National Institute for Health and Care Excellence

Draft for consultation

RRT and conservative management

Initiating RRT

NICE guideline <number>

Evidence review

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Draft for Consultation

These evidence reviews were developed by the National Guideline Centre

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ISBN:

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1.1 Review question: When should RRT be initiated?

1.2 Introduction

The need to start dialysis is influenced by a number of different factors including signs and symptoms of uraemia, biochemical measurements or eGFR. These factors may also influence timing of transplantation. The precise timing of initiation of renal replacement therapy is likely to have an impact of the cost and infrastructure of dialysis services as well as clinical outcomes. This review identifies the specific factors that should be considered when discussing decisions about starting renal replacement therapy or conservative management.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People requiring RRT for deteriorating CKD, who are previously RRT naïve. Stratified by age: • <2 years • 2 to <18 years • 18 to <70 years • ≥70 years
Intervention and Comparisons	Comparing initiating strategies for RRT, including but not restricted to: Initiating RRT based on eGFR; Initiating RRT at "early" eGFR Initiating RRT based on eGFR; Initiating RRT at "late" eGFR Initiating RRT based on symptoms; Initiating RRT based on moderate symptoms Initiating RRT based on symptoms; Initiating RRT based on severe symptoms

Outcomes	Critical:
	• Quality of life
	• Symptom scores/functional measures
	• Mortality
	• Hospitalisation
	• Other healthcare resource use
	• Time to failure of RRT form
	
	Important:
	• Psychological distress and mental wellbeing
	• Cognitive impairment
	• Patient/family/carer experience of care
	• Growth (in children)
	• Malignancy
	• Adverse Events
	  ○ Infections
	  ○ vascular access issues
	  ○ dialysis access issues
	  ○ acute transplant rejection episodes

Study design	RCTs Non-randomised studies (NRS) to be considered if insufficient RCT evidence found on a comparison basis, only if adjusted for key confounders: • Age • Ethnicity • Comorbidities Health at baseline

1.4 Clinical evidence

1.4.1 Included studies

One RCT was included in the review for the initiation of dialysis[8-10, 13, 16, 28], two non-randomised studies[1, 15] were included in the review for the optimum timing of transplantation.

These studies are summarised in Table 2 below. Evidence from these studies are summarised in the clinical evidence summaries below. See also the study selection flow chart in appendix B, study evidence tables in appendix E, GRADE tables in appendix G and forest plots in appendix H.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

There were no trials looking at symptom-based strategies, and no trials including children or looking specifically at the special populations outlined in the protocol (people with diabetes, people from BAME groups). We found no evidence on the outcomes of symptom score / functional measures or time to failure of RRT form.

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
IDEAL study [10]	Early vs Late by eGFR value Early dialysis, n=404: Aim to commence the chosen form of dialysis when the estimated GFR 10.0-14.0 ml/min • Ave eGFR at dialysis 12.0ml/min. 81% started dialysis at eGFR 10.0-14.0, Late dialysis, n=424: Aim to commence the chosen form of dialysis when the estimated GFR is 5.0-7.0 ml/min. Could be started on dialysis at GFR >7.0 if the treating physician recommended this	Adults aged 18 and older – no upper age limit Progressive kidney disease (including failing transplant) with eGFR 10.0 to 15.0 ml/min/1.73m^2 Average time since first seen by nephrologist around 30 months Prevalence of diabetes ~43% Ethnicity 72%	Critical: • Quality of Life • Mortality • Hospitalisation • Other healthcare resource use Important: • Adverse events ○ Infections ○ Dialysis access issues	RCT Setting: Australia and New Zealand Results reported for overall cohort and for HD and PD subgroups Difference between actual mean starting eGFRs less than the difference between the intended starting eGFR ranges

Study	Intervention and comparison	Population	Outcomes	Comments
	• Ave eGFR at dialysis 9.8ml/min. 24% started dialysis at eGFR 5.0-7.0	white Australia & New Zealand		Population included 3.4% who were not fully RRT naïve (failing transplant)
Akkina 2008[1]	Early vs late transplantation by eGFR Transplant at eGFR <10.0ml/min, n = 324 Transplant at eGFR 10.0-14.9ml/min, n = 217 Transplant at eGFR >/=15ml/min, n = 130	Adults aged 18 and older (mean not stated) First, pre-emptive, kidney only transplant USA	Critical: • Mortality • Graft failure	NRS
Ishani 2003[15]	Early vs late transplantation by eGFR Transplant at eGFR <15ml/min, n = 3622 Transplant at eGFR >/=15ml/min, n = 424	Adults aged 18 and older (mean 42, SD 12) First, pre-emptive, kidney transplant USA	Critical: • Graft failure	NRS

