing data excluded)*
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Tangri, 2016

Bibliographic Reference	Tangri, N.; Grams, M.E.; Levey, A.S.; Coresh, J.; Appel, L.J.; Astor, B.C.; Chodick, G.; Collins, A.J.; Djurdjev, O.; Raina Elley, C.; Evans, M.; Garg, A.X.; Hallan, S.I.; Inker, L.A.; Ito, S.; Jee, S.H.; Kovesdy, C.P.; Kronenberg, F.; Heerspink, H.J.L.; Marks, A.; Nadkarni, G.N.; Navaneethan, S.D.; Nelson, R.G.; Titze, S.; Sarnak, M.J.; Stengel, B.; Woodward, M.; Iseki, K.; Multinational assessment of accuracy of equations for predicting risk of kidney failure ameta-analysis; JAMA - Journal of the American Medical Association; 2016; vol. 315 (no. 2); 164-174

Study Characteristics

Study design	Meta-analysis Individual data meta-analysis from 31 cohorts
Study details	Study location 30 countries, 4 continents Study dates 2012 - 2015 Duration of follow-up 2 years Sources of funding CKD-PC Data Coordination Centre, National Kidney Foundation, National Institute of Diabetes and Digestive and Kidney Diseases.
Inclusion criteria	CKD criteria Stage 3-5 (eGFR < 60 ml/min and absence of kidney failure at baseline, defined as treatment by dialysis or kidney transplant).
Exclusion criteria	Participants with missing data at baseline
Sample characteristics	Sample size Total=721357 (617604 from North America, 103753 from Non-North America). Female 33% Mean age (SD) 74 (10)
Prognostic factors	KFRE 4 variable ESRD at 2 years and 5 years

Outcome	C-statistic	
Section	**Question**	**Answer**
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes *(Meta-analysis)*
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	Probably yes
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Yes
	3.2 Was a pre-specified or standard outcome definition used?	Probably yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Probably yes
	3.5 Was the outcome determined without knowledge of predictor information?	Probably yes
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Yes
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	Yes
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	No
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Waheed, 2013

Bibliographic Reference	Waheed S; Matsushita K; Astor BC; Hoogeveen RC; Ballantyne C; Coresh J; Combined association of creatinine, albuminuria, and cystatin C with all-cause mortality and cardiovascular and kidney outcomes.; Clinical journal of the American Society of Nephrology : CJASN; 2013; vol. 8 (no. 3)

Study Characteristics

Study design	Prospective cohort study
Study details	Study location USA Study setting Atherosclerosis Risk in Communities (ARIC) study: population-based cohort Study dates 1987-1989 Duration of follow-up Median follow up of 11.2 years Sources of funding National Heart, Lung, and Blood Institute. Siemens Healthcare Diagnostics provided the reagents and loan of a BNII instrument to conduct the cystatin C assays.
Inclusion criteria	Age 45-64 years
Exclusion criteria	Participants with missing baseline data Race Race other than African American and white Cardiovascular disease at baseline
Sample characteristics	Sample size eGFRcreatinine only: n=219 ACR only: n=476 eGFR cystatin only: n= 476 eGFRcreatine and eGFRcystatin: n=185 eGFRcreatinine and ACR: n=24 eGFR cystatin and ACR: n=63 All 3 markers abnormal: n=96 Female 54.2% - 61.6% Mean age (SD) 63 years Diabetes 15%
Prognostic factors	urinary ACR and cystatin c Creatinine and urinary ACR ACR calculated from a random urine sample from urine albumin and urine creatinine concentrations. Jaffe method used to measure urine creatinine, whereas urine albumin was measured using the nephelometric method. Creatinine and cystatin C Creatinine and cystatin c and urinary ACR
Reference Factor (s)	No CKD

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes

Section	Question	Answer
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	Probably yes
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Yes
	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	Probably yes
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Yes
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	Probably yes *(However only N=5 with outcome with eGFRcreatinine + ACR)*
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	No *(Excluded from analysis.)*
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low *(With some risk of bias for*

Section	Question	Answer
		eGFRcreatinine + ACR due to low event rate.)
	Concerns for applicability	Low

Wang, 2019

Bibliographic Reference	Wang, Y.; Nguyen, F.N.H.L.; Allen, J.C.; Lew, J.Q.L.; Tan, N.C.; Jafar, T.H.; Validation of the kidney failure risk equation for end-stage kidney disease in Southeast Asia; BMC Nephrology; 2019; vol. 20 (no. 1); 451

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Singapore Study setting Nine primary care clinics Study dates 2010 - 2013 Duration of follow-up 2 and 5 years Sources of funding SingHealth Analytics and Research Technologies
Inclusion criteria	Age 40 years or older Other Visited any primary care clinic at least twice with two visits at least 1 year apart. CKD criteria Not pregnant Creatinine had ≥2 serum creatinine measurements taken at least 3 months apart to calculate eGFR by CKD-EPI equation
Exclusion criteria	Without ACR Developed ESRD before baseline
Sample characteristics	Sample size N=17444 Female 51% Mean age (SD) 75 (9)
Prognostic factors	KFRE 4 variable ESRD at 2 and 5 years
Outcome	Brier score

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes

Section	Question	Answer
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Probably yes
	2.2 Were predictor assessments made without knowledge of outcome data?	No information
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Yes
	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	No information
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Yes
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	Yes
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	Yes
	4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of control participants) accounted for appropriately?	Probably yes
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Whitlock, 2017

Bibliographic Reference	Whitlock, R.H.; Chartier, M.; Komenda, P.; Hingwala, J.; Rigatto, C.; Walld, R.; Dart, A.; Tangri, N.; Validation of the kidney failure risk equation in Manitoba; Canadian Journal of Kidney Health and Disease; 2017; vol. 4; 5372

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Canada Study setting Manitoba Centre for Health Policy - individual level data (laboratory data, hospital discharge, physician records) Study dates 2006-2007 Duration of follow-up 5 years Sources of funding Department of Health of the Province of Manitoba
Inclusion criteria	Age > 18 years CKD criteria Creatinine Serum creatinine and urine ACR measured between Oct 2006 - March 2007
Exclusion criteria	Without ACR And eGFR
Sample characteristics	Sample size N=1512 Female Approximately 50% Mean age (SD) Stage 3: 67 (13), Stage 4-5: 66 (14) Diabetes Stage 3: 76.6%, Stage 4-5: 73.1%
Prognostic factors	KFRE 4 variable 5 years follow-up
Outcome	C-statistic

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	No *(Retrospective)*
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low

Section	Question	Answer
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Yes
	3.2 Was a pre-specified or standard outcome definition used?	No information *(No definition of kidney failure provided.)*
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	No information
	3.5 Was the outcome determined without knowledge of predictor information?	No
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Yes
	Overall risk of bias for outcome or its determination domain	High
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	Yes
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	Yes
	4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of control participants) accounted for appropriately?	Yes
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Winnicki, 2018

Bibliographic Reference	Winnicki, Erica; McCulloch, Charles E; Mitsnefes, Mark M; Furth, Susan L; Warady, Bradley A; Ku, Elaine; Use of the Kidney Failure Risk Equation to Determine the Risk of Progression to End-stage Renal Disease in Children With Chronic Kidney Disease.; JAMA pediatrics; 2018; vol. 172 (no. 2); 174-180

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location

	USA Study setting the Chronic Kidney Disease in Children (CKiD) study: 57 clinical sites. Study dates January 2005 - July 2013 Duration of follow-up 1, 2 and 5 years Sources of funding National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute.
Inclusion criteria	CKD criteria eGFR < 60 ml/min
Exclusion criteria	Participants with missing baseline data hyperoxaluria
Sample characteristics	Sample size N=603 Female 37.3% Median age 12 (IQR: 8-15)
Prognostic factors	KFRE 8 variable ESRD at 1, 2 and 5 years
Outcome	C-statistic

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	No
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Yes
	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes

Section	Question	Answer
	3.5 Was the outcome determined without knowledge of predictor information?	No
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Yes
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	Yes
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	No *(Omitted from analysis)*
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	Overall risk of bias for analysis domain	High
Overall Risk of bias and Applicability	Risk of bias	Some
	Concerns for applicability	Low

Appendix F – Forest plots

F.1 Combination of measurements

Figure 1: All-cause mortality: REGARDS study

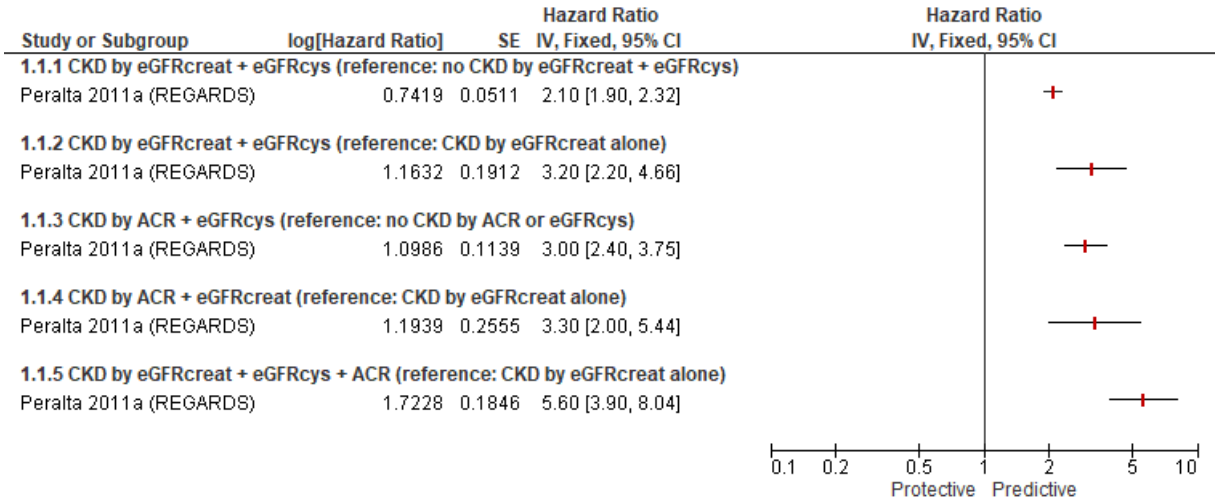


Figure 2: All-cause mortality: ARIC study

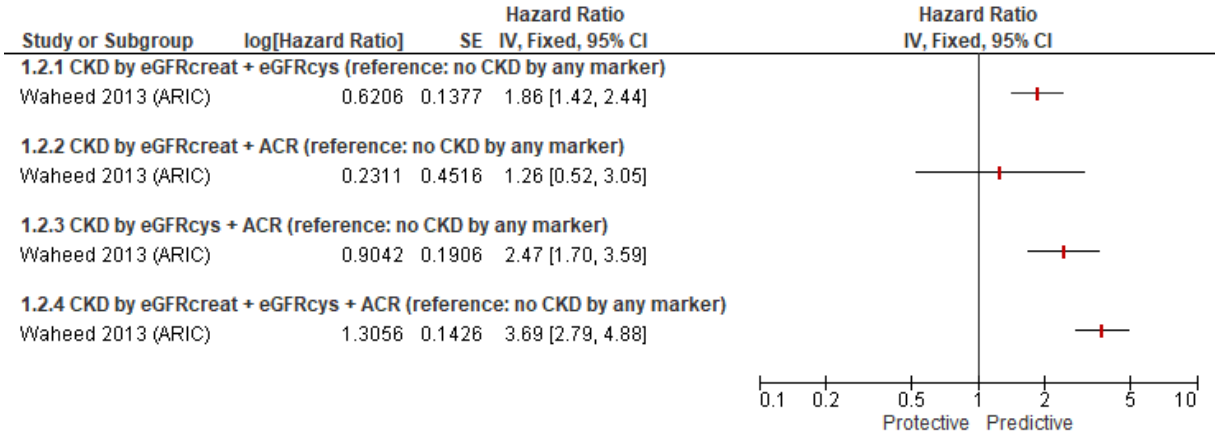


Figure 3: All-cause mortality: CHS and MESA studies

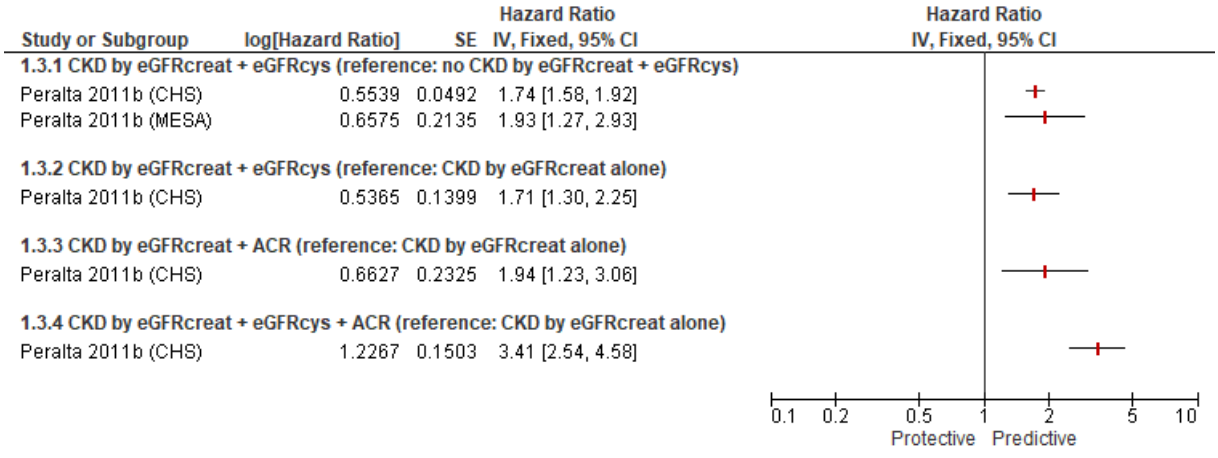


Figure 4: End-stage renal disease: ARIC, CHS and REGARDS studies

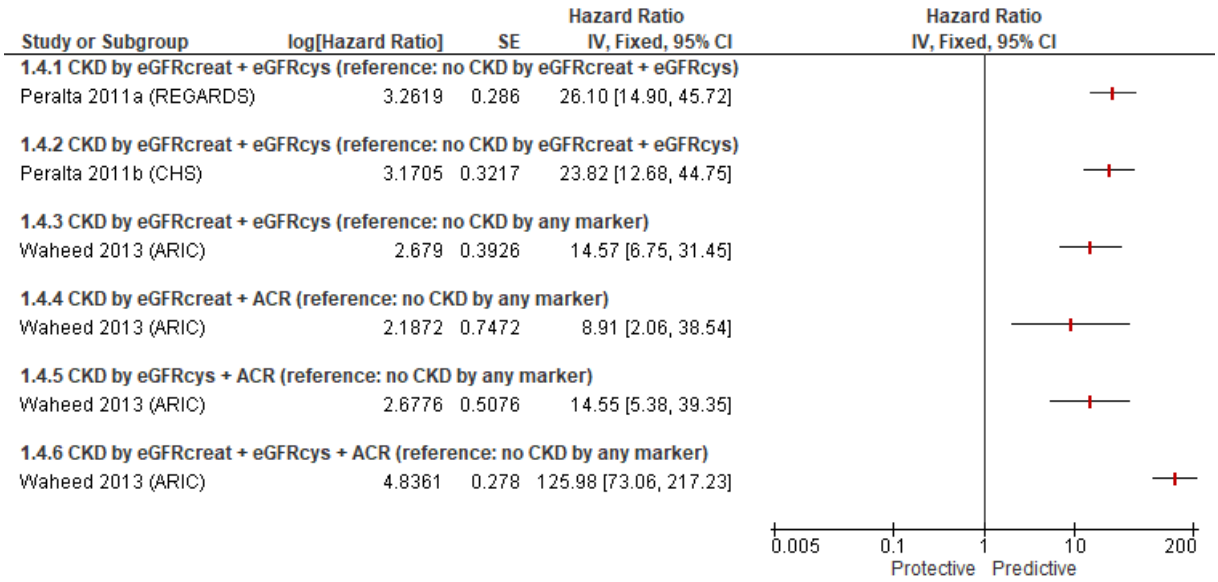
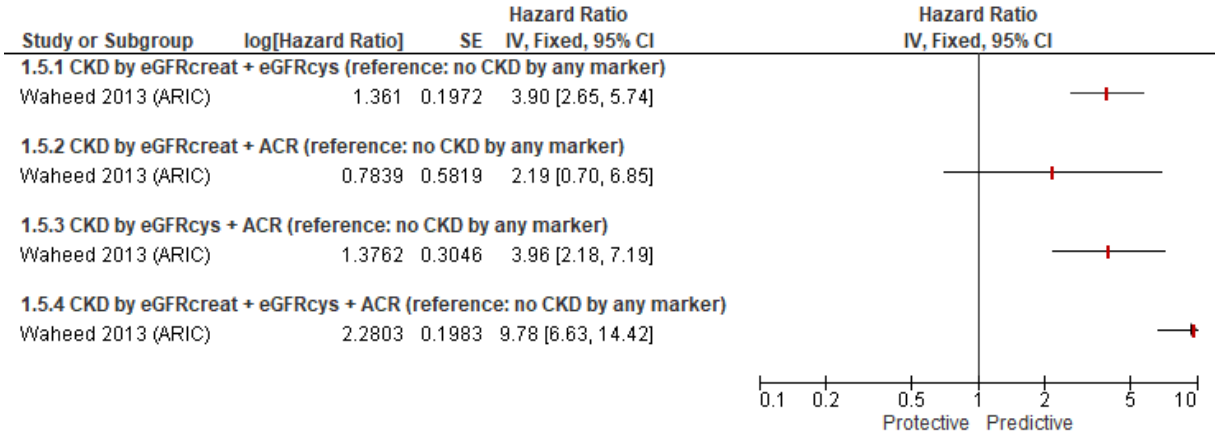
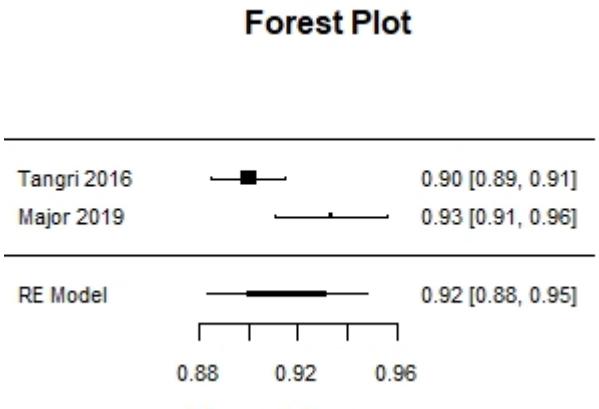


Figure 5 Acute kidney injury: ARIC study



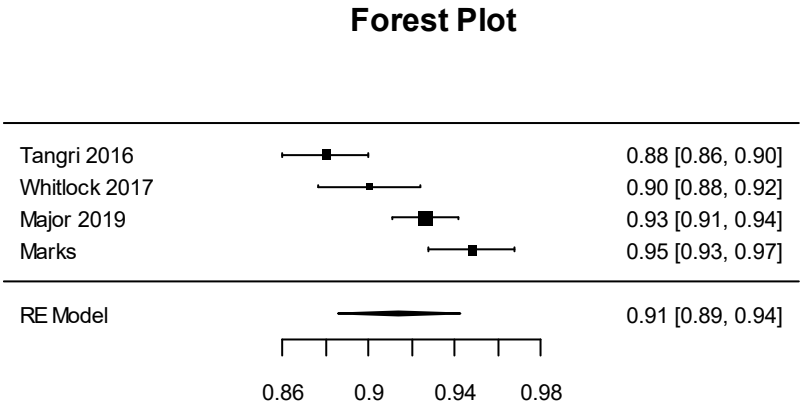
F.2 Prediction equations: c-statistics

Figure 6: KFRE 4 variable, 2 years



RE model, I^2= 82.3%

Figure 7: KFRE 4 variable, 5 years



RE model, I^2= 88.3%

Appendix G – GRADE tables

G.1 Combination of measurements

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of measures	Reference	Relative (95% CI)	Absolute	
All-cause mortality: REGARDS - CKD by eGFRcreat + eGFRcys (reference: no CKD by eGFRcreat + eGFRcys) **Higher HR means combination of measures is predictive of all-cause mortality**											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	799/2055 (38.9%)	1104/22361 (4.9%)	HR 2.1 (1.9 to 2.32)	5 more per 100 (from 4 more to 6 more)	HIGH
All-cause mortality: REGARDS - CKD by eGFRcreat + eGFRcys (reference: CKD by eGFRcreat alone) **Higher HR means combination of measures is predictive of all-cause mortality**											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	223/1172 (19%)	32/701 (4.6%)	HR 3.2 (2.2 to 4.66)	9 more per 100 (from 5 more to 15 more)	HIGH
All-cause mortality: REGARDS - CKD by ACR + eGFRcys (reference: no CKD by ACR or eGFRcys) **Higher HR means combination of measures is predictive of all-cause mortality**											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	105/415 (25.3%)	863/19876 (4.3%)	HR 3 (2.4 to 3.75)	8 more per 100 (from 6 more to 11 more)	HIGH

All-cause mortality: REGARDS - CKD by ACR + eGFRcreat (reference: CKD by eGFRcreat alone) **Higher HR means combination of measures is predictive of all-cause mortality**											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/148 (18.2%)	32/701 (4.6%)	HR 3.3 (2 to 5.44)	10 more per 100 (from 4 more to 18 more)	HIGH
All-cause mortality: REGARDS - CKD by eGFRcreat + eGFRcys + ACR (reference: CKD by eGFRcreat alone) **Higher HR means combination of measures is predictive of all-cause mortality**											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	276/883 (31.3%)	32/701 (4.6%)	HR 5.6 (3.9 to 8.04)	18 more per 100 (from 12 more to 27 more)	HIGH
All-cause mortality: ARIC - CKD by eGFRcreat + eGFRcys (reference: no CKD by any marker) **Higher HR means combination of measures is predictive of all-cause mortality**											
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	IR 32.7 per 1000 person-year	IR 10.5 per 1000 person-year	HR 1.86 (1.42 to 2.44)	-[3]	HIGH
All-cause mortality: ARIC - CKD by eGFRcreat + ACR (reference: no CKD by any marker) **Higher HR means combination of measures is predictive of all-cause mortality**											
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	IR 23.3 per 1000 person-year	IR 10.5 per 1000 person-year	HR 1.26 (0.52 to 3.05)	-[3]	MODERATE
All-cause mortality: ARIC - CKD by eGFRcys + ACR (reference: no CKD by any marker) **Higher HR means combination of measures is predictive of all-cause mortality**											

1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	IR 50.4 per 1000 person-year	IR 10.5 per 1000 person-year	HR 2.47 (1.70 to 3.61)	-[3]	HIGH
All-cause mortality: ARIC - CKD by eGFRcreat + eGFRcys + ACR (reference: no CKD by any marker) **Higher HR means combination of measures is predictive of all-cause mortality**											
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	IR 70.5 per 1000 person-year	IR 10.5 per 1000 person-year	HR 3.69 (2.79 to 4.87)	-[3]	HIGH
All-cause mortality: CHS - CKD by eGFRcreat + eGFRcys (reference: no CKD by eGFRcreat + eGFRcys) **Higher HR means combination of measures is predictive of all-cause mortality**											
1	observational studies[5]	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Total 689	Total 3639	HR 1.74 (1.58 to 1.93)	-[7]	MODERATE
All-cause mortality: MESA - CKD by eGFRcreat + eGFRcys (reference: no CKD by eGFRcreat + eGFRcys) **Higher HR means combination of measures is predictive of all-cause mortality**											
1	observational studies[8]	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Total 269	Total 5759	HR 1.93 (1.27 to 2.92)	-[7]	MODERATE
All-cause mortality: CHS - CKD by eGFRcreat + eGFRcys (reference: CKD by eGFRcreat alone) **Higher HR means combination of measures is predictive of all-cause mortality**											
1	observational studies[5]	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	262/380 (68.9%)	71/170 (41.8%)	HR 1.71 (1.3 to 2.25)	19 more per 100 (from 9 more to 29 more)	MODERATE

All-cause mortality: CHS - CKD by eGFRcreat + ACR (reference: CKD by eGFRcreat alone) **Higher HR means combination of measures is predictive of all-cause mortality**											
1	observational studies[5]	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/39 (74.4%)	71/170 (41.8%)	HR 1.94 (1.23 to 3.06)	23 more per 100 (from 7 more to 39 more)	MODERATE
All-cause mortality: CHS - CKD by eGFRcreat + eGFRcys + ACR (reference: CKD by eGFRcreat alone) **Higher HR means combination of measures is predictive of all-cause mortality**											
1	observational studies[5]	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	181/200 (90.5%)	71/170 (41.8%)	HR 3.41 (2.54 to 4.58)	42 more per 100 (from 33 more to 50 more)	MODERATE
End stage renal disease: REGARDS - CKD by eGFRcreat + eGFRcys (reference: no CKD by eGFRcreat + eGFRcys) **Higher HR means combination of measures is predictive of end stage renal disease**											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	144/2055 (7%)	17/22361 (0.08%)	HR 26.1 (14.9 to 45.72)	2 more per 100 (from 1 more to 3 more)	HIGH
End stage renal disease: CHS - CKD by eGFRcreat + eGFRcys (reference: no CKD by eGFRcreat + eGFRcys) **Higher HR means combination of measures is predictive of end stage renal disease**											
1	observational studies[5]	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Total 689	Total 3639	HR 23.82 (12.68 to 44.76)	-[7]	MODERATE
End stage renal disease: ARIC - CKD by eGFRcreat + eGFRcys (reference: no CKD by any marker) **Higher HR means combination of measures is predictive of end stage renal disease**											

1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	IR 5.5 per 1000 person-year	IR 0.4 per 1000 person-year	HR 14.57 (6.75 to 31.46)	-[3]	HIGH
End stage renal disease: ARIC - CKD by eGFRcreat + ACR (reference: no CKD by any marker) **Higher HR means combination of measures is predictive of end stage renal disease**											
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	IR 8.2 per 1000 person-year	IR 0.4 per 1000 person-year	HR 8.91 (2.06 to 38.49)	-[3]	HIGH
End stage renal disease: ARIC - CKD by eGFRcys + ACR (reference: no CKD by any marker) **Higher HR means combination of measures is predictive of end stage renal disease**											
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	IR 9.1 per 1000 person-year	IR 0.4 per 1000 person-year	HR 14.55 (5.38 to 39.32)	-[3]	HIGH
End stage renal disease: ARIC - CKD by eGFRcreat + eGFRcys + ACR (reference: no CKD by any marker) **Higher HR means combination of measures is predictive of end stage renal disease**											
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	IR 60.9 per 1000 person-year	IR 0.4 per 1000 person-year	HR 125.98 (73.06 to 217.22)	-[3]	HIGH
Acute kidney injury: ARIC - CKD by eGFRcreat + eGFRcys (reference: no CKD by any marker) **Higher HR means combination of measures is predictive of acute kidney injury**											

1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	IR 18.0 per 1000 person-year	IR 3.0 per 1000 person-year	HR 3.90 (2.65 to 5.74)	-[3]	HIGH
Acute kidney injury: ARIC - CKD by eGFRcreat + ACR (reference: no CKD by any marker) **Higher HR means combination of measures is predictive of acute kidney injury**											
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	IR 12.2 per 1000 person-year	IR 3.0 per 1000 person-year	HR 2.19 (0.70 to 6.9)	-[3]	MODERATE
Acute kidney injury: ARIC - CKD by eGFRcys + ACR (reference: no CKD by any marker) **Higher HR means combination of measures is predictive of acute kidney injury**											
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	IR 23.7 per 1000 person-year	IR 3.0 per 1000 person-year	HR 3.96 (2.18 to 7.18)	-[3]	HIGH
Acute kidney injury: ARIC - CKD by eGFRcreat + eGFRcys + ACR (reference: no CKD by any marker) **Higher HR means combination of measures is predictive of acute kidney injury**											
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	IR 43.5 per 1000 person-year	IR 3.0 per 1000 person-year	HR 9.78 (6.63 to 14.43)	-[3]	HIGH

