

## RRT and conservative management

### When to assess for RRT

*NICE guideline*

*Intervention evidence review*

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the National Guideline Centre*



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# 1 <sup>1</sup> When to assess for RRT

## 1.1 <sup>2</sup> Review question: When should people with progression to <sup>3</sup> later stages of CKD be assessed for RRT?

### 1.2 <sup>4</sup> Introduction

<sup>5</sup> The NICE guideline on Chronic Kidney Disease in adults (CG182) makes recommendations  
<sup>6</sup> about when people should be initially referred to nephrology services in secondary care.  
<sup>7</sup> Recommendations are needed on when the process of assessment and preparation for RRT  
<sup>8</sup> or conservative management should commence. This review applies to people requiring  
<sup>9</sup> referral to secondary care renal services and those already in these services but who are not  
<sup>10</sup> yet having assessment for RRT.

### 1.3 <sup>11</sup> PICO table

<sup>12</sup> For full details see the review protocol in appendix A.

<sup>13</sup> **Table 1: PICO characteristics of review question**

<b>Population</b>	Children, young people and adults with CKD stage 3 to 5  Stratified by: <ul style="list-style-type: none"> <li>• Age (&lt;2, 2 to &lt;18, 18 to &lt;70, ≥70)</li> <li>• BAME vs non-BAME</li> <li>• Diabetes mellitus vs no diabetes mellitus</li> </ul>
<b>Intervention(s)</b>	Assessment for RRT; Early
<b>Comparison(s)</b>	Assessment for RRT; Late
<b>Outcomes</b>	<p>Critical</p> <ul style="list-style-type: none"> <li>• Patient, family/carer health-related QoL (continuous)</li> <li>• Mortality (dichotomous and time to event)</li> <li>• Hospitalisation (rates or continuous)</li> <li>• Time to failure of RRT form (time to event)</li> </ul> <p>Important</p> <ul style="list-style-type: none"> <li>• Late referral rates (rates or dichotomous)</li> <li>• Pre-emptive transplantation rates (rates or dichotomous)</li> <li>• Proportion starting on modality of choice (rates or dichotomous)</li> <li>• Proportion receiving RRT after assessment (rates or dichotomous)</li> <li>• Symptom scores and functional measures (continuous)</li> <li>• Psychological distress and mental wellbeing (continuous)</li> <li>• Cognitive impairment (dichotomous)</li> <li>• Patient, family/carer experience of care (continuous)</li> <li>• Growth (continuous)</li> <li>• Malignancy (dichotomous)</li> <li>• Adverse events <ul style="list-style-type: none"> <li>○ Infections (dichotomous)</li> <li>○ Vascular access issues (dichotomous)</li> <li>○ Dialysis access issues (dichotomous)</li> <li>○ Acute transplant rejection episodes (dichotomous)</li> </ul> </li> </ul>

<b>Study design</b>	RCTs only, if insufficient RCT evidence, NRS that adjust for key confounders (age, ethnicity, comorbidities and baseline health) will be included
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## 1.4 1 Clinical evidence

### 1.4.1 2 Included studies

3 No randomised studies were identified. One non-randomised study was included in the  
4 review;<sup>58</sup> this is summarised in Table 2 below. Evidence from this study is summarised in the  
5 clinical evidence summary below (Table 3).

6 See also the study selection flow chart in appendix C, study evidence tables in appendix D,  
7 GRADE tables in appendix F and forest plots in appendix E.

### 1.4.2 8 Excluded studies

9 See the excluded studies list in appendix I.

### 1.4.3 0 Summary of clinical studies included in the evidence review

11 **Table 2: Summary of studies included in the evidence review**

Study	Intervention and comparison	Population	Outcomes	Comments
Winkelmayer 2003 <sup>58</sup>  Retrospective cohort study N=3014	Early versus late nephrologist referral  (1) Early, n= 1975, patients who saw a nephrologist >90 days before their first chronic dialysis  (2) Late, n=1039, patients who were not seen >90 days before their first chronic dialysis	Adults who had been diagnosed with a renal disease >1 year before first dialysis – no lower or upper age limit  Prevalence of diabetes of 45%  Ethnicity 74% white	Critical: • Mortality (0-90 days, 90 days -1 year)	Setting: USA

12 See appendix D for full evidence tables.

13

14

### 1.4.4 1 Quality assessment of clinical studies included in the evidence review

2 **Table 3: Clinical evidence summary: Late referral versus early referral**

Late compared to early referral for RRT					
Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with early referral	Risk difference with late (95% CI)
All-cause mortality	3014 (1 study) 90 days	VERY LOW <sup>1</sup> due to risk of bias	HR 1.75 (1.48 to 2.08)	235 per 1000	139 more per 1000 (from 92 more to 192 more)
All-cause mortality	2178 (1 study) 90 days-1 year	VERY LOW <sup>1</sup> due to risk of bias	HR 1.03 (0.84 to 1.26)	274 per 1000	7 more per 1000 (from 38 fewer to 58 more)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias					

3

4 See appendix F for full GRADE tables.

5



## **1.5 1 Economic evidence**

### **1.5.1 2 Included studies**

3 No relevant health economic studies were included.

### **1.5.2 4 Excluded studies**

5 No health economic studies that were relevant to this question were identified but excluded  
6 due to assessment of limited applicability or methodological limitations.

7 See also the health economic study selection flow chart in appendix G.

8

### 1.5.3 1 Unit costs

- 2 Relevant current UK unit costs were provided to the committee to aid consideration of cost effectiveness. Costs of nephrology outpatient  
3 appointments are summarised in Table 4. Costs of CKD-related inpatient admissions are summarised in Table 5. If a patient starts dialysis  
4 urgently requiring inpatient admission this will incur an additional inpatient stay cost (as well as the hospital dialysis costs recorded separately).  
5 Access-related costs are summarised in Table 6.

6 **Table 4: UK NHS reference costs 2015/16 for nephrology outpatient appointments**

Currency code	Currency description	No. of attendances	National average unit cost
<b>Consultant led</b>			
WF01A	Non-Admitted Face to Face Attendance, Follow-Up	576,355	£153
WF01B	Non-Admitted Face to Face Attendance, First	88,492	£194
WF01C	Non-Admitted Non-Face to Face Attendance, Follow-Up	9,450	£86
WF01D	Non-Admitted Non-Face to Face Attendance, First	1,399	£72
WF02A	Multiprofessional Non-Admitted Face to Face Attendance, Follow-Up	29,964	£169
WF02B	Multiprofessional Non-Admitted Face to Face Attendance, First	2,951	£206
WF02C	Multiprofessional Non-Admitted Non Face to Face Attendance, Follow-Up	11	£139
<b>Non-consultant led</b>			
WF01A	Non-Admitted Face to Face Attendance, Follow-Up	92,331	£108
WF01B	Non-Admitted Face to Face Attendance, First	6,947	£130
WF01C	Non-Admitted Non-Face to Face Attendance, Follow-Up	8,587	£45
WF01D	Non-Admitted Non-Face to Face Attendance, First	328	£96
WF02A	Multiprofessional Non-Admitted Face to Face Attendance, Follow-Up	452	£135
WF02B	Multiprofessional Non-Admitted Face to Face Attendance, First	24	£139

7 Source: NHS reference costs 2015/16<sup>10</sup>

8 **Table 5: UK NHS reference costs 2015/16 for CKD inpatient admissions**

Admission	Currency code	Currency description	Number of FCEs	National average unit cost	Weighted average
Elective inpatient	LA08G	Chronic Kidney Disease with Interventions, with CC Score 6+	155	£6,344	£2,369