1 See appendix E for full evidence tables.

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1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Early vs Late dialysis initiation based on eGFR (early=10-14 ml/min, late=5-7 ml/min)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Late initiation	Risk difference with Early (95% CI) Clinical difference based on point estimate (TBC)
Quality of life AQoL. Scale from: 0 to 1. Higher is better.	642 (1 study) 3.6 years	LOW[a] due to risk of bias		The mean AQoL score in the control groups was 0.57	The mean quality of life - hd or pd in the intervention groups was 0 higher (0.03 lower to 0.03 higher)
Combined, all-cause mortality, dichotomous	828 (1 study) 3.6 years	MODERATE[a] due to risk of bias	RR 1.03 (0.86 to 1.23)	366 per 1000	11 more per 1000 (from 51 fewer to 84 more)
HD planned, all-cause mortality, dichotomous	362 (1 study) 3.6 years	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.95 (0.69 to 1.3)	309 per 1000	15 fewer per 1000 (from 96 fewer to 93 more)
PD planned, all-cause mortality, dichotomous	466 (1 study) 3.6 years	LOW[a,b] due to risk of bias, imprecision	RR 1.06 (0.86 to 1.31)	412 per 1000	25 more per 1000 (from 58 fewer to 128 more)
Combined, all-cause mortality, time to event	828 (1 study) 3.6 years	LOW[b] due to imprecision	HR 1.04 (0.83 to 1.3)	366 per 1000	11 more per 1000 (from 51 fewer to 81 more)
HD planned, all-cause mortality, time to event	362 (1 study) 3.6 years	VERY LOW[a,b] due to risk of bias, imprecision	HR 0.97 (0.66 to 1.43)	309 per 1000	8 fewer per 1000 (from 93 fewer to 102 more)
PD planned, all-cause mortality, time to event	466 (1 study) 3.6 years	LOW[b] due to imprecision	HR 1.04 (0.79 to 1.37)	412 per 1000	12 more per 1000 (from 69 fewer to 105 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Late initiation	Risk difference with Early (95% CI) Clinical difference based on point estimate (TBC)
Combined, hospitalisation: average days spent as inpatient	642 (1 study) 3 years	MODERATE[a] due to risk of bias		The mean hospitalisation: average days spent as inpatient in the control groups was 40 days	The mean hospitalisation: average days spent as inpatient in the intervention groups was 8 higher (1.2 lower to 17.2 higher)
Combined, hospitalisations per person over study duration	642 (1 study) 3 years	LOW[a] due to risk of bias		The mean hospitalisations in the control groups was 8 admissions	The mean hospitalisations in the intervention groups was 0 higher (0.93 lower to 0.93 higher)
Combined, non-admitted hospital visits per person over study duration	642 (1 study) 3 years	LOW[a] due to risk of bias		The mean non-admitted hospital visits in the control groups was 15 contacts	The mean non-admitted hospital visits in the intervention groups was 0 higher (2.73 lower to 2.73 higher)
Combined, GP and allied HCP visits per person over study duration	642 (1 study) 3 years	LOW[a] due to risk of bias		The mean visits in the control groups was 29 contacts	The mean visits in the intervention groups was 0 higher (5.57 lower to 5.57 higher)
Combined, Infection events	828 (1 study) 3.6 years	LOW[a,b] due to risk of bias, imprecision	RR 0.89 (0.75 to 1.06)	410 per 1000	45 fewer per 1000 (from 103 fewer to 25 more)
HD planned, infection events	362 (1 study) 3.6 years	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.93 (0.71 to 1.22)	377 per 1000	26 fewer per 1000 (from 109 fewer to 83 more)
PD planned, infection events	466 (1 study) 3.6 years	LOW[a,b] due to risk of bias, imprecision	RR 0.86 (0.69 to 1.07)	438 per 1000	61 fewer per 1000 (from 136 fewer to 31 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Late initiation	Risk difference with Early (95% CI) Clinical difference based on point estimate (TBC)
Combined, need for access revision	828 (1 study) 3.6 years	LOW[a,b] due to risk of bias, imprecision	RR 1.04 (0.86 to 1.25)	347 per 1000	14 more per 1000 (from 49 fewer to 87 more)
HD planned, need for access revision	362 (1 study) 3.6 years	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.09 (0.85 to 1.39)	393 per 1000	35 more per 1000 (from 59 fewer to 153 more)
PD planned, need for access revision	466 (1 study) 3.6 years	VERY LOW[a,b] due to risk of bias, imprecision	RR 1 (0.76 to 1.31)	309 per 1000	0 fewer per 1000 (from 74 fewer to 96 more)

a 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
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 4: Clinical evidence summary: Transplant at >15 eGFR vs Transplant at <15 eGFR

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Transplant at <15 eGFR	Risk difference with Transplant at >15 eGFR (95% CI)
Graft failure	4046 (1 study) 3 years	VERY LOW[1,2] due to risk of bias, imprecision	HR 0.95 (0.69 to 1.31)	Moderate	
				-[3]	-[3]

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Transplant at <15 eGFR	Risk difference with Transplant at >15 eGFR (95% CI)
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 3 No control group risk available					

1 **Table 5: Clinical evidence summary: Transplant at >15 eGFR vs Transplant at <10 eGFR**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Transplant at <10 eGFR	Risk difference with Transplant at >15 eGFR (95% CI)
Mortality	454 (1 study) 1 years	VERY LOW[1,2] due to risk of bias, imprecision	HR 1.35 (0.89 to 2.05)	Moderate	
				-[3]	-[3]
Graft failure	454 (1 study) 1 years	VERY LOW[1,2] due to risk of bias, imprecision	HR 1.96 (1.10 to 3.49)	Moderate	
				-[3]	-[3]
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 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 3 No control group risk available					

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3 **Table 6: Clinical evidence summary: Transplant at 10-14.9 eGFR vs Transplant at <10 eGFR**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Transplant at <10 eGFR	Risk difference with Transplant at 10-14.9 eGFR (95% CI)
Mortality	541 (1 study) 1 years	VERY LOW[1,2] due to risk of bias, imprecision	HR 0.99 (0.69 to 1.42)	Moderate	
				-[3]	-[3]
Graft failure	541	VERY LOW[1]	HR 1.89	Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Transplant at <10 eGFR	Risk difference with Transplant at 10-14.9 eGFR (95% CI)
	(1 study) 1 years	due to risk of bias	(1.14 to 3.12)	-[3]	-[3]

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
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 No control group risk available

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2 See appendix G for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

One health economic study was identified with a relevant comparison and has been included in this review.[13] This is summarised in the health economic evidence profile below (Table 4) and the health economic evidence table in Appendix F.

See also the health economic study selection flow chart in Appendix C.

1.5.2 Excluded studies

No potentially includable economic studies have been excluded due to applicability and/or quality.