[1] Peralta 2011a (REGARDS prospective cohort study)
[2] Waheed 2013 (ARIC prospective cohort study)
[3] Only number of events, total person-time in years and crude incidence rates per 1000 person-year were reported
[4] Confidence interval crosses line of no effect
[5] Peralta 2011b (CHS prospective cohort study)
[6] Study at moderate risk of bias

[7] Only total participants were reported
[8] Peralta 2011b (MESA prospective cohort)

IR: incidence rate

G.2 Prediction equations to predict kidney failure or end stage renal disease (ESRD)

G.2.1 C-statistics

No. of studies	Study design	Sample size	C-statistic (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
KFRE 4 variable, 2 years follow-up								
2 (Major 2019; Tangri 2016)	Retrospective and prospective cohort	756896	0.92 (0.88, 0.95)	No serious	No serious[1]	No serious	No serious	High
KFRE 4 variable in children, 2 years follow-up								
Winnicki 2017	Retrospective cohort	603	0.86 (0.81-0.90)	No serious	N/A[2]	No serious	No serious	High
KFRE 4 variable, 3 years follow-up								
Lennartz 2016	Prospective cohort	406	0.91 (0.83-0.99)	No serious	N/A[2]	No serious	No serious	High
KFRE 4 variable, 5 years follow-up								
4 (Major 2019; Marks 2015; Tangri 2016; Whitlock 2017)	Retrospective and prospective cohort	760682	0.91 (0.89-0.94)	No serious	No serious[1]	No serious	No serious	High
KFRE 4 variable in children, 5 years follow-up								
Winnicki 2017	Retrospective cohort	603	0.81 (0.77-0.83)	No serious	N/A[2]	No serious	No serious	High
KFRE 8 variable in children, 1 years follow-up								
Winnicki 2017	Retrospective cohort	603	0.91 (0.87-0.94)	No serious	N/A[2]	No serious	No serious	High
KFRE 8 variable in children, 2 years follow-up								

No. of studies	Study design	Sample size	C-statistic (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Winnicki 2017	Retrospective cohort	603	0.87 (0.82-0.91)	No serious	N/A[2]	No serious	No serious	High
KFRE 8 variable in children, 5 years follow-up								
Winnicki 2017	Retrospective cohort	603	0.82 (0.78-0.85)	No serious	N/A[2]	No serious	No serious	High
RRT prediction tool, 5 years follow-up								
Marks 2015	Prospective cohort	2274	0.93 (0.90-0.96)	No serious	N/A[2]	No serious	No serious	High

1. *Despite high statistical heterogeneity, confidence intervals were high in studies and the committee were confident*

2. *Single study contributed to outcome.*

G.2.2 Brier scores

No. of studies	Study design	Sample size	Brier score	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
KFRE 4 variable in elderly (mean age 75 years), 2 years follow-up								
Wang 2019	Retrospective cohort	17271	7.9% Bias: 3.4% (-7.8, 11.2%)	No serious	N/A[1]	No serious	N/A[2]	High
KFRE 4 variable (mean age 75 years), 5 years follow-up								
Wang 2019	Retrospective cohort	17271	6.2% Bias: 4.5% (-1.4, 5.9%)	No serious	N/A[1]	No serious	N/A[2]	High

1. *Inconsistency not applicable as result from single study.*

2. *Imprecision not calculable.*

G.2.3 R^2 statistic

No. of studies	Study design	Sample size	R^2 statistic	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
KFRE 4 variable, 3 years follow-up								
Lennartz 2016	Prospective cohort	406	0.29 (37.7%)	No serious	N/A[1]	No serious	N/A[2]	High

1. *Inconsistency not applicable as result from single study.*

2. *Imprecision not calculable.*

G.2.4 Sensitivity and specificity to start RRT

No. of studies	Study design	Sample size	Sensitivity	Specificity	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
KFRE 4 variable, 5 years follow-up									
Marks 2015	Prospective cohort	2274	0.84	0.89	No serious	N/A[1]	No serious	N/A[2]	High
RRT prediction tool, 5 years follow-up									
Marks 2015	Prospective cohort	2274	0.56	0.96	No serious	N/A[1]	No serious	N/A[2]	High

1. *Inconsistency not applicable as result from single study.*

2. *Imprecision not calculable.*

Appendix H – Economic evidence study selection

Appendix I – Economic evidence tables

No economic evidence was identified for this review question.

Below is the economic evaluation checklist for the original economic model, see Appendix J for the full model.

Study identification **Original model 2020**		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	See section J.3.1 for a description and discussion of the population included in the study
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	

Study identification Original model 2020		
Category	**Rating**	**Comments**
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

Appendix J – Health economic model

J.1 Introduction

The review questions this analysis addresses are:

- What is the best combination of measures of kidney function and markers of kidney damage to identify increased risk of progression in adults, children and young people with CKD?
- Are kidney failure prediction equations good predictors of progression, kidney failure or end-stage renal disease?

In particular, the committee were interested in whether the kidney failure risk equations (KFRE) are a more effective tool to guide referral to secondary care than the recommendations in the 2014 NICE chronic kidney disease guideline, which specify independent referral thresholds for eGFR and ACR. In particular, they were interested if the KFRE resulted in more people being identified in line with the recommendations in the NICE renal replacement therapy guideline, which specifies that people should referred 1 year before start of renal replacement therapy, and whether this would lead to improvements in long-term outcomes.

Table 13 summarises the decision problem which this analysis is designed to address. The full protocol for the clinical review is available in appendix A. There are a number of differences between the clinical review protocol and the economic decision problem. Based on the results of the clinical review, the model was focused on adults and the 4-variable version of the KFRE. Additionally, whilst the clinical review looked at predictive accuracy studies, as this was the data expected to be available, the economic model looks at the effectiveness of the different referral rules, as the model enables us to extrapolate the predictive accuracy data from the clinical studies to look at long-term outcomes.

Table 13 Health economic decision problem

Population	Adults with chronic kidney disease stages 3-5, currently being managed in primary care
Interventions	Rules for referral to secondary care based on the 4 variable kidney failure risk equations
Comparators	Rules for referral to secondary care using independent thresholds for eGFR and ACR – in particular the rules specified in the 2014 NICE guideline (eGFR<30 ml/min/1.73m^2 or ACR≥70 mg/mmol, unless known to be caused by diabetes and already appropriately treated).
Outcomes	• Accuracy for predicting progression to end stage renal disease [ESRD] (sensitivity/specificity/positive and negative predictive values) • QALYs • Costs

The economic literature review conducted alongside the clinical review did not find any economic evaluations that address the review question, and therefore it was agreed an original model would be of value.

J.2 Methods

J.2.1 Model overview

The aim of this model is to compare the cost-effectiveness of different referral rules from primary to secondary care for people with CKD. It does this in four stages.

Stage 1 – The predictive accuracy of each of the referral rules is estimated. This is done by applying each of the referral rules to an individual's baseline measurements, and then comparing the result of that referral rule to whether the person does or does not go on to ESRD within the specified time horizon. Sensitivity, specificity, and positive and negative predictive values for each referral rule are calculated, and these results are given in section J.3.2.

Stage 2 – For each individual in the dataset, the time at which they are first referred to secondary care is estimated (assuming they are not referred at baseline). This is done by combining their baseline measurements with data on the natural history of the progression of CKD, and the recommended monitoring schedule in the guideline (which depends on eGFR and ACR). As well as estimating the time of referral, this part of the model also calculates each individual's estimated monitoring costs, based on the time they are monitored in primary and secondary care.

Stage 3 – For people who go on to dialysis, a 3 state Markov model (people who have subsequently had a transplant post starting dialysis, people who have not subsequently had a transplant post stating dialysis, and people who have died) is used to estimate long-term outcomes. Outcomes for people post initiation of dialysis are different based on the time at which the person was referred to secondary care, with people referred earlier having better post-dialysis outcomes.

Stage 4 – Similarly to stage 3, a Markov model is also used to estimate long-term outcomes for people who have a pre-emptive kidney transplant (i.e. without going on to dialysis first). Outcomes for people post-transplant are different based on the time at which the person was referred to secondary care, with people referred earlier having better post-transplant outcomes.

J.2.1.1 Population(s)

Adults with chronic kidney disease stages 3-5, currently being managed in primary care

There was insufficient UK evidence for the accuracy of the KFRE in children identified from the clinical review and the KFRE has not been validated in the UK for children, and therefore this analysis was restricted to adults. The population was set as CKD stages 3-5 to match the UK validation study for the KFRE equations (Major 2019). This study required people to have an eGFR <60 ml/min/1.73m^2 to be eligible for inclusion. Full details of the population in the Major study are given in section J.3.1.

J.2.1.2 Interventions

The majority of the evidence identified in the clinical review was based on the 4-variable KFRE equation, and therefore this was the one selected for the model, as the committee agreed there was not sufficient evidence of benefit from the extra variables included in the 8-variable equation. 5-year rather than 2-year risks were used, to ensure enough people progressed to ESRD over the time horizon to enable estimation of the accuracy of the different referral rules.

The decision rules tested match those reported in Major 2019, which include the 2014 NICE referral criteria, criteria based solely on various KFRE risk cut-offs, and referral rules that combine the KFRE with either a separate eGFR or a separate ACR threshold. Six referral rules were tested in total:

- 2014 NICE criteria: eGFR<30 ml/min/1.73m^2 **or** ACR≥70 mg/mmol
- KFRE ≥3% risk of ESRD over 5 years
- KFRE ≥5% risk of ESRD over 5 years
- KFRE ≥15% risk of ESRD over 5 years

- KFRE ≥5% risk of ESRD over 5 years **or** eGFR<30 ml/min/1.73m^2
- KFRE ≥5% risk of ESRD over 5 years **or** ACR≥70 mg/mmol

The committee also considered whether to look at referral rules that combined the KFRE at 3% with eGFR or ACR criteria, similarly to the last two bullet points above. However, given that using the KFRE at 3% alone already led to a high number of false positives (see section J.3.2) they were confident these rules would not be optimal ones, as they could only lead to equal or higher false positive rates.

J.2.1.3 Type of evaluation, time horizon, perspective, discount rate

As per the NICE reference case, this evaluation is a cost–utility analysis (reporting health benefits in terms of QALYs), conducted from the perspective of the NHS/PSS. It assesses costs and health benefits using a lifetime horizon and uses a discount rate of 3.5% per annum for both costs and health benefits.

J.2.2 Model structure (referral rules and monitoring)

J.2.2.1 Background

The population modelled is based on that reported in Major 2019. This was a UK validation study of the 4-variable KFRE equation. That study obtained electronic patient record data for 35,539 people meeting the criteria for CKD (2 CKD-EPI eGFR values < 60 ml/min/1.73 m^2 more than 90 days apart and a recorded quantifiable urine proteinuria measurement). These data spanned from 1st December 2004 to 1st November 2016, and were taken from patients registered with GP practices in the East Leicestershire and Rutland, Leicester City, Nene, and West Leicestershire Clinical Commissioning Groups. These data were then linked to the Leicester Renal network, which contains data on ESRD events.

The paper applies the standard 4-variable KFRE to predict risk of ESRD at 2 and 5 years, but recalibrates the baseline risk to be more accurate for a primary care UK population. The original KFRE equations give two- and five-year risks as follows:

- Five-year risk: $1 - 0.9365^{\exp(\beta sum)}$
- Two-year risk: $1 - 0.9832^{\exp(\beta sum)}$

where βsum = -0.2201 × (age/10 – 7.036) + 0.2467 × (male – 0.5642) – 0.5567 × (eGFR/5 – 7.222) + 0.4510 × (logACR – 5.137)

For the above equation, eGFR is reported in ml/min/1.73m^2 and ACR in mg/g. The recalibrated risks from Major 2019 use the same β coefficients, but recalibrate the baseline risk to the UK primary care population as follows:

- Five-year risk: $1 - 0.9570^{\exp(\beta sum)}$
- Two-year risk: $1 - 0.9878^{\exp(\beta sum)}$

The recalibrated five-year risk is the data used to populate the model.

The individual patient data used in the Major study are freely available alongside the journal article. The data provided and used in this analysis are:

- Baseline age, sex, eGFR and ACR (enables calculation of the 4-variable KFRE)
- Follow-up time
- Censoring events – death and progression to ESRD (if a person progresses to ESRD and then dies, they are coded in the dataset as ESRD)
- An identifier as to whether the person was known to secondary care nephrology services at baseline

The definition of ESRD used in the study was progression to either dialysis or transplantation. The original paper does not separate out these two events, but additional data was provided by the authors on which individuals progressed to dialysis and which to transplantation. We thank the authors of Major 2019 for providing us with this additional data. The committee noted there would be a proportion of people who would meet the criteria for dialysis/transplant, but would choose conservative management instead, and these would not be captured in the Major study. However, they agreed this was not a substantial issue with the predictive accuracy data, as there would be no reason to believe there would be any difference in the predictive accuracy of the rules based on the treatment choices that people would subsequently make

From the data provided, it is possible to calculate whether or not a person would meet the criteria for referral to secondary care at baseline, based on each of the referral rules being evaluated. In line with the 2019 Major paper, this analysis was restricted to the 15,830 people in the dataset known not to be in contact with secondary care nephrology services at baseline (as the purpose of the analysis is to look at referral rules in to secondary care, and therefore people already being managed in secondary care are not relevant). This dataset contains 89 people who progress to ESRD within 5 years.

J.2.2.2 Model structure

Each of the six referral rules is applied to the baseline measurements for each individual in the dataset, and compared to whether that person does or does not progress to ESRD over 5 years in order to calculate predictive accuracy (results reported in section J.3.2), as well as looking at whether the demographics of the populations referred by the rules are different.

Individuals who are either referred at baseline by all the referral rules (0.9% of the individuals in the original dataset), or referred at baseline by none of them (91.6% of individuals in the original dataset), are then excluded from any further analysis, as we expect the downstream consequences for those people to be the same, regardless of which referral rule is used. People who would be differentially referred by different rules are then classified in to one of three groups, based on their clinical trajectory:

- People who do not progress to ESRD within 5 years
- People who go on to dialysis within 5 years (this include people who may then subsequently go on to have a kidney transplant)
- People who receive a pre-emptive kidney transplant within 5 years

For all three of these groups, we calculate the differential costs of monitoring based on how long they are monitored in primary care and how long in secondary care. Additionally, for the second and third bullet points we assess the long-term outcomes associated with dialysis (section J.2.3) and transplant (section J.2.4), based on the time they are referred. Some of the people who do not progress to ESRD within 5 years will of course progress to ESRD after 5 years. However, since the KFRE equations modelled are only attempting to predict ESRD occurring within 5 years, it is expected that outcomes for these people will not be impacted by a differential referral choice made more than 5 years before they enter ESRD.

J.2.2.3 Monitoring costs and referral time

For people who are referred at baseline, they receive the cost of a secondary care referral at baseline, and then a proportion of their future monitoring appointments are assumed to be in primary care, and a proportion in secondary care (see section J.2.2.4 for cost details). An individual's monitoring schedule depends on their eGFR and ACR measurements, and is based on the schedule recommended in the guideline (Table 14). The only modification made is that where the guideline does not recommend a single specific frequency (for example, where it recommends at least 2 monitoring appointments per year) we assume they receive exactly that many appointments.

Table 14 Number of monitoring appointments per year

	ACR<3 mg/mmol	ACR 3-30 mg/mmol	ACR>30 mg/mmol
eGFR≥90	1	1	1
eGFR 60-89	1	1	1
eGFR 45-59	1	1	2
eGFR 30-44	2	2	2
eGFR 15-29	2	2	3
eGFR <15	4	4	4

At each monitoring appointment, a person's current eGFR and ACR measurements are used to calculate when their next monitoring appointment will take place. Then, we predict what their eGFR and ACR will be at that next monitoring appointment, based on average population declines in eGFR and increases in ACR (see section J.2.2.6). This process is continued for a time horizon of five years (the duration our baseline KFRE calculations are designed to be predicting ESRD risk over).

For people not referred at baseline, we perform an equivalent process of predicting their future monitoring schedule and their eGFR and ACR value at each monitoring appointment. At each subsequent monitoring appointment, it is checked to see if the person would now meet the criteria for referral to secondary care. People accrue the costs of primary care monitoring up until that point, then the cost of a secondary care referral at the time they do meet the criteria for referral. After the point of referral, a proportion of their future monitoring appointments are assumed to be in primary care, and a proportion in secondary care, as for people referred to secondary care at baseline (see section J.2.2.4 for cost details). Again, this process is carried on for the five-year horizon which the KFRE is predicting risk over.

The output of this first stage of the model is a cost of monitoring and referral for each person in the dataset and each referral rule that could be applied to them, as well as the time at which the person is referred to secondary care (or the fact that they reach the five-year time horizon without having been referred to secondary care).

J.2.2.4 Parameters (costs)

There are different monitoring costs depending on the referral time to secondary care. Before an initial referral to secondary care, patients start by being monitored in primary care, with GP appointments. The cost used for a GP appointment is one that also includes the cost of direct care staff (i.e. practice nurses) and therefore should also account for the staff time for tests undertaken as part of GP monitoring. The costs of tests themselves are not included, as it is assumed the same tests would be conducted at a primary care monitoring visit as at a secondary care one, and therefore there would be no difference in test costs between the two options.

When a patient is referred to secondary care, they will have an initial appointment with secondary care nephrology services. It was felt by the guideline committee that a combination of consultant and non-consultant outpatient appointment costs should be used to account for variation in practice across the country. A new referral appointment was expected to last longer than a standard monitoring appointment, potentially lasting around half an hour, with further tests being conducted if they have not been done by the GP. NHS reference costs contain a specific category for a first outpatient appointment with nephrology services, and therefore an average of the consultant and non-consultant led costs was used (weighted by the total number of appointments in each category). For the first appointment 92.8% were consultant led and 7.2% were non-consultant led; for follow up appointments 91.1% were consultant led and 8.9% were non-consultant led.

There are a proportion of patients who are referred to secondary care, have the new referral appointment, after which it is felt that they can be monitored in primary care and are therefore referred back. Additionally, some people may have a combination of primary and secondary care monitoring, after an initial secondary care referral. The committee supplied an estimate of the proportion of post-initial referral monitoring that takes place in secondary care from their knowledge of practice in their own clinics, and a range of possible values for this were tested in sensitivity analyses. Patients referred back to primary care accrue the cost of GP appointments for their subsequent monitoring, whilst those who continue to be monitored in secondary care receive the costs of outpatient nephrology follow-up visits. As for initial referral costs, these were taken from NHS reference costs, as a weighted average of the costs of consultant led and non-consultant led appointments.

Table 15: Monitoring inputs

Parameter	Value	PSA distribution	Source
GP appointment	£33.19		Curtis 2019
First outpatient nephrology visit	£219.63		NHS reference costs 2018/19
Subsequent outpatient nephrology visits	£159.17		NHS reference costs 2018/19
Proportion of monitoring in secondary care post referral	0.2	Beta (12.09, 48.37)	Assumption

J.2.2.5 Parameters (quality of life)

Since the model assumes that different referral times to secondary care only impact on outcomes once a person has entered ESRD, it follows that there will be no differences in quality of life or mortality for people before they enter ESRD, regardless of the time they are referred. Therefore, for individuals who do not enter ESRD, total QALYs will be identical for all referral rules, and therefore are not necessary to include in the analysis. Similarly, for people who do enter ESRD, total QALYs will be identical for all referral rules up until the point they enter ESRD, and again it is therefore not necessary to estimate QALYs for this time period. Consequently, the model does not contain a quality of life estimate for people with CKD who have not entered ESRD.

J.2.2.6 Parameters (epidemiology)

Estimates of average eGFR decline over time were based on an individual patient data meta-analysis of over 3.5 million people with CKD but without ESRD, coming from 14 separate CKD cohorts (Grams 2019). Thirteen of those cohorts report eGFR decline rates for people with a baseline eGFR<60, with 122,664 people in total in that subpopulation. Mean annual eGFR declines for each cohort were taken from the 2-years mixed effects models reported in the paper, and then a random-effects meta-analysis was conducted to estimate mean annual eGFR decline in the population.

No equivalent large cohort studies were identified providing data on ACR progression over time. Therefore, these parameters were based on data reported in a Health Technology Assessment report on early referral strategies for people with markers of renal disease (Black 2010). This study reports that people with an ACR<30 have a 2% probability of moving to ACR≥30 in 1 year, and people with an ACR of 30-299 have a 2.8% probability of moving to an ACR≥300 over 1 year. Since this model requires specific ACR values rather than ranges, an estimate of the mean increase in ACR needed over 1 year in order to have the correct number of people transition between those categories was made. Specifically, all the people in our dataset (from Major 2019) with a baseline ACR<30 were extracted, and

what average increase in ACR would be needed for 2% to reach an ACR of 30-299 within 1 year was estimated. Similarly, all the people in the dataset with a baseline ACR of 30-299 were extracted, and what average increase in ACR would be needed for 2.8% to reach an ACR >300 within 1 year was estimated.

ACR increases were assumed to be multiplicative rather than additive, to reflect the fact we would expect people with higher ACR values at baseline to also have faster increases in ACR over time. Since no data was available for people with ACRs greater than 300, these were assumed to increase at the same rate as those with an ACR 30-299.

The estimate mean eGFR declines and ACR increases are shown in Table 16.

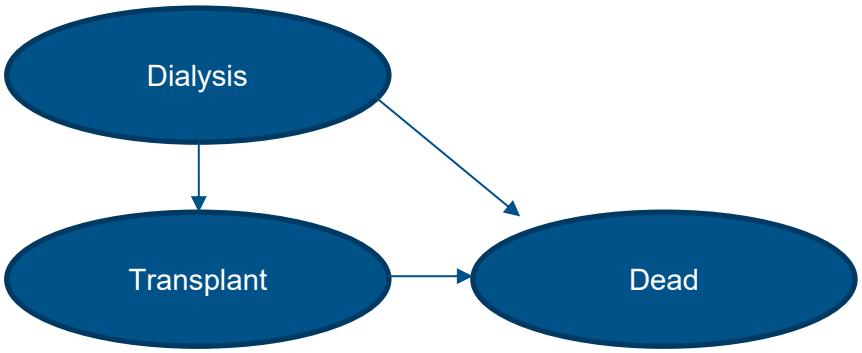
Table 16 Epidemiological parameters

Parameter	Value	PSA distribution	Source
Annual eGFR decline [ml/min/1.73m^2]	-1.145	Normal (-1.145, 0.191)	Grams 2019
1-year multiplicative increase in ACR [mg/mmol] (starting ACR<30)	1.288	Lognormal (0.253, 0.000096)	Black 2010 and Major 2019
1-year multiplicative increase in ACR [mg/mmol] (starting ACR≥30)	1.459	Lognormal (0.377, 0.000108)	Black 2010 and Major 2019

J.2.3 Model structure (dialysis)

For people who begin dialysis within 5 years of the start of the model (the time horizon over which the KFRE equations used are trying to predict risk), the three state Markov model shown in Figure 8 is used to estimate their long-term outcomes. An individual starts in the dialysis state and remains there until they either die or have a kidney transplant. Thus, the dialysis state contains all individuals who have not yet progressed to transplant or death, including those who have discontinued dialysis for any other reason, and outcomes represent the average outcomes for that group, not just for remaining on dialysis. Similarly, the post-transplant state contains all individuals who have had a kidney transplant after starting on dialysis, even if they have had additional subsequent procedures (a second transplant or a return to dialysis).

Figure 8 Model structure - dialysis



Since this analysis is based on an individual patient dataset, each person in the model starts with a different set of baseline characteristics (in particular a different age) that affect their estimated outcomes. The model is therefore run as a set of within person cohort studies (i.e. we estimate mean outcomes for an individual using the probability of being in each state over time). Thus, unlike a normal cohort model, which estimates numbers of people in each state

over time, this model estimates the probability of being in each state over time, for each individual in the dataset, and then aggregates their results. For the simple model structure used, this gives equivalent answers to running a series of individual simulations for each person and averaging the results.

J.2.3.1 Parameters (natural history)

Natural history data for people starting on dialysis were based on an analysis of data supplied by the UK Renal Registry of the Renal Association. We thank all the UK renal centres for providing data to the UK Renal Registry and Anna Casula from the UK Renal Registry for the statistical analysis she undertook. The interpretation and reporting of these data are the responsibility of NICE and the guideline committee and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.

Data were provided on rates of mortality and transplantation over 10 years for people starting on any form of dialysis, with the data divided into four age ranges (<50, 50-64, 65-74, 75+), with the data shown in Table 17, Table 18, Table 19 and Table 20, respectively. For mortality, data were censored at loss to follow-up and transplantation, and therefore represent mortality rates for people not receiving a transplant within a given year.

Additionally, data was provided on rates of mortality (Table 21, Table 22 and Table 23) and graft failure (Table 24, Table 25 and Table 26) for people having a kidney transplant (excluding pre-emptive transplants). Unlike for dialysis, people aged 75 and older were not considered a separate category, due to the low number of transplantations taking place in this age group, and were instead combined with those aged 65 and older. For mortality, data were censored at loss to follow-up, whilst for graft failure, data were censored at loss to follow-up and mortality, and therefore represent people surviving to require either a second transplant or to move on to dialysis.

The analyses used a UK cohort of adults starting dialysis or receiving a transplant between January 2005 and December 2017 with follow-up to the end of 2018.