Admission	Currency code	Currency description	Number of FCEs	National average unit cost	Weighted average
Elective inpatient	LA08H	Chronic Kidney Disease with Interventions, with CC Score 3-5	327	£4,420	
Elective inpatient	LA08J	Chronic Kidney Disease with Interventions, with CC Score 0-2	686	£3,475	
Elective inpatient	LA08K	Chronic Kidney Disease without Interventions, with CC Score 11+	74	£2,737	
Elective inpatient	LA08L	Chronic Kidney Disease without Interventions, with CC Score 8-10	151	£2,368	
Elective inpatient	LA08M	Chronic Kidney Disease without Interventions, with CC Score 5-7	317	£1,782	
Elective inpatient	LA08N	Chronic Kidney Disease without Interventions, with CC Score 3-4	437	£1,446	
Elective inpatient	LA08P	Chronic Kidney Disease without Interventions, with CC Score 0-2	1,362	£1,281	
Non-elective long stay	LA08G	Chronic Kidney Disease with Interventions, with CC Score 6+	764	£7,122	£3,398
Non-elective long stay	LA08H	Chronic Kidney Disease with Interventions, with CC Score 3-5	610	£5,083	
Non-elective long stay	LA08J	Chronic Kidney Disease with Interventions, with CC Score 0-2	541	£3,826	
Non-elective long stay	LA08K	Chronic Kidney Disease without Interventions, with CC Score 11+	480	£3,939	
Non-elective long stay	LA08L	Chronic Kidney Disease without Interventions, with CC Score 8-10	963	£3,405	
Non-elective long stay	LA08M	Chronic Kidney Disease without Interventions, with CC Score 5-7	1,655	£2,967	
Non-elective long stay	LA08N	Chronic Kidney Disease without Interventions, with CC Score 3-4	1,416	£2,446	
Non-elective long stay	LA08P	Chronic Kidney Disease without Interventions, with CC Score 0-2	1,761	£2,085	£687
Non-elective short stay	LA08H	Chronic Kidney Disease with Interventions, with CC Score 3-5	13	£988	
Non-elective short stay	LA08J	Chronic Kidney Disease with Interventions, with CC Score 0-2	13	£793	
Non-elective short stay	LA08K	Chronic Kidney Disease without Interventions, with CC Score 11+	126	£613	
Non-elective short stay	LA08L	Chronic Kidney Disease without Interventions, with CC Score 8-10	378	£570	
Non-elective short stay	LA08M	Chronic Kidney Disease without Interventions, with CC Score 5-7	923	£552	
Non-elective short stay	LA08N	Chronic Kidney Disease without Interventions, with CC Score 3-4	1,012	£592	
Non-elective short stay	LA08P	Chronic Kidney Disease without Interventions, with CC Score 0-2	2,234	£808	£379
Day case	LA08J	Chronic Kidney Disease with Interventions, with CC Score 0-2	2	£604	
Day case	LA08K	Chronic Kidney Disease without Interventions, with CC Score 11+	9	£670	
Day case	LA08L	Chronic Kidney Disease without Interventions, with CC Score 8-10	11	£311	
Day case	LA08M	Chronic Kidney Disease without Interventions, with CC Score 5-7	137	£331	
Day case	LA08N	Chronic Kidney Disease without Interventions, with CC Score 3-4	408	£340	
Day case	LA08P	Chronic Kidney Disease without Interventions, with CC Score 0-2	1,940	£389	

Admission	Currency code	Currency description	Number of FCEs	National average unit cost	Weighted average
Regular Day or Night Admissions	LA08L	Chronic Kidney Disease without Interventions, with CC Score 8-10	2	£359	£365
Regular Day or Night Admissions	LA08M	Chronic Kidney Disease without Interventions, with CC Score 5-7	7	£355	
Regular Day or Night Admissions	LA08N	Chronic Kidney Disease without Interventions, with CC Score 3-4	10	£337	
Regular Day or Night Admissions	LA08P	Chronic Kidney Disease without Interventions, with CC Score 0-2	1,652	£365	

1 Source: NHS reference costs 2015/16<sup>10</sup>

2 Abbreviations: FCE = finished consultant episodes

3 **Table 6: UK NHS reference costs 2015/16 for dialysis access-related inpatient and outpatient procedures**

Currency description	Currency code	Admission	Number of FCEs	National average unit cost	Weighted average
<b>HD access: tunnelled line</b>					
<b>Adults</b>					
Insertion of Tunnelled Central Venous Catheter, 19 years and over	YR41A	Elective inpatient	544	£1,558	£1,149
		Non-elective long stay	280	£2,157	
		Non-elective short stay	1,042	£2,043	
		Day case	3573	£750	
		Regular Day or Night Admissions	73	£1,038	
		Out-patient	2	£368	
Attention to Central Venous Catheter, 19 years and over	YR43A	Elective inpatient	752	£1,062	£383
		Non-elective long stay	9	£3,738	
		Non-elective short stay	946	£917	
		Day case	44697	£354	
		Regular Day or Night Admissions	10651	£407	
		Out-patient	90	£98	
Removal of Central Venous Catheter, 19 years and over	YR44A	Elective inpatient	314	£1,043	£570
		Non-elective long stay	25	£4,336	

Currency description	Currency code	Admission	Number of FCEs	National average unit cost	Weighted average
		Non-elective short stay	797	£1,109	
		Day case	6880	£459	
		Regular Day or Night Admissions	793	£727	
		Out-patient	95	£198	
<b>Children</b>					
Insertion of Tunnelled Central Venous Catheter, 18 years and under	YR41B	Elective inpatient	114	£2,886	£2,367
		Non-elective long stay	11	£5,926	
		Non-elective short stay	77	£2,536	
		Day case	145	£1,640	
		Regular Day or Night Admissions	3	£343	
Attention to Central Venous Catheter, 18 years and under	YR43B	Elective inpatient	95	£1,209	£650
		Non-elective long stay	8	£4,672	
		Non-elective short stay	232	£712	
		Day case	2392	£654	
		Regular Day or Night Admissions	353	£342	
Removal of Central Venous Catheter, 18 years and under	YR44B	Elective inpatient	172	£1,533	£1,323
		Non-elective long stay	11	£16,682	
		Non-elective short stay	164	£1,243	
		Day case	894	£1,163	
		Regular Day or Night Admissions	80	£708	
<b>HD access: AV fistula or graft</b>					
Open Arteriovenous Fistula, Graft or Shunt Procedures	YQ42Z	Elective inpatient	2735	£2,451	£2,012
		Non-elective long stay	144	£3,661	
		Non-elective short stay	306	£1,826	
		Day case	5291	£1,763	
		Regular Day or Night Admissions	9	£665	
		Out-patient	28	£199	
Attention to Arteriovenous	YR48Z	Elective inpatient	647	£1,715	£1,433

Currency description	Currency code	Admission	Number of FCEs	National average unit cost	Weighted average
Fistula, Graft or Shunt		Non-elective long stay	140	£2,824	
		Non-elective short stay	359	£2,079	
		Day case	2978	£1,235	
		Regular Day or Night Admissions	17	£523	
		Out-patient	3	£228	
<b>PD access: PD catheter</b>					
Renal Replacement Peritoneal Dialysis Associated Procedures	LA05Z	Elective inpatient	892	£1,819	£1,148
		Non-elective long stay	32	£5,701	
		Non-elective short stay	297	£1,288	
		Day case	1,588	£996	
		Regular Day or Night Admissions	46	£339	
		Out-patient	470	£71	

1 Source: NHS reference costs 2015/16<sup>10</sup>

2 Abbreviations: FCE = finished consultant episodes

3 (a) HRG YR43A/B Attention to Central Venous Catheter, includes OPCS L921 Fibrin sheath stripping of access catheter, L922 Wire brushing of access catheter, L923  
4 Thrombolysis of access catheter, L928 Other specified unblocking of access catheter, L929 Unspecified unblocking of access catheter, L913 Attention to central venous  
5 catheter NEC

6 (b) HRG YQ42 includes OPCS L746 Creation of graft fistula for dialysis, L741 Insertion of arteriovenous prosthesis, L742 Creation of arteriovenous fistula NEC, L743 Attention  
7 to arteriovenous shunt, L744 Banding of arteriovenous fistula, L745 Thrombectomy of arteriovenous fistula, L748 Other specified arteriovenous shunt, L749 Unspecified  
8 arteriovenous shunt, L752 Repair of acquired arteriovenous fistula

9 (c) HRG YR48 includes OPCS L746 Injection of radiocontrast substance into arteriovenous fistula

10 (d) HRG LA05 includes OPCS X411 Insertion of ambulatory peritoneal dialysis catheter, X412 Removal of ambulatory peritoneal dialysis catheter, X418 Other specified  
11 placement of ambulatory apparatus for compensation for renal failure, X419 Unspecified placement of ambulatory apparatus for compensation for renal failure, X421  
12 Insertion of temporary peritoneal dialysis catheter, X428 Other specified placement of other apparatus for compensation for renal failure, X429 Unspecified placement of  
13 other apparatus for compensation for renal failure.