1.5.3 Summary of studies included in the economic evidence review

Table 7: Health economic evidence profile: early versus late initiation of dialysis

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty

Harris 2011[13] (Australia)	Partially applicable [(a)]	Minor limitations [(b)]	• Within-RCT (IDEAL[10] economic subgroup) analysis
			• Cost-utility analysis (QALYs)
			• Population: progressive CKD, GFR 10-15, initiating dialysis
			• Comparators:
			  ○ Later initiation of dialysis (median time to dialysis initiation 7.3 months)
			  ○ Earlier initiation of dialysis (median time to dialysis initiation 1.9 months)
			• Follow-up: up to 8 years, median 4.1 years in both arms
				£8235[(c)]	0.09 QALYs lost	Later initiation of dialysis is dominant (lower costs and higher QALYs)	• Probability cost effective not reported (only graphically) but probability late initiation dominant was 72%.
							• Conclusion robust to sensitivity analyses.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Australian/New Zealand resource use data (2000-2008) and Australian unit costs (2008) may not reflect current NHS context. Non-NICE reference case discount rate (5% in base case analysis, 3% and 0% in sensitivity analysis) and utility instrument used - AQOL 6D (administered to patients in trial, Australian population time trade off-derived valuation tariff).

(b) Within-trial analysis but reflects full body of evidence for this question as only one clinical study identified. It is unclear if the trial duration is sufficient to reflect important difference in costs and QALYs, however given the lack of difference in clinical outcomes in the RCT this is not judged to be a serious limitation. Some sources of funding are from industry however primary funding is not.

(c) 2008 Australian dollars converted to UK pounds.[23] Cost components incorporated: Dialysis, transportation for dialysis, hospital admissions, non-admitted hospital treatment, out-of-hospital visits to physicians and other health professionals, investigations, pharmaceuticals.

1.6 Resource impact

The recommendations made based on this review (see section 1.9) are not expected to have a substantial impact on resources.

1.7 Evidence statements

1.7.1 Clinical evidence statements

Early vs late dialysis initiation

No evidence was identified for symptom scores and functional measures, time to failure of RRT modality, psychological distress and mental wellbeing, cognitive impairment, experience of care, growth, malignancy and acute transplant rejection episodes.

There was no clinically important difference for quality of life (1 study, low quality), dichotomous all-cause mortality (1 study, moderate quality (combined), very low quality (HD only), low quality (PD only)), time to event all-cause mortality (1 study, low quality (combined), very low quality (HD only), low quality (PD only)), hospitalisation days (1 study, moderate quality), hospitalisations (1 study, low quality), hospital visits (1 study, low quality), GP and healthcare professional visits (1 study, low quality), infection events (1 study, low quality (combined), very low quality (HD only), low quality (PD only)), need for access revision (1 study, low quality (combined), very low quality (HD only, PD only).

Early vs late pre-emptive transplantation

Transplant at >15 eGFR vs Transplant at <15 eGFR

No evidence was identified for quality of life, mortality, symptom scores and functional measures, hospitalisation, psychological distress and mental wellbeing, cognitive impairment, experience of care, growth, malignancy and acute transplant rejection episodes.

There was no clinically important difference for graft failure (1 study, very low quality).

Transplant at >15 eGFR vs Transplant at <10 eGFR

No evidence was identified for quality of life, symptom scores and functional measures, hospitalisation, psychological distress and mental wellbeing, cognitive impairment, experience of care, growth, malignancy and acute transplant rejection episodes.

There was a clinically important harm of early transplant for graft failure and mortality (1 study, very low quality).

Transplant at 10-14.9 eGFR vs Transplant at <10 eGFR

No evidence was identified for quality of life, symptom scores and functional measures, hospitalisation, psychological distress and mental wellbeing, cognitive impairment, experience of care, growth, malignancy and acute transplant rejection episodes.

There was a clinically important harm of early transplant for graft failure (1 study, very low quality).

There was no clinically important difference for mortality (1 study, very low quality).

1.7.2 Health economic evidence statements

- One cost–utility analysis found that later initiation was dominant (less costly and more effective) compared to earlier initiation. This analysis was assessed as partially applicable with minor limitations.

1.8 Recommendations

Starting renal replacement therapy

A1. Follow the recommendations on referral criteria in NICE's guideline on chronic kidney disease in adults.

A2. Consider starting dialysis at an estimated glomerular filtration rate (eGFR) of around 5 to 7 ml/min/1.73 m2, or earlier if indicated by the impact of symptoms of uraemia on daily living, biochemical measures or uncontrollable fluid overload.

A3. Ensure the decision to start dialysis is made jointly by the person (or, where appropriate, their family members or carers) and their healthcare team.

A4. Before starting dialysis in response to symptoms, be aware that some non-specific symptoms may be caused by non-renal conditions.

1.8.1 Research recommendations

RR1. What is the most clinical and cost effective strategy for timing of pre-emptive transplantation?

See also the rationale in appendix J.

1.9 Rationale and impact

1.9.1 Why the committee made the recommendations

The committee agreed that when to start dialysis is a complex decision that should take into account a number of factors (estimated glomerular filtration rate [eGFR], symptoms, patient preference, biochemistry and fluid overload). Evidence suggested that there was no overall harm or benefit of starting dialysis at an eGFR of around 5 to 7 ml/min/1.73 m2 or earlier if indicated by symptoms. However, there was evidence that starting at an eGFR of 5 to 7 ml/min per 1.73 m2 was cost saving compared with an earlier start. The committee noted that some patients prefer to have an agreed starting point (eGFR) and that the recommended level broadly reflects current practice for adults and children. However, some people may need dialysis before the eGFR reaches this value because they have symptoms that are affecting normal daily activities. The committee agreed that it was not appropriate only to start dialysis when symptoms are reported, because some people with slowly progressing chronic kidney disease may not recognise and report symptoms that indicate dialysis is needed. The committee agreed that it is important to establish whether the symptoms are due to uraemia, for example fatigue and depression or not and to discuss their impact on daily life.