Table 17 Post-dialysis survival data for people aged <50 at initiation, censored at loss to follow-up

	Survival (%)	N at risk	N died	N transplanted	N lost
Start	100.0	19,372			
1 year	94.9	13,578	873	3,381	1,540
2 years	89.4	9,122	659	2,785	1,012
3 years	83.6	6,079	500	1,883	660
4 years	77.6	4,063	371	1,177	468
5 years	72.3	2,734	240	765	324
6 years	66.5	1,896	193	432	213
7 years	59.7	1,308	170	239	179
8 years	53.9	911	113	115	169
9 years	48.2	634	86	86	105
10 years	43.0	398	60	44	132

Table 18 Post-dialysis survival data for people aged 50-64 at initiation, censored at loss to follow-up

	Survival (%)	N at risk	N died	N transplanted	N lost
Start	100.0	25,025			

	Survival (%)	N at risk	N died	N transplanted	N lost
1 year	89.9	18,492	2,573	1,688	2,272
2 years	79.8	13,547	1,703	1,613	1,629
3 years	71.1	9,687	1,335	1,387	1,138
4 years	62.3	6,744	1,083	1,036	824
5 years	53.6	4,608	838	732	132
6 years	45.5	3,137	617	421	433
7 years	38.3	2,122	446	232	132
8 years	31.2	1,417	358	104	243
9 years	25.5	908	235	75	199
10 years	20.6	585	154	18	151

Table 19 Post-dialysis survival data for people aged 65-74 at initiation, censored at loss to follow-up

	Survival (%)	N at risk	N died	N transplanted	N lost
Start	100.0	23,763			
1 year	81.1	17,041	4,275	526	1,921
2 years	68.8	12,693	2,443	501	1,404
3 years	57.7	9,325	1,921	407	1,040
4 years	47.7	6,758	1,526	280	761
5 years	38.3	4,732	1,237	162	627
6 years	30.8	3,313	877	109	433
7 years	24.2	2,249	660	47	357
8 years	18.3	1,457	513	15	264
9 years	14.3	961	296	6	194
10 years	10.6	573	229	<=5	<=5

Table 20 Post-dialysis survival data for people aged 75 plus at initiation, censored at loss to follow-up

	Survival (%)	N at risk	N died	N transplanted	N lost
Start	100.0	23,485			
1 year	73.3	15,586	6,032	50	1,817
2 years	57.4	11,066	3,228	23	1.269
3 years	43.8	7,603	2,504	18	941
4 years	32.7	5,045	1,835	14	709
5 years	23.8	3,285	1,292	<=5	<=5
6 years	16.6	1,984	932	<=5	<=5
7 years	11.4	1,181	580	<=5	<=5
8 years	7.7	680	355	<=5	<=5
9 years	5.0	348	223	<=5	<=5
10 years	3.3	177	103	<=5	<=5

Table 21 Post-transplant survival data for people aged <50 at transplant, censored at loss to follow-up

	Survival (%)	N at risk	N died	N lost
Start	100.0	14,389		
1 year	98.5	13,113	210	1,066
2 years	97.7	11,990	106	1,017
3 years	96.9	10,870	94	1,026
4 years	95.8	9,719	113	1,038
5 years	94.7	8,622	103	994
6 years	93.5	7,437	107	1,078
7 years	92.0	6,403	111	923
8 years	90.5	5,347	94	962
9 years	89.0	4,364	83	900
10 years	87.1	3,357	82	925

Table 22 Post-transplant survival data for people aged 50-64 at transplant, censored at loss to follow-up

	Survival (%)	N at risk	N died	N lost
Start	100.0	10,427		
1 year	96.4	9,103	362	962
2 years	94.1	8,089	205	809
3 years	91.7	7,014	196	879
4 years	89.3	6,033	173	808
5 years	86.0	5,074	206	753
6 years	83.2	4,183	157	734
7 years	80.0	3,385	149	649
8 years	76.1	2,666	149	570
9 years	71.5	1,996	143	527
10 years	67.2	1,392	104	500

Table 23 Post-transplant survival data for people aged 65+ at transplant, censored at loss to follow-up

	Survival (%)	N at risk	N died	N lost
Start	100.0	4,089		
1 year	92.3	3,316	301	472
2 years	87.5	2,771	163	382
3 years	82.9	2,294	133	344
4 years	77.9	1,882	129	283
5 years	73.0	1,493	111	278
6 years	66.5	1,102	119	272
7 years	59.8	805	99	198
8 years	51.6	562	100	143
9 years	44.6	369	67	126
10 years	40.2	228	30	111

Table 24 Graft failure rates for people aged <50 at transplant, censored at death and loss to follow-up

	N at risk	N with graft failure – move to dialysis	N with graft failure – re-transplant	N died	N lost	Graft survival (%)
Start	14,389					100.0
1 year	12,480	663	0	182	1,064	95.3
2 years	11,163	251	0	75	991	93.3
3 years	9,924	221	10	60	948	91.3
4 years	8,686	201	9	76	952	89.2
5 years	7,564	162	13	65	882	87.3
6 years	6,385	174	12	60	933	85.0
7 years	5,341	179	12	62	791	82.3
8 years	4,359	128	11	50	793	80.0
9 years	3,459	88	11	47	754	78.0
10 years	2,578	93	8	42	738	75.4

Table 25 Graft failure rates for people aged 50-64 at transplant, censored at death and loss to follow-up

	N at risk	N with graft failure – move to dialysis or re-transplant	N died	N lost	Intact graft (%)
Start	10,427				100.0
1 year	8,647	538	303	939	94.7
2 years	7,560	133	160	794	93.1
3 years	6,495	110	151	804	91.7
4 years	5,505	103	142	745	90.1
5 years	4,563	100	159	683	88.3
6 years	3,712	75	119	657	86.7
7 years	2,975	59	106	572	85.2
8 years	2,326	54	101	494	83.5
9 years	1,713	43	110	460	81.8
10 years	1,199	37	73	404	79.8

Table 26 Graft failure rates for people aged 65+ at transplant, censored at death and loss to follow-up

	N at risk	N with graft failure – move to dialysis or re-transplant	N died	N lost	Intact graft (%)
Start	4,089				100.0
1 year	3,134	233	263	459	94.0
2 years	2,581	48	132	373	92.4
3 years	2,123	31	108	319	91.2
4 years	1,726	26	105	266	90.0

	N at risk	N with graft failure – move to dialysis or re-transplant	N died	N lost	Intact graft (%)
5 years	1,357	24	88	257	88.6
6 years	988	26	95	248	86.6
7 years	722	11	75	180	85.5
8 years	497	9	85	131	84.2
9 years	322	6	54	115	83.0
10 years	203	7	22	90	80.8

J.2.3.2 Parameters (effect of referral time)

The effect of referral time on outcomes post the initiation of dialysis was estimated based on an update of a published Cochrane review (Smart 2014). This review included both prospective and retrospective cohort studies, and looked at the impact on post-dialysis outcomes of early referral versus late referral to secondary care services. A variety of definitions of early versus late referral were used in the papers included in the review, with cut-offs of between 1 month and 6 months prior to the initiation of dialysis marking the boundary between early and late referral. An update of this review was conducted, to include studies published after 2014, and this update is described in full in section J.6. This update of the review also updated the analysis methods used (e.g. selection of fixed- versus random-effects meta-analysis models) to be consistent with those used in the rest of the guideline.

Five outcomes from the Cochrane review were considered for inclusion in the model, with two ultimately being included – mortality and length of hospital stay at dialysis initiation. For both of these outcomes there was a clear benefit of early referral demonstrated, and the committee agreed these were both outcomes where it would be expected that early referral (and hence more time to prepare for dialysis initiation) could improve outcomes. The Cochrane review contains four timepoints at which mortality data were reported; 3/4 months, 6 months, 1 year and 5 years. However, only one study reported data at 6 months, and therefore the committee agreed it was appropriate to exclude this timepoint, and only include those for which multiple studies were available.

The three outcomes considered for inclusion in the model but ultimately rejected were quality of life, dialysis type and patient characteristics/comorbidities. Quality of life was excluded solely due to the lack of good quality data available. It was only reported in a small number of studies, using different instruments, and there was no clear evidence of differences between people referred early and late, and therefore the committee agreed it was better not to include any quality of life differences in the model. The review did show that people referred early were significantly more likely to have peritoneal dialysis (rather than haemodialysis) compared to those referred late. The committee agreed this finding made sense, as often there was more time needed for discussion with patients before peritoneal dialysis was used. However, they decided this data should not be included in the model, as they agreed that doing so might result in double counting of the benefits. For example, if peritoneal dialysis were to be associated with improved mortality, this would already be captured in the mortality outcomes itself, and therefore modelling differences in peritoneal versus haemodialysis outcomes was not necessary.

For the data on patient characteristics/comorbidities, the committee agreed it was not of interest to include this in the model, but the purpose of this data was rather to assess the potential risk of selection bias from the fact the review is composed entirely of observational studies. In particular, if the people referred late for dialysis were worse off in other ways (more advances CKD, worse disease control, higher levels of comorbidities) then this could

account for the differences in outcomes between early and late referral, rather than it being the result of the referral itself. The committee noted that it was never possible to entirely rule out this possibility when using observational data. However, they were reassured by the conclusion of the Cochrane review that: “differences in mortality and hospitalisation data between the two groups were not explained by differences in prevalence of comorbid disease or serum phosphate. However, early referral was associated with better preparation and placement of dialysis access.” They therefore agreed it was likely the benefits found in the review were truly associated with early referral, and therefore these benefits were appropriate to include in the analysis.

The committee discussed the appropriate cut-off to use for early versus late referral. The NICE guideline on renal replacement therapy recommends referral one year before initiation of dialysis is necessary, and therefore they agreed they wanted to use a cut-off as close to that as the data would allow. However, they also agreed they wanted to make use of all the studies found in the Cochrane review, regardless of the cut-off used, to ensure there was sufficient data available. They therefore set the cut-off for early versus late referral in the modelling at six months, the upper end of the range of definitions used in the studies in the 2014 Cochrane review, but agreed that all studies should be included in the meta-analysis, regardless of the cut-off used within the individual study. They noted the Cochrane review did contain subgroup analyses looking at the impact of using different cut-offs, and that larger differences in mortality were found using a six-month cut-off than one at three months or one month, and were therefore confident the choice made was a conservative one, with regard to the benefits estimated for early referral.

Full details of the update of the Cochrane review are given in section J.6, and the final parameters include in the model are shown in Table 27.

Table 27 Effects of earlier referral to secondary care on dialysis outcomes

Parameter	Value	PSA distribution	Source
Relative risk of mortality at 3 months (early versus late referral)	0.47	Lognormal (-0.755, 0.060)	Update of Smart 2014
Relative risk of mortality at 1 year (early versus late referral)	0.54	Lognormal (-0.616, 0.006)	Update of Smart 2014
Relative risk of mortality at 5 years (early versus late referral)	0.68	Lognormal (-0.386, 0.014)	Update of Smart 2014
Decrease in length of initial hospital stay (days; early versus late referral)	10.47	Normal (10.47, 6.37)	Update of Smart 2014

J.2.3.3 Combining natural history and effects of referral time

To generate transition probabilities for the Markov models described in section J.2.3, the natural history data from section J.2.3.1 need to be combined with the relative effect data in section J.2.3.2. Beginning with mortality data for people aged <50 at initiation of dialysis (shown in Table 28), the cumulative hazard H(t) each year is calculated from the survival probability S(t) in Table 17 as:

$$H(t) = -\ln[S(t)]$$

This hazard represents the average hazard in the mixed population of people who are referred early and late for dialysis. From these hazards, we estimate mortality in this mixed population at 3 months, 1 year and 5 years (the three points at which we have relative effect data for early versus late referrals). From these average mortality data M(t), the relative risks for mortality in people referred early versus late RR_{EL}, and the proportion of people who are referred early at present $Prop_E$ we can calculate mortality for people referred early $M_E(t)$ and $M_L(t)$ at each time point as follows:

$$M_L(t) = M(t)/((1 - Prop_E) + Prop_E * RR_{EL})$$

$$M_E = M_L * RR_{EL}$$

These probabilities are then converted back into cumulative hazards for both early and late referrals at each of the three time points. Hazards at intermediate time points (e.g. 2 years) are calculated by interpolating between the cumulative hazards, using the relative hazards at each point in time. For example, the cumulative hazard at 2 years for people who were referred early is estimated as being the same proportion of the difference between the 1 year and 5 year cumulative hazard for people referred early as the 2 year hazard is between the 1 and 5 year hazards in the full population. From year 6 onwards, it is assumed the hazards are the same in the two groups, due to the absence of relative effect data beyond that timepoint.

These hazards can then be converted to 1-year transition probabilities (T) for year x as follows:

$$T(x) = 1 - \exp\left[H(x) - H(x-1)\right]$$

Finally, these 1-year transition probabilities are converted to 3-month (the cycle length of the model) transition probabilities (T') as follows, assuming that within a given year, the probability of death is the same of each 3-month cycle.

$$T'(x) = 1 - \exp\left(\frac{\ln\left[T(x)\right]}{4}\right)$$

Table 28 Mortality rates per cycle for people aged <50 at dialysis initiation

	Cumulative hazard (full population)	Cumulative hazard (early referral)	Probability of death per 3-month cycle (early referral)	Cumulative hazard (late referral)	Probability of death per 3-month cycle (late referral)
Start	0	0		0	
First 3 months	0.01319	0.00918	0.00914	0.01963	0.01944
3 months-1 year	0.05277	0.03947	0.01005	0.07436	0.01808
Year 2	0.11178	0.08894	0.01229	0.15007	0.01875
Year 3	0.17871	0.14506	0.01393	0.23593	0.02124
Year 4	0.25320	0.20753	0.01550	0.33151	0.02361
Year 5	0.32415	0.26702	0.01476	0.42254	0.02250
Year 6	0.40819	0.35106	0.02079	0.50658	0.02079
Year 7	0.51632	0.45919	0.02667	0.61471	0.02667
Year 8	0.61852	0.56139	0.02523	0.71691	0.02523
Year 9	0.72952	0.67239	0.02737	0.82791	0.02737
Year 10	0.84439	0.78726	0.02831	0.94278	0.02831

Similar calculations are performed for people aged 50-64, 65-74 and 75+ at dialysis initiation (applying the same relative risks to the different baseline rates for each age group), with the results given in Table 29, Table 30 and Table 31, respectively. For all age groups, mortality rates for years 11 and onwards are assumed to be the same as in year 10. In order to avoid this method potentially producing unrealistically low mortality rates as people age, data on all course age and sex-specific mortality were also taken from the Office for National Statistics, and each person's mortality was set as the maximum of either the mortality estimated from the UK Renal Registry data or all-cause mortality for their age and sex (thus, mortality can never be lower than average all-cause mortality).

Table 29 Mortality rates per cycle for people aged 50-64 at dialysis initiation

	Cumulative hazard (full population)	Cumulative hazard (early referral)	Probability of death per 3-month cycle (early referral)	Cumulative hazard (late referral)	Probability of death per 3-month cycle (late referral)
Start	0	0		0	
First 3 months	0.02943	0.02042	0.02021	0.04396	0.04300
3 months-1 year	0.11771	0.08730	0.02205	0.16819	0.04057
Year 2	0.22508	0.17463	0.02160	0.31539	0.03613
Year 3	0.34080	0.26875	0.02326	0.47405	0.03889
Year 4	0.47374	0.37687	0.02667	0.65630	0.04454
Year 5	0.62399	0.49908	0.03009	0.86231	0.05020
Year 6	0.78708	0.66217	0.03995	1.02540	0.03995
Year 7	0.95857	0.83366	0.04197	1.19689	0.04197
Year 8	1.16344	1.03853	0.04993	1.40175	0.04993
Year 9	1.36845	1.24354	0.04996	1.60677	0.04996
Year 10	1.57760	1.45269	0.05094	1.81591	0.05094

Table 30 Mortality rates per cycle for people aged 65-74 at dialysis initiation

	Cumulative hazard (full population)	Cumulative hazard (early referral)	Probability of death per 3-month cycle (early referral)	Cumulative hazard (late referral)	Probability of death per 3-month cycle (late referral)
Start	0	0		0	
First 3 months	0.05228	0.03614	0.03550	0.07854	0.07553
3 months-1 year	0.20911	0.15320	0.03827	0.30522	0.07278
Year 2	0.37417	0.28195	0.03168	0.55937	0.06156
Year 3	0.55007	0.41916	0.03372	0.83020	0.06547
Year 4	0.74020	0.56746	0.03640	1.22294	0.07057
Year 5	0.95946	0.73849	0.04186	1.46053	0.08094
Year 6	1.17892	0.95795	0.05339	1.67999	0.05339
Year 7	1.41878	1.19780	0.05820	1.91985	0.05820
Year 8	1.69914	1.47817	0.06769	2.20022	0.06769
Year 9	1.94687	1.72590	0.06005	2.44794	0.06005
Year 10	2.24639	2.02542	0.07215	2.74747	0.07215

Table 31 Mortality rates per cycle for people aged 75+ at dialysis initiation

	Cumulative hazard (full population)	Cumulative hazard (early referral)	Probability of death per 3-month cycle (early referral)	Cumulative hazard (late referral)	Probability of death per 3-month cycle (late referral)
Start	0	0		0	
First 3 months	0.07754	0.05340	0.05200	0.11726	0.11064
3 months-1 year	0.31016	0.22407	0.05530	0.46481	0.10939
Year 2	0.55467	0.40042	0.04313	1.00789	0.12696
Year 3	0.82529	0.59558	0.04762	1.60895	0.13952
Year 4	1.11868	0.80719	0.05152	2.26061	0.15034
Year 5	1.43494	1.03527	0.05543	2.96304	0.16105
Year 6	1.79336	1.39369	0.08571	3.32146	0.08571
Year 7	2.16832	1.76865	0.08948	3.69642	0.08948
Year 8	2.55838	2.15871	0.09291	4.08649	0.09291
Year 9	3.00477	2.60511	0.10560	4.53288	0.10560
Year 10	3.40641	3.00674	0.09553	4.93452	0.09553

The data in Table 17, Table 18, Table 19 and Table 20 were also used to estimate annual rates of transplant for people on dialysis, calculated as the proportion of people alive on dialysis at the start of a year who receive a transplant within that year, which are then converted to 3 month rates to match the cycle length of the model. Because mortality data are censored at transplant, they represent mortality rates for people not receiving a transplant within a given year. Therefore, the mortality rates estimated above are applied to people alive at the start of a cycle who do not then have a transplant within that cycle.

Table 32 Post-dialysis transplant rates per 3-month cycle, by age at dialysis initiation

	Age <50	Age 50-64	Age 65-74	Age 75+
Year 1	0.04590	0.01731	0.0056	0.0005
Year 2	0.05577	0.02256	0.0074	0.0004
Year 3	0.05616	0.02664	0.0081	0.0004
Year 4	0.05238	0.02788	0.0076	0.0004
Year 5	0.05081	0.02832	0.0060	0.0000
Year 6	0.04209	0.02367	0.0083	0.0000
Year 7	0.03312	0.01903	0.0036	0.0000
Year 8	0.02274	0.01248	0.0017	0.0000
Year 9	0.02449	0.01350	0.0010	0.0000
Year 10	0.01782	0.0050	0.0000	0.0000

From year 11 onwards, transplant rates are assumed to be zero (there is a clear pattern of decreasing transplant rates as you approach year 10, in all age groups).

For people who go on to have a transplant after dialysis, rates of mortality per cycle are calculated from the data in Table 21, Table 22 and Table 23, and presented in Table 33. As for people on dialysis, mortality rates for years 11 and onwards are assumed to be the same as in year 10, and each person's mortality was set as the maximum of either the mortality estimated from the UK Renal Registry data or all-cause mortality for their age and sex (thus, mortality can never be lower than average all-cause mortality).

Similarly, rates of graft failure per cycle are calculated from the data in Table 24, Table 25 and Table 26, and presented in Table 34. For both mortality and graft failure cases, survival data were converted to hazards, and then those hazards converted to probability of death/graft failure per cycle.

For people who have graft failure post-transplant but survive, a proportion will have a second transplant, and a proportion will go on to dialysis, either permanently or until a second transplant is carried out. For simplicity in the modelling (and because the purpose of this analysis is not to compare different options for RRT), all people suffering graft failure are assumed to receive a second transplant, and then their subsequent downstream outcomes (mortality and rates of further graft failure) are assumed to be the same as for someone receiving their first transplant (it is likely that outcomes may be somewhat worse for people after a second or subsequent transplant, but in the absence of data to quantify this the committee agreed it was a reasonably assumption). People who have additional graft failures remain in that state, but receive the costs of graft failure for each subsequent event.

Table 33 Mortality rates per cycle for people post-transplant, by age at transplant

	Age <50	Age 50-64	Age 65+
Year 1	0.00378	0.00916	0.01996
Year 2	0.00211	0.00589	0.01321
Year 3	0.00206	0.00654	0.01324
Year 4	0.00274	0.00664	0.01544
Year 5	0.00280	0.00924	0.01635
Year 6	0.00331	0.00843	0.02285
Year 7	0.00399	0.00981	0.02608
Year 8	0.00407	0.01238	0.03633
Year 9	0.00426	0.01522	0.03554
Year 10	0.00530	0.01544	0.02573

Table 34 Graft failure rates per cycle for people post-transplant, by age at transplant

	Age <50	Age 50-64	Age 65+
Year 1	0.01200	0.01360	0.01532
Year 2	0.00525	0.00411	0.00426
Year 3	0.00551	0.00391	0.00331
Year 4	0.00561	0.00431	0.00340
Year 5	0.00538	0.00495	0.00389
Year 6	0.00662	0.00454	0.00549
Year 7	0.00810	0.00441	0.00322
Year 8	0.00716	0.00507	0.00381
Year 9	0.00615	0.00522	0.00363
Year 10	0.00841	0.00624	0.00664

J.2.3.4 Parameters (costs)

Costs related to length of stay for the hospitalisation where dialysis is initiated were estimated from NHS reference costs, using the cost of excess bed days. Excess bed days are not included in the 2018/19 version of the NHS reference costs, and therefore this cost was taken from the 2017/18 reference costs instead. There is no specific excess bed day cost related to dialysis, and therefore the categories for chronic kidney disease (with interventions) were used instead.

Long-term costs of dialysis are not included in the base analysis of this model. This is consistent with the approach taken both in previous NICE CKD guidelines, and in the NICE guideline on renal replacement therapy. A full explanation of the reasoning behind this is given in section 1.2.6.1 (P38) of the modelling report for the renal replacement therapy guideline. However, in brief, dialysis as an intervention does not meet the standard NICE criteria for cost-effectiveness, and its use in the NHS is therefore justified not solely by the amount of extra health it generates, but based on a broader set of decision-making criteria. This causes problems when dialysis is then included as a downstream consequence of another decision (as is the case in this model) as it can lead to counterintuitive results. For example, an intervention with a higher mortality rate can appear to be more cost-effective, solely because people die before reaching a stage of needing dialysis, and therefore those costs are saved. Because the purpose of this analysis is not to evaluate the cost-effectiveness of dialysis, and because the long-term annual costs of providing dialysis are not affected by referral time, excluding these costs from the model removes these potentially incoherent results.

Costs associated with kidney transplants for people after they had been on dialysis were also excluded from the base-case analysis. Whilst including transplant costs does not cause the same issues as including dialysis costs (since transplantation is a cost-effective intervention) it can nevertheless cause inconsistencies when one set of costs is included and the other excluded. In particular, when people switch from dialysis to transplant, this will lead to the model estimating an increase in costs (since dialysis costs are excluded) when in fact in reality the long-term costs of transplantation are considerably lower than remaining on dialysis. This means the model includes no costs after the start of renal replacement therapy, and only QALYs are accrued after that time point.

However, in order to match the NICE reference case, a scenario analysis was conducted including the costs of dialysis (section J.2.7.3) and subsequent transplantation. To estimate the costs of dialysis to include in this scenario analysis, we took the average cost of each type of dialysis session from NHS Reference costs, an estimate of the number of sessions per cycle for each type of dialysis from NICE Technology Appraisal 117, and the proportions of people receiving each of the types of dialysis from the UK Renal Registry. All the data used are shown in Table 35. A potential error was identified in the 2018/19 reference costs when performing this analysis. In the code “Renal dialysis away from base - Home Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over”, which usually has activity levels of a few hundred per trust submitting, a submission of 42,681 events from Salford NHS trust was received, with a very different estimated unit cost from both the other submissions this year, and from the costs in previous years. Communication with NHS Improvement revealed this was the first year a submission had been made from Salford for this code, and it was not clear whether the definition used was the same as had been submitted by other trusts for this code. Therefore, this code was excluded from the analysis when dialysis costs were estimated.

In line with the NICE renal replacement therapy guideline, transport costs were also included for a proportion of people receiving hospital and satellite dialysis (78%, taken from a 2010 audit on patient transport, which was confirmed by the committee to still reflect the current situation around payment of patient transport costs). The cost of £4,058 per person estimated in the renal replacement therapy guideline was inflated to 2019 prices using the consumer price index, giving an estimate of £4,392 per person.

Table 35 Dialysis costing

Type of dialysis	Cost per session	Number of sessions per 3-month cycle	Cost of 3-month cycle (including transport costs)	Proportion
Home haemodialysis	£212.15	52.0	£11,031.52	4.8%

Type of dialysis	Cost per session	Number of sessions per 3-month cycle	Cost of 3-month cycle (including transport costs)	Proportion
Hospital haemodialysis	£153.78	39.0	£7,095.70	32.3%
Satellite haemodialysis	£153.27	39.0	£7,075.63	50.5%
Continuous ambulatory peritoneal dialysis	£66.16	91.3	£6,040.81	5.0%
Automated peritoneal dialysis	£75.88	91.3	£6,927.65	7.3%

An additional 15% was added on top of the reference costs for dialysis and transport costs, to account for access procedures, out-patient appointments, and management of complications. This again follows the methodology used in the renal replacement therapy guideline.

For people who go on to have a transplant after dialysis, the costs of transplantation (to include in the same sensitivity analysis as dialysis costs) are estimated as a weighted average of the costs of living and deceased donor transplant (using an estimate of 29% of transplants coming from living donors taken from the UK Renal registry), and the costs of immunosuppressive therapy are assumed to the same as after a pre-emptive transplant. The full details of how these costs were estimated is provided in section J.2.4.4.

Table 36 Cost data - dialysis model

Parameter	Value	PSA distribution	Source
Cost per extra day in hospital at dialysis initiation	£339		NHS reference costs 2017/18
Cost per 3 months of dialysis	£8,283		NHS reference costs 2018/19
Cost of kidney transplant	£12,680		NHS reference costs 2018/19
Cost per 3 months of immunosuppressive therapy	£2,083		Costs from NHS drug tariff (Sep 2020); quantity for weighting from PCA (Mar 2019)

J.2.3.5 Parameters (quality of life)

Data on quality of life (reported using the EQ-5D-3L) for people on dialysis were taken from a published systematic review and meta-analysis (Liem 2008). That analysis separately estimated utilities for people on haemodialysis (0.56) and peritoneal dialysis (0.58). The committee agreed that is was plausible that quality of life would be higher for people on peritoneal dialysis, but were not confident in using these separate estimates, as on average people starting on peritoneal dialysis are younger and healthier, and therefore the difference may at least partially be explained by this, rather than relating to the dialysis type itself. The studies on haemodialysis and peritoneal dialysis were therefore combined together to create a single estimate for quality of life on dialysis.

The average age of the populations in the studies (across both haemodialysis and peritoneal dialysis) was 61.4 years and the populations were 41% female, and standard age adjustments (Kind 1999) were applied to that mean utility reported in the study when estimating utilities for an individual.

For individuals who progress from dialysis to transplant, the same utilities were used as for people receiving a pre-emptive transplant. The full detail on how this value was estimated is given in section J.2.4.5.

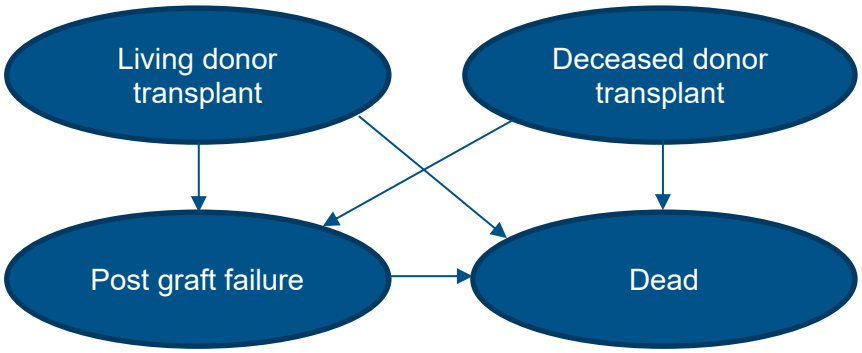
Table 37: Quality of life values – dialysis model

Parameter	Value	PSA distribution	Source
Quality of life on dialysis	0.565	Beta (204.85, 157.72)	Liem 2008
Quality of life post-transplant	0.827	Beta (809.58, 169.36)	Li 2017

J.2.4 Model structure (pre-emptive transplant)

For people who have a pre-emptive transplant within 5 years of the start of the model (the time horizon over which the KFRE equations used are trying to predict risk), the four state Markov model shown in Figure 9 is used to estimate their long-term outcomes. An individual has a probability of beginning in either the living donor transplant or deceased donor transplant states, based on the time at which they are referred to secondary care (see section J.2.4.3). People remain in these states until they die or experience graft failure. People experiencing graft failure then remain in the post-graft failure state for the remainder of the model, or until they die.