14

15

16

## 1.6 1 Resource impact

2 The recommendations made based on this review (see section 1.8) are not expected to have  
3 a substantial impact on resources.

## 1.7 4 Evidence statements

### 1.7.1 5 Clinical evidence statements

6 There was no evidence identified for quality of life, hospitalisation, time to failure of RRT  
7 form, late referral rates, pre-emptive transplantation rates, proportion starting on modality of  
8 choice, proportion receiving RRT after assessment, symptom scores/functional measures,  
9 psychological distress and mental wellbeing, cognitive impairment, experience of care,  
10 growth, malignancy or adverse events.

11 There was no clinically important difference in all-cause mortality from day 90 to 1 year (1  
12 study, very low quality evidence).

13 There was a clinically important harm of late referral for all-cause mortality in the first 90 days  
14 (1 study, very low quality evidence).

### 1.7.2 5 Health economic evidence statements

16 • No relevant economic evaluations were identified.

## 1.8 17 Recommendations

18 E1. Start assessment for RRT or conservative management at least 1 year before therapy is  
19 likely to be needed, including for those with a failing transplant.

## 1.9 20 Rationale and impact

### 1.9. 21 Why the committee made the recommendations

22 Some evidence indicated that earlier referral to nephrology services improved survival on  
23 RRT at 90 days. The committee were interested in the timing of referral for assessment for  
24 RRT and used their experience to recommend that this should be at least 1 year before RRT  
25 is likely to be needed. They agreed that this would provide time for clinical and psychological  
26 preparation for dialysis or pre-emptive transplantation, and give the person, family members  
27 and carers enough time to think about the options. The committee acknowledged that there  
28 might be possible harms and costs for people who were referred but did not go on to need  
29 RRT, but they agreed that these were outweighed by the benefits of early referral for most  
30 people.

### 1.9.2 1 Impact of the recommendations on practice

32 The recommendation generally reflects current practice so there should be no significant  
33 change in practice or substantial resource impact to the NHS in England.

34  
35

## 1.10 The committee's discussion of the evidence

### 1.10.2 Interpreting the evidence

#### 1.10.1.1 The outcomes that matter most

- 4 Critical outcomes were mortality, quality of life, hospitalisation, symptom scores and time to
- 5 failure of RRT.
- 6 Other important outcomes were numbers of measures of mental wellbeing and cognitive
- 7 impairment, malignancy and adverse events. Growth is considered an important outcome in
- 8 children. We were also interested in outcomes representing people's experience of care.

#### 1.10.1.2 The quality of the evidence

10 The GC noted that the only study identified for this review did not specifically assess the  
11 importance of the timing of referral for RRT assessment but rather assessed the importance  
12 of the timing of a nephrology referral. A nephrology referral may be for a variety of reasons  
13 other than assessment for RRT, including investigating the aetiology of the condition and  
14 actions to treat and monitor the condition and preserve renal function. The assessment for  
15 RRT happens within renal services, but often requires transfer of patient care from an  
16 individual consultant-led review to a multidisciplinary review. This usually follows recognition  
17 that the person with kidney disease has now reached a stage where plans need to be made  
18 to manage the progressive nature of their condition, and the multidisciplinary team is needed  
19 to cover all aspects of the person's care and future care plans. Therefore, the committee  
20 agreed that this evidence was appropriate to include but noted that it did not exactly mirror  
21 the target intervention of the review

22 The committee noted that the evidence identified in this review represented a comparison  
23 between very late referral versus not very late referral. The very late referral group perhaps  
24 more accurately represented people having an unplanned start to dialysis, although the  
25 population had been documented as having a diagnosis of CKD for at least one year. The  
26 committee noted the impact of the study being set in the US with a different primary care  
27 system than in the UK.

28 The committee noted that referral to nephrologist is only a proxy for the full multidisciplinary  
29 assessment required.

#### 1.10.1.3 Benefits and harms

31 The evidence showed at 90 days there was a harm of late referral in terms of higher mortality  
32 compared to earlier referral. At 90 days to a year the difference in mortality was no longer  
33 clinically different

34 The committee discussed how practically the amount of time required for assessment  
35 reflects both the speed of accomplishing the various tasks involved in assessment but also  
36 the time needed for people to deliberate over decisions that have to be made in this period.

37 The committee noted that alongside the more obvious benefits of early referral (for example  
38 ensuring full preparation and assessment, avoiding unplanned starts and improving pre-  
39 emptive transplantation rates) there are potential harms of early referral in the form of  
40 unnecessary treatment or psychological burden for people who are referred for consideration  
41 of RRT but then never go on to require it. Therefore when considering when to refer for  
42 assessment there is a need to balance allowing sufficient time to prepare for RRT with  
43 minimising referral of those that will never receive it.



1 The committee discussed the difficulty in predicting when a person may require renal  
2 replacement therapy. The consensus of the committee was that people should be referred  
3 for assessment at least 12 months before renal replacement therapy needs to be initiated.  
4 This is to enable the person time to make an informed decision about their treatment options,  
5 to allow vascular access to be created and other psychological and clinical assessments and  
6 investigations to occur.

### **1.10.2 Cost effectiveness and resource use**

8 No relevant health economic studies were identified.

9 The potential benefits of assessing people earlier described above (reducing unplanned  
10 starters and increasing pre-emptive transplant rates) may result in lower resource use and  
11 benefits to patients that may increase QALYs. The committee highlighted that reducing  
12 unplanned starters would be expected to reduce costs because they will generally require a  
13 hospital admission for a number of days and it is likely it will also require additional access  
14 procedures. Improving access to pre-emptive transplant was also considered likely to result  
15 in better outcomes for patients and may reduce costs (due to avoiding starting dialysis and  
16 reducing transplant failure).

17 However, conversely the potential harms described above (assessment in people who do not  
18 go on to need RRT) would increase resource use and could potentially have a negative  
19 impact on patient QALYs if quality of life was reduced. The cost of this would relate to  
20 outpatient appointments for general assessment for RRT and, in parallel, assessment and  
21 tests to assess suitability for transplant. A series of healthcare contacts with doctors and/or  
22 nurses is required to support the decision making process. If dialysis access is created, this  
23 will be associated with resource use such as an outpatient appointment with a surgeon,  
24 scans, the surgery itself and follow-up.

25 No studies were available that allowed quantitative assessment of this trade-off. However,  
26 the committee felt that referring people at least 1 year before it is anticipated they would  
27 need RRT was practical and would strike a reasonable balance between maximising  
28 adequate assessment and preparation without unduly increasing the number of people being  
29 assessed. The committee highlighted that this generally reflects current practice should not  
30 be a significant change in practice or have a substantial resource impact to the NHS in  
31 England.