Evidence on the timing of pre-emptive transplant was limited and contradictory, with one study showing a clinically important benefit of transplanting at an eGFR of less than 10 ml/min/1.73 m2 but another showing no difference. The committee agreed to make a research recommendation on this to guide future practice.

1.9.2 Impact of the recommendations on practice

The recommendations reflect common practice for adults and children, and so are not likely to involve a change of practice for most NHS providers or have a substantial resource impact for the NHS in England. If providers need to change from an earlier to a later initiation strategy, this is likely to be cost saving due to a reduction in time on dialysis.

1.10 The committee's discussion of the evidence

1.10.1 Interpreting the evidence

1.10.1.1 The outcomes that matter most

The committee considered that quality of life, mortality, symptom scores/functional measures, hospitalisation, other healthcare resource use and time to modality failure as the critical outcomes to judge the success of a strategy for initiation. A number of other important outcomes were identified included patient-reported outcome measures and adverse events. No evidence was found for symptom scores or functional measures.

1.10.1.2 The quality of the evidence

Dialysis

The majority of evidence was moderate to low quality. The evidence was mostly downgraded due to risk of bias (due to factors including lack of blinding, protocol violations) and imprecision. Randomised evidence was only available for the over 18 age group, only for the comparison of starting dialysis early based on eGFR vs late on eGFR. Early was defined as 10.0 to 14.0 ml per minute per 1.73m2 of body surface (using the Cockcroft-Gault (CG) equation) and late 5.0 to 7.0 ml per minute. Randomised evidence was available for haemodialysis and peritoneal dialysis, combined and sub-grouped.

The committee noted that there was not a large difference in the actual eGFR(CG) for starting dialysis between the two groups due to the fact that 76% of participants in the late group started earlier than eGFR(CG) 7ml/min. These protocol violations were done at the "physician's discretion" and the majority were due to symptoms of uraemia.

Whilst the committee welcomed the fact that there was a randomised trial, it was noted that only a small proportion of those eligible were enrolled in the study, and that this may lead to selection bias. It was also raised that the study had been done in Australia/New-Zealand, and although there appeared to be a similar patient-mix, there may be problems in generalising this to a UK population. The committee also highlighted in particular, the use of the Cockroft-Gault equation for estimating GFR; as decisions in the UK are based on the MDRD method. While it is not possible to convert the early and late eGFR categories to MDRD (as the conversion will vary with the individual), the paper does give the average eGFR-MDRD where the early and late groups actually started dialysis, which were presented to the group (see below for more detail).

Among the outcomes, mortality and healthcare utilisation had been reported fully, but quality of life (AQOL) was presented in summary only. The quality of life outcome had also been affected by incomplete data, meaning the GRADE rating was of low quality. Outcomes for peritoneal and haemodialysis was presented combined (to maximise precision) and separately, where available. Although mortality outcomes had been downgraded once or twice for imprecision, it was noted that they were all close around the line of no effect, and the group was fairly confident this could be regarded as no clinical difference, despite the powering of the study. However, since this was an intention to treat analysis, most of those analysed in the late group did not start late, and we do not have information separately for those that did not start dialysis until they had very low eGFR.

Transplant

The evidence for the timing of transplant was very low quality. The only outcomes reported for this comparison were mortality and graft failure. Although the studies did adjust for the key confounders specified by the committee, there were still concerns regarding the selection bias from the non-randomised studies. It was plausible this bias could affect results in either

direction, those selected for very early transplant may be those that healthcare professionals expect to deteriorate rapidly while those that only get a transplant late may be harmed by the longer time without adequate renal replacement. The committee also noted that the mean eGFR in the one study that reported this suggested that the early transplant group (eGFR >15ml/min) involved transplantation at a very early stage compared to current UK practice (mean eGFR in early group of 22ml/min).

1.10.1.3 Benefits and harms

Dialysis

There was a clinically important benefit for early initiation of RRT for infection events in the peritoneal dialysis group. There was no clinically important difference for all other outcomes considered.

The committee agreed that overall there appeared to be no benefit or harm to initiating RRT early compared with late. However due to the number of protocol violations in the late starting group, this was not sufficient evidence to recommend that all people start RRT as late as the intended eGFR range from the evidence included. The actual average GFR-CG when participants started dialysis was 12.0 ml/min in the early group and 9.8 ml/min in the late group: in terms of a measure more commonly used in the UK, this was equivalent to GFR-MDRD, 9.0 ml/min early and 7.2 ml/min late. This eGFR difference equated to the people in the late group starting dialysis an average of 5.60 months later.

The committee discussed whether, with this evidence it would be possible to make a recommendation that discouraged the routine use of a concrete eGFR threshold of, say eGFR-MDRD of 10 ml/min, regardless of the preference or symptom status of the person with CKD. However, it was felt that there was a risk of using wholly symptom-based criteria as this might present a risk to those people who do not develop symptoms or in people whom the symptoms are not recognised as needing RRT. Since there is no per-protocol evidence from the IDEAL-study, it remains unclear whether those actually started at very low eGFR might be disadvantaged.

The committee discussed whether this evidence from an adult population could be extrapolated to make recommendations for children patients. It was felt that this was reasonable. The committee noted that the wording of the recommendations is appropriate for children however in practice concerns over the consequences of uraemia on growth and the developing brain in children may lead to children with high levels of urea starting dialysis sooner than adults.

The committee agreed that the evidence identified was sufficient to recommend a strategy for initiating dialysis either at around eGFR of 5-7ml/min or earlier if indicated by the impact of symptoms of uraemia on daily living, biochemical measures or uncontrollable fluid overload.