Figure 9 Model structure - pre-emptive transplant



Since this analysis is based on an individual patient dataset, each person in the model starts with a different set of baseline characteristics (in particular a different age) that affect their estimated outcomes. The model is therefore run as a set of within person cohort studies (i.e. we estimate mean outcomes for an individual using the probability of being in each state over time). Thus, unlike a normal cohort model, which estimates numbers of people in each state over time, this model estimates the probability of being in each state over time, for each individual in the dataset, and then aggregates their results. For the simple model structure used, this gives equivalent answers to running a series of individual simulations for each person and averaging the results.

J.2.4.1 Parameters (natural history)

As for dialysis, natural history data for people having a pre-emptive kidney transplant were based on an analysis of data supplied by the UK Renal Registry of the Renal Association. We thank all the UK renal centres for providing data to the UK Renal Registry and Anna Casula from the UK Renal Registry for the statistical analysis she undertook. The interpretation and reporting of these data are the responsibility of NICE and the guideline committee and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.

Data was provided on rates of mortality (Table 38, Table 39 and Table 40) and graft failure (Table 41, Table 42 and Table 43) over 10 years for people having a pre-emptive kidney transplant, with the data divided into three age ranges (<50, 50-64, 65+). Unlike for dialysis, people aged 75 and older were not considered a separate category, due to the low number of transplantations taking place in this age group.

The analyses used a UK cohort of adults having a pre-emptive transplant between January 2005 and December 2017 with follow-up to the end of 2018. For mortality, data were censored at loss to follow-up, whilst for graft failure, data were censored at loss to follow-up and mortality, and therefore represent people surviving to require either a second transplant or to move on to dialysis.

Table 38 Post-transplant survival data for people aged <50 at pre-emptive transplant, censored at loss to follow-up

	Survival (%)	N at risk	N died	N lost
Start	100.0	3,486		
1 year	99.3	3,149	22	315
2 years	98.9	2,805	15	329
3 years	98.2	2,494	17	294
4 years	97.8	2,201	10	283
5 years	97.4	1,901	9	291
6 years	96.8	1,599	10	292
7 years	96.0	1,328	12	259
8 years	95.1	1,085	12	231
9 years	94.2	839	9	237
10 years	93.1	610	8	221

Table 39 Post-transplant survival data for people aged 50-64 at pre-emptive transplant, censored at loss to follow-up

	Survival (%)	N at risk	N died	N lost
Start	100.0	2,199	34	237
1 year	98.4	1,928	20	251
2 years	97.3	1,657	15	197
3 years	96.4	1,445	15	202
4 years	95.3	1,228	23	202
5 years	93.3	1,003	21	190
6 years	91.2	792	11	157
7 years	89.7	624	20	145
8 years	86.4	459	8	140
9 years	84.6	311	7	96
10 years	82.2	208	<=5	75

Table 40 Post-transplant survival data for people aged 65+ at pre-emptive transplant, censored at loss to follow-up

	Survival (%)	N at risk	N died	N lost
Start	100.0	843		
1 year	96.2	710	30	103
2 years	93.3	568	19	123
3 years	89.3	456	23	89

	Survival (%)	N at risk	N died	N lost
4 years	86.2	351	14	91
5 years	82.4	266	14	71
6 years	78.1	183	12	71
7 years	74.6	122	8	53
8 years	69.0	83	7	32
9 years	65.4	56	<=5	<=5
10 years	57.6	35	<=5	<=5

Table 41 Graft failure rates for people aged <50 at pre-emptive transplant, censored at death and loss to follow-up

	Intact graft (%)	N at risk	N with graft failure – move to dialysis or re-transplant	N died	N lost
Start	100.0	3,486			
1 year	98.4	3,087	55	20	324
2 years	96.8	2,699	45	13	330
3 years	95.3	2,358	41	12	288
4 years	93.9	2,041	31	6	280
5 years	92.4	1,734	29	8	270
6 years	90.8	1,441	28	<=5	265
7 years	89.4	1,180	21	8	232
8 years	87.7	937	20	9	214
9 years	86.0	715	16	6	200
10 years	84.1	511	14	<=5	190

Table 42 Graft failure rates for people aged 50-64 at pre-emptive transplant, censored at death and loss to follow-up

	Intact graft (%)	N at risk	N with graft failure – move to dialysis or re-transplant	N died	N lost
Start	100.0	2,199			
1 year	97.8	1,881	45	33	240
2 years	96.7	1,596	21	14	250
3 years	96.1	1,385	9	14	188
4 years	94.7	1,167	18	9	191
5 years	93.5	939	14	22	192
6 years	92.2	723	11	15	190
7 years	91.0	568	9	7	139
8 years	89.9	419	6	16	127
9 years	89.1	278	<=5	<=5	131
10 years	88.3	181	<=5	<=5	88

Table 43 Graft failure rates for people aged 65+ at pre-emptive transplant, censored at death and loss to follow-up

	Intact graft (%)	N at risk	N with graft failure – move to dialysis or re-transplant	N died	N lost
Start	100.0	843			
1 year	98.2	698	14	26	105
2 years	97.6	554	<=5	<=5	123
3 years	97.0	446	<=5	<=5	85
4 years	95.2	335	7	13	91
5 years	93.9	250	<=5	<=5	69
6 years	93.1	174	<=5	<=5	65
7 years	91.3	115	<=5	<=5	49
8 years	91.3	78	<=5	<=5	30
9 years	89.5	51	<=5	<=5	26
10 years	86.8	30	<=5	<=5	20

J.2.4.2 Parameters (effect of referral time)

Articles considered during preliminary reading indicated that outcomes for kidney transplants from living donors were likely to be better than outcomes for recipients of kidneys from deceased donors. We expect that early referral to secondary care would increase the likelihood of a patient receiving a transplant from a living donor as it would increase the available time to find a clinically suitable match to a living donor. The proportions of living and deceased donor types (and thus the consequences of transplant) would therefore differ by referral strategy, making it necessary to capture the differences in transplant outcomes between donor types in the model.

For each individual receiving a pre-emptive transplant, the probability of them receiving either a living or deceased donor transplant needs to be estimated. Across all individuals receiving a pre-emptive transplant in the UK, 74.5% receive a living donor transplant (Annual report on kidney transplantation 2018/19). This was assumed to represent the proportion for someone listed for pre-emptive transplant 12 months before the transplant is carried out. This choice matches the 1 year target for beginning assessment for RRT in the NICE renal replacement therapy guideline, but the exact value is not critical, as we are not interested in the absolute amount of living versus deceased donor transplants carried out, but rather the increase in the proportion of living donor transplants carried out for people referred to secondary care earlier.

To estimate the impact of referral time on the probability of receiving a living donor transplant, we use data from the UK Renal Registry on the proportion of people receiving a transplant within the first year of going on to dialysis. 6.2% of people going on to dialysis receive a transplant within one year, of which we assume 28% are living donor transplants, the overall proportion of kidney transplants that come from living donors (UK Renal Registry 22nd Annual Report). Thus, 1.7% of people going on to dialysis receive a living donor transplant within 1 year. Assuming those transplants occur at a constant rate throughout the year and assuming that, for example, a person receiving a living donor transplant 2 months after dialysis could have received the same transplant pre-emptively had they been referred at least 2 months earlier. As a person who was referred 1 year earlier would have had a 74.5% chance of getting a transplant from a living donor (the proportion assumed for pre-emptive transplants at 1 year) rather than a 28% chance of getting a living a donor (the proportion for all transplants). From this we can calculate a person has an additional 3.88%

chance of receiving a living donor for each month earlier they are referred to secondary care and listed for a pre-emptive transplant (in the absence of evidence on the distribution of this increase it is assumed to be constant). This also implies that a person has a 3.88% reduction in their chance of receiving a living donor transplant for each month later they are referred to secondary care. The probability of getting a living donor is capped at 90%, as it is assumed that there cannot be certainty of finding a living donor for a patient regardless of how early they are referred. This implicitly means that there is no additional benefit in being referred more than 16 months before a transplant needs to take place.

A pragmatic literature search was conducted to identify the best source of evidence to model the differences in long term outcomes between people receiving a living donor and a deceased donor transplant. Details of the search and study selection are outlined in section J.7.

The base-case analysis uses a hazard ratio of 0.83 (95% CI: 0.50, 1.40) for graft failure from living versus deceased donors, taken from Yohanna (2020) based in Cananda and a hazard ratio for mortality of 0.92 (95% CI: 0.58, 1.45), taken from the same study. Alternative scenarios explored a hazard ratio for graft failure of 1 (section J.2.7.5), and a hazard ratio of 0.70 (95% CI: 0.66, 0.73) taken from pooling the hazard ratios for age groups reported in Molnar 2012 (section J.2.7.4) based on eight European countries (Austria, Spain, Denmark, Finland, The Netherlands, Norway, Sweden, UK) .

Table 44 Effects of earlier referral to secondary care on transplant outcomes

Parameter	Value	PSA distribution	Source
Proportion of pre-emptive transplants coming from living donors if a person is referred to secondary care 12 months before transplant	74.5%	Beta (53.94, 19.41)	Annual report on kidney transplantation 2018/19
Proportion of all transplants coming from living donors	29%	Beta (1015, 2447)	UK Renal Registry 22nd Annual Report
Increase (decrease) in proportion of pre-emptive transplants coming from living donors for each month earlier (later) a person is referred to secondary care	3.88%	N/A - derived from proportion of pre-emptive transplants from living donors and proportion of all transplants from living donors, and therefore will update as those values change	Estimated based on data from Annual report on kidney transplantation 2018/19 and UK Renal Registry 22nd Annual Report
Hazard ratio for graft failure (living versus deceased donor)	0.83	Lognormal (-0.186, 0.069)	Yohanna (2020)
Hazard ratio for mortality (living versus deceased donor)	0.92	Lognormal (-0.083, 0.055)	Yohanna (2020)

J.2.4.3 Combining natural history and effects of referral time

To generate transition probabilities for the Markov models described in section J.2.4, the natural history data from section J.2.4.1 need to be combined with the relative effect data in section J.2.4.2. Beginning with mortality data for people aged <50 at pre-emptive transplant

(shown in Table 45), the cumulative hazard H(t) each year is calculated from the survival probability S(t) in Table 38 as:

$$H(t) = -\ln [S(t)]$$

This hazard represents the average hazard in the mixed population of people receiving living donor and deceased donor transplant. We can estimate the cumulative hazard for living and deceased donors separately using the hazard ratio for mortality in living versus deceased donors HR_{LD}, and the proportion of people who receive a living $Prop_{LD}$ versus deceased $Prop_{DD}$ donor transplant as follows:

$$H_{DD}(t) = H(t)/(Prop_{DD} + Prop_{LD} * HR_{LD})$$

$$H_{LD} = H_{DD} * HR_{LD}$$

These hazards can then be converted to 1-year transition probabilities (T) for year x as follows:

$$T(x) = 1 - \exp [H(x) - H(x-1)]$$

Finally, these 1-year transition probabilities are converted to 3-month (the cycle length of the model) transition probabilities (T') as follows, assuming that within a given year, the probability of death is the same of each 3-month cycle.

$$T'(x) = 1 - \exp \left(\frac{\ln [T(x)]}{4}\right)$$

Table 45 Mortality rates per cycle for people aged <50 at pre-emptive transplant

	Cumulative hazard (full population)	Cumulative hazard (living donor)	Probability of death per 3-month cycle (living donor)	Cumulative hazard (deceased donor)	Probability of death per 3-month cycle (deceased donor)
Start	0	0		0	
Year 1	0.00655	0.00641	0.00160	0.00697	0.00174
Year 2	0.01156	0.01131	0.00122	0.01229	0.00133
Year 3	0.01799	0.01760	0.00157	0.01913	0.00171
Year 4	0.02230	0.02181	0.00105	0.02371	0.00114
Year 5	0.02665	0.02607	0.00106	0.02834	0.00116
Year 6	0.03237	0.03167	0.00140	0.03442	0.00152
Year 7	0.04046	0.03958	0.00198	0.04302	0.00215
Year 8	0.05062	0.04952	0.00248	0.05383	0.00270
Year 9	0.06010	0.05880	0.00232	0.06391	0.00252
Year 10	0.07135	0.06980	0.00275	0.07587	0.00299

Similar calculations are performed for people aged 50-64 and 65+ at pre-emptive transplant (applying the same hazard ratios to the different baseline rates for each age group), with the results given in Table 46 and Table 47, respectively. For all age groups, mortality rates for years 11 and onwards are assumed to be the same as in year 10. In order to avoid this method potentially producing unrealistically low mortality rates as people age, data on all-cause age and sex-specific mortality were also taken from the Office for National Statistics, and each person's mortality was set as the maximum of either the mortality estimated from the UK Renal Registry data or all-cause mortality for their age and sex (thus, mortality can never be lower than average all-cause mortality).

Similar calculations are also performed to estimate graft failure rates for people receiving living and deceased donors in each of the age categories, with the results given in Table 48, Table 49 and Table 50. As with mortality, rates of graft failure in year 11 onwards were assumed to be the same as in year 10. The data on graft failure rates obtained from the UK Renal Registry were censored at death. Therefore, the probabilities estimated were only applied to the proportion of people alive at the end of each cycle in the model.

Table 46 Mortality rates per cycle for people aged 50-64 at pre-emptive transplant

	Cumulative hazard (full population)	Cumulative hazard (living donor)	Probability of death per 3-month cycle (living donor)	Cumulative hazard (deceased donor)	Probability of death per 3-month cycle (deceased donor)
Start	0	0		0	
Year 1	0.01624	0.01589	0.00396	0.01727	0.00431
Year 2	0.02739	0.02680	0.00272	0.02913	0.00296
Year 3	0.03707	0.03626	0.00236	0.03942	0.00257
Year 4	0.04837	0.04732	0.00276	0.05143	0.00300
Year 5	0.06924	0.06774	0.00509	0.07363	0.00553
Year 6	0.09250	0.09049	0.00567	0.09836	0.00616
Year 7	0.10830	0.10595	0.00386	0.11516	0.00419
Year 8	0.14572	0.14256	0.00911	0.15495	0.00990
Year 9	0.16743	0.16379	0.00529	0.17804	0.00575
Year 10	0.19629	0.19204	0.00704	0.20874	0.00765

Table 47 Mortality rates per cycle for people aged 65+ at pre-emptive transplant

	Cumulative hazard (full population)	Cumulative hazard (living donor)	Probability of death per 3-month cycle (living donor)	Cumulative hazard (deceased donor)	Probability of death per 3-month cycle (deceased donor)
Start	0	0		0	
Year 1	0.03893	0.38084	0.00948	0.04140	0.10295
Year 2	0.06925	0.06775	0.00739	0.07364	0.00803
Year 3	0.11364	0.11117	0.01080	0.12084	0.01173
Year 4	0.14827	0.14505	0.00843	0.15766	0.00916
Year 5	0.19372	0.18952	0.01105	0.20600	0.01201
Year 6	0.24677	0.24142	0.01289	0.26241	0.01401
Year 7	0.29303	0.86673	0.01125	0.31160	0.01222
Year 8	0.37160	0.36354	0.01903	0.13515	0.02067
Year 9	0.42489	0.41568	0.01295	0.45182	0.01407
Year 10	0.55163	0.53966	0.03052	0.58659	0.03313

Table 48 Graft failure rates per cycle for people aged <50 at pre-emptive transplant

	Cumulative hazard (full population)	Cumulative hazard (living donor)	Probability of graft failure per 3-month cycle (living donor)	Cumulative hazard (deceased donor)	Probability of graft failure per 3-month cycle (deceased donor)
Start	0	0		0	
Year 1	0.01661	0.01578	0.00394	0.19015	0.00474
Year 2	0.03212	0.03053	0.00368	0.03678	0.00443
Year 3	0.04831	0.04591	0.00384	0.05531	0.00462
Year 4	0.06249	0.05939	0.00336	0.07156	0.00405
Year 5	0.07845	0.07455	0.00378	0.08982	0.00456
Year 6	0.09613	0.09135	0.00419	0.11007	0.00505
Year 7	0.11254	0.10696	0.00389	0.12886	0.00469
Year 8	0.13132	0.12480	0.00445	0.15036	0.00536
Year 9	0.15132	0.14382	0.00474	0.17327	0.00571
Year 10	0.17359	0.16498	0.00528	0.19877	0.00635

Table 49 Graft failure rates per cycle for people aged 50-64 at pre-emptive transplant

	Cumulative hazard (full population)	Cumulative hazard (living donor)	Probability of graft failure per 3-month cycle (living donor)	Cumulative hazard (deceased donor)	Probability of graft failure per 3-month cycle (deceased donor)
Start	0	0		0	
Year 1	0.02195	0.02086	0.00520	0.02513	0.00626
Year 2	0.03404	0.03235	0.00287	0.03898	0.00346
Year 3	0.04016	0.03816	0.00145	0.04598	0.00175
Year 4	0.05448	0.05177	0.00340	0.06238	0.00409
Year 5	0.06737	0.06403	0.00306	0.07714	0.00368
Year 6	0.08083	0.07682	0.00319	0.09255	0.00385
Year 7	0.09466	0.08996	0.00328	0.10839	0.00395
Year 8	0.10651	0.10122	0.00281	0.12195	0.00338
Year 9	0.11512	0.10940	0.00204	0.13181	0.00246
Year 10	0.12418	0.11802	0.00215	0.14219	0.00259

Table 50 Graft failure rates per cycle for people aged 65+ at pre-emptive transplant

	Cumulative hazard (full population)	Cumulative hazard (living donor)	Probability of graft failure per 3-month cycle (living donor)	Cumulative hazard (deceased donor)	Probability of graft failure per 3-month cycle (deceased donor)
Start	0	0		0	
Year 1	0.18021	0.01713	0.00427	0.02063	0.00515
Year 2	0.02436	0.02316	0.00151	0.02790	0.00181
Year 3	0.03014	0.02864	0.00137	0.03451	0.00165
Year 4	0.04877	0.04635	0.00442	0.05584	0.00532

	Cumulative hazard (full population)	Cumulative hazard (living donor)	Probability of graft failure per 3-month cycle (living donor)	Cumulative hazard (deceased donor)	Probability of graft failure per 3-month cycle (deceased donor)
Year 5	0.06282	0.05970	0.00333	0.07193	0.00401
Year 6	0.07151	0.06796	0.00206	0.08188	0.00248
Year 7	0.09134	0.08680	0.00470	0.10458	0.00566
Year 8	0.09134	0.08680	0	0.10458	0
Year 9	0.11038	0.10491	0.00452	0.12639	0.00544
Year 10	0.14213	0.13507	0.00751	0.16274	0.00905

For people who have graft failure but survive, a proportion will have a second transplant, and a proportion will go on to dialysis, either permanently or until a second transplant is carried out. For simplicity in the modelling (and because the purpose of this analysis is not to compare different options for RRT), all people moving to the post graft failure state are assumed to receive a second transplant, and then their subsequent downstream outcomes (mortality and rates of further graft failure) are assumed to be the same as someone receiving a non-pre-emptive transplant (i.e. receiving a transplant after going on to dialysis). People in the post-graft failure state who have additional graft failures remain in that state, but receive the costs of graft failure for each subsequent event. These parameter values are the same as for people who receive a transplant post-dialysis and are given in section J.2.3.3

J.2.4.4 Parameters (costs)

Costs of transplantation were taken from NHS reference costs, averaging across all relevant costs (elective and non-elective, short- and long-stay). There is a single set of codes for the cost of living donor transplant, whilst the cost for deceased donor transplant was taken as the average of the cost of heart beating and non-heart beating donors, weighted by the number of each type of procedure.

People in the post-transplantation state incur the cost of ongoing immunosuppression. People were assumed to use immediate-release tacrolimus and mycophenolate mofetil, with average doses of 0.2 mg/kg/day for tacrolimus and 2g/day for mycophenolate mofetil taken from an HTA report (Jones-Hughes 2016). Some patients cannot tolerate this dose and mycophenolate mofetil is lowered to 1.5g/day. Other patients may have reasons that they cannot take tacrolimus and mycophenolate and therefore move onto either cheaper or more expensive alternative treatments. It was therefore agreed that using 0.2 mg/kg/day of tacrolimus and 2g/day of mycophenolate mofetil was an appropriate average to use in the model, even though not all patients would receive that exact regimen.

Costs for tacrolimus and mycophenolate mofetil were taken from the NHS drug tariff and weighted by usage data for each product and dose taken from the NHS Prescription Cost Analysis. Estimates of the cost per mg for tacrolimus are given in Table 51 whilst 2g/day of mycophenolate mofetil costs £0.55 (all products have the same cost in the drug tariff).

Table 51 Cost per mg for tacrolimus

Product	Cost per mg	Usage (items)
Prograf 0.5mg	2.48	17384
Prograf 1 mg	1.61	42783
Prograf 5 mg	1.19	1976
Adoport 0.5 mg	2.48	9586
Adoport 0.75 mg	1.38	418

Product	Cost per mg	Usage (items)
Adoport 1 mg	1.61	23803
Adoport 2 mg	1.11	4272
Adoport 5 mg	1.19	2409
Weighted average cost per mg	1.59	

Total costs of tacrolimus and mycophenolate mofetil were estimated for a three-month period (the cycle length of the model).

For people experiencing graft failure, it is assumed they receive an additional kidney transplant, which is costed as a weighted average of living and deceased transplant costs, using the proportion of transplants that are from living donors from the Renal Registry (29%). It is possible the costs for an additional transplant post-graft failure may differ from the costs of a primary transplant, depending on the reason for the graft failure, but no data was identified to estimate a different cost. People continue to receive the costs of the same immunosuppressive therapy following a second or subsequent transplant as following an initial transplant.

Table 52: Transplant inputs

Parameter	Value	PSA distribution	Source
Cost of kidney transplant (deceased donor)	£12,838		NHS reference costs 2018/19
Cost of kidney transplant (living donor)	£12,292		NHS reference costs 2018/19
Cost per 3 months of immunosuppressive therapy	£2,083		Costs from NHS drug tariff (Sep 2020); quantity for weighting from PCA (Mar 2019)

J.2.4.5 Parameters (quality of life)

Data on quality of life (reported using the EQ-5D-5L) for people receiving a transplant were taken from a recent UK study, which included 512 people who have received a transplant within the last 6 months (Li 2017). The average age of the population in the study was estimated as 51 years (data were only reported for age ranges) and the population was 40% female, and standard age adjustments (Kind 1999) were applied to that mean utility reported in the study when estimating utilities for an individual.

Whilst there are some studies that appear to show people with a living donor transplant may have a higher quality of life than people with a deceased donor transplant, the committee agreed not to include this in the model as they felt there was no strong hypothesis as to why people with a functioning living donor kidney should have a higher quality of life than people with a functioning deceased donor kidney. They also agreed that any differences found in observational data may simply represent differences between people who receive a living versus deceased donor transplant, rather than being a result of the different type of transplant itself. They also noted that although it is plausible quality of life would be lower for people on a second or further line transplant post graft-failure, there was no evidence to parameterise this and therefore the same utility was applied to people in the post-graft failure state.

Table 53: Transplant quality of life

Parameter	Value	PSA distribution	Source
Quality of life post-transplant	0.827	Beta (809.58, 169.36)	Li 2017

J.2.5 Summary of key assumptions

- Estimates of the predictive accuracy of the different referral rules are based entirely on the Major 2019 UK validation study, and therefore if that study is not representative of the UK population, the results of this model will similarly not be.
- The model assumes that the monitoring schedule recommended in the NICE CKD guideline is followed, as if it is not this will result in tests taking place at different times, and therefore estimates of referral time being inaccurate.
- The model assumes that eGFR and ACR progression for individuals can reasonably be approximated using average population declines. If the known between person heterogeneity in progression significantly affects either referral times or progression to ESRD, then this source of heterogeneity is not captured in the model.
- The model assumes the key benefits of early referral to nephrology are on improvements in outcomes after people enter ESRD. Benefits that may be accrued before end stage renal disease, delays to when ESRD is reached, and the possibility that more people may receive pre-emptive transplants rather than need to go on to dialysis if they are referred earlier, are all potential benefits of early referral not captured by the model.
- The model assumes that the benefit of early referral for people who go on to receive a pre-emptive transplant is moderated through the mechanism that a higher proportion of people referred earlier will receive a transplant from a living donor, and outcomes from living donor transplants are better than from deceased donor transplants.

J.2.6 Sensitivity analyses

J.2.6.1 Deterministic sensitivity analyses

A series of deterministic sensitivity analyses were run, looking at the impact on the results of varying individual parameters in the model. For parameters where 95% confidence intervals were available, the parameter was set to the upper and lower end of those confidence intervals. Where no such confidence interval was available, the committee specified plausible ranges over which the parameters were varied. For situations where multiple parameters feed into the same part of the model structure (e.g. ACR progression over time for people in different ACR categories, or post-dialysis mortality at different timepoints) these parameters were varied together in the same analysis. However, it should be noted when interpreting these results that setting multiple parameters all to the 95th percentile of a distribution will create an overall set of numbers that is more extreme than the 95th percentile (unless the outcomes are perfectly correlated).

The results of the deterministic sensitivity analyses are given in section J.3.4.1, together with the values tested for each parameter.

J.2.6.2 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was conducted, to quantify uncertainty in the true values of input parameters. Distributions are assigned to the parameter values in the model, and then a random value from each of these distributions is drawn for each of 2,000 iterations. Then, for each of these iterations, costs, QALYs and net-benefits are calculated for each strategy. This process allows uncertainty around model results to be characterised in terms of the

proportion of iterations in which each comparator provides the optimal balance of costs and QALYs at a particular threshold.

Except where differences are described below, standard distributions were used for the different data types in the model, and parameterised using data on uncertainty from the same primary sources as the parameters themselves (in the form of either standard deviations/errors or confidence intervals. Specifically, relative risks were parameterised used log-normal distributions, mean differences on a natural scale using normal distributions, probabilities (bounded between 0 and 1) using beta distributions, and utilities also using beta distributions (whilst not technically bounded at 0, it was agreed that for the population in this model, it was implausible average population utility values would be below 0).

The parameter for the proportion of pre-emptive transplants from living donors referrals 12 months before transplant (74.5%) was taken from the Annual report on kidney transplantation 2018/19 (Figures 5.8 and 5.9). The rates of deceased and living donor pre-emptive transplants reported do not total to 1, implying that the appropriate denominator for the rates is total number of all transplants (rather than pre-emptive transplants). Total number of transplants for centres are reported in Figure 5.3 of the report; these totals were used to estimate absolute numbers of living and deceased donor pre-emptive transplants. These values were used to inform the shape parameters for the beta distribution applied in the PSA, with the alpha parameter equalling the average number of living donor pre-emptive transplants (53.94) and the beta parameter equalling the average number of deceased donor pre-emptive transplants (19.41).