### **1.10.3 Other considerations**

33 None.

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# 1 Appendices

## 2 Appendix A: Review protocols

3 Table 7: Review protocol: When to assess for RRT

Field	Content
Review question	When should people progressing through later stages of CKD be assessed for RRT?
Type of review question	Intervention
Objective of the review	Identify evidence of clinical and cost effectiveness of different timing strategies for RRT assessment
Eligibility criteria – population / disease / condition / issue / domain	Children, young people and adults with CKD stage 3 to 5  Stratified by: <ul style="list-style-type: none"> <li>• Age (&lt;2, 2 to &lt;18, 18 to &lt;70, ≥70)</li> <li>• BAME vs non-BAME</li> <li>• DM vs no DM</li> </ul>
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	<ul style="list-style-type: none"> <li>• Early assessment by eGFR (e.g. 15-20/20-25/25-30ml/min)</li> <li>• Late assessment by eGFR (e.g. 10-15ml/min)</li> <li>• Early assessment by time from start of dialysis (either actual or estimated from risk tool – e.g. Tangri score)</li> <li>• Late assessment by time from start of dialysis (either actual or estimated from risk tool – e.g. Tangri score)</li> </ul> <p>Assessment to include at minimum consultation with RRT specialist healthcare professional, aimed at decision making around RRT/conservative management and/or preparation for RRT</p>
Eligibility criteria – comparator(s) / control or reference (gold) standard	Any early strategy compared with any late strategy
Outcomes and prioritisation	<p>Critical</p> <ul style="list-style-type: none"> <li>• Patient, family/carer health-related QoL (continuous)</li> <li>• Mortality (dichotomous and time to event)</li> <li>• Hospitalisation (rates or continuous)</li> <li>• Time to failure of RRT form (time to event)</li> </ul> <p>Important</p> <ul style="list-style-type: none"> <li>• Symptom scores and functional measures (continuous)</li> <li>• Late referral rates (rates or dichotomous)</li> <li>• Pre-emptive transplantation rates (rates or dichotomous)</li> <li>• Proportion starting on modality of choice (rates or dichotomous)</li> <li>• Proportion receiving RRT after assessment (rates or dichotomous)</li> <li>• Psychological distress and mental wellbeing (continuous)</li> <li>• Cognitive impairment (dichotomous)</li> <li>• Patient, family/carer experience of care (continuous)</li> </ul>

	<ul style="list-style-type: none"> <li>• Growth (continuous)</li> <li>• Malignancy (dichotomous)</li> <li>• Adverse events <ul style="list-style-type: none"> <li>○ Infections (dichotomous)</li> <li>○ Vascular access issues (dichotomous)</li> <li>○ Dialysis access issues (dichotomous)</li> <li>○ Acute transplant rejection episodes (dichotomous)</li> </ul> </li> </ul> <p>When outcomes are reported at multiple timepoints, the later timepoints will be prioritised. All outcomes must be reported after at least 4 weeks of the intervention under investigation. The outcomes of mortality and hospitalisation must be reported after at least 6 months.</p> <p>For quality of life, symptom scores/functional measures, psychological distress/mental wellbeing and experience of care, any validated measures will be accepted.</p> <p>Absolute MIDs of 30 per 1000 will be used for mortality and modality failure. Absolute MIDs of 100 per 1000 will be used for all other outcomes dichotomous outcomes. Where relative MIDs are required (if absolute effects are unavailable), 0.90 to 1.11 will be used for mortality and modality failure. The default relative MIDs of 0.8 to 1.25 will be used for all other dichotomous outcomes. Default continuous MIDs of 0.5x SD will be used for all continuous outcomes, except where published, validated MIDs exist.</p>
Eligibility criteria – study design	RCTs only, if insufficient RCT evidence, NRS that adjust for key confounders (age, ethnicity, comorbidities and baseline health) will be included
Other inclusion exclusion criteria	
Proposed sensitivity / subgroup analysis, or meta-regression	Different modalities of RRT
Selection process – duplicate screening / selection / analysis	No duplicate screening was deemed necessary for this question, for more information please see the separate Methods report for this guideline.
Data management (software)	<ul style="list-style-type: none"> <li>• Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5).</li> <li>• GRADEpro was used to assess the quality of evidence for each outcome.</li> <li>• Endnote was used for bibliography, citations, sifting and reference management.</li> </ul>
Information sources – databases and dates	<p>Clinical search databases to be used: Medline, Embase, Cochrane Library Date: All years</p> <p>Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2014 NHSEED, HTA – all years</p> <p>Language: Restrict to English only Supplementary search techniques: backward citation searching Key papers: Not known</p>
Identify if an update	Not an update
Author contacts	<a href="https://www.nice.org.uk/guidance/indevelopment/gid-ng10019">https://www.nice.org.uk/guidance/indevelopment/gid-ng10019</a>



Highlight if amendment to previous protocol	Not an amendment
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendices of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’ developed by the international GRADE working group <a href="http://www.gradeworkinggroup.org/">http://www.gradeworkinggroup.org/</a>
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jan Dudley in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

1

## 2 Table 8: Health economic review protocol

<b>Review question</b>	<b>All questions – health economic evidence</b>
<b>Objectives</b>	To identify economic studies relevant to any of the review questions.

<p><b>Search criteria</b></p>	<ul style="list-style-type: none"> <li>• Populations, interventions and comparators must be as specified in the individual review protocol above.</li> <li>• Studies must be of a relevant economic study design (cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-consequences analysis, comparative cost analysis).</li> <li>• Studies must not be a letter, editorial or commentary, or a review of economic evaluations. (Recent reviews will be ordered although not reviewed; the bibliographies will be checked for relevant studies, which will then be ordered.)</li> <li>• Unpublished reports will not be considered unless submitted as part of a call for evidence.</li> <li>• Studies must be in English.</li> </ul>
<p><b>Search strategy</b></p>	<p>An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix B.2 Health economics literature search strategy.</p>
<p><b>Review strategy</b></p>	<p>Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.</p> <p>Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the 2012 NICE guidelines manual.<sup>39</sup> Each included study is summarised in an economic evidence profile and an evidence table. Any excluded studies are detailed in the excluded studies table with the reason for exclusion in Appendix I.</p> <p><b>Inclusion and exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• If a study is rated as both ‘Directly applicable’ and with ‘Minor limitations’ then it will be included in the guideline.</li> <li>• If a study is rated as either ‘Not applicable’ or with ‘Very serious limitations’ then it will usually be excluded from the guideline.</li> <li>• If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both then there is discretion over whether it should be included.</li> </ul> <p><b>Where there is discretion</b></p> <p>The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the Committee if required. The ultimate aim is to include economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the Committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. For example, if a high quality study from a UK perspective is available a similar study from another country’s perspective may be excluded.</p> <p>The health economist will be guided by the following hierarchies.</p> <p><i>Setting:</i></p> <ul style="list-style-type: none"> <li>• UK NHS (most applicable).</li> <li>• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).</li> <li>• OECD countries with predominantly private health insurance systems (for example, Switzerland).</li> <li>• Studies set in non-OECD countries or in the USA will have been excluded before being assessed for applicability and methodological limitations.</li> </ul> <p><i>Economic study type:</i></p> <ul style="list-style-type: none"> <li>• Cost-utility analysis (most applicable).</li> <li>• Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis,</li> </ul>

<p>cost-consequences analysis).</p> <ul style="list-style-type: none"> <li>• Comparative cost analysis.</li> <li>• Non-comparative cost analyses including cost-of-illness studies will have been excluded before being assessed for applicability and methodological limitations.</li> </ul> <p><i>Year of analysis:</i></p> <ul style="list-style-type: none"> <li>• The more recent the study, the more applicable it will be.</li> <li>• Studies published in 2001 or later but that depend on unit costs and resource data entirely or predominantly from before 2001 will be rated as 'Not applicable'.</li> <li>• Studies published before 2001 will have been excluded before being assessed for applicability and methodological limitations.</li> </ul> <p><i>Quality and relevance of effectiveness data used in the economic analysis:</i></p> <ul style="list-style-type: none"> <li>• The more closely the clinical effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.</li> <li>• The following will be rated as 'Very serious limitations' and excluded: economic analyses undertaken as part of clinical studies that are excluded from the clinical review; economic models where relative treatment effects are based entirely on studies that are excluded from the clinical review; comparative costing analyses that only look at the cost of delivering dialysis (as current UK NHS reference costs are considered a more relevant estimate of this for the guideline); within-trial economic analyses based on non-randomised studies that do not meet the minimum adjustment criteria outlined in the main review protocol.</li> </ul>
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## 1 Appendix B: Literature search strategies

### B.1.2 Clinical search literature search strategy

3 The literature searches for this review are detailed below and complied with the methodology  
4 outlined in Developing NICE guidelines: the manual 2014, updated 2017  
5 [https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-](https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869)  
6 [pdf-72286708700869](https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869)

7 *For more detailed information, please see the Methodology Review.*

8 Searches were constructed using a PICO framework where population (P) terms were  
9 combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are  
10 rarely used in search strategies for interventions as these concepts may not be well  
11 described in title, abstract or indexes and therefore difficult to retrieve. Search filters were  
12 applied to the search where appropriate.