Transplant

The evidence showed a clinically important harm for early transplant for both graft failure and mortality, although the magnitude of the effect varied across comparisons and studies. The committee noted that given the concerns over the quality of the evidence (related to the very early eGFR of transplantation and the non-randomised study design), they had little confidence in those outcomes being repeated in prospective randomised trials.

The benefits of transplanting early are that it would presumably increase the rates of pre-emptive transplantation but transplanting too early would lead to the use of organs in people who did not yet acutely require them, potentially denying those who did. Furthermore, transplanting too early may shorten the amount of function gained from an individual transplant, in the period before graft failure occurs.

The committee noted that in the modalities review (Evidence report B), there was evidence of a benefit of pre-emptive transplant as opposed to transplant after dialysis. Taken alongside the evidence in this review, the committee agreed that an overall strategy of prioritising an aim to transplant before the need for dialysis was appropriate. However there was no evidence to support aiming for an early pre-emptive transplant. The committee agreed that the evidence in this review was not sufficient to support specifically aiming for a late pre-emptive transplant.

1.10.2 Cost effectiveness and resource use

Dialysis

An Australian cost–utility (QALY) analysis based on the IDEAL RCT (the only study identified in the clinical review) suggested that the late initiation strategy in the trial would be a dominant strategy – that is, it would have lower costs with better health outcomes (QALYs). It found an average increase in costs of around £8000 per patient associated with the early start group compared to the late start group, primarily due to more time on dialysis.

While the study was judged to be partially applicable due to the non-UK NHS setting and differences in methods to the NICE reference case, the committee concluded that it was a reasonable basis for decision making that supported the use of a later initiation strategy due to the lower costs associated with it. The committee were not confident that there would be a net health benefit with later initiation (mean QALYs were greater in the study) having considered the clinical evidence. However, even if health outcomes were equivalent the later initiation strategy would still be cost effective given it is cost saving.

The committee discussed that current practice in the UK for adults and children is somewhat variable but is generally more similar to the later initiation strategy in the IDEAL trial. On this basis, the recommendation was not considered likely to have a substantial resource impact for England. The committee noted that generally if a change is required it will be moving from an earlier to a later initiation criteria and this would be likely to be cost saving based on the evidence identified.

Transplant

No published economic evaluations were identified.

The modalities review discusses the trade-offs for pre-emptive transplant versus non-pre-emptive transplant and concluded that pre-emptive transplant should be recommended.

In this review, the committee considered evidence relating to the timing of pre-emptive transplant. Earlier pre-emptive transplant could be associated with higher costs as a transplant will have a limited life and so undertaking pre-emptive transplantation too early you may use up some of the transplant longevity at a time when you did not actually need RRT. This may mean that people will require a further transplant or dialysis. However, conversely, outcomes may be better when transplanting into a healthier patient. The clinical evidence however suggested that earlier pre-emptive transplant had increased graft failure compared with later pre-emptive transplant and this would be associated with higher costs due to the need for further transplant or dialysis. It also suggested increased mortality which would translate to lower QALYs, although the committee did not have much confidence in this clinical evidence. Overall, the committee did not consider the evidence to support undertaking pre-emptive transplant earlier than is current practice or specifying a particular time point to aim for.

1.10.3 Other factors the committee took into account

The committee noted that various equations for estimating GFR produce slightly different results and for this reason they used the term 'around' in the recommendation on when to initiate renal replacement therapy.

The committee noted that some patients may prefer to be presented with a fixed point at which to start RRT or to start RRT before the onset of major symptoms.

The symptoms of uraemia are varied and may include itching, nausea, tiredness, depression and anxiety. In addition there are some very serious complications of uremia including pericarditis and seizures. As a number of symptoms are associated with non-renal conditions, the committee noted the importance of establishing whether the symptoms are due to uraemia or non-renal conditions, the latter being unlikely to respond to initiating RRT. The extent to which symptoms may impact on daily life is highly variable and this needs to be taken into account when deciding to initiate dialysis. Furthermore, the decision when to initiate RRT is complex and takes account of multiple sources of information, the wishes and needs of the patient, carer and their family and through balancing the potential benefit of treatment against the burden of that treatment.

Examples of measures of biochemistry that may be considered are:

1. Uraemia in children. This may prompt consideration of earlier initiation of RRT due to concerns about its effects on growth and the developing brain
2. Elevated potassium levels
3. Uncontrolled metabolic acidosis

The presence of fluid overload is an important indicator for dialysis due to the association with poor cardiovascular outcomes.

The committee highlighted that people who require combined kidney-pancreas transplant will often have to wait for longer and this should be taken into account.

The committee noted that in their experience it is common for people to delay starting RRT for example due to difficulty accepting that their condition has deteriorated. In some situations this delay may be appropriate as long as it is fully informed, however in others, particularly if people delay preparing for initiating RRT, it may lead to worse clinical outcomes.

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Appendices

Appendix A: Review protocols

Table 8: Review protocol: Initiating RRT

Field	Content
Review question	When should RRT be initiated?
Type of review question	Intervention
Objective of the review	What is the clinical and cost effectiveness of various strategies for the timing of initiating RRT?
Eligibility criteria – population/disease/condition/issue/domain	People requiring RRT for deteriorating CKD. Stratified by: Age (<2, 2 to 18, >18 to 70, >70) DM vs no DM
Eligibility criteria – intervention(s)	Any strategy for initiating RRT (e.g. at eGFR 10-15ml/min vs eGFR 5-10ml/min, transplantation at estimated 6 months prior to requirement for RRT vs transplantation at requirement for RRT).
Eligibility criteria – comparator(s)/control or reference (gold) standard	As above
Outcomes and prioritisation	Critical Patient, family/carer health-related quality of life (continuous) Symptom scores and functional measures (continuous) Mortality (dichotomous and time to event) Hospitalisation (rates or continuous) Other healthcare resource use (rates or dichotomous) Time to failure of RRT form (time to event) Important Psychological distress and mental wellbeing (continuous) Cognitive impairment (dichotomous) Patient, family and carer experience of care (continuous) Growth (continuous) Malignancy (dichotomous) Adverse events Infections (dichotomous) Vascular access issues (dichotomous) Dialysis access issues (dichotomous) Acute transplant rejection episodes (dichotomous) Strategy: 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. For the outcomes of quality of life, symptom scores/functional measures, psychological distress/mental wellbeing and experience of care – any validated measure will be accepted. 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