There are three sources of costs for the model, from NHS reference costs, from the Personal Social Services Research Unit (PSSRU, Curtis 2019) and the NHS drug tariff. None had standard deviations associated with them in the primary sources so each was assessed separately to see if and which distribution could be applied to it. For NHS reference costs there were multiple ways that a standard deviation could be found. It would be possible to assess the different trusts that have supplied the data to the NHS reference costs and calculate a standard deviation between them. However, NHS reference costs have not published that data this year and therefore the data from last year would have to be assessed. It was felt that while it is unlikely that there will be much difference from previous years, as different trusts supply different data each year last year's data would not necessarily be fully applicable to this year. As using this trust data would already be a proxy for the standard deviation, using last year's data would be adding more uncertainty into the analysis. Therefore, it was decided not to use trust data. Another option for the NHS reference costs would be to use data over time. It would be possible to take the past 5 years of data and take a standard deviation from that data. However again this would be a proxy for the standard deviation, and it was felt that a standard deviation over time would be different to the standard deviation required for this analysis. Therefore, it was decided not to add the NHS reference costs into the probabilistic sensitivity analysis. This was felt to be unlikely to be a major limitation, as that data should represent the true costs paid across a large number of individuals (and therefore only be subject to limited sampling uncertainty) and is in line with the approach taken in many economic evaluations.

The only value that was obtained from the PSSRU was the cost of a GP appointment. There was no standard deviation around the cost but there was a confidence interval around the duration of the appointment; this was (9.22,9.23) with a mean of 9.22. Therefore, there is little uncertainty around the length of a regular GP appointment. No evidence was discovered that stated there is a systematic difference in the length of a CKD GP appointment and therefore the regular GP appointment length was used. It was felt that given the small confidence interval varying the cost of GP appointments in the probabilistic sensitivity analysis would have no effect and therefore the deterministic sensitivity analysis would give a better indication of variation (as any meaningful differences would be likely to be due to systematic variation, and not sampling uncertainty).

The final set of cost inputs was the cost of immunosuppressive therapy drugs. There were limited options for getting a standard deviation for the drug costs. It was decided to exclude all the costs from the probabilistic sensitivity analysis and instead do a scenario analysis where all the costs were varied together. This scenario analysis is described in section J.2.7.6.

The individual population dataset used in the model was bootstrapped in each sample of the probabilistic sensitivity analysis. That is, a new set of patient data was created by sampling, with replacement, from the initial dataset. Thus, in each iteration, some individuals will not appear in the dataset, some will appear once (as in the base-case analysis) and some will appear multiple times. This has the effect of varying all the parameters derived from that individual person dataset (diagnostic accuracy of the referral rules, prevalence of ESRD, proportions of dialysis versus transplant etc.) whilst preserving the within-person correlations from the original dataset. It should be noted this has the effect of correctly accounting for sampling variability in the original dataset, but cannot adjust for bias caused if the original set of data was unrepresentative (as it can only resample from within the data that was collected).

Full distributions are given in the parameters tables in the sections above. Normal and log-normal distributions are parameterised as a mean and variance, whilst all other distributions have the standard interpretation.

J.2.7 Scenario analyses

J.2.7.1 eGFR and ACR non-decliners

There is considerable between person variability in eGFR trajectories over time. In the base-case analysis it is assumed that all individuals decline over time at the mean annual eGFR decline rate. In this sensitivity analysis a proportion of individuals were assumed not to decline in eGFR over time (40.5%; taken from a published individual patient data meta-analysis [Coresh 2014] with a two-year time horizon), and this was applied to individuals who do not go on to enter ESRD (individuals who will go on to develop ESRD are all assumed to decline). For individuals who do decline, a new and higher estimated eGFR decline was estimated, to ensure the mean decline remains the same across the full population. No similar data was available for the proportion of people who do not increase in ACR, so this was also set at the same value in this analysis.

J.2.7.2 Alternative threshold for what counts as early referral for dialysis

In the base-case analysis, early referral is taken as being referred to secondary care more than 6 months before the initiation of dialysis, as this is the earliest time frame for which there was data available in the Smart 2014 Cochrane review used to estimate the relative effects of early referral. In current UK practice the aim is actually to have people referred 1 year prior to initiation of dialysis, and therefore a sensitivity analysis was conducted using this as the threshold for early referral, and applying the relative effects to people referred more than 1 year before dialysis. Only one study from the update of the Smart Cochrane review (Selim) provided data on the impact of referral before/after one year, and that study only reported outcomes at 5 years, and therefore this analysis used the same relative risks as the analysis using a threshold of 6 months.

J.2.7.3 Including costs of dialysis

The base case analysis excludes the long-term costs of dialysis, in line with the approach taken both in previous NICE CKD guidelines, and in the NICE guideline on renal replacement therapy. It similarly excludes the costs associated with transplantation for people who have a transplant after having been on dialysis (although costs of pre-emptive transplantation are

included). In order to have an analysis matching the NICE reference case, a scenario analysis was conducted including the costs of dialysis and subsequent transplantation. See section J.2.3.4 for full details on how the costs of dialysis were estimated.

J.2.7.4 Alternative source for hazard ratio of graft failure and mortality rates

In the base case analysis, hazard ratios for graft failure and mortality were taken from Yohanna 2020, which was identified as the best available source for this data. An alternative data source (Molnar 2012) was also identified, which reported hazard ratios for graft failure and mortality across different age groups. Scenario analyses were run based on hazard ratios for graft failure (0.70) and mortality (0.68) pooled across age groups from that study.

J.2.7.5 Excluding outcomes for people with a pre-emptive transplant

The data linking referral times to outcomes is considerably less certain for pre-emptive transplants than for people who begin on dialysis. In particular, the hazard ratios for graft failure and mortality between living and deceased donors are not statistically significant in the paper chosen for the base-case analysis (Yohanna 2020), whilst the relative risks for mortality are significant in the analysis for early referral for dialysis. Therefore, a scenario analysis was conducted that assumes there are no differences in outcomes based on referral time for people who receive a pre-emptive transplant (this is done by setting the hazard ratios for both graft failure and mortality to 1). The model will thus give the same outcomes for people who receive a pre-emptive transplant, regardless of the time at which they are referred, and therefore the only differences in post-ESRD outcomes will be for people who initially receive dialysis.

J.2.7.6 Varying costs

It was decided not to include costs in the probabilistic sensitivity analysis (see section J.2.6.2), and so to assess the effect of costs on the result it was decided to do a scenario analysis varying all the cost parameters in the model simultaneously. After looking at all the deterministic sensitivity analyses for the costs, it was assessed if increasing or decreasing each cost item increases or decreases the difference between the two most cost-effective referral rules. Then, all the changes that increased the difference were included together in one analysis, and similarly all the changes that decreased the difference were included together. This should give the most extreme differences that can be attributed to changes in cost parameters alone.

J.3 Results

J.3.1 Baseline characteristics of sample

The full details of the sample in the Major 2019 paper are provided in the original publication. Briefly, the sample had a mean age of 75.9 years, was 57.5% female, with a mean baseline eGFR of 48.2 ml/min/1.73m^2, and a mean baseline ACR of 11.8 mg/mmol.

For the subsample used in this analysis (people known to have not previously been referred to secondary care nephrology services) the baseline characteristics were broadly similar, with a mean age of 76.1 years, 58.0% of the population being female, a mean baseline eGFR of 48.9 ml/min/1.73m^2, and a mean baseline ACR of 10.2 mg/mmol.

The Major study does not report details on the ethnicity of the participants in the study (these data are not needed for calculating the KFRE equations). However, for the four CCGs from which data was extracted, the overall profiles of those areas are:

- East Leicestershire and Rutland (90.6% white, 6.5% Asian, 0.6% black, 2.3% other)

- Leicester City (51.0% white, 35.7% Asian, 5.1% black, 8.2% other)
- Nene (90.4% white, 3.7% Asian, 2.4% black, 3.4% other)
- West Leicestershire (91.7% white, 5.2% Asian, 0.6% black, 2.5% other)
- Average across 4 included CCGs (82.0% white, 11.7% Asian, 2.3% black, 4.1% other)
- England overall (84.6% white, 7.6% Asian, 3.2% black, 4.7% other)
- Renal Registry, England (74.8% white, 13.0% Asian, 7.5% black, 4.7% other, 5.4 missing)

Ethnicity data for CCGs were taken from a 2018 NHS audit on health inequalities.

J.3.2 Predictive accuracy

Table 54 contains data on predictive accuracy for each of the 4 referral rules. The four accuracy metrics reported are:

- Sensitivity – the probability that a person who will go into ESRD within 5 years is referred at baseline using a given rule
- Specificity – the probability that a person who will not go into ESRD within 5 years is not referred at baseline using a given rule
- Positive predictive value – the probability that a person who is referred at baseline using a given rule will go into ESRD within 5 years
- Negative predictive value – the probability that a person who is not referred at baseline using a given rule will not go into ESRD within 5 years

These numbers match those reported in Major 2019, with the exception that in that paper, positive and negative predictive values are mislabelled as sensitivities and specificities. The table also reports the numbers of referrals, and the characteristics of those referred (age, sex, eGFR, ACR), as well as the number of people who will go into ESRD within 5 years who are not referred at baseline.

Table 54 Predictive accuracy data

Referral rule	2014 NICE criteria (eGFR <30 or ACR ≥ 70)	KFRE ≥3%	KFRE ≥5%	KFRE ≥15%	KFRE ≥5% or eGFR < 30	KFRE ≥5% or ACR ≥70
Sensitivity	53.9% (43.0, 64.6)	53.9% (43.0, 64.6)	47.2% (36.5, 58.1)	27.0% (18.1, 37.4)	47.2% (36.5, 58.1)	61.8% (50.9, 71.9)
Specificity	94.7% (94.3, 95.1)	93.4% (93.0, 93.8)	96.4% (96.1, 96.7)	99.2% (99.1, 99.4)	95.2% (94.8, 95.5)	95.0% (94.7, 95.4)
Positive predictive value	5.5% (4.1, 7.2)	4.4% (3.3, 5.8)	6.8% (5.0, 9.1)	16.7% (11.0, 23.8)	5.2% (3.8, 7.0)	6.6% (5.0, 8.5)
Negative predictive value	99.7% (99.6, 99.8)	99.7% (99.6, 99.8)	99.7% (99.6, 99.8)	99.6% (99.5, 99.7)	99.7% (99.6, 99.8)	99.8% (99.7, 99.8)
Number of referrals	879 (5.6%)	1,084 (6.9%)	615 (3.8%)	144 (0.9%)	803 (5.1%)	836 (5.3%)
No of people not referred who enter ESRD within 5 years	41 (46.1%)	41 (46.1%)	47 (52.8%)	62 (73.0%)	47 (52.8%)	34 (38.2%)
Mean age of referrals	76.3	76.3	75.2	70.3	77.3	73.8
Female referrals	58.4%	55.9%	54.3%	47.2%	59.4%	52.8%

Referral rule	2014 NICE criteria (eGFR <30 or ACR ≥ 70)	KFRE ≥3%	KFRE ≥5%	KFRE ≥15%	KFRE ≥5% or eGFR < 30	KFRE ≥5% or ACR ≥70
Mean eGFR of referrals (ml/min/1.73m^2)	32.7	30.5	27.7	21.6	27.5	34.0
Mean ACR of referrals (mg/mmol)	77.3	50.6	64.8	130.8	50.5	86.0

The 2014 NICE criteria are strictly better than the KFRE ≥3% referral rule, as less people are referred to secondary care without any additional cases of ESRD being missed. Conversely the 2014 NICE criteria are strictly worse than the hybrid rule of referring someone with a KFRE ≥5% or ACR ≥70, as the NICE criteria have both lower sensitivity and specificity (meaning more people will be referred using the NICE criteria, but more cases of ESRD will be missed). The KFRE ≥5% or ACR ≥70 criteria refer people who are, on average, younger, more likely to be male, and with higher mean eGFR and ACR than the 2014 NICE criteria.

J.3.3 Base-case cost–utility results

Base case analysis results are presented in Table 55. The results are total costs and QALYs for all the individuals in the dataset (remembering that QALYs are only included for people after progression to ESRD). Net-benefits are calculated at £20,000 per QALY, by multiplying the number of QALYs accrued by a strategy by 20,000, and then subtracting the costs of that strategy. The two best referral rules appear to be the 2014 NICE criteria and the composite of the KFRE at 5% or ACR > 70. It appears that the composite of the KFRE at 5% or ACR > 70 is better than the 2014 NICE criteria but only by a very small amount. The other referral rules were either not sensitive enough (meaning a large QALY loss from people referred late for dialysis) or not specific enough (meaning high costs of unnecessary referrals). For example, KFRE at 15% saves a considerable amount of money on monitoring costs compared to the other rules. However, it finds considerably less patients who will go on to ESRD, resulting in a loss of QALYs, and therefore the overall net benefit is lower.

Table 55 Base-case results

Strategy	Costs	QALYs	Net monetary benefit at £20,000 per QALY
2014 NICE criteria	£1,122,440	190.79	£2,693,328
KFRE ≥3%	£1,147,831	189.03	£2,632,856
KFRE ≥5%	£1,080,299	187.19	£2,663,485
KFRE ≥15%	£886,880	171.63	£2,545,646
KFRE ≥5% or eGFR < 30	£1,117,324	187.19	£2,626,460
KFRE ≥5% or ACR ≥70	£1,120,944	190.90	£2,697,108

Some preliminary testing was done on referral rules involving a composite of the KFRE at 3% and either ACR > 70 or eGFR <30. However, those rules both had poor specificities, leading to poor net-benefits (£2,621,121 and £2,643,704) for those two rules in the base-case, and therefore no further work was done on those rules, as they were worse than the equivalent strategy using a KFRE threshold of 5%.

Table 56 shows a breakdown of the costs for the different referral rules. As would be expected, more specific referral strategies are associated with lower monitoring costs, whilst more sensitive strategies are associated with lower hospitalisation costs for dialysis initiation, as less people are referred late and therefore accrue those additional costs. Costs associated with pre-emptive transplants are relatively similar for the two groups, as the model only predicts small differences in outcomes for people receiving pre-emptive transplants (differences in downstream consequences are much more significant for people on dialysis).

Table 56 Cost breakdown for base-case results

Strategy	Monitoring and referral	Additional costs of hospitalisation at dialysis initiation for people referred late	Cost of pre-emptive transplants (including immunosuppressants and costs of managing graft failure)
2014 NICE criteria	£657,666	£7,004	£457,770
KFRE ≥3%	£675,573	£13,745	£458,513
KFRE ≥5%	£601,191	£20,470	£458,638
KFRE ≥15%	£351,149	£77,836	£457,895

Strategy	Monitoring and referral	Additional costs of hospitalisation at dialysis initiation for people referred late	Cost of pre-emptive transplants (including immunosuppressants and costs of managing graft failure)
KFRE ≥5% or eGFR < 30	£638,216	£20,470	£458,638
KFRE ≥5% or ACR ≥70	£655,427	£7,004	£458,513

J.3.4 Sensitivity analysis

J.3.4.1 Deterministic sensitivity analyses

The results of the deterministic sensitivity analyses undertaken are presented in Table 57. All results are presented as net monetary benefits for the strategies at £20,000 per QALY. In the base-case analysis, the 2014 NICE criteria come out as the second most cost-effective strategy, after the composite of the KFRE at 5% and ACR ≥70. Results are highlighted in red in the table below if this pattern of which two strategies are best changes in any given analysis.

For the majority of parameters changing the values do not make a difference to the results, meaning the results are robust to parameter uncertainty. The top two strategies stay as "KFRE ≥5% or ACR ≥70" and the 2014 NICE criteria. The parameter changes which do make a difference to the conclusions of the model are:

- Setting the average rates of eGFR decline to the upper end of the 95% confidence interval causes the 2014 NICE criteria to become the most cost-effective strategy, with the "KFRE ≥5% or ACR ≥70" becoming the 2nd most cost-effective. This is perhaps unsurprising, since one would expect that if eGFR rates are declining significantly faster, a strategy that involves an eGFR cut-off is likely to become more effective. It should also be noted that the recommendations already contain advice for people who are rapidly declining in eGFR (defined as a sustained decrease in GFR of 25% or more, and a change in GFR category or sustained decrease in GFR of 15 ml/min/1.73 m^2 or more within 12 months), and therefore this population should be captured, whatever other referral rules are used.
- Setting the mortality hazard ratio for living donor versus deceased donor transplants to the upper end of the 95% confidence interval also causes the 2014 NICE criteria to become the most cost-effective strategy, with the "KFRE ≥5% or ACR ≥70" becoming the 2nd most cost-effective. However, this would imply that getting a deceased donor kidney leads to better outcomes that getting a living donor kidney, which the committee did not believe was plausible. They therefore agreed the uncertainty around pre-emptive transplants was dealt with better in the scenario analysis that exclude all differences between strategies for people receiving pre-emptive transplants (see section J.3.4.3).
- Setting the three relative risks for dialysis mortality to the upper end of the 95% confidence interval of the relative risk of dialysis mortality showed that KFRE ≥15% was the best referral rule. Thus, if there are considerably smaller benefits from early referral for dialysis than estimated in this model, then using the most specific referral rule becomes the best option, as sensitivity becomes more important than sensitivity. As noted in section J.2.6.1, this analysis involves setting three parameters to the upper end of their 95% confidence intervals, and therefore represents an analysis more extreme than the 95th percentile of our uncertainty in these parameters.

Table 57 Deterministic sensitivity analyses

Parameter	Value used	2014 NICE criteria	KFRE ≥3%	KFRE ≥5%	KFRE ≥15%	KFRE ≥5% or eGFR < 30	KFRE ≥5% or ACR ≥70
Cost GP monitoring (25% decrease)	£24.89	£2,748,205	£2,686,808	£2,720,091	£2,609,439	£2,681,700	£2,752,050
Cost GP monitoring (25% increase)	£41.49	£2,638,452	£2,578,903	£2,606,878	£2,481,852	£2,571,219	£2,642,166
Cost of first secondary care assessment (25% decrease)	£164.72	£2,751,814	£2,692,313	£2,714,416	£2,561,339	£2,681,464	£2,755,284
Cost of first secondary care assessment (25% increase)	£274.54	£2,634,842	£2,573,399	£2,612,553	£2,529,952	£2,571,455	£2,638,933
Cost of secondary care monitoring (25% decrease)	£119.38	£2,744,398	£2,688,355	£2,706,262	£2,553,964	£2,675,785	£2,747,863
Cost of secondary care monitoring (25% increase)	£198.96	£2,642,258	£2,577,356	£2,620,708	£2,537,327	£2,577,134	£2,646,353
Proportion of monitoring in secondary care after initial referral (Committee specified lower limit)	10%	£2,774,175	£2,720,715	£2,731,203	£2,558,815	£2,704,545	£2,777,457
Proportion of monitoring in secondary care after initial referral (Committee specified upper limit)	30%	£2,612,481	£2,544,997	£2,595,766	£2,532,476	£2,548,374	£2,616,759
Annual eGFR decline (lower limit of 95% CI)	2.000	£2,671,881	£2,611,301	£2,628,310	£2,550,315	£2,600,907	£2,670,341

Parameter	Value used	2014 NICE criteria	KFRE ≥3%	KFRE ≥5%	KFRE ≥15%	KFRE ≥5% or eGFR < 30	KFRE ≥5% or ACR ≥70
Annual eGFR decline (upper limit of 95% CI)	0.288	£2,713,727	£2,634,983	£2,650,270	£2,601,427	£2,600,089	£2,736,650
Annual ACR increase (lower limit of 95% CI)	1.263 (ACR<30) 1.429 (ACR ≥ 30)	£2,697,090	£2,636,381	£2,668,846	£2,553,892	£2,630,880	£2,701,046
Annual ACR increase (upper limit of 95% CI)	1.313 (ACR<30) 1.488 (ACR ≥ 30)	£2,689,949	£2,628,801	£2,658,382	£2,539,005	£2,622,802	£2,692,563
Mortality HR for living transplants (lower limit of 95% CI)	0.582	£2,690,675	£2,636,201	£2,663,567	£2,539,730	£2,636,542	£2,700,453
Mortality HR for living transplants (upper limit of 95% CI)	1.456	£2,695,954	£2,630,222	£2,663,483	£2,550,904	£2,626,458	£2,694,474
Graft failure HR for living transplants (lower limit of 95% CI)	0.496	£2,693,968	£2,634,074	£2,663,438	£2,545,021	£2,626,413	£2,968,326
Graft failure HR for living transplants (upper limit of 95% CI)	1.390	£2,692,985	£2,632,013	£2,663,816	£2,546,476	£2,626,791	£2,696,266
Cost of transplant (25% decrease)	£9,219 (living donor) £9,629 (deceased donor)	£2,704,833	£2,644,229	£2,675,036	£2,557,328	£2,638,011	£2,708,481
Cost of transplant (25% increase)	£15,365 (living donor) £16,048 (deceased donor)	£2,681,822	£2,621,482	£2,621,932	£2,533,961	£2,614,907	£2,685,734
Cost of immunosuppressive therapy (25% decrease)	£1,562	£2,796,315	£2,736,160	£2,766,642	£2,648,485	£2,729,617	£2,800,412
Cost of immunosuppressive therapy (25% increase)	£2,603	£2,590,539	£2,529,750	£2,560,525	£2,443,003	£2,523,500	£2,594,002

Parameter	Value used	2014 NICE criteria	KFRE ≥3%	KFRE ≥5%	KFRE ≥15%	KFRE ≥5% or eGFR < 30	KFRE ≥5% or ACR ≥70
Quality of life on transplant (lower limit of 95% CI)	0.803	£2,609,842	£2,550,032	£2,581,463	£2,468,456	£2,544,438	£2,613,548
Quality of life on transplant (upper limit of 95% CI)	0.850	£2,773,336	£2,712,229	£2,742,088	£2,619,619	£2,705,063	£2,777,186
Relative risk of dialysis mortality (lower limit of 95% CI)	0.2908 (3 months) 0.4540 (1 year) 0.5391 (5 years)	£2,783,154	£2,701,888	£2,712,853	£2,419,381	£2,675,828	£2,786,934
Relative risk of dialysis mortality (upper limit of 95% CI)	0.7597 (3 months) 0.6286 (1 year) 0.8572 (5 years)	£2,607,971	£2,567,531	£2,617,185	£2,666,771	£2,580,160	£2,611,751
Extra length of stay at dialysis initiation (lower limit of 95% CI)	5.523	£2,696,638	£2,639,350	£2,673,156	£2,582,423	£2,636,131	£2,700,418
Extra length of stay at dialysis initiation (upper limit of 95% CI)	15.417	£2,690,019	£2,626,361	£2,653,813	£2,508,869	£2,616,788	£2,693,799
Cost excess bed day (25% decrease)	£254.57	£2,695,079	£2,636,292	£2,668,602	£2,565,105	£2,631,577	£2,698,859
Cost excess bed day (25% increase)	£424.29	£2,691,577	£2,629,419	£2,658,367	£2,526,186	£2,621,342	£2,695,357
Quality of life on dialysis (lower limit of 95% CI)	0.514	£2,582,699	£2,523,674	£2,555,311	£2,453,502	£2,518,286	£2,586,479
Quality of life on dialysis (upper limit of 95% CI)	0.616	£2,803,958	£2,742,038	£2,771,658	£2,637,789	£2,734,633	£2,807,737

J.3.4.2 Probabilistic sensitivity analysis

Results from the PSA where all uncertainty described in section J.2.6.2 are included are given in Table 58. Mean costs, QALYs and NMBs are calculated by averaging each of these metrics across the 2,000 simulations of the PSA. The mean NMBs calculated here are very similar (both in magnitude and ranking) to the base-case results in section J.3.3. The "KFRE ≥5% or ACR ≥70" rule has an approximately 50% probability of being the most cost-effective, with non-negligible probabilities for the 2014 NICE criteria, the ""KFRE ≥5%" rule and the "KFRE ≥15%" rule.

Table 58 Main PSA results (including pre-emptive transplant)

Strategy	Mean costs	Mean QALYs	Net monetary benefit at £20,000 per QALY	Probability most cost-effective at £20,000 per QALY
2014 NICE criteria	£1,110,120	188.48	£2,693,328	22.0%
KFRE ≥3%	£1,140,943	186.88	£2,632,856	0%
KFRE ≥5%	£1,070,469	184.58	£2,663,485	14.6%
KFRE ≥15%	£873,057	169.89	£2,545,646	13.7%
KFRE ≥5% or eGFR < 30	£1,107,924	184.58	£2,626,460	0%
KFRE ≥5% or ACR ≥70	£1,112,187	188.77	£2,697,108	49.7%

The situation where the "KFRE ≥15%" rule comes out as most cost-effective will be those where there is less additional benefit from earlier referral for dialysis, and therefore the additional monitoring costs to identify these people are not justified. These situations are likely to be either where the relative risks for post-dialysis mortality are less favourable for early referral, or where the overall prevalence of ESRD is lower, and therefore there are less people who will benefit from early referral.

Two of the three remaining rules both use the KFRE at a threshold of 5%. Whether or not also using ACR greater than 70 as part of that rule is something that is hard for this model to assess. This is because in practice the rule used is to refer people who have an ACR at less 70, unless this is known to be caused by diabetes and already appropriately treated. The model does not have data on whether an individual has well treated diabetes, and therefore can only simulate a hard cut-off of 70 in ACR, without this distinction.

The two rules which both include using the KFRE at a threshold of 5% have a combined probability of 64.3% of being the most cost-effective option, compared to 22.0% for the 2014 NICE criteria. Therefore, this analysis would consider it to be three times more likely that the KFRE are the optimal approach than the 2014 NICE criteria.

J.3.4.3 Scenario analyses

The results of the scenario analyses undertaken are presented in Table 60. For three of the analyses (including a proportion of people who do not decline in eGFR, using the hazard ratios from Molnar 2012 for pre-emptive transplant outcomes, and excluding the outcomes for pre-emptive transplant) the conclusions did not change from the base-case analysis.

Include costs of dialysis and subsequent transplants When costs of dialysis (and post-dialysis transplantation) were included in the model the KFRE ≥15% was the best referral rule. This is an unsurprising finding, since because dialysis is itself not a cost-effective intervention based on the standard NICE criteria, including these costs means any other

choices that lead to more people being alive on dialysis will also not be cost-effective. Therefore, in this case, the KFRE ≥15% is benefiting from having a low sensitivity, as people then do not survive for as long on dialysis (as more are referred late) and therefore lower costs are incurred. The committee agreed it was appropriate to ignore the results of this analysis, as it is clear society/the health care system has made a choice it is appropriate to pay for dialysis, and therefore the results of other analyses should reflect that decision, which this sensitivity analysis does not.

Changing the definition of early referral to 1 year

When the definition of early referral was changed to one year, the "KFRE ≥5% or ACR ≥70" referral rule remained the most cost-effective, but "KFRE ≥5%" was now the second most cost-effective rule, with a larger gap before the 2014 NICE criteria, which are now only the third best referral rule. The committee noted that the data on benefits of early referral, based on the Smart 2014 Cochrane, had an upper limit of six months as the definition of early referral, and therefore they could not be confident how much further benefit would occur using a threshold of one year, and therefore the results of this analysis were not robust. However, they noted this analysis demonstrated an important finding from the model.

At the start of the model, considerably more people were correctly identified as progressing to ESRD over five years using the "KFRE ≥5% or ACR ≥70" than the 2014 NICE criteria with a sensitivity of 62% compared to 54% (thus 8% more people are correctly identified). One year before people enter ESRD there is still a significant proportion of people who the model predicts will be identified using the "KFRE ≥5% or ACR ≥70" but not using the 2014 NICE criteria, hence why the analysis using a threshold of one year for early referral shows significant benefits from using the KFRE criteria. However, by 6 months before people enter ESRD the same number of people are identified using both rules (presumably because close to the time of kidney failure, an eGFR based cut-off will become increasingly predictive). Therefore, the earlier it is felt to be important to identify people in advance of entering ESRD, the more value will be provided by using the equations. The committee noted that whilst there was not data available to this analysis specific to a threshold of 1 year for early referral, this was the time horizon recommended by the NICE renal replacement therapy guideline, and therefore a rule that identified people before that threshold would make it easier to fulfil the recommendations in that guideline.