13 **Table 9: Database date parameters and filters used**

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 11 December 2017	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 11 December 2017	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2017 Issue 12 of 12 CENTRAL to 2017 Issue 11	None

Database	Dates searched	Search filter used
	of12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	

- 1 1. Line 81 (Medline) and line 75 (Embase) were added to the search strategy to reduce the
- 2 number of items retrieved for observational studies as the overall results from the search
- 3 were very large.
- 4 This was checked to ensure that relevant studies were not excluded.

#### 5 Medline (Ovid) search terms

1.	exp Renal Replacement Therapy/
2.	((renal or kidney) adj2 replace*).ti,ab.
3.	(hemodiafilt* or haemodiafilt* or (biofilt* adj1 acetate-free)).ti,ab.
4.	(hemodialys* or haemodialys*).ti,ab.
5.	((kidney* or renal) adj3 (transplant* or graft*)).ti,ab.
6.	capd.ti,ab.
7.	dialys*.ti,ab.
8.	(artificial adj1 kidney*).ti,ab.
9.	or/1-8
10.	limit 9 to English language
11.	letter/
12.	editorial/
13.	news/
14.	exp historical article/
15.	Anecdotes as Topic/
16.	comment/
17.	case report/
18.	(letter or comment*).ti.
19.	or/11-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animals/ not humans/
23.	Animals, Laboratory/
24.	exp animal experiment/
25.	exp animal model/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	10 not 28
30.	randomized controlled trial.pt.
31.	controlled clinical trial.pt.
32.	randomi#ed.ti,ab.
33.	placebo.ab.
34.	drug therapy.fs.
35.	randomly.ti,ab.
36.	trial.ab.

37.	groups.ab.
38.	or/30-37
39.	Clinical Trials as topic.sh.
40.	trial.ti.
41.	or/30-33,35,39-40
42.	Meta-Analysis/
43.	Meta-Analysis as Topic/
44.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
45.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
46.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
47.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
48.	(search* adj4 literature).ab.
49.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
50.	cochrane.jw.
51.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
52.	or/42-51
53.	29 and (41 or 52)
54.	exp Renal Replacement Therapy/
55.	((renal or kidney*) adj2 replace*).ti,ab.
56.	(hemodiafilt* or haemodiafilt* or haemofilt* or hemofilt*).ti,ab.
57.	(hemodialys* or haemodialys*).ti,ab.
58.	((kidney* or renal or pre-empt* or preempt*) adj3 (transplant* or graft*)).ti,ab.
59.	(capd or apd or ccpd or dialys*).ti,ab.
60.	or/54-59
61.	letter/
62.	editorial/
63.	news/
64.	exp historical article/
65.	Anecdotes as Topic/
66.	comment/
67.	case report/
68.	(letter or comment*).ti.
69.	or/61-68
70.	randomized controlled trial/ or random*.ti,ab.
71.	147 not 148
72.	animals/ not humans/
73.	Animals, Laboratory/
74.	exp Animal Experimentation/
75.	exp Models, Animal/
76.	exp Rodentia/
77.	(rat or rats or mouse or mice).ti.
78.	or/72-77
79.	60 not 78

80.	limit 79 to English language
81.	(mycophenolic acid or azathioprine or sirolimus or everolimus or tacrolimus or cyclosporin* or steroid or calcineurin inhibitor or anaemi* or anemi* or vitamin d or immunosuppres*).ti. <sup>1</sup>
82.	80 not 81
83.	Epidemiologic studies/
84.	Observational study/
85.	exp Cohort studies/
86.	(cohort adj (study or studies or analys* or data)).ti,ab.
87.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
88.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
89.	Controlled Before-After Studies/
90.	Historically Controlled Study/
91.	Interrupted Time Series Analysis/
92.	(before adj2 after adj2 (study or studies or data)).ti,ab.
93.	or/83-92
94.	Registries/
95.	Management Audit/ or Clinical Audit/ or Nursing Audit/ or Medical Audit/
96.	(registry or registries).ti,ab.
97.	(audit or audits or auditor or auditors or auditing or auditable).ti,ab.
98.	or/94-97
99.	93 or 98
100.	82 and 99
101.	100 not 53
102.	53 or 101

#### 1 Embase (Ovid) search terms

1.	exp *renal replacement therapy/
2.	((renal or kidney) adj2 replace*).ti,ab.
3.	(hemodiafilt* or haemodiafilt* or (biofilt* adj1 acetate-free)).ti,ab.
4.	(hemodialys* or haemodialys*).ti,ab.
5.	((kidney* or renal) adj3 (transplant* or graft*)).ti,ab.
6.	capd.ti,ab.
7.	dialys*.ti,ab.
8.	(artificial adj1 kidney*).ti,ab.
9.	or/1-8
10.	limit 9 to English language
11.	letter.pt. or letter/
12.	note.pt.
13.	editorial.pt.
14.	case report/ or case study/
15.	(letter or comment*).ti.
16.	or/11-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17

19.	animal/ not human/
20.	nonhuman/
21.	exp Animal Experiment/
22.	exp Experimental Animal/
23.	animal model/
24.	exp Rodent/
25.	(rat or rats or mouse or mice).ti.
26.	or/18-25
27.	10 not 26
28.	random*.ti,ab.
29.	factorial*.ti,ab.
30.	(crossover* or cross over*).ti,ab.
31.	((doubl* or singl*) adj blind*).ti,ab.
32.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
33.	crossover procedure/
34.	single blind procedure/
35.	randomized controlled trial/
36.	double blind procedure/
37.	or/28-36
38.	systematic review/
39.	meta-analysis/
40.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
41.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
42.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
43.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
44.	(search* adj4 literature).ab.
45.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
46.	cochrane.jw.
47.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
48.	or/38-47
49.	27 and (37 or 48)
50.	*renal replacement therapy/
51.	((renal or kidney*) adj2 replace*).ti,ab.
52.	(hemodiafilt* or haemodiafilt* or haemofilt* or hemofilt*).ti,ab.
53.	(hemodialys* or haemodialys*).ti,ab.
54.	((kidney* or renal or pre-empt* or preempt*) adj3 (transplant* or graft*)).ti,ab.
55.	(capd or apd or ccpd or dialys*).ti,ab.
56.	or/50-55
57.	letter.pt. or letter/
58.	note.pt.
59.	editorial.pt.
60.	case report/ or case study/
61.	(letter or comment*).ti.