Field	Content
	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.
Eligibility criteria – study design	RCT, if insufficient evidence is found for any specified comparisons non-randomised studies will be considered but only if outcomes are adjusted for the following key confounders: Age Ethnicity Health at baseline Co-morbidities
Other inclusion exclusion criteria	Crossover studies are not appropriate for assessment of initiation. Any studies where the RRT is being delivered for acute kidney injury, not in the context of chronic kidney disease, will be excluded. Any studies where the RRT is being delivered in a level 2 or 3 care setting, will be excluded.
Proposed sensitivity/sub-group analysis, or meta-regression	BAME vs non-BAME Aged ≥80 vs aged <80 T1DM vs T2DM
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)	Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). GRADEpro was used to assess the quality of evidence for each outcome. Endnote was used for bibliography, citations, sifting and reference management.
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library Date: All years Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2014 NHSEED, HTA – all years Language: Restrict to English only Supplementary search techniques: backward citation searching Key papers: Not known
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10019
Highlight if amendment to previous protocol	Not an amendment
Search strategy – for one database	For details please see appendix D of the full guideline
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or F (economic evidence tables) of the full guideline.

Field	Content
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or F (economic evidence tables) of the full guideline.
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 http://www.gradeworkinggroup.org/
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 methods chapter of the full 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 in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by 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 guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	NGC is funded by NICE and hosted by Royal College of Physicians
Name of sponsor	NGC is funded by NICE and hosted by Royal College of Physicians
Roles of sponsor	NICE funds NGC to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered

Table 9: Health economic review protocol

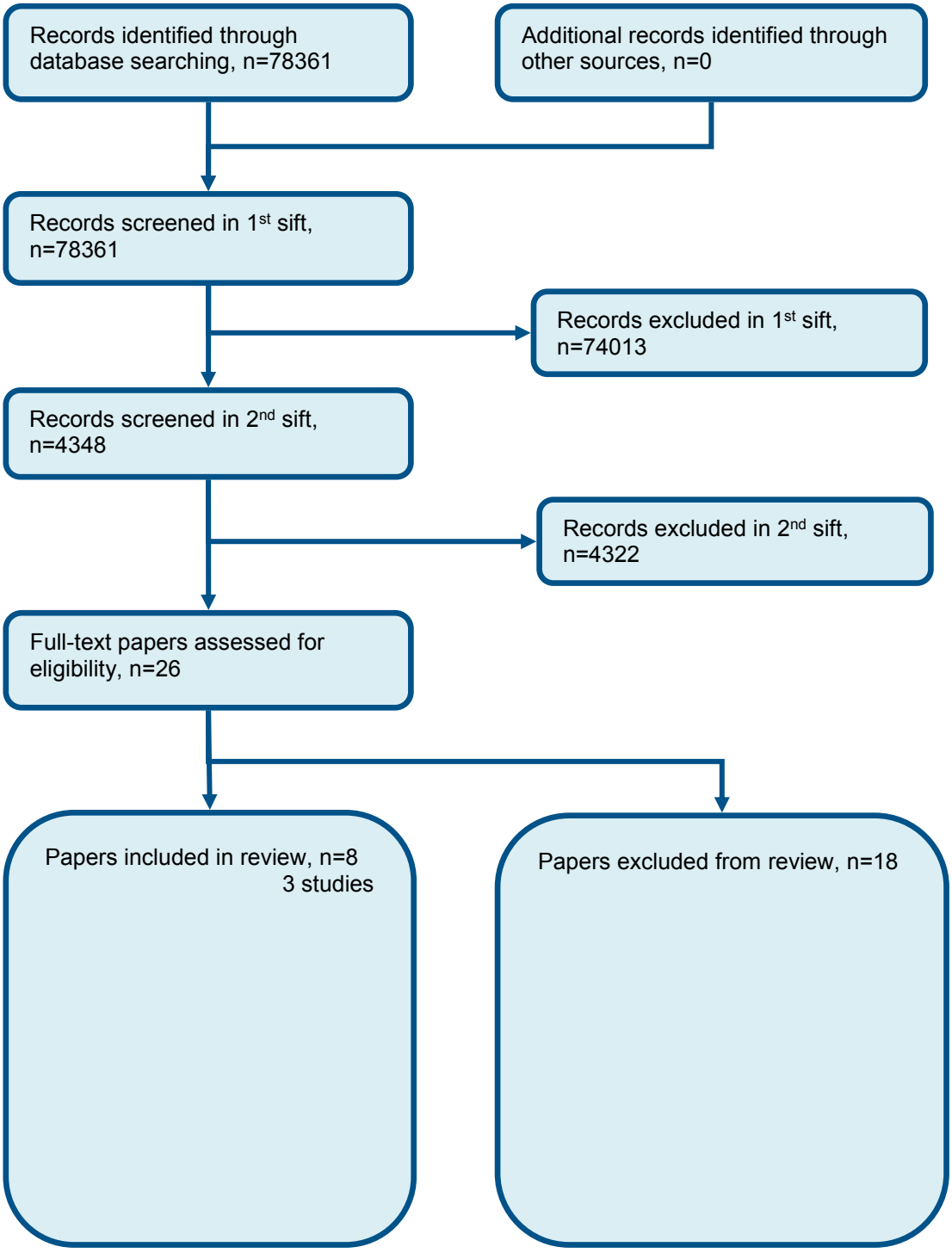
Review question	All questions – health economic evidence
Objectives	To identify economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the individual review protocol above. • Studies must be of a relevant economic study design (cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-consequences analysis, comparative cost analysis). 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.)

	• Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix D.2 Health economics literature search strategy.
Review strategy	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. 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.[21] 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. **Inclusion and exclusion criteria** If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** 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. The health economist will be guided by the following hierarchies. *Setting:* UK NHS (most applicable). OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). OECD countries with predominantly private health insurance systems (for example, Switzerland). Studies set in non-OECD countries or in the USA will have been excluded before being assessed for applicability and methodological limitations. *Economic study type:* Cost-utility analysis (most applicable). Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequences analysis). Comparative cost analysis. Non-comparative cost analyses including cost-of-illness studies will have been excluded before being assessed for applicability and methodological limitations. *Year of analysis:* The more recent the study, the more applicable it will be. 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'. Studies published before 2001 will have been excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the economic analysis:* 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. 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.

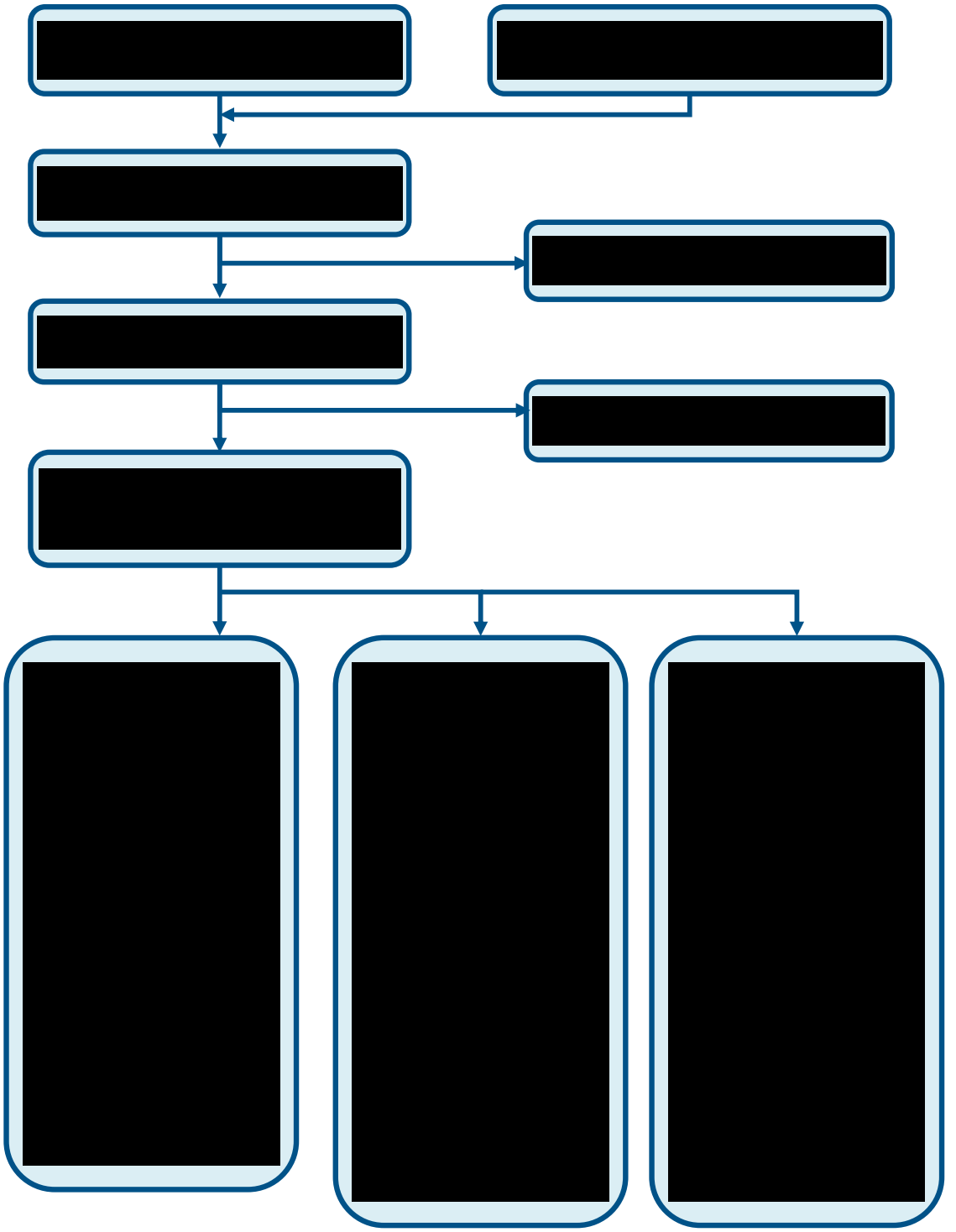
Appendix B: Clinical evidence study selection

Figure 1: Flow chart of clinical study selection for the review of initiating RRT



Appendix C: Health economic evidence study selection

Figure 2: 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

Appendix D: Literature search strategies

D.1 Clinical search literature search strategy

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

For more detailed information, please see the Methodology Review.