Cost scenario analysis

Due to it not being feasible to vary costs in the probabilistic sensitivity analysis scenario analyses varying all the cost parameters simultaneously was done (see section J.2.7.6). For each of the costs the direction of change that led to the largest difference between the NICE criteria and the "KFRE ≥5% or ACR ≥70" rule in net-benefit was identified and then a version of the model was run setting all cost parameters to that value (and a similar analysis was also performed moving all costs in the opposite direction).

To find the largest possible difference between the NICE criteria and the "KFRE ≥5% or ACR ≥70" rule the cost of first secondary care assessment, cost of secondary care monitoring and the cost of transplant needed to be increased and the cost of GP monitoring, cost of immunosuppressive therapy and cost of excess bed days decreased. Thus, in the line with the deterministic sensitivity analyses, the values used were:

Table 59: Cost scenario analysis, inputs (largest difference)

Largest Difference	
Parameter	**Value**
Cost of GP monitoring	£24.89
Cost of first secondary care assessment	£274.54
Cost of secondary care monitoring	£198.96

Largest Difference	
Parameter	**Value**
Cost of transplant	£15,365 (Living donor) £16047.50 (deceased donor)
Cost of immunosuppressive therapy	£1,562.25
Cost of excess bed day	£254.57
Smallest Difference	
Cost of GP monitoring	£41.49
Cost of first secondary care assessment	£164.72
Cost of secondary care monitoring	£119.38
Cost of transplant	£9,219 (Living donor) £9628.50 (deceased donor)
Cost of immunosuppressive therapy	£2,603.75
Cost of excess bed day	£424.29

When changing all these parameters the “KFRE ≥5% or ACR ≥70” rule still came out as the most cost-effective option, £4,920 ahead of the current NICE criteria in mean net monetary benefit at £20,000/QALY.

To find the smallest possible difference between the NICE criteria and the “KFRE ≥5% or ACR ≥70” rule the cost of first secondary care assessment, cost of secondary care monitoring and the cost of transplant were decreased, and the cost of GP monitoring, cost of immunosuppressive therapy and cost of excess bed days increased. Thus, the values used were:

Similarly to changing the parameters in Table 59, changing the parameters to find the smallest difference found that the “KFRE ≥5% or ACR ≥70” rule was still the preferred referral method, and £2,640 ahead of the current NICE criteria in mean net monetary benefit at £20,000/QALY.

This showed that the model is not very sensitive to changing costs and therefore there is more confidence in the result that KFRE ≥5% or ACR ≥70 is a more precise referral rule than the current NICE criteria.

Table 60 Scenario analyses

Parameter	2014 NICE criteria	KFRE ≥3%	KFRE ≥5%	KFRE ≥15%	KFRE ≥5% or eGFR < 30	KFRE ≥5% or ACR ≥70
Including a proportion of people who do not decline in eGFR	£2,719,124	£2,655,516	£2,691,852	£2,655,795	£2,649,184	£2,725,983
Changing the definition of early referral to 1 year	£2,624,832	£2,569,390	£2,642,474	£2,545,646	£2,605,449	£2,653,070
Include costs of dialysis and subsequent transplants	-£2,077,454	-£2,076,288	-£1,997,852	-£1,500,707	-£2,034,877	-£2,073,674
Using Molnar for transplant HRs	£2,691,813	£2,635,392	£2,663,548	£2,541,657	£2,626,523	£2,699,645
Excluding outcomes for pre-emptive transplants	£2,693,695	£2,631,989	£2,663,603	£2,546,998	£2,626,578	£2,696,242

J.4 Discussion

J.4.1 Principal findings

The model consistently found that the best two referral rules were “KFRE ≥5% or ACR ≥70” and the 2014 NICE criteria. All other referral rules tested were less cost-effective than these two rules. This was because they either had too low a sensitivity, meaning that more patients who will need RRT are not identified and therefore not referred which means the opportunity to prepare for RRT is missed, or too low a specificity, leading to increase monitoring costs from unnecessary referrals to secondary care.

The “KFRE ≥5% or ACR ≥70” referral rule came out as more cost-effective than the 2014 NICE criteria, but only by a small margin in the base-case analysis. The earlier it is deemed important to identify people in advance of RRT, the more advantage the KFRE based rule has over the 2014 NICE criteria. For example, the margin is larger if 1 year is used as the cut-off for a sufficiently early referral, rather than 6 months.

J.4.2 Strengths and limitations of the analysis

The majority of the sensitivity analyses found that the best referral rule was “KFRE ≥5% or ACR ≥70”. The model was relatively robust to both parameter uncertainty and many of the scenario analyses tested, meaning that we are confident the “KFRE ≥5% or ACR ≥70” provides benefits over the 2014 NICE criteria, even if the magnitude of those benefits is small.

The analysis is based predominantly around the Major 2019 UK validation study of the KFRE equations. This is the only UK validations study for the equations, and therefore there is no second set of data on predictive accuracy to which these results can be compared. Therefore, if the results in the Major study are in some way unrepresentative of England as a whole, that will not be appropriately captured in the analysis.

A second issue with the analysis is the Major stuudy was taken as a cross-section of data at a single point of time, which does not represent what happens in the real world. In the real world a patient would be assessed by the referral rule at each monitoring appointments; meaning that if a patient is not referred at a single appointment then they might get referred at the next one. Whilst the model does simulate eGFR and ACR progression over time in an attempt to address this issue, these simulated data will necessarily be at higher risk of error than if longitudinal data had been available for the individuals in the Major study.

The impact of early referral on post-dialysis outcomes was based on a meta-analysis of cohort studies. Whilst considered effort was made in the Cochrane review used as this basis for this analysis to assess the potential for selection bias, and no evidence for it was found, there is still necessarily more uncertainty in these data than would be the case for equivalent results from randomised controlled trials. Additionally, since data were only available on the impact of referral on post-dialysis outcomes, this means the model is not able to account for differences that occur before renal replacement is necessary. For example, it is possible that earlier referral may either delay the onset of kidney failure or enable more people to receive pre-emptive transplants rather than go on to dialysis at all. These potential additional benefits of earlier referral are not currently possible to capture in the analysis.

In May 2020, the organ donation rules in England changed to be an ‘Opt out’ system rather than an ‘Opt in’ system (Organ Donation 2020). This means that patients who have not stated a preference on organ donation are assumed to be willing to donate their organs. This was introduced to increase the number of available organs for patients who require a new

organ. However, as this new system has been introduced recently there is no data on the real-world changes to the number of available organs. This meant that the data used in the model was based on the previous organ donation rules. However, with the new rules the number of available organs will only increase not decrease and therefore the values in the model are a lower bound of available organs. With more kidneys available more patients are likely to be able to have a transplant and not have to go onto dialysis. It will be a few years before sufficient data is available to estimate the impact these changes may have on practice, and therefore how they may affect the most appropriate referral rules to use.

J.4.3 Comparison with other CUAs

The KFRE are new equations that have not existed long enough for there to be other cost-effectiveness analyses that have been conducted using them. Therefore, it is not possible to compare the results obtained with any similar published work. Other studies that have attempted to assess the place for the KFRE in practice (such as Hingwala 2017 in Canada) have been restricted to looking at clinical outcomes and predictions and did not consider cost-effectiveness.

However, the approach this analysis has taken is similar as the NICE guideline on renal replacement therapy and conservative management (NG107) when assessing the comparative cost-effectiveness of different forms of haemodialysis. That analysis also used data from the UK Renal Registry to build a natural history model, to which relative effects were then applied.

J.4.4 Conclusions

Using the “KFRE ≥5% or ACR ≥70” is the most cost-effective referral rule for identifying patients at risk of end stage renal disease over the next 5 years, and who will benefit from referral to secondary care. However, the benefits of using this referral rule are only modest, compared to using the criteria from the 2014 NICE guideline.

J.5 References

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Kim, Do Hyoung; Kim, Myounghee; Kim, Ho; Kim, Yong-Lim; Kang, Shin-Wook; Yang, Chul Woo; Kim, Nam-Ho; Kim, Yon Su; Lee, Jung Pyo; Early referral to a nephrologist improved patient survival: prospective cohort study for end-stage renal disease in Korea.; PloS one; 2013; vol. 8 (no. 1); e55323

Kind P, Hardman G, Macran S. (1999) UK population norms for EQ-5D. CHE Discussion Paper 175, University of York, UK

Kumar, S.; Jeganathan, J.; Amruthesh; Timing of nephrology referral: Influence on mortality and morbidity in chronic kidney disease; Nephro-Urology Monthly; 2012; vol. 4 (no. 3); 578-581

Li B, Cairns JA, Draper H, Dudley C, MD, Forsythe JL, Johnson RJ, Metcalfe W, Oniscu GC, Ravanan R, Robb ML, Roderick P, Tomson CR, Watson CJE, Bradley JA (2017) Estimating Health-State Utility Values in Kidney Transplant Recipients and Waiting-List Patients Using the EQ-5D-5L 20(7): 976–984 doi: 10.1016/j.jval.2017.01.011

Liem YS, Bosch JL, Hunink MG. Preference-based quality of life of patients on renal replacement therapy: a systematic review and meta-analysis. Value Health. 2008;11(4):733-741. doi:10.1111/j.1524-4733.2007.00308.x

Major RW, Shepherd D, Medcalf JF, Xu G, Gray LJ, Brunskill NJ (2019) The Kidney Failure Risk Equation for prediction of end stage renal disease in UK primary care: An external validation and clinical impact projection cohort study. PLoS Med 16(11): e1002955.

Molnar M, Streja E, Kovesdy CP, Shah A, Huang E, Bunnapradist S, Krishnan M, Kopple JD, Kalantar-Zadeh K (2012) Age and the associations of living donor and expanded criteria donor kidneys with kidney transplant outcomes. Am J Kidney Dis; 59(6) :841-8. doi: 10.1053/j.ajkd.2011.12.014.

NHS Blood and Transplant (2019) Annual report on kidney transplantation. Accessed at: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16778/nhsbt-kidney-transplantation-annual-report-2018-19.pdf

NHS Digital (2019) Prescription Cost Analysis - England, 2018. Accessed at: https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/2018

NHS Improvement (2018) National schedule of reference costs 2017-18. Accessed at: https://improvement.nhs.uk/resources/reference-costs/

NHS Improvement (2019) National schedule of reference costs 2018-19. Accessed at: https://www.england.nhs.uk/national-cost-collection/#ncc1819

NICE (2007) Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy: https://www.nice.org.uk/guidance/ta117

Office for National Statistics (2019) National life tables: UK. Accessed at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables

Organ Donation (2020) Organ Donation Law in England. Accessed at: https://www.organdonation.nhs.uk/uk-laws/organ-donation-law-in-england/

Park, Ji In; Kim, Myounghee; Kim, Ho; An, Jung Nam; Lee, Jeonghwan; Yang, Seung Hee; Cho, Jang-Hee; Kim, Yong-Lim; Park, Ki-Soo; Oh, Yun Kyu; Lim, Chun Soo; Kim, Dong Ki; Kim, Yon Su; Lee, Jung Pyo; Not early referral but planned dialysis improves quality of life and depression in newly diagnosed end stage renal disease patients: a prospective cohort study in Korea.; PloS one; 2015; vol. 10 (no. 2); e0117582

Selim, Gjulsen; Stojceva-Taneva, Olivera; Spasovski, Goce; Tozija, Liljana; Grozdanovski, Risto; Georgievska-Ismail, Ljubica; Zafirova-Ivanovska, Beti; Dzekova, Pavlina; Trajceska, Lada; Gelev, Saso; Mladenovska, Daniela; Sikole, Aleksandar; Timing of nephrology referral and initiation of dialysis as predictors for survival in hemodialysis patients: 5-year follow-up analysis.; International urology and nephrology; 2015; vol. 47 (no. 1); 153-60

Smart NA, Dieberg G, Ladhani M, Titus T. Early referral to specialist nephrology services for preventing the progression to end-stage kidney disease. Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD007333. DOI: 10.1002/14651858.CD007333.pub2.

UK Renal Registry (2020) UK Renal Registry 22nd Annual Report – data to 31/12/2018, Bristol, UK. Available from https://www.renalreg.org/publications-reports/

Yanay, Noa Berar; Scherbakov, Lubov; Sachs, David; Peleg, Nana; Slovodkin, Yakov; Gershkovich, Regina; Effect of early nephrology referral on the mortality of dialysis patients in Israel.; The Israel Medical Association journal : IMAJ; 2014; vol. 16 (no. 8); 479-82

Yohanna S, Naylor K, McArthur E, Lam N, Austin P, Habbous S, McCallum M, Ordon M, Knoll G, Kim, J, Garg A (2020) A Propensity Score-weighted Comparison of Outcomes Between Living and Standard Criteria Deceased Donor Kidney Transplant Recipients. Transplantation: June Volume Online First. doi: 10.1097/TP.0000000000003337.

J.6 Appendix 1 – Cochrane review update

The Smart 2014 Cochrane review was identified as the best source of evidence for differences in dialysis outcomes for people referred early versus late in advance of needing dialysis (see section 107 for full details of how the review was used). The Cochrane review was published in 2014 and therefore it was important to update it with more recently published evidence.

J.6.1 Review details

The Cochrane review searched for papers up until 8th February 2012. Therefore, to update the search, a systematic search was carried out to identify papers published between 2012 and 2020, with 2993 papers being identified. These references were screened on their titles and abstracts. 59 full texted were obtained and reviewed, of which 8 studies were identified as being relevant and include in the final review.

The search strategy is below in Table 61 and Table 62, and the Prisma diagram showing the study selection is given in Figure 10.

Table 61 Databases searched

Databases	Date searched	Version/files	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	11th Jun 2020	Issue 6 of 12, June 2020	185
Cochrane Database of Systematic Reviews (CDSR)	11th Jun 2020	Issue 6 of 12, June 2020	0
Embase (Ovid)	11th Jun 2020	Embase <1974 to 2020 Week 23>	2436
MEDLINE (Ovid)	11th Jun 2020	Ovid MEDLINE(R) <1946 to June 09, 2020>	1011
MEDLINE In-Process (Ovid)	11th Jun 2020	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to June 09, 2020>	167
MEDLINE Epub Ahead of Print[b]	11th Jun 2020	Ovid MEDLINE(R) Epub Ahead of Print <June 09, 2020>	27

Table 62 Search strategies

Databases
Database: Ovid MEDLINE(R) <1946 to June 09, 2020> Search Strategy: --- 1 Kidney Diseases/ (83555) 2 Renal Insufficiency/ (15717) 3 exp Renal Insufficiency, Chronic/ (114250) 4 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (73932) 5 ((kidney* or renal*) adj1 insufficien*).tw. (21355) 6 ckd*.tw. (23699) 7 ((kidney* or renal*) adj1 fail*).tw. (86828) 8 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (35763) 9 (esrd* or eskd*).tw. (14489) 10 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3470) 11 exp Renal Dialysis/ (113200) 12 (haemodialys* or hemodialys* or dialys*).tw. (143369) 13 ((kidney* or renal*) adj1 replac*).tw. (11571) 14 (pre-dialys* or predialys*).tw. (4583) 15 or/1-14 (377773) 16 "Referral and Consultation"/ (66074) 17 (refer or referral* or referred).tw. (262291) 18 consult*.tw. (108100) 19 or/16-18 (385844) 20 15 and 19 (7081) 21 Cohort Studies/ (262259) 22 cohort.tw. (443724) 23 clinical trial.pt. (522637) 24 Evaluation Studies.pt. (0) 25 "Outcome Assessment (Health Care)"/ (72065) 26 Treatment Outcome/ (967809) 27 or/21-26 (1925539)

28 20 and 27 (1838)

29 (refer or referral* or referred).ti. (18432)

30 15 and 29 (487)

31 28 or 30 (2174)

32 limit 31 to ed=20120201-20200611 (1061)

33 limit 32 to english language (1015)

34 animals/ not humans/ (4672742)

35 33 not 34 (1011)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to June 09, 2020>

Search Strategy:

---

1 Kidney Diseases/ (0)

2 Renal Insufficiency/ (0)

3 exp Renal Insufficiency, Chronic/ (0)

4 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (9773)

5 ((kidney* or renal*) adj1 insufficien*).tw. (1151)

6 ckd*.tw. (4697)

7 ((kidney* or renal*) adj1 fail*).tw. (6560)

8 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (5019)

9 (esrd* or eskd*).tw. (2063)

10 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

11 exp Renal Dialysis/ (0)

12 (haemodialys* or hemodialys* or dialys*).tw. (12168)

13 ((kidney* or renal*) adj1 replac*).tw. (1956)

14 (pre-dialys* or predialys*).tw. (391)

15 or/1-14 (27136)

16 "Referral and Consultation"/ (0)

17 (refer or referral* or referred).tw. (43980)

18 consult*.tw. (15129)

19 or/16-18 (57464)

20 15 and 19 (923)

21 Cohort Studies/ (0)

22 cohort.tw. (72090)

23 clinical trial.pt. (429)

24 Evaluation Studies.pt. (26)

25 "Outcome Assessment (Health Care)"/ (0)

26 Treatment Outcome/ (0)

27 or/21-26 (72533)

28 20 and 27 (112)

29 (refer or referral* or referred).ti. (2854)

30 15 and 29 (67)

31 28 or 30 (167)

32 limit 31 to english language (167)

Database: Ovid MEDLINE(R) Epub Ahead of Print <June 09, 2020>

Search Strategy:

---

1 Kidney Diseases/ (0)

2 Renal Insufficiency/ (0)

3 exp Renal Insufficiency, Chronic/ (0)

4 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (1419)

5 ((kidney* or renal*) adj1 insufficien*).tw. (147)

6 ckd*.tw. (716)

7 ((kidney* or renal*) adj1 fail*).tw. (811)

8 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (746)

9 (esrd* or eskd*).tw. (313)

10 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

11 exp Renal Dialysis/ (0)

12 (haemodialys* or hemodialys* or dialys*).tw. (1789)

13 ((kidney* or renal*) adj1 replac*).tw. (323)

14 (pre-dialys* or predialys*).tw. (61)

15 or/1-14 (3966)

16 "Referral and Consultation"/ (0)

17 (refer or referral* or referred).tw. (6696)

18 consult*.tw. (2625)

19 or/16-18 (9046)

20 15 and 19 (131)

21 Cohort Studies/ (0)

22 cohort.tw. (17010)

23 clinical trial.pt. (24)

24 Evaluation Studies.pt. (0)

25 "Outcome Assessment (Health Care)"/ (0)

26 Treatment Outcome/ (0)

27 or/21-26 (17034)

28 20 and 27 (25)

29 (refer or referral* or referred).ti. (433)

30 15 and 29 (5)

31 28 or 30 (27)

32 limit 31 to english language (27)

Database: Embase <1974 to 2020 Week 23>

Search Strategy:

---

1 Kidney Disease/ (104350)

2 exp kidney failure/ (358754)

3 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (125835)

4 ((kidney* or renal*) adj1 insufficien*).tw. (30266)

5 ckd*.tw. (51469)

6 ((kidney* or renal*) adj1 fail*).tw. (133619)

7 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (59431)

8 (esrd* or eskd*).tw. (28045)

9 exp renal replacement therapy/ (186646)

10 exp dialysis/ (182725)

11 (haemodialys* or hemodialys* or dialys*).tw. (215672)

12 ((kidney* or renal*) adj1 replac*).tw. (22815)

13 (predialys* or pre-dialys*).tw. (7285)

14 or/1-13 (668696)

15 Patient Referral/ (112949)

16 Patient Scheduling/ (1267)

17 Consultation/ (108484)

18 (refer or referral* or referred).tw. (488802)

19 consult*.tw. (206592)

20 or/15-19 (735301)

21 14 and 20 (20328)

22 Cohort Analysis/ (585321)

23 Longitudinal Study/ (140217)

24 Prospective Study/ (605518)

25 Follow Up/ (1546729)

26 Evaluation/ (170422)

27 Treatment Outcome/ (846883)

28 Clinical Trial/ (976504)

29 cohort.tw. (910166)

30 or/22-29 (4253542)

31 21 and 30 (7025)

32 (refer or referral* or referred).ti. (32744)

33 14 and 32 (1134)

34 31 or 33 (7699)

35 limit 34 to dc=20120202-20200611 (5263)

36 limit 35 to english language (5183)

37 nonhuman/ not human/ (4632489)

38 36 not 37 (5148)

39 limit 38 to (conference abstract or conference paper or "conference review") (2709)

40 38 not 39 (2439)

Cochrane Library

#1 MeSH descriptor: [Kidney Diseases] this term only 3331

#2 MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees 6569

#3 MeSH descriptor: [Renal Insufficiency] this term only 1533

#4 (((chronic* or progressi*) near/1 (renal* or kidney*))):ti,ab,kw 10135

#5 (((kidney* or renal*) near/1 insufficien*)):ti,ab,kw 5345

#6 (ckd*):ti,ab,kw 4812

#7 (((kidney* or renal*) near/1 fail*)):ti,ab,kw 16040

#8 (((endstage* or end-stage* or "end stage*") near/1 (renal* or kidney*))):ti,ab,kw 4402

#9 ((esrd* or eskd*)):ti,ab,kw 2015

#10 MeSH descriptor: [Chronic Kidney Disease-Mineral and Bone Disorder] this term only 86

#11 MeSH descriptor: [Renal Replacement Therapy] explode all trees 8619

#12 (haemodialys* or hemodialys* or dialys* or predialys* or pre-dialys*):ti,ab,kw 17848

#13 ((kidney* or renal*) near/1 replac*):ti,ab,kw 2167

#14 {OR #1-#13} 38759

#15 MeSH descriptor: [Referral and Consultation] this term only 1813

#16 (refer or referral* or referred):TI,AB,KW 27589

#17 (consult*):TI,AB,KW 16999

#18 #15 or #16 or #17 40902

#19 #14 and #18 875

#20 (refer or referral* or referred):ti 1408

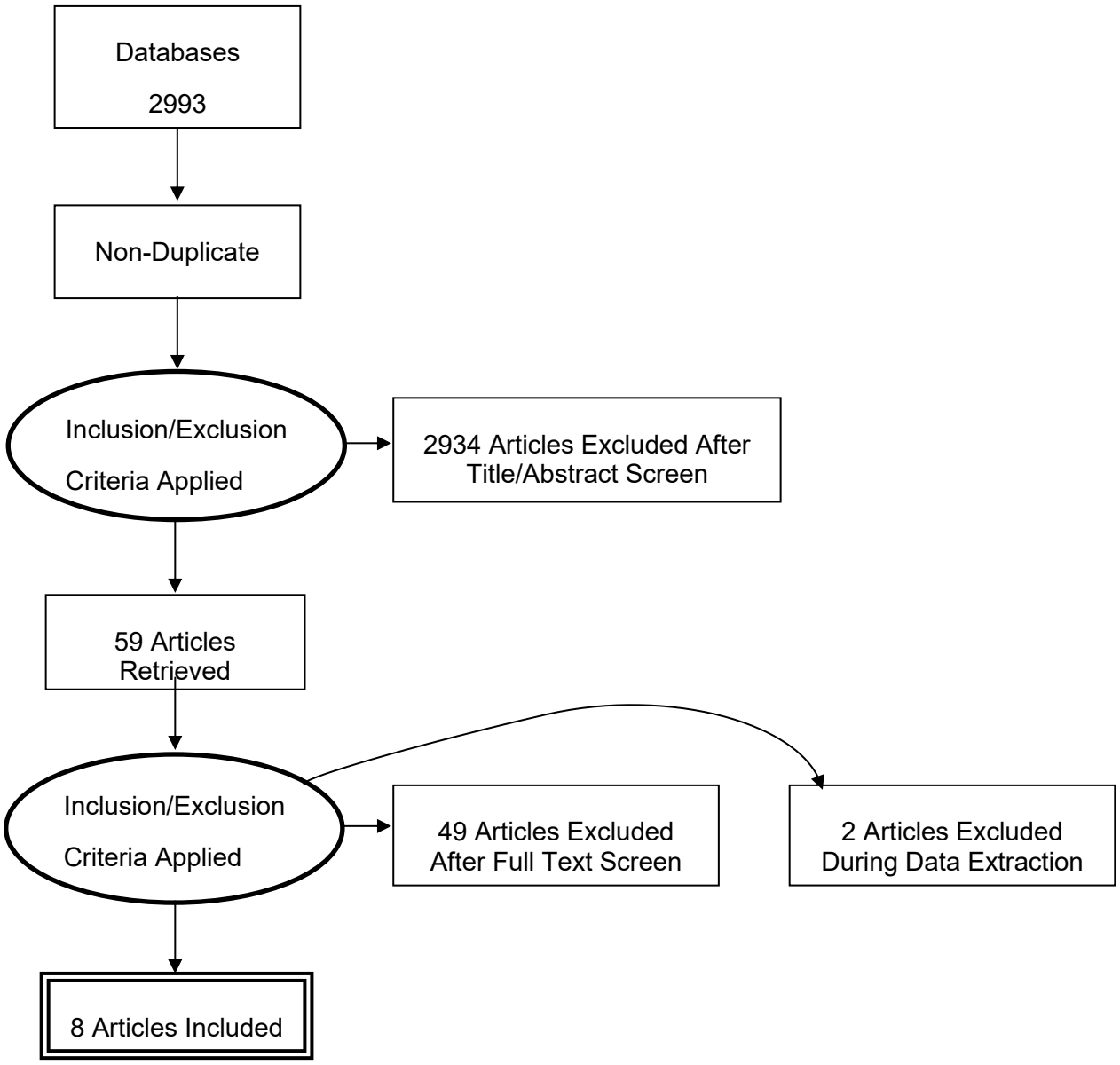
#21 #14 and #20 22

#22 #19 or #21 with Publication Year from 2012 to 2020, with Cochrane Library publication date Between Feb 2012 and Jun 2020, in Trials 550

#23 "conference":pt or (clinicaltrials or trialsearch):so 489248

#24 #22 not #23 185

Figure 10 PRISMA diagram



J.6.2 Excluded studies

See Table 63 for the list of excluded studies with reasons for exclusions.