62.	or/57-61
63.	randomized controlled trial/ or random*.ti,ab.
64.	62 not 63
65.	animal/ not human/
66.	nonhuman/
67.	exp Animal Experiment/
68.	exp Experimental Animal/
69.	animal model/
70.	exp Rodent/
71.	(rat or rats or mouse or mice).ti.
72.	or/64-71
73.	56 not 72
74.	limit 73 to English language
75.	(mycophenolic acid or azathioprine or sirolimus or everolimus or tacrolimus or cyclosporin* or steroid or calcineurin inhibitor or anaemi* or anemi* or vitamin d or immunosuppres*).ti. <sup>1</sup>
76.	74 not 75
77.	Clinical study/
78.	Observational study/
79.	family study/
80.	longitudinal study/
81.	retrospective study/
82.	prospective study/
83.	cohort analysis/
84.	follow-up/
85.	cohort*.ti,ab.
86.	84 and 85
87.	(cohort adj (study or studies or analys* or data)).ti,ab.
88.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
89.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
90.	(before adj2 after adj2 (study or studies or data)).ti,ab.
91.	or/77-83,86-90
92.	register/
93.	medical audit/
94.	(registry or registries).ti,ab.
95.	(audit or audits or auditor or auditors or auditing or auditable).ti,ab.
96.	or/92-95
97.	91 or 96
98.	76 and 97
99.	98 not 49
100.	49 or 99

## 1 Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Renal Replacement Therapy] explode all trees
#2.	((renal or kidney*) near/2 replace*).ti,ab



#3.	(hemodiafilt* or haemodiafilt* or haemofilt* or hemofilt*):ti,ab
#4.	(hemodialys* or haemodialys*):ti,ab
#5.	((kidney* or renal or pre-empt* or preempt*) near/3 (transplant* or graft*)):ti,ab
#6.	(capd or apd or ccpd or dialys*):ti,ab
#7.	(biofilt* near/1 acetate-free):ti,ab
#8.	(artificial near/1 kidney*):ti,ab
#9.	(or #1-#8)

## B.2.1 Health Economics literature search strategy

2 Health economic evidence was identified by conducting a broad search relating to renal  
3 replacement therapy population in NHS Economic Evaluation Database (NHS EED – this  
4 ceased to be updated after March 2015) and the Health Technology Assessment database  
5 (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for  
6 Research and Dissemination (CRD). Additional searches were run on Medline and Embase  
7 for health economics.

### 8 Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline & Embase	2014 – 11 December 2017	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA & NHS EED- Inception – 11 December 2017	None

### 9 Medline (Ovid) search terms

1.	exp Renal Replacement Therapy/
2.	((renal or kidney) adj2 replace*).ti,ab.
3.	(hemodiafilt* or haemodiafilt* or (biofilt* adj1 acetate-free)).ti,ab.
4.	(hemodialys* or haemodialys*):ti,ab.
5.	((kidney* or renal) adj3 (transplant* or graft*)):ti,ab.
6.	capd.ti,ab.
7.	dialys*.ti,ab.
8.	(artificial adj1 kidney*).ti,ab.
9.	or/1-8
10.	limit 9 to English language
11.	letter/
12.	editorial/
13.	news/
14.	exp historical article/
15.	Anecdotes as Topic/
16.	comment/
17.	case report/
18.	(letter or comment*).ti.
19.	or/11-18
20.	randomized controlled trial/ or random*.ti,ab.

21.	19 not 20
22.	animals/ not humans/
23.	Animals, Laboratory/
24.	exp animal experiment/
25.	exp animal model/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	10 not 28
30.	Economics/
31.	Value of life/
32.	exp "Costs and Cost Analysis"/
33.	exp Economics, Hospital/
34.	exp Economics, Medical/
35.	Economics, Nursing/
36.	Economics, Pharmaceutical/
37.	exp "Fees and Charges"/
38.	exp Budgets/
39.	budget*.ti,ab.
40.	cost*.ti.
41.	(economic* or pharmaco?economic*).ti.
42.	(price* or pricing*).ti,ab.
43.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
44.	(financ* or fee or fees).ti,ab.
45.	(value adj2 (money or monetary)).ti,ab.
46.	or/30-45
47.	29 and 46

#### 1 Embase (Ovid) search terms

1.	exp renal replacement therapy/
2.	((renal or kidney) adj2 replace*).ti,ab.
3.	(hemodiafilt* or haemodiafilt* or (biofilt* adj1 acetate-free)).ti,ab.
4.	(hemodialys* or haemodialys*).ti,ab.
5.	((kidney* or renal) adj3 (transplant* or graft*)).ti,ab.
6.	capd.ti,ab.
7.	dialys*.ti,ab.
8.	(artificial adj1 kidney*).ti,ab.
9.	or/1-8
10.	limit 9 to English language
11.	letter.pt. or letter/
12.	note.pt.
13.	editorial.pt.
14.	case report/ or case study/

15.	(letter or comment*).ti.
16.	or/11-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animal/ not human/
20.	nonhuman/
21.	exp Animal Experiment/
22.	exp Experimental Animal/
23.	animal model/
24.	exp Rodent/
25.	(rat or rats or mouse or mice).ti.
26.	or/18-25
27.	10 not 26
28.	*health economics/
29.	exp *economic evaluation/
30.	exp *health care cost/
31.	exp *fee/
32.	budget/
33.	funding/
34.	budget*.ti,ab.
35.	cost*.ti.
36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*).ab.
39.	(financ* or fee or fees).ti,ab.
40.	(value adj2 (money or monetary)).ti,ab.
41.	or/28-40
42.	27 and 41

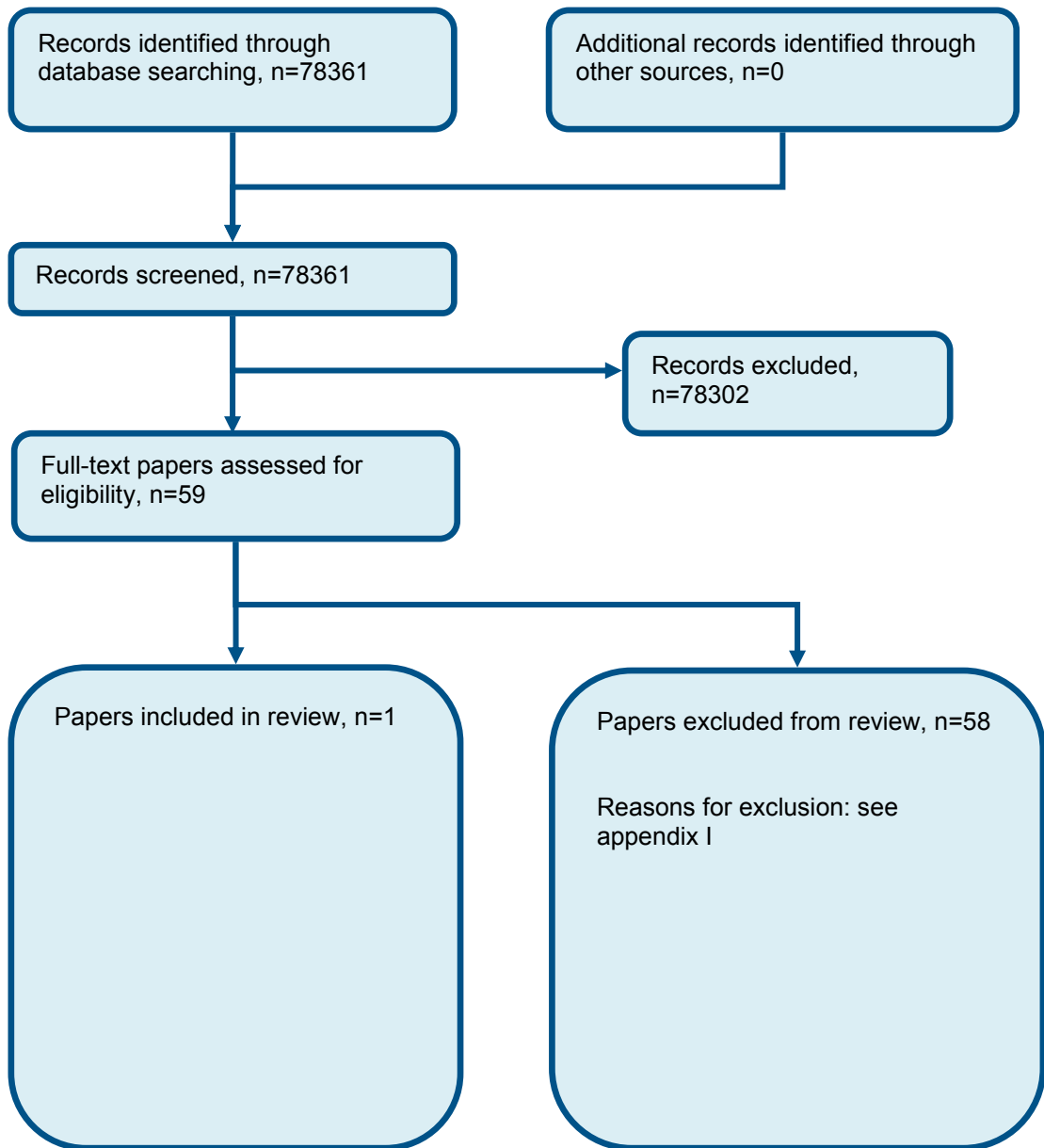
## 1 NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Renal Replacement Therapy EXPLODE ALL TREES
#2.	(((renal or kidney) adj2 replace*))
#3.	((hemodiafilt* or haemodiafilt* or (biofilt* adj1 acetate-free)))
#4.	((hemodialys* or haemodialys*))
#5.	(((kidney* or renal) adj3 (transplant* or graft*)))
#6.	(capd)
#7.	(dialys*)
#8.	((artificial adj1 kidney*))
#9.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