Table 63: Excluded Studies

Study	Reason for exclusion
Akbari, Ayub, Grimshaw, Jeremy, Stacey, Dawn et al. (2012) Change in appropriate referrals to nephrologists after the introduction of automatic reporting of the estimated glomerular filtration rate. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 184(5): e269-76	- Study does not contain factors of interest
Alebiosu, C O (2001) Detrimental effects of late referral for dialysis. African journal of health sciences 8(12): 89-92	- Full text paper not available
Anees, Muhammad, Hussain, Yasir, Ibrahim, Muhammad et al. (2018) Outcome of Chronic	- Data not reported in an extractable format

Study	Reason for exclusion
Kidney Disease Patients on the Basis of Referral to Nephrologist: A One-Year Follow-up Study. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP 28(4): 304-307	
Anees, Muhammad, Mumtaz, Asim, Nazir, Muhammad et al. (2007) Referral pattern fof hemodialysis patients to nephrologists. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP 17(11): 671-4	- Full text paper not available
Auguste, Bourne L and Naimark, David M J (2017) Re: Timely Referral to Outpatient Nephrology Care Slows Progression and Reduces Treatment Costs of Chronic Kidney Diseases. Kidney international reports 2(4): 779	- Not a peer-reviewed publication
Baer, Gernot; Lameire, Norbert; Van Biesen, Wim (2010) Late referral of patients with end-stage renal disease: an in-depth review and suggestions for further actions. NDT plus 3(1): 17-27	- Review article but not a systematic review
Bahadi, A., El Farouki, M.R., Zajjari, Y. et al. (2017) Initiating hemodialysis in Morocco: Impact of late referral. Nephrologie et Therapeutique 13(7): 525-531	- Study not reported in English
Beaud, F.; Pruijm, M.; Peytremann-Bridevaux, I. (2015) Preterminal chronic renal failure: It is never too early to refer to the specialist. Revue Medicale Suisse 11(493): 2085	- Study not reported in English
Blunt, Ian; Bardsley, Martin; Strippoli, Giovanni F M (2015) Pre-dialysis hospital use and late referrals in incident dialysis patients in England: a retrospective cohort study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 30(1): 124-9	- Data not reported in an extractable format
Boudville, Neil; Muthucumarana, Kalindu; Inderjeeth, Charles (2012) Limited referral to nephrologists from a tertiary geriatric outpatient clinic despite a high prevalence of chronic kidney disease and anaemia. BMC geriatrics 12: 43	- Study does not contain factors of interest
Buttigieg, Jesmar, Mercieca, Liam, Saliba, Arielle et al. (2016) Chronic kidney disease referral practices among non-nephrology specialists: A single-centre experience. European journal of internal medicine 29: 93-7	- Study does not contain factors of interest
Campbell, Garland Adam and Bolton, Warren Kline (2011) Referral and comanagement of the patient with CKD. Advances in chronic kidney disease 18(6): 420-7	- Review article but not a systematic review
Campbell, Kellie H, Smith, Sandy G, Hemmerich, Joshua et al. (2011) Patient and provider determinants of nephrology referral in older adults with severe chronic kidney disease: a survey of provider decision making. BMC nephrology 12: 47	- Study does not contain factors of interest
Chambers, Shirley, Healy, Helen, Hoy, Wendy E et al. (2018) Health service utilisation during the last year of life: a prospective, longitudinal study of	- Study does not contain a relevant intervention

Study	Reason for exclusion
the pathways of patients with chronic kidney disease stages 3-5. BMC palliative care 17(1): 57	
Chen, Yun-Yi, Chen, Likwang, Huang, Jenq-Wen et al. (2019) Effects of Early Frequent Nephrology Care on Emergency Department Visits among Patients with End-stage Renal Disease. International journal of environmental research and public health 16(7)	- Study does not contain factors of interest
Cornec-Le Gall, Emilie, Audrezet, Marie-Pierre, Renaudineau, Eric et al. (2017) PKD2-Related Autosomal Dominant Polycystic Kidney Disease: Prevalence, Clinical Presentation, Mutation Spectrum, and Prognosis. American journal of kidney diseases : the official journal of the National Kidney Foundation 70(4): 476-485	- Study does not contain factors of interest
Dattolo, Pietro, Michelassi, Stefano, Amidone, Marco et al. (2015) Structured clinical follow-up for CKD stage 5 may safely postpone dialysis. Journal of nephrology 28(4): 463-9	- Study does not contain factors of interest
De Wilde, M; Speeckaert, M; Van Biesen, W (2018) Can increased vigilance for chronic kidney disease in hospitalised patients decrease late referral and improve dialysis-free survival?. BMC nephrology 19(1): 74	- Study does not contain factors of interest
Farooq, Z., Mehmood, A., Saeed, S. et al. (2010) Early versus late arterio-venous fistulae: impact on failure rate. Journal of Ayub Medical College, Abbottabad : JAMC 22(3): 179-181	- Study does not contain factors of interest
Foote, Celine, Clayton, Philip A, Johnson, David W et al. (2014) Impact of estimated GFR reporting on late referral rates and practice patterns for end-stage kidney disease patients: a multilevel logistic regression analysis using the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). American journal of kidney diseases : the official journal of the National Kidney Foundation 64(3): 359-66	- Study does not contain factors of interest
Gander, Jennifer C, Zhang, Xingyu, Plantinga, Laura et al. (2018) Racial disparities in preemptive referral for kidney transplantation in Georgia. Clinical transplantation 32(9): e13380	- Study does not contain factors of interest
Gerntholtz, T., Paget, G., Hsu, P. et al. (2015) Management of patients with chronic kidney disease. South African Medical Journal 105(3): 237	- Study does not contain factors of interest
Guerra, Daiane Cristina, Rodrigues Neto Angeloco, Larissa, Furtado, Wander R et al. (2014) Late referral for chronic kidney disease patients: nutritional point of view. Nutricion hospitalaria 31(3): 1286-93	- Study does not contain factors of interest
Gulla, Joy, Neri, Pamela M, Bates, David W et al. (2017) User Requirements for a Chronic Kidney Disease Clinical Decision Support Tool to Promote Timely Referral. International journal of medical informatics 101: 50-57	- Study does not contain factors of interest

Study	Reason for exclusion
Harum, Peggy (2012) Referrals needed to impact survival. Nephrology news & issues 26(1): 18	- Not a peer-reviewed publication
Higuchi, Satoshi, Nakaya, Izaya, Yoshikawa, Kazuhiro et al. (2017) Potential Benefit Associated With Delaying Initiation of Hemodialysis in a Japanese Cohort. Kidney international reports 2(4): 594-602	- Study does not contain factors of interest
Hirsch, Sheldon (2011) A defense of early renal referral: preventing progression to end-stage renal disease. Archives of internal medicine 171(22): 2064-2067	- Not a peer-reviewed publication
Hughes, Stephanie A, Mendelssohn, Joshua G, Tobe, Sheldon W et al. (2013) Factors associated with suboptimal initiation of dialysis despite early nephrologist referral. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 28(2): 392-7	- Study does not contain factors of interest
Inaguma, Daijo, Ando, Ryoichi, Ikeda, Masato et al. (2011) Nephrologist care for 12 months or more increases hemodialysis initiation with permanent vascular access. Clinical and experimental nephrology 15(5): 738-744	- Study does not contain factors of interest
Inston, Nicholas and Lok, Charmaine E (2019) Improving precision in prediction: Using kidney failure risk equations as a potential adjunct to vascular access planning. The journal of vascular access 20(1): 95-97	- Study does not contain factors of interest
Jones, Ruth K, Hampton, David, O'Sullivan, Daniel J et al. (2013) Diabetes and renal disease: who does what?. Clinical medicine (London, England) 13(5): 460-4	- Study does not contain factors of interest
Jun, Min and Hemmelgarn, Brenda R (2014) Automated estimated GFR reporting and late referral: are we expecting automatic benefits?. American journal of kidney diseases : the official journal of the National Kidney Foundation 64(3): 319-21	- Not a peer-reviewed publication
Kim, Suh Min, Han, Ahram, Ahn, Sanghyun et al. (2019) Timing of referral for vascular access for hemodialysis: Analysis of the current status and the barriers to timely referral. The journal of vascular access 20(6): 659-665	- Study does not contain factors of interest
Lee, Jeonghwan, Lee, Jung Pyo, Park, Ji In et al. (2014) Early nephrology referral reduces the economic costs among patients who start renal replacement therapy: a prospective cohort study in Korea. PloS one 9(6): e99460	- Study does not contain factors of interest
Liu, Ping, Quinn, Robert R, Oliver, Matthew J et al. (2018) Association between Duration of Predialysis Care and Mortality after Dialysis Start. Clinical journal of the American Society of Nephrology : CJASN 13(6): 893-899	- Data not reported in an extractable format
Lonnemann, Gerhard, Duttlinger, Johannes, Hohmann, David et al. (2017) Timely Referral to Outpatient Nephrology Care Slows Progression	- Data not reported in an extractable format

Study	Reason for exclusion
and Reduces Treatment Costs of Chronic Kidney Diseases. Kidney international reports 2(2): 142-151	
Major, Rupert W, Shepherd, David, Medcalf, James F et al. (2019) The Kidney Failure Risk Equation for prediction of end stage renal disease in UK primary care: An external validation and clinical impact projection cohort study. PLoS medicine 16(11): e1002955	- Paper used to estimate predictive accuracy of the different referral rules
Marron, Belen, Ostrowski, Janusz, Torok, Marietta et al. (2016) Type of Referral, Dialysis Start and Choice of Renal Replacement Therapy Modality in an International Integrated Care Setting. PloS one 11(5): e0155987	- Study does not contain a relevant intervention
Menon, Rena, Mohd Noor, Fariz Safhan, Draman, Che Rosle et al. (2012) A retrospective review of diabetic nephropathy patients during referral to the sub-urban nephrology clinic. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia 23(5): 1109-14	- Study does not contain factors of interest
Minutolo, Roberto, Lapi, Francesco, Chiodini, Paolo et al. (2014) Risk of ESRD and death in patients with CKD not referred to a nephrologist: a 7-year prospective study. Clinical journal of the American Society of Nephrology : CJASN 9(9): 1586-93	- Study does not contain a relevant intervention
Muneer, Abulkashem; Al Nusairat, Ibrahim; Kabir, Mohd Zahangir (2004) Clinical profiles of chronic renal failure patients at referral to nephrologist. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia 15(4): 468-72	- Study does not contain a relevant intervention
Okaka, Enajite I; Adejumo, Oluseyi A; Akinbodewa, Ayodeji A (2020) Late referral and associated factors among chronic kidney disease outpatients in Southern Nigeria. Annals of African medicine 19(1): 47-52	- Systematics differences, differences between groups that cannot be adjusted for e.g. visiting non-medical practitioners, having a blood transfusion first or not having good insurance
Okazaki, Masaki, Inaguma, Daijo, Imaizumi, Takahiro et al. (2018) Unfavorable effects of history of volume overload and late referral to a nephrologist on mortality in patients initiating dialysis: a multicenter prospective cohort study in Japan. BMC nephrology 19(1): 65	- Study does not contain factors of interest
Oliva-Damaso, N., Oliva-Damaso, E., Rodriguez-Perez, J.C. et al. (2019) Improved nephrology referral of chronic kidney disease patients: Potential role of smartphone apps. Clinical Kidney Journal 12(6): 767-770	- Not a peer-reviewed publication
Quaglia, Marco; Canavese, Caterina; Stratta, Piero (2011) Early nephrology referral: how early is early enough?. Archives of internal medicine 171(22): 2065-2067	- Not a peer-reviewed publication
Shavit, Linda and Slotki, Itzchak (2014) Early nephrology referral for the chronic kidney disease patient: seeing the light or groping in the dark?.	- Not a peer-reviewed publication

Study	Reason for exclusion
The Israel Medical Association journal : IMAJ 16(8): 506-8	
Shechter, Steven M; Skandari, M Reza; Zalunardo, Nadia (2014) Timing of arteriovenous fistula creation in patients With CKD: a decision analysis. American journal of kidney diseases : the official journal of the National Kidney Foundation 63(1): 95-103	- Study does not contain factors of interest
Slinin, Yelena, Greer, Nancy, Ishani, Areef et al. (2015) Timing of dialysis initiation, duration and frequency of hemodialysis sessions, and membrane flux: a systematic review for a KDOQI clinical practice guideline. American journal of kidney diseases : the official journal of the National Kidney Foundation 66(5): 823-36	- Study does not contain factors of interest
Smart, Neil A, Dieberg, Gudrun, Ladhani, Maleeka et al. (2014) Early referral to specialist nephrology services for preventing the progression to end-stage kidney disease. The Cochrane database of systematic reviews: cd007333	- Duplicate reference
Sulowicz, Wladyslaw and Stompor, Tomasz P (2004) Timely referral to the nephrologist: essential to optimizing patient outcomes. Hemodialysis international. International Symposium on Home Hemodialysis 8(3): 233-43	- Review article but not a systematic review
Udayaraj, Udaya P; Haynes, Richard; Winearls, Christopher G (2011) Late presentation of patients with end-stage renal disease for renal replacement therapy--is it always avoidable?. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 26(11): 3646-51	- Data not reported in an extractable format

J.6.3 Included studies

Eight papers were included in the review update from 7 different cohort studies, Kim 2013 and Park 2015 were from the same cohort study. The studies had different definitions of early and late referrals, 3 months (Diegoli 2015, Kumar 2012), 16 weeks (Hommel 2012), 6 months (Hayashi 2016) and 1 year (Kim 2013, Park 2015, Selim 2015) before the start of renal replacement therapy.

There are two different timings within the review; there is the time between being referred to a nephrologist and starting renal replacement therapy, and mortality which is the time between renal replacement therapy starting and the time of death.

The evidence table below has been completed in line with the evidence tables completed in the Smart 2014 Cochrane review.

The risk of bias tool used in the Cochrane review was the Newcastle-Ottawa Scale, and therefore the same risk of bias tool was used in the update. The Newcastle-Ottawa Scale uses 10 questions to look at different element of the studies, including the participant selection, comparability, and outcomes. Each question was then awarded a star if it was considered appropriately done with no risk of bias within that element. The Cochrane review then used an overall rating based on the number of stars attained. A rating of high required eight stars, moderate level cohort studies acquired a score of six to seven stars, low level four to five

stars and very low level scored three stars or less, therefore the same rating was used in this update.

Diegoli, 2015

Bibliographic Reference	Diegoli, Henrique; Silva, Marcelo Castro Goncalves; Machado, Diogo Spengler Barcelos; Cruz, Carlos Eduardo Rilling da Nova; Late nephrologist referral and mortality assotiation in dialytic patients.; Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia; 2015; vol. 37 (no. 1); 32-7

Study details

Methods	Retrospective cohort study
Participants	111 patients starting dialysis at a reference clinic between 1 January 2008 and 31 December 2011
Intervention(s)	Early nephology referral as defined as 90 days before the start of renal replacement therapy
Outcomes	Mortality

Study arms

Early Referral (N = 44)
Referred 90 days or more before the start of renal replacement therapy

Late Referral (N = 67)
Referred less than 90 days before the start of renal replacement therapy

Section	Question	Answer
Bias	Selective reporting (reporting bias)	Low risk *(Looked at mortality)*
	Other bias	High risk *(Retrospective)*
	Selection: representativeness of exposed cohort	Low risk *(All patients referred during 2008-2011 to cancer centre)*
	Selection: non exposed cohort	Low risk *(All patients referred during 2008-2011 to cancer centre)*
	Selection: ascertainment of exposure	Low risk *(Medical records)*
	Selection: demonstration that outcome of interest was not present at the start of the study	High risk *(All patients had started RRT)*

Section	Question	Answer
	Comparability of cohorts on basis of design or analysis	Low risk *(Looked at other baseline characteristics)*
	Outcome: assessment	Low risk *(Death - from records)*
	Outcome: follow-up length	High risk *(Data extracted a year after end of enrolment)*
	Outcome: adequacy of follow- up	Low risk *(100%)*
	Overall quality of study	Moderate *(6 Stars)*

Hayashi, 2016

Bibliographic Reference	Hayashi, Terumasa; Kimura, Tomonori; Yasuda, Keiko; Sasaki, Koichi; Obi, Yoshitsugu; Nagayama, Harumi; Ohno, Motoki; Uematsu, Kazusei; Tamai, Takehiro; Nishide, Takahiro; Rakugi, Hiromi; Isaka, Yoshitaka; Early Nephrology Referral 6 Months Before Dialysis Initiation Can Reduce Early Death But Does Not Improve Long-Term Cardiovascular Outcome on Dialysis.; Circulation journal : official journal of the Japanese Circulation Society; 2016; vol. 80 (no. 4); 1008-16

Study details

Methods	Retrospective cohort study
Participants	604 patients from Rinku General Medical Centre or 5 hospitals with dialysis centres
Intervention(s)	Early referral defined as 6 months or more before then start of renal replacement therapy
Outcomes	Mortality

Study arms

Early Referral (N = 258) Referred to a nephrologist 6 months or before the first chronic dialysis
Late Referral (N = 346) Referred to a nephrologist less than 6 months before the first chronic dialysis

Section	Question	Answer
Bias	Selective reporting (reporting bias)	Low risk *(No obvious exclusions)*
	Other bias	High risk *(Retrospective)*
	Selection: representativeness of exposed cohort	Low risk *(consecutive patients who started dialysis between 2001 and 2009 at 6 hospitals)*
	Selection: non exposed cohort	Low risk *(consecutive patients who started dialysis between 2001 and 2009 at 6 hospitals)*
	Selection: ascertainment of exposure	Low risk *(From medical records)*
	Selection: demonstration that outcome of interest was not present at the start of the study	High risk *(All patients had started RRT)*
	Comparability of cohorts on basis of design or analysis	Low risk *(Looked at the differences between groups)*
	Outcome: assessment	Low risk *(Death, from records)*
	Outcome: follow-up length	High risk *(Lowest follow up length was 1 month)*
	Outcome: adequacy of follow- up	Low risk *(100% Patients excluded if lost to follow up)*
	Overall quality of study	Moderate *(6 Stars)*

Hommel, 2012

Bibliographic Reference	Hommel, Kristine; Madsen, Mette; Kamper, Anne-Lise; The importance of early referral for the treatment of chronic kidney disease: a Danish nationwide cohort study.; BMC nephrology; 2012; vol. 13; 108

Study details

Methods	Retrospective cohort study
Participants	4495 patients itentified in the Danish Nephrology Registry between 1999-2006

Intervention(s)	Early referral defined as 16 weeks or before the start of renal replacement therapy
Outcomes	Mortality, peritoneal dialysis

Study arms

Early Referral (N = 2768) Referred 16 weeks or more before the start of renal replacement therapy
Late Referral (N = 1727) Referred less than 16 weeks before the start of renal replacement therapy

Section	Question	Answer
Bias	Selective reporting (reporting bias)	Low risk *(No obvious omissions)*
	Other bias	High risk *(Retrospective)*
	Selection: representativeness of exposed cohort	Low risk *(Chronic RRT patients 1999-2006 in Denmark)*
	Selection: non exposed cohort	Low risk *(Chronic RRT patients 1999-2006 in Denmark)*
	Selection: ascertainment of exposure	Low risk *(From registries)*
	Selection: demonstration that outcome of interest was not present at the start of the study	High risk *(All patients had started RRT)*
	Comparability of cohorts on basis of design or analysis	Low risk *(Characteristics were statistically compared)*
	Outcome: assessment	Low risk *(Data from mandatory database)*
	Outcome: follow-up length	Low risk *(At least one year follow up)*
	Outcome: adequacy of follow- up	Low risk *(100%)*
	Overall quality of study	Moderate *(7 Stars)*

Kim, 2013

Bibliographic Reference	Kim, Do Hyoung; Kim, Myounghee; Kim, Ho; Kim, Yong-Lim; Kang, Shin-Wook; Yang, Chul Woo; Kim, Nam-Ho; Kim, Yon Su; Lee, Jung Pyo; Early referral to a nephrologist improved patient survival: prospective cohort study for end-stage renal disease in Korea.; PloS one; 2013; vol. 8 (no. 1); e55323

Study details

Methods	Retrospective cohort study (subsection of the Comprehensive Prospective Study of the Clinical Research Centre for End Stage Renal Disease)
Participants	511 patients from 31 hospital or clinics participating in the Comprehensive Prospective Study of the Clinical Research Centre for End Stage Renal Disease
Intervention(s)	Early referral defined as at least a year before starting renal replacement therapy
Outcomes	Mortality

Study arms

Early Referral (N = 302) Referral defined as 1 year or more before the start of renal replacement therapy
Late Referral (N = 209) Referral defined as less than a year before the start of renal replacement therapy

Section	Question	Answer
Bias	Selective reporting (reporting bias)	Low risk *(Looked at mortality)*
	Other bias	High risk *(Retrospective)*
	Selection: representativeness of exposed cohort	Low risk *(All patients with ESRD were included)*
	Selection: non exposed cohort	Low risk *(All patients with ESRD were included)*
	Selection: ascertainment of exposure	Low risk *(Clinical records)*
	Selection: demonstration that outcome of interest was not present at the start of the study	High risk *(All patients had started dialysis)*
	Comparability of cohorts on basis of design or analysis	Low risk *(Assessed differences)*
	Outcome: assessment	Low risk *(Data from clinical records)*

Section	Question	Answer
	Outcome: follow-up length	High risk *(Death in external hospitals extracted before the end of recruitment)*
	Outcome: adequacy of follow- up	Low risk *(100%)*
	Overall quality of study	Moderate *(6 Stars)*

Kumar, 2012

Bibliographic Reference	Kumar, S.; Jeganathan, J.; Amruthesh; Timing of nephrology referral: Influence on mortality and morbidity in chronic kidney disease; Nephro-Urology Monthly; 2012; vol. 4 (no. 3); 578-581

Study details

Methods	Retrospective analysis of a prospectively collected dataset
Participants	50 patients in a tertiary care hospital
Intervention(s)	Early nephrology referral defined as 3 months or more before the start of renal replacement therapy
Outcomes	Mortality

Study arms

Early Referral (N = 18) Defined as 3 months or more before the start of renal replacement therapy
Late Referral (N = 32) Defined as less than 3 months before the start of renal replacement therapy

Section	Question	Answer
Bias	Selective reporting (reporting bias)	Low risk *(Looked at mortality)*
	Other bias	High risk *(Retrospective)*
	Selection: representativeness of exposed cohort	Low risk *(All patients referred to hospital for nephology)*

Section	Question	Answer
	Selection: non exposed cohort	Low risk *(All patients referred to hospital for nephology)*
	Selection: ascertainment of exposure	Low risk *(From medical records)*
	Selection: demonstration that outcome of interest was not present at the start of the study	Low risk *(Chronic kidney disease but not yet ESRD)*
	Comparability of cohorts on basis of design or analysis	Low risk *(Assessed differences)*
	Outcome: assessment	Low risk *(Data from records)*
	Outcome: follow-up length	Low risk *(Follow up for a year)*
	Outcome: adequacy of follow- up	Low risk *(100%)*
	Overall quality of study	High *(8 Stars)*

Park, 2015

Bibliographic Reference	Park, Ji In; Kim, Myounghee; Kim, Ho; An, Jung Nam; Lee, Jeonghwan; Yang, Seung Hee; Cho, Jang-Hee; Kim, Yong-Lim; Park, Ki-Soo; Oh, Yun Kyu; Lim, Chun Soo; Kim, Dong Ki; Kim, Yon Su; Lee, Jung Pyo; Not early referral but planned dialysis improves quality of life and depression in newly diagnosed end stage renal disease patients: a prospective cohort study in Korea.; PloS one; 2015; vol. 10 (no. 2); e0117582

Study details

Methods	Retrospective cohort study (subgroup of the Clinical Research Centre for End Stage Renal Disease)
Participants	643 patients from 31 hospital or clinics participating in the Clinical Research Centre for End Stage Renal Disease
Intervention(s)	Early referral is defined as a year or more before the start of renal replacement therapy
Outcomes	Kidney Disease Quality of Life Short Form 36 (KDQOL-36), Beck's Depression Inventory (BDI)

Study arms

Early Referral (N = 390)
Defined as referred a year or more before the start of renal replacement therapy

Late Referral (N = 253)
Defined as referred less than a year before the start of renal replacement therapy

Section	Question	Answer
Bias	Selective reporting (reporting bias)	High risk *(Mortality not reported)*
	Other bias	High risk *(Retrospective)*
	Selection: representativeness of exposed cohort	Low risk *(All patients with ESRD were included)*
	Selection: non exposed cohort	Low risk *(All patients with ESRD were included)*
	Selection: ascertainment of exposure	Low risk *(Clinical records)*
	Selection: demonstration that outcome of interest was not present at the start of the study	High risk *(All patients had started dialysis)*
	Comparability of cohorts on basis of design or analysis	Low risk *(Assessed differences)*
	Outcome: assessment	Low risk *(Questioned patients directly)*
	Outcome: follow-up length	Low risk *(1 year for all patients)*
	Outcome: adequacy of follow- up	Low risk *(100%)*
	Overall quality of study	Moderate *(7 Stars)*

Selim, 2015

Bibliographic Reference Selim, Gjulsen; Stojceva-Taneva, Olivera; Spasovski, Goce; Tozija, Liljana; Grozdanovski, Risto; Georgievska-Ismail, Ljubica; Zafirova-Ivanovska, Beti; Dzekova, Pavlina; Trajceska, Lada; Gelev, Saso; Mladenovska, Daniela; Sikole, Aleksandar; Timing of nephrology referral and initiation of dialysis as predictors for survival in hemodialysis patients: 5-year follow-up analysis.; International urology and nephrology; 2015; vol. 47 (no. 1); 153-60

Study details

Methods	Retrospective cohort study
Participants	190 patients starting haemodialysis between January 1994 and December 2004 at a haemodialysis unit
Intervention(s)	Early referral defined as a year or more before the start of renal replacement therapy
Outcomes	Mortality

Study arms

Early Referral (N = 64)
Early referral defined as a year or more before the start of renal replacement therapy

Late Referral (N = 126)
Late referral defined as less than a year before the start of renal replacement therapy

Section	Question	Answer
Bias	Selective reporting (reporting bias)	Low risk *(Reported mortality)*
	Other bias	High risk *(Retrospective)*
	Selection: representativeness of exposed cohort	Low risk *(Patients starting HD at a HD unit)*
	Selection: non exposed cohort	Low risk *(Patients starting HD at a HD unit)*
	Selection: ascertainment of exposure	Low risk *(Medical records)*
	Selection: demonstration that outcome of interest was not present at the start of the study	High risk *(Patients starting HD)*
	Comparability of cohorts on basis of design or analysis	Low risk *(Assessed differences)*
	Outcome: assessment	Low risk *(Clinical records)*
	Outcome: follow-up length	Low risk *(5 years or death)*
	Outcome: adequacy of follow- up	Low risk *(100%)*
	Overall quality of study	Moderate *(7 Stars)*

Yanay, 2014

Bibliographic Reference	Yanay, Noa Berar; Scherbakov, Lubov; Sachs, David; Peleg, Nana; Slovodkin, Yakov; Gershkovich, Regina; Effect of early nephrology referral on the mortality of dialysis patients in Israel.; The Israel Medical Association journal : IMAJ; 2014; vol. 16 (no. 8); 479-82

Study details

Methods	Retrospective cohort study
Participants	200 patients that started haemodialysis at a centre between January 2006 and December 2009
Intervention(s)	Definition of early referral as 3 months or more before the start of renal replacement therapy
Outcomes	Mortality

Study arms

Early Referral (N = 118)
Defined as 3 months or more before the start of renal replacement therapy

Late Referral (N = 82)
Defined as less than 3 months before the start of renal replacement therapy

Section	Question	Answer
Bias	Selective reporting (reporting bias)	High risk *(Looked at mortality)*
	Other bias	High risk *(Retrospective)*
	Selection: representativeness of exposed cohort	Low risk *(Started RRT at centre)*
	Selection: non exposed cohort	Low risk *(Started RRT at centre)*
	Selection: ascertainment of exposure	Unclear risk *(Does not say)*
	Selection: demonstration that outcome of interest was not present at the start of the study	High risk *(Patients recruited at start of RRT)*
	Comparability of cohorts on basis of design or analysis	Low risk *(Corrected for differences)*
	Outcome: assessment	Unclear risk *(Does not say)*

Section	Question	Answer
	Outcome: follow-up length	Low risk *(At least 3 years)*
	Outcome: adequacy of follow- up	Low risk *(All patients followed up)*
	Overall quality of study	Low *(5 Stars)*

J.6.4 Results

Most of the studies added further evidence towards the outcomes already defined in the original Cochrane review. Further outcomes that were identified in the review were 3 year mortality in studies with 3-month definition of early versus late referral; Kidney Disease Quality of Life – 36 (KDQOL-36) physical and mental components at 3 months and 12 months, and the Beck Depression Inventory (BDI) at 3 months and 12 months.