2

# 1 Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of when to assess for RRT



2

## 1 Appendix D: Clinical evidence tables

Study	Winkelmayer 2003 <sup>58</sup>
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=3014)
Countries and setting	Conducted in USA; Setting: New Jersey
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	General population
Subgroup analysis within study	Not applicable
Inclusion criteria	Incident peritoneal and haemodialysis patients enrolled in the Medicaid, Medicare, or Pharmaceutical Assistance for the Aged and Disabled programs in the state of New Jersey who had progressed chronically rather than acutely to end-stage renal failure. Patients had been diagnosed with a renal disease > 1 year before first dialysis.
Exclusion criteria	Patients who received only a single dialysis and survived > 1 month thereafter or who received a limited series of dialysis treatments and survived >2 months.
Recruitment/selection of patients	Cohort of 3014 patients starting dialysis between 1991 and mid-1996.
Age, gender and ethnicity	Age - Other: <45 year: early 3%, late 3%; 45-54 years: early 4%, late 6%; 55-64 years: early 9%, late 8%; 65-74 years: early 45%, late 39%; 75-84 years: early 35%, late 36%; >85 years: early 5%; late 8%. Gender (M:F): 1/1. Ethnicity: White: early referrals 75%, late referrals 73%; Black: early referrals 20%, late referrals 19%; Other early referrals 5%, late referrals 9%
Further population details	
Indirectness of population	No indirectness
Interventions	(n=1975) Intervention 1: Assessment for RRT - Early. Patients who saw a nephrologist >90 days before their first chronic dialysis were labelled as early referrals. Duration 1 year. Concurrent medication/care: N/A  (n=1039) Intervention 2: Assessment for RRT - Late. Patients who saw nephrologist at any other time apart from >90 days before their first chronic dialysis. Duration 1 year. Concurrent medication/care: N/A

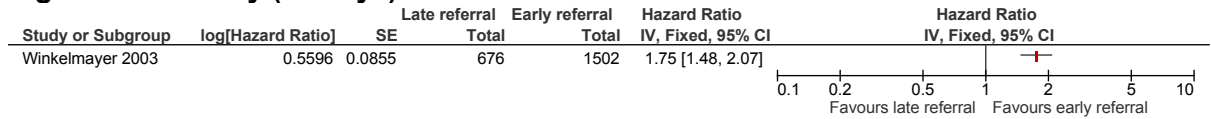
Study	Winkelmayer 2003 <sup>58</sup>
Funding	Academic or government funding (Supported by grants from the Agency for Health Care Research and Quality and the National Institute on Aging)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LATE versus EARLY</p> <p>Protocol outcome 1: Mortality                      - Actual outcome for General population: Mortality at 1-90 days; Group 1: Observed events 363 n=1039 ; Group 2: Observed events 465 n=1975; HR 1.75; Lower CI 1.48 to Upper CI 2.08                      Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0                      - Actual outcome for General population: Mortality at 1 year; Group 1: Observed events 190 n=676 ; Group 2: Observed events 411 n=1502; HR 1.03; Lower CI 0.84 to Upper CI 1.25                      Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 363, Reason: Death, transplanted, censored by timing of referral and time period.; Group 2 Number missing: 473, Reason: Death, transplanted, censored by timing of referral and time period.</p>	
Protocol outcomes not reported by the study	Quality of life patient/family/carer ; Symptom scores and functional measurers ; Hospitalisation ; Time to failure of RRT ; Late referral rates ; Pre-emptive transplantation rates ; Proportion starting on modality of choice ; Proportion receiving RRT after assessment ; Psychological distress and mental wellbeing ; Cognitive impairment ; Patient/family/carer experience of care ; Growth ; Malignancy ; Adverse event

1  
2

# 1 Appendix E: Forest plots

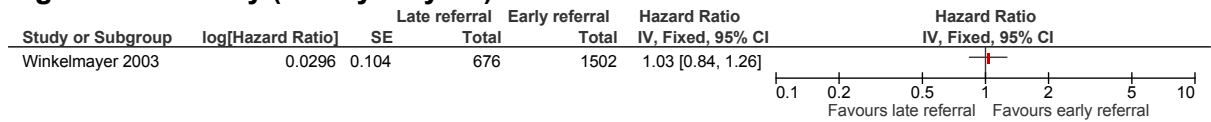
## E.1.2 Late referral versus early referral for RRT in people 3 diagnosed with chronic renal failure

Figure 2: Mortality (90 days)



4

Figure 3: Mortality (90 days-1 year)



5

6

# 1 Appendix F: GRADE tables

2 Table 11: Clinical evidence profile: Late referral versus early referral for RRT in people diagnosed with chronic renal failure

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Late	Early referral	Relative (95% CI)	Absolute		
<b>All-cause mortality (follow-up 90 days)</b>												
1	observational studies	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	363/1039 (34.9%)	465/1975 (23.5%)	HR 1.75 (1.48 to 2.08)	139 more per 1000 (from 92 more to 192 more)	⊕○○○ VERY LOW	CRITICAL
<b>All-cause mortality (follow-up 90 days-1 year)</b>												
1	observational studies	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	190/676 (28.1%)	411/1502 (27.4%)	HR 1.03 (0.84 to 1.26)	7 more per 1000 (from 38 fewer to 58 more)	⊕○○○ VERY LOW	CRITICAL

3 <sup>1</sup> Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of  
4 bias

5 <sup>2</sup> Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

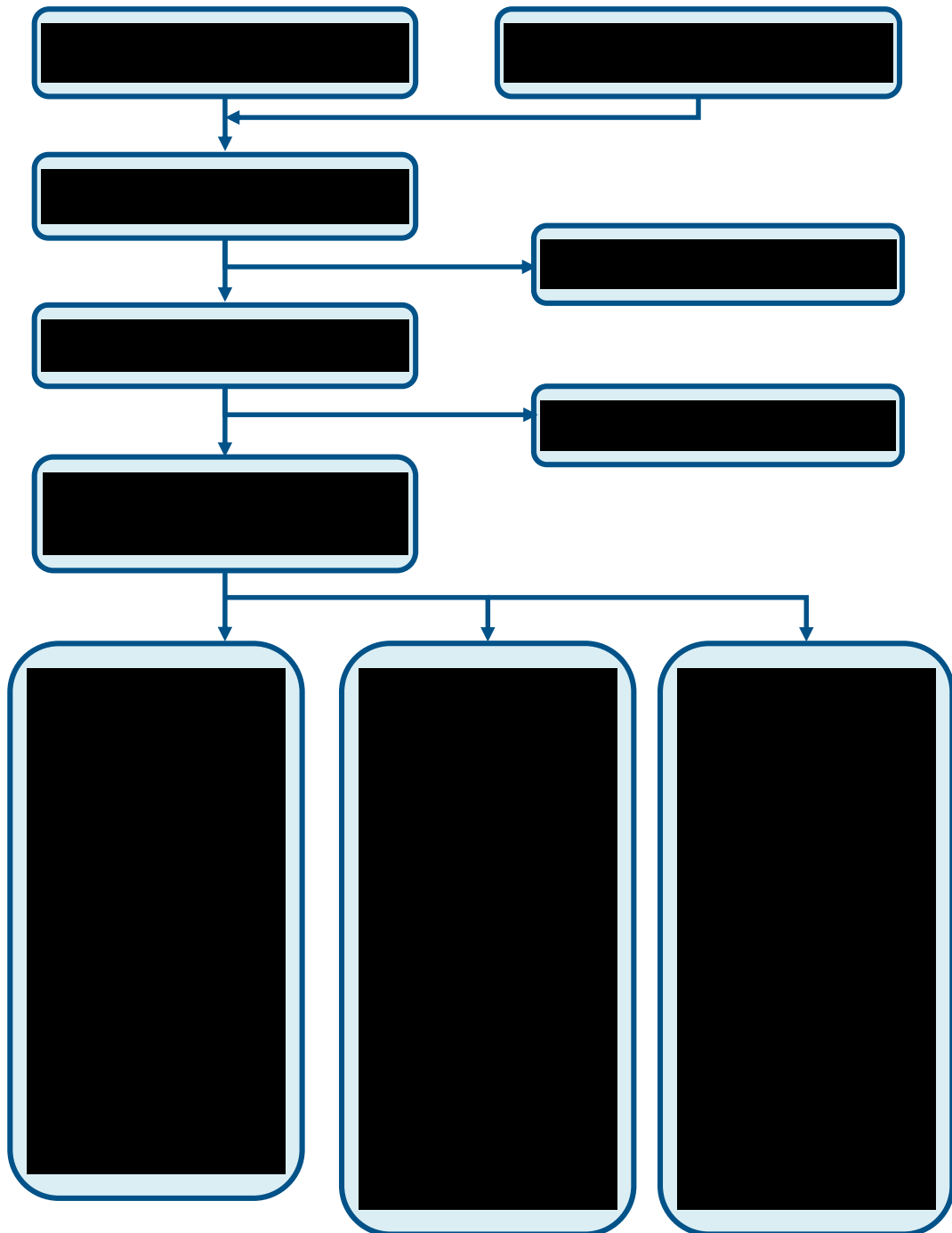
6

7



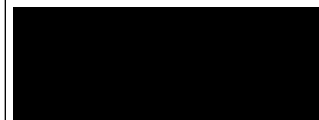
# 1 Appendix G: Health economic evidence selection

Figure 4: Flow chart of economic study selection for the guideline



A = starting RRT  
B = modality of RRT, subgroups and CM  
C = sequencing  
D = planning for RRT  
E = When to assess  
F = what to assess  
G = Indicators for switching or stopping RRT  
I = diet and fluids  
J = frequency of review  
L = decision support interventions  
M = coordinating care

*Note: Reviews H and K do not have an economic component*



# 1 **Appendix H: Health economic evidence tables**

2 None.

3

4

# 1 Appendix I: Excluded studies

## I.1.2 Excluded clinical studies

3 Table 12: Studies excluded from the clinical review

Study	Exclusion reason
Arora 2015 <sup>1</sup>	Not review population
Avorn 2002 <sup>2</sup>	Inappropriate comparison. No adjustment for confounders
Ballerini 2002 <sup>3</sup>	Non-English study
Caskey 2003 <sup>4</sup>	No adjustment for confounders
Chen 2010 <sup>5</sup>	No adjustment for confounders
Chow 2008 <sup>6</sup>	No adjustment for confounders
Churchill 1997 <sup>7</sup>	Systematic review - references checked
Curtis 2002 <sup>8</sup>	Not review population. No adjustment for confounders
De Jager 2011 <sup>9</sup>	No adjustment for confounders
Dogan 2005 <sup>11</sup>	No adjustment for confounders
Ellis 1998 <sup>12</sup>	No adjustment for confounders
Gallego 2003 <sup>13</sup>	Non-English study
Goransson 2001 <sup>14</sup>	No adjustment for confounders
Hasegawa 2009 <sup>15</sup>	Inappropriate comparison
Hayashi 2016 <sup>16</sup>	No adjustment for confounders
Helal 2010 <sup>17</sup>	Abstract only
Herget-Rosenthal 2010 <sup>18</sup>	Not review population. No adjustment for confounders
Hoffmann 2006 <sup>19</sup>	Non-English study
Hommel 2012 <sup>20</sup>	No adjustment for confounders
Ilhan 2013 <sup>21</sup>	No adjustment for confounders
Inaguma 2011 <sup>22</sup>	No adjustment for confounders
Jakubovic 2013 <sup>23</sup>	Inappropriate comparison
Jungers 1993 <sup>27</sup>	No adjustment for confounders
Jungers 1997 <sup>26</sup>	Non-English study
Jungers 2001 <sup>25</sup>	No adjustment for confounders
Jungers 2006 <sup>24</sup>	No adjustment for confounders
Kessler 2003 <sup>28</sup>	No adjustment for confounders
Kim 2013 <sup>29</sup>	No adjustment for confounders
Kumar 2012 <sup>30</sup>	No adjustment for confounders
Lameire 1997 <sup>32</sup>	No adjustment for confounders. No relevant outcomes
Lameire 1999 <sup>31</sup>	No adjustment for confounders. No relevant outcomes
Lhotta 2003 <sup>33</sup>	No adjustment for confounders
Lin 2003 <sup>35</sup>	Not review population. No adjustment for confounders
Lin 2004 <sup>34</sup>	No adjustment for confounders
Lorenzo 2004 <sup>36</sup>	Not review population. No adjustment for confounders
Mezei 2010 <sup>37</sup>	Conference abstract only
Nakamura 2007 <sup>38</sup>	No adjustment for confounders
Parameswaran 2011 <sup>40</sup>	No adjustment for confounders
Pena 2006 <sup>41</sup>	No adjustment for confounders

Study	Exclusion reason
Ratcliffe 1984 <sup>42</sup>	No adjustment for confounders
Ravani 2003 <sup>43</sup>	No adjustment for confounders
Roubicek 2000 <sup>44</sup>	No adjustment for confounders
Sabath 2003 <sup>45</sup>	Non-English study
Schmidt 1998 <sup>46</sup>	No adjustment for confounders
Sesso 1996 <sup>47</sup>	Inappropriate comparison
Shiao 2008 <sup>48</sup>	No adjustment for confounders
Stack 2003 <sup>49</sup>	Not review population
Van Biesen 1998 <sup>51</sup>	No adjustment for confounders
Van Biesen 1999 <sup>50</sup>	No adjustment for confounders
Wijewickrama 2010 <sup>52</sup>	Conference abstract only
Winkelmayer 2001 <sup>53</sup>	Inappropriate comparison. No adjustment for confounders
Winkelmayer 2001 <sup>54</sup>	Inappropriate comparison
Winkelmayer 2002 <sup>57</sup>	Inappropriate comparison
Winkelmayer 2007 <sup>56</sup>	No relevant outcomes
Winkelmayer 2011 <sup>55</sup>	Inappropriate comparison
Wu 2003 <sup>59</sup>	No adjustment for confounders
Yang 2017 <sup>60</sup>	Inappropriate comparison
Yokoyama 2009 <sup>61</sup>	Not review population

## I.2.1 Excluded health economic studies

- 2 Studies that meet the review protocol population and interventions and economic study  
3 design criteria but have not been included in the review based on applicability and/or  
4 methodological quality are summarised below with reasons for exclusion.

5 **Table 13: Studies excluded from the health economic review**

Reference	Reason for exclusion
None.	

6

7

8