For the two outcomes that were ultimately included in the model (mortality and length of stay at dialysis initiation), the final meta-analyses are shown in Figure 11, Figure 12, Figure 13 and Figure 14. All four forest plots show that early referral has a significant benefit compared to late referral. When looking at the mortality it appears that early referral prevents death closer to the start of dialysis, with the effect becoming smaller as a larger duration of time has passed since dialysis initiation.

GRADE confidence ratings for these results are given in Table 64. The overall quality of the evidence was rated as low to moderate, with higher confidence in the mortality at 3/4 months than at 1 year or 5 years.

It appears that early referral is important in reducing mortality in patients that start renal replacement therapy. Just after commencement of renal replacement therapy it appears being referred early reduces mortality by as much as 50%. This seems to be logical as early referral gives the physician and patient time to prepare for the treatment. It also appears that the benefit in mortality reduces the longer it has been since the start of renal replacement therapy. This makes sense as other factors are more likely to become involved the further from the start of renal replacement therapy, in particular that by five years a sizeable proportion of the people who started on dialysis will either have died or subsequently received a transplant.

Figure 11 Mortality at 3/4 months

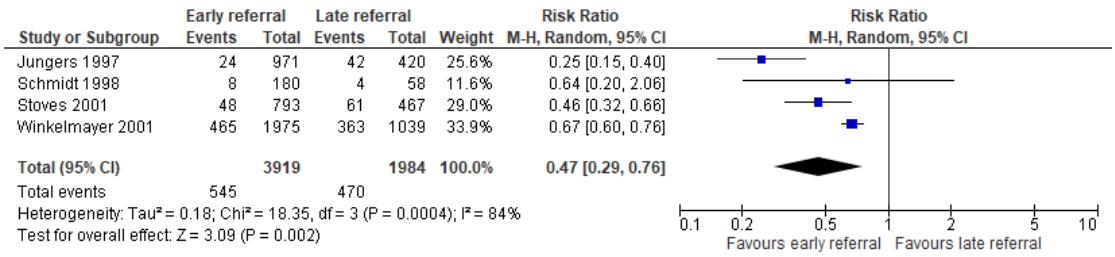


Figure 12 Mortality at 1 year

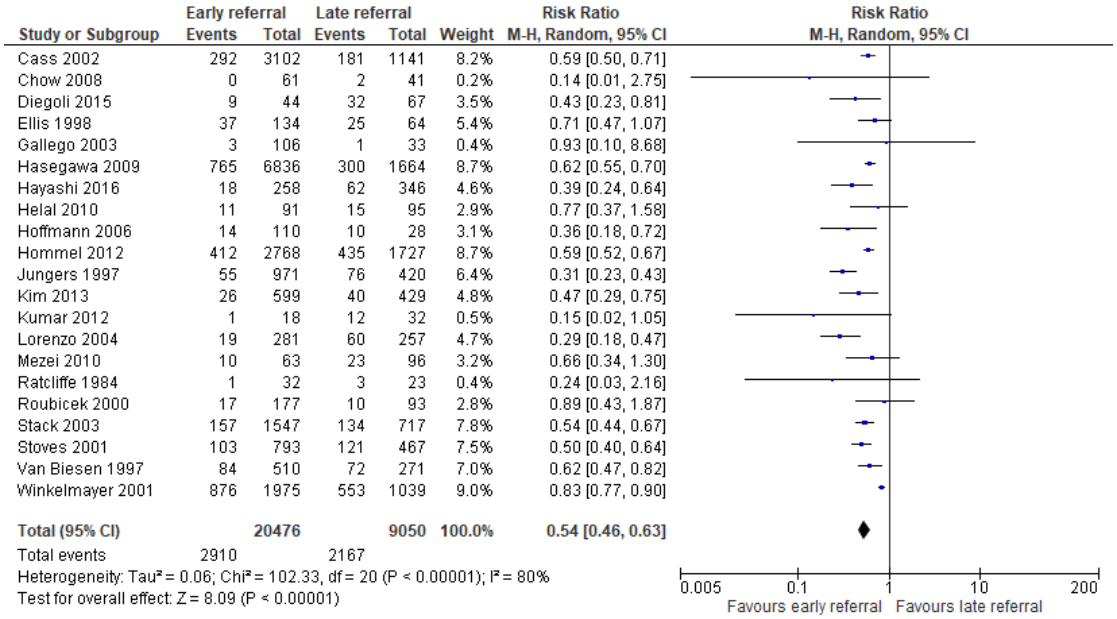


Figure 13 Mortality at 5 years

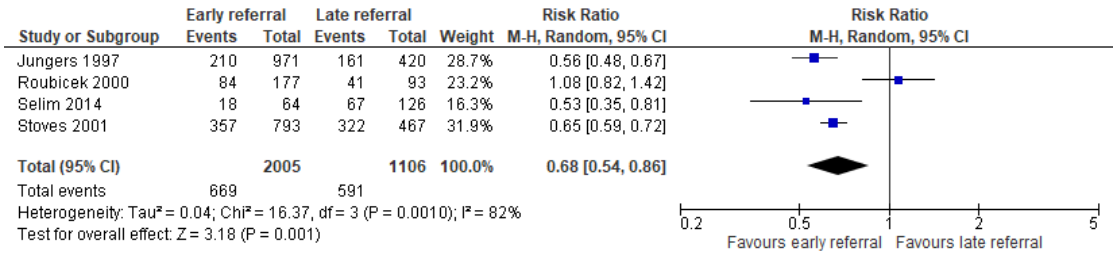


Figure 14 Duration of hospital stay

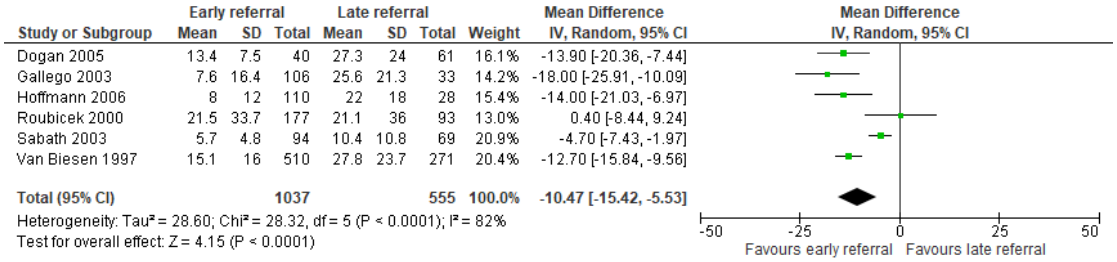


Table 64 GRADE table for early versus late referral

No. of studies	Study design[a]	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Mortality at 3/4 months after dialysis initiation (lower values favour early referral)								
4	Retrospective cohort studies	5,903	RR 0.47 (0.29, 0.76)	Serious[b]	Not serious	Not serious[c]	Not serious	Moderate
Mortality at 1 year after dialysis initiation (lower values favour early referral)								
21	Prospective and retrospective cohort studies	29,526	RR 0.54 (0.46, 0.63)	Serious[b]	Not serious	Serious[d]	Not serious	Low
Mortality at 5 years after dialysis initiation (lower values favour early referral)								
4	Retrospective cohort studies	3,111	RR 0.68 (0.54, 0.86)	Serious[b]	Not serious	Serious[e]	Not serious	Low
Duration of hospital stay at dialysis initiation in days (lower values favour early referral)								
6	Prospective and retrospective cohort studies	1,592	MD -10.47 (-15.42, -5.53)	Serious[b]	Not serious	Serious[e]	Not serious	Low

a. Despite the studies being cohorts rather than randomised controlled trials, the quality of the evidence was started as high rather than low. This was because the Cochrane review put considerable effort in to ruling out systematic differences between the two groups, and therefore we are confident the groups are relatively well matched at baseline.
b. >33.3% of weighted data have high risk of bias, but the finding was only downgrade once due to the fact that reasons for the high risk of bias (e.g. retrospective outcome measurement) are less likely to be a problem when the outcome is mortality or hospitalisation (identified from patients records), as recall bias is unlikely to be an issue.
c. High levels of statistical heterogeneity, but the outcome was not downgraded because all the studies agreed there is a meaningful improvement in mortality from early referral.
d. High levels of statistical heterogeneity, but the outcome was only downgraded once because all the studies agreed there is an improvement in mortality from early referral, and most agree there is a meaningful improvement.
e. High levels of statistical heterogeneity, but the outcome was only downgraded once because there was a consistent pattern of improvement from early referral, with at worst studies not being able to detect a difference between the groups.

J.7 Appendix 2 – Link between donor status and graft failure rates

Several articles and websites that were considered during preliminary reading indicated that outcomes for kidney transplants were likely to differ by donor type. These sources suggested that recipients of kidneys from living donors were likely to have better outcomes than recipients of kidneys from deceased donors. Differences in transplant outcomes would likely translate to differences in the costs and QALYs associated with transplant donor types.

If referral time does not affect whether a patient receives a transplant from a living donor, the proportions of living and deceased donor types would be the same in transplants across all referral strategies. The overall consequences of a transplant would remain the same for all strategies and so disaggregating transplant outcomes by donor type would not be expected to change the incremental differences in costs and QALYs between referral strategies.

However, we expect that earlier referral to secondary care would increase the likelihood of a patient receiving a transplant from a living donor as it would increase the available time to find a clinically suitable match to a living donor. This means the proportions of living and deceased donor types (and thus the consequences of transplant) would differ by referral strategy. It is therefore necessary to capture the differences in transplant outcome between donor types in the model, as this will affect the incremental costs and QALYs between referral strategies.

During preliminary reading, Roodnat 2003 was initially identified as potential source to model the difference in outcomes between donor types. The paper reports the hazard ratio for the risk of graft failure as 1.9157 (95% CI: 1.3359 to 2.7472) between recipients of deceased and living donor transplants. However, transplant services are expected to have changed since publication of this paper (for example due to improvements in immunosuppressants). We therefore conducted a pragmatic literature search to identify other potential sources of evidence to inform this parameter. The search specifically aimed to identify a comparative statistic (such as a hazard ratio or odds ratio) for the risk of graft failure for transplants from living and deceased donors. This comparative statistic was then combined with UK Renal Registry data on graft failures in transplant patients and used to estimate the number of graft failures for the different referral strategies.

A targeted search of literature published since 2003 exploring kidney donor type yielded 623 results. After screening on title and abstract, 44 included studies were identified for full-text screening. Of these, 6 articles included comparative analyses of the risk of graft failure in transplants from living and deceased donors. A summary of the identified studies is presented in Table 65.

Table 65: Studies comparing risk of graft failure in transplants from living and deceased donors

Paper	Country	Comparison(s)
Almasi-Hashianai (2018)	Iran	Deceased vs related living donors, unrelated vs related living donors
Englum (2015)	USA	Living vs standard criteria deceased donors stratified by age of donor (<60 years, 60-64 years, 65-69 years, ≥70 years), expanded criteria vs standard criteria deceased donors
Molnar (2012)	USA	Living vs standard criteria deceased donors, living vs expanded criteria deceased donors, expanded criteria vs standard criteria deceased donors, all stratified by age of recipient (18-34

Paper	Country	Comparison(s)
		years, 15-54 years, 55-64 years, 65-69 years, 70-74 years, ≥75 years)
Nemati (2014)	Iran	Deceased vs related living donors
Saatchi (2013)	Iran	Deceased vs living donors
Yohanna (2020)	Canada	Standard criteria deceased vs living donors

In the UK, patients may receive kidney transplants from either related or unrelated living donors. Almasi-Hashianai (2018) and Nemati (2014) compare transplants from deceased donors with living donors who were related to the recipient, but do not include comparisons which pool the transplants from living donors that were related and unrelated to recipients. As the hazard ratios from these studies do not reflect the risk between transplants from living and deceased donors in the UK, both studies were excluded.

The comparisons in Englum (2015) were stratified by living donor age and did not compare risk of graft failure in transplants from deceased donors versus living donors pooled across all ages. As the renal registry data does not include information about donor age, it would not be possible to pool the reported hazard ratios to estimate this comparison. On this basis, Englum (2015) was also excluded.

The suitability of using the remaining three studies (Molnar (2012), Saatchi (2013) and Yohanna (2020)) were evaluated to establish which study population best reflected UK transplant patients and services.

Transplant services and populations are likely to vary by healthcare system, with different allocation rules, variation in transportation of organs and differences in donor supply. We assumed that Canada's healthcare system was the most similar to the UK's on the basis that Canada is a high-income OECD country with single-payer universal healthcare. We also assumed that these similarities in healthcare systems would translate to similarities in the configuration of transplant services. On this basis, the transplant services in Yohanna (2020) are assumed to be most comparable to the UK.

The deceased donor study population in Yohanna (2020) is restricted to standard criteria deceased donors. Molnar (2012) reports hazard ratios for standard and expanded criteria deceased donors (expanded criteria include donors over 60 years or between 50 and 59 years with a history of hypertension and/or donor serum creatinine >1.5mg/dL and/or a cerebrovascular event as the cause of death). The proportion of expanded criteria donations used increased directly with the age categories, ranging from 7% of all transplants in the 18-35 year group to 43% in the ≥75 year group. Although, it does not explicitly mention criteria, the UK's policy for deceased donor organ allocation makes reference to donors aged 70 years and older, implying that the expanded criteria are used in at least some patients in the UK. This suggests that the analyses from Molnar (2012) may better represent the organs transplanted from deceased donors in the UK than those used in the Yohanna (2020) analyses. Saatchi (2013) does not report whether deceased donors met the standard or expanded criteria.

This prompted a consideration of the relative importance of difference in healthcare system and difference in deceased donor type on the generalisability to the UK transplant population. There is uncertainty about the proportion of transplants from expanded criteria deceased donors in the UK; the UK Renal Registry 2017 annual report did not outline the information required for this estimate. Hazard ratios in Molnar (2012) indicate that the risk of graft failure in transplants from living versus all deceased donors is similar to the risk from living versus standard criteria deceased donors across all recipient age ranges. In the absence of an analysis using a proportion of expanded criteria deceased donors that represents the UK, and given that risk of graft failure appears only minimally affected, we concluded that the difference in deceased donor type was less of a limitation than difference in healthcare system when applying results to the UK setting.

On this basis, the living versus deceased donor hazard ratio from Yohanna (2020) was used in the base-case analysis. The study provided propensity-score weighted analyses for all-cause and death-censored graft failure; the latter was used in the analysis as we did not consider that death with a functioning kidney was relevant when assessing the benefits of referral strategies. A scenario analysis explored the use of the fully-adjusted analyses from the Molnar (2012) study. Molnar (2012) outlined hazard ratios for subgroups based on age of recipient and did not report a hazard ratio for the total study population. To compare the results of the Molnar (2012) study with the Yohanna (2020) study, the age-based hazard ratios from the former study were pooled into a hazard ratio for the total study population. Hazard ratios from Saatchi (2013) were not explored as the evidence from Molnar (2012) and Yohanna (2020) was considered to be more representative of the UK with respect to donor type and healthcare system. Hazard ratios for the base-case and scenario are reported in Table 66.

Whilst searching for comparative statistics had focused on graft failure, both the Yohanna (2020) and Molnar (2012) studies also reported all-cause mortality for recipients of living versus deceased donors. These are reported in Table 66. As with graft failure, the hazard ratios from Molnar (2012) are pooled across different age groups.

Table 66: Graft failure and mortality hazard ratios for transplants from living donors compared to deceased donors

Paper	Graft failure HR (95% CI)	Mortality HR (95% CI)
Yohanna (2020)	0.83 (0.50,1.40)	0.92 (0.58,1.45)
Molnar (2012)*	0.70 (0.66,0.73)	0.68 (0.64,0.71)

*Pooled across reported age groups

These values were then combined with the data from the UK Renal Registry and used to estimate transition probabilities for the Markov model. Details of this analysis are outlined in J.2.4.3. Details of the related scenario analysis are outlined in J.2.6.1.

Appendix K – Excluded studies

Study	Reason for exclusion
Astor, BC, Shafi, T, Hoogeveen, RC et al. (2012) Novel markers of kidney function as predictors of ESRD, cardiovascular disease, and mortality in the general population. American journal of kidney diseases 59(5): 653-662	- Does not include a combination of measures.
Bansal, Nisha, Katz, Ronit, De Boer, Ian H et al. (2015) Development and validation of a model to predict 5-year risk of death without ESRD among older adults with CKD. Clinical journal of the American Society of Nephrology : CJASN 10(3): 363-71	- Does not include any outcomes of interest. [Does not include progression to ESRD]
Bansal, Nisha, Katz, Ronit, Himmelfarb, Jonathan et al. (2016) Markers of kidney disease and risk of subclinical and clinical heart failure in African Americans: the Jackson Heart Study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 31(12): 2057-2064	- Does not include a combination of measures.
Bevc, Sebastjan, Hojs, Nina, Knehtl, Masa et al. (2019) Cystatin C as a predictor of mortality in elderly patients with chronic kidney disease. The aging male : the official journal of the International Society for the Study of the Aging Male 22(1): 62-67	- Does not include a combination of measures.
Bloomfield, G S, Yi, S S, Astor, B C et al. (2013) Blood pressure and chronic kidney disease progression in a multi-racial cohort: the Multi-Ethnic Study of Atherosclerosis. Journal of human hypertension 27(7): 421-6	- Does not include any outcomes of interest.
Chang, Wen Xiu, Asakawa, Shinichiro, Toyoki, Daigo et al. (2015) Predictors and the Subsequent Risk of End-Stage Renal Disease - Usefulness of 30% Decline in Estimated GFR over 2 Years. PloS one 10(7): e0132927	- Retrospective study design. [No combined predictors included.]
Dart, A.; Komenda, P.; Tangri, N. (2018) Time to implement the kidney failure risk equation into pediatric practice. JAMA Pediatrics 172(2): 122-123	- Review (non-systematic)
Fenton, Anthony, Jesky, Mark D, Webster, Rachel et al. (2018) Association between urinary free light chains and progression to end stage renal disease in chronic kidney disease. PloS one 13(5): e0197043	- KFRE not used in validation cohort.
Fung, Colman Siu Cheung, Wan, Eric Yuk Fai, Chan, Anca Ka Chun et al. (2017) Association of estimated glomerular filtration rate and urine albumin-to-creatinine ratio with incidence of cardiovascular diseases and mortality in chinese patients with type 2 diabetes mellitus - a population-based retrospective cohort study. BMC nephrology 18(1): 47	- Does not include a combination of measures.
Furth, Susan L, Pierce, Chris, Hui, Wun Fung et al. (2018) Estimating Time to ESRD in Children With CKD. American journal of kidney diseases :	- Does not include a combination of measures.

Study	Reason for exclusion
the official journal of the National Kidney Foundation 71(6): 783-792	
Go, Alan S, Yang, Jingrong, Tan, Thida C et al. (2018) Contemporary rates and predictors of fast progression of chronic kidney disease in adults with and without diabetes mellitus. BMC nephrology 19(1): 146	- Retrospective study design. [No combined predictors included.]
Grams, Morgan E, Li, Liang, Greene, Tom H et al. (2015) Estimating time to ESRD using kidney failure risk equations: results from the African American Study of Kidney Disease and Hypertension (AASK). American journal of kidney diseases : the official journal of the National Kidney Foundation 65(3): 394-402	- KFRE not used in validation cohort.
Grams, Morgan E, Sang, Yingying, Ballew, Shoshana H et al. (2018) Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. Kidney international 93(6): 1442-1451	- KFRE not used in validation cohort.
Hui, Xuan, Matsushita, Kunihiro, Sang, Yingying et al. (2013) CKD and cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study: interactions with age, sex, and race. American journal of kidney diseases : the official journal of the National Kidney Foundation 62(4): 691-702	- Does not include any outcomes of interest.
Ku, Elaine, Kopple, Joel D, McCulloch, Charles E et al. (2018) Associations Between Weight Loss, Kidney Function Decline, and Risk of ESRD in the Chronic Kidney Disease in Children (CKiD) Cohort Study. American journal of kidney diseases : the official journal of the National Kidney Foundation 71(5): 648-656	- Does not include a combination of measures.
Landray, M.J., Emberson, J.R., Blackwell, L. et al. (2010) Prediction of ESRD and death among people with CKD: The chronic renal impairment in Birmingham (CRIB) prospective cohort study. American Journal of Kidney Diseases 56(6): 1082-1094	- Calculator not in use
Lees, Jennifer S, Welsh, Claire E, Celis-Morales, Carlos A et al. (2019) Glomerular filtration rate by differing measures, albuminuria and prediction of cardiovascular disease, mortality and end-stage kidney disease. Nature medicine 25(11): 1753-1760	- Does not include a combination of measures.
Lewis, Julia, Greene, Tom, Appel, Lawrence et al. (2004) A comparison of iothalamate-GFR and serum creatinine-based outcomes: acceleration in the rate of GFR decline in the African American Study of Kidney Disease and Hypertension. Journal of the American Society of Nephrology : JASN 15(12): 3175-83	- Does not include CKD.
Lim, Cynthia C, Teo, Boon Wee, Ong, Peng Guan et al. (2015) Chronic kidney disease, cardiovascular disease and mortality: A prospective cohort study in a multi-ethnic Asian	- Cross-sectional study design.

Study	Reason for exclusion
population. European journal of preventive cardiology 22(8): 1018-26	
Matsushita, Kunihiro; Ballew, Shoshana H; Coresh, Josef (2016) Cardiovascular risk prediction in people with chronic kidney disease. Current opinion in nephrology and hypertension 25(6): 518-523	- Review (non-systematic)
Matsushita, Kunihiro, Coresh, Josef, Sang, Yingying et al. (2015) Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. The lancet. Diabetes & endocrinology 3(7): 514-25	- Meta-analysis which includes mixed population. Checked for relevant studies including CKD..
Matsushita, Kunihiro, Selvin, Elizabeth, Bash, Lori D et al. (2010) Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD Study equation for estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study. American journal of kidney diseases : the official journal of the National Kidney Foundation 55(4): 648-59	- Does not include a combination of measures.
McCudden, Christopher, Akbari, Ayub, White, Christine A et al. (2018) Individual patient variability with the application of the kidney failure risk equation in advanced chronic kidney disease. PloS one 13(6): e0198456	- Does not include any outcomes of interest.
McQuarrie, Emily P, Traynor, Jamie P, Taylor, Alison H et al. (2014) Association between urinary sodium, creatinine, albumin, and long-term survival in chronic kidney disease. Hypertension (Dallas, Tex. : 1979) 64(1): 111-7	- Does not include a combination of measures.
Methven, Shona, Gasparini, Alessandro, Carrero, Juan J et al. (2017) Routinely measured iohexol glomerular filtration rate versus creatinine-based estimated glomerular filtration rate as predictors of mortality in patients with advanced chronic kidney disease: a Swedish Chronic Kidney Disease Registry cohort study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 32(suppl2): ii170-ii179	- Does not include a combination of measures. [Also includes some with renal replacement therapy.]
Ng, Derek K, Schwartz, George J, Warady, Bradley A et al. (2017) Relationships of Measured Iohexol GFR and Estimated GFR With CKD-Related Biomarkers in Children and Adolescents. American journal of kidney diseases : the official journal of the National Kidney Foundation 70(3): 397-405	- Does not address review question. [Study on estimation of GFR.]
Nitsch, D, Nonyane, BA, Smeeth, L et al. (2011) CKD and hospitalization in the elderly: a community-based cohort study in the United Kingdom. American journal of kidney diseases 57(5): 664-672	- Does not address review question.
Odden, Michelle C, Amadu, Abdul-Razak, Smit, Ellen et al. (2014) Uric acid levels, kidney	- Study design not included [Survey study]

Study	Reason for exclusion
function, and cardiovascular mortality in US adults: National Health and Nutrition Examination Survey (NHANES) 1988-1994 and 1999-2002. American journal of kidney diseases : the official journal of the National Kidney Foundation 64(4): 550-7	
Rebholz, Casey M, Grams, Morgan E, Matsushita, Kunihiro et al. (2015) Change in novel filtration markers and risk of ESRD. American journal of kidney diseases : the official journal of the National Kidney Foundation 66(1): 47-54	- Does not include a combination of measures.
Sebastiao, Y.V., Cooper, J.N., Becknell, B. et al. (2020) Prediction of kidney failure in children with chronic kidney disease and obstructive uropathy. Pediatric Nephrology	- Secondary publication [Related to Winicki 2017]
Shardlow, Adam, McIntyre, Natasha J, Fluck, Richard J et al. (2016) Chronic Kidney Disease in Primary Care: Outcomes after Five Years in a Prospective Cohort Study. PLoS medicine 13(9): e1002128	- Does not include a combination of measures.
Tangri, Navdeep, Inker, Lesley A, Hiebert, Brett et al. (2017) A Dynamic Predictive Model for Progression of CKD. American journal of kidney diseases : the official journal of the National Kidney Foundation 69(4): 514-520	- KFRE not used in validation cohort. [Additionally, study design (testing a dynamic model) is not included.]
Tarantini, Luigi, McAlister, Finlay Aleck, Barbati, Giulia et al. (2016) Chronic kidney disease and prognosis in elderly patients with cardiovascular disease: Comparison between CKD-EPI and Berlin Initiative Study-1 formulas. European journal of preventive cardiology 23(14): 1504-13	- Does not address review question.
Turin, T.C., Ahmed, S.B., Tonelli, M. et al. (2014) Kidney function, albuminuria and life expectancy. Canadian Journal of Kidney Health and Disease 1(1): 33	- Does not include a combination of measures. - Does not include any outcomes of interest.
Tynkevich, Elena, Flamant, Martin, Haymann, Jean-Philippe et al. (2015) Urinary creatinine excretion, measured glomerular filtration rate and CKD outcomes. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 30(8): 1386-94	- Does not include a combination of measures.
Van Pottelbergh, Gijs, Vaes, Bert, Adriaensen, Wim et al. (2014) The glomerular filtration rate estimated by new and old equations as a predictor of important outcomes in elderly patients. BMC medicine 12: 27	- Does not address review question. [Estimation of GFR study.]
Walther, Carl P, Gutierrez, Orlando M, Cushman, Mary et al. (2018) Serum albumin concentration and risk of end-stage renal disease: the REGARDS study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 33(10): 1770-1777	- Does not include a combination of measures.

Appendix L – Research recommendations – full details

L.1.1 Research recommendation

What is the accuracy of the kidney failure risk equation in adults, children and young people with CKD from black, Asian and minority ethnic groups living on the UK?

L.1.2 Why this is important

The kidney failure risk equation has been recommended as one of the criteria to refer adults with CKD to secondary care. The risk equation was validated in the UK but adults, children and young people with CKD from black, Asian and minority ethnic groups were underrepresented. It is important to investigate the accuracy of the equation to identify the risk of renal replacement therapy in this population.

L.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the application of the kidney failure risk equation in adults, children and young people with CKD from black, Asian and minority ethnic groups.
Relevance to NICE guidance	The kidney failure risk equation has been recommended in this guideline and there is a lack of data on adults, children and young people with CKD from black, Asian and minority ethnic groups.
Relevance to the NHS	The outcome would affect the referral to secondary care of adults, children and young people with CKD from black, Asian and minority ethnic groups.
National priorities	High
Current evidence base	Minimal
Equality considerations	Ethnicity

L.1.4 Modified PICO table

Population	Adults, children and young people with CKD from black, Asian and minority ethnic groups living on the UK
Prognostic factor	Kidney failure risk equation
Covariates	• Age • Gender • Hypertension • Diabetes • Family origin
Outcome	• Prognostic performance: • Calibration (goodness of measures.eg. R2; Brier score, Hosmer-Lemeshow test) • Discrimination (eg. sn/sp; AUC from ROC, AUROC; c-statistic)
Study design	Validation cohorts
Timeframe	Long term
Additional information	None