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

Table 10: 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
Embase (OVID)	1974 – 11 December 2017	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2017 Issue 12 of12 CENTRAL to 2017 Issue 11 of12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

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)

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)

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)

D.2 Health Economics literature search strategy

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

Table 11: 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

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

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Appendix E: Clinical evidence tables

Study (subsidiary papers)	IDEAL trial: Cooper 2010[10] (Whalley 2013[28], Johnson 2012[16], Collins 2011[8], Harris 2011[13], Cooper 2004[9])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=828)
Countries and setting	Conducted in Australia, New Zealand; Setting: 32 centres in Australia and New Zealand
Line of therapy	1st line
Duration of study	Intervention + follow up: median time from randomisation to end of follow-up for each group was 3.64 years (0.03-9.15) and 3.57 years (0.02-8.78)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: eGFR was determined by the Cockcroft-Gault equation corrected for body-surface area
Stratum	General population: Stratified according to centre, planned method of dialysis and presence/not of diabetes mellitus (type 1 or 2 not specified)
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with progressive chronic kidney disorder (including patients with a failing transplant) with an estimated GFR 10.0 to 15.0ml/min/1.73m² who were planning for dialysis, either HD or PD
Exclusion criteria	<18y, eGFR<10ml/min, plans to receive a transplant from a living donor within the next 12 months, recent diagnosis of cancer likely to affect survival, or were unable to provide written informed consent
Recruitment/selection of patients	Aimed to recruit 800. 2982 patients screened, 828 randomised (2154 excluded: 868 did not meet inclusion criteria; 681 declined; 340 physician's decision; 106 other; 159 were registered but not randomised), 769 started dialysis within follow-up period
Age, gender and ethnicity	Age - Mean (SD): 60.2(12.8)/60.5(12.3) years. Gender (M:F): 286:542. Ethnicity: In each group, percentage White 70.0/72.9, Asian 9.2/8.5, Maori 6.5/5.7, Pacific Islander 5.7/5.9, Aboriginal or Torres Strait islander 3.2/2.1, Other 5.2/5.0
Further population details	
Extra comments	Average time in months since first seen by a nephrologist, median (IQR) 32.5(9.8-84.2) / 29.4(9.8-75). Planned dialysis method %: CAPD 57.7/54.9; HD 42.3/45.1. Ave GFR at recruitment 13.0(1.4)/13.1(1.4). Cause of kidney disease in each group (%): diabetes 33.9/34.0, glomerulonephritis 16.1/17.2, Poly-cystic Kidney 10.1/11.1, failing transplant 3.2/3.5. Coexisting conditions (%): DM 42.6/43.2, CVD 39.6/38.2, CHF 4.5/6.4. Smoking status (%): current 11.4/11.1, former 50.7/47.2, never 37.9/41.8. Medication (%): ACE-i 48.8/47.6, ARB 21.0/23.1, statin 56.7/55.7, EPO 40.1/41.5. Blood parameters, mean (SD): Creatinine

Study (subsidiary papers)	IDEAL trial: Cooper 2010[10] (Whalley 2013[28], Johnson 2012[16], Collins 2011[8], Harris 2011[13], Cooper 2004[9])
	532(131)/528(122); Albumin 38.5(5.1)/38.4(4.8); Phosphate 1.8(0.4)/1.8(0.4)
Indirectness of population	No indirectness
Interventions	(n=404) Intervention 1: Initiating RRT based on eGFR - Initiating RRT at "early" eGFR. Commence the chosen form of dialysis when the estimated GFR was 10.0-14.0 ml/min. Duration Ave 3.6y. Concurrent medication/care: The method of dialysis and regimen was up to the treating physician. Physicians were asked to consider timely placement of access, but there was no requirement for placement of temporary access to meet study timing requirements. Dialysis clearance targets were recommended at Kt/V of 2.0 for PD (2.2 for automated PD) and more than 3.6 for HD. It was also recommended that participants received dietary advice, management of anaemia and hyperphosphataemia, and treatment from hypertension as recommended in contemporary guidelines Comments: 383 of 404 started dialysis before the end of follow-up. The average time to starting dialysis was 1.8(1.6-2.2) months. The average GFR at commencement of dialysis was 12.0ml/min, and 19% started at GFR<10.0. (n=424) Intervention 2: Initiating RRT based on eGFR - Initiating RRT at "late" eGFR. Commence the chosen form of dialysis when the estimated GFR is 5.0-7.0 ml/min. To receive routine medical care before this. Patients allocated to this group could be started on dialysis at GFR >7.0 if the treating physician recommended this. Duration ave 3.57 years. Concurrent medication/care: The method of dialysis and regimen was up to the treating physician. Physicians were asked to consider timely placement of access, but there was no requirement for placement of temporary access to meet study timing requirements. Dialysis clearance targets were recommended at Kt/V of 2.0 for PD (2.2 for automated PD) and more than 3.6 for HD. It was also recommended that participants received dietary advice, management of anaemia and hyperphosphataemia, and treatment from hypertension as recommended in contemporary guidelines Comments: 386 of 424 started dialysis before the end of follow-up. The average time to starting dialysis was 7.4(6.2-8.2) months. The average GFR at commencement of dialysis was 9.8ml/min, and 76% started at GFR>7.0
Funding	Study funded by industry (Study was funded by grants from governmental (Australian MRC and health ministers advisory council), non-governmental (Australian/New Zealand doctor's societies), and charitable (NZ heart association) organisations, as well as industry (Baxter healthcare, Amgen Australia and Janssen-Cilag). Authors had received consulting fees from a variety of healthcare companies)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EARLY EGFR versus LATE EGFR Protocol outcome 1: Quality of life	

Study (subsidiary papers)	IDEAL trial: Cooper 2010[10] (Whalley 2013[28], Johnson 2012[16], Collins 2011[8], Harris 2011[13], Cooper 2004[9])
- Actual outcome for General population: AQoL score at follow-up (ave 3.6y); Other: Regression analysis between-group difference: 0.00 (95%CI -0.03 to 0.03) (Regression analysis over time: small decrease); Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Mortality - Actual outcome for General population: All-cause mortality at follow-up (ave 3.6y); Group 1: 152/404, Group 2: 155/424; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for General population: All-cause mortality (HR) at follow-up (ave 3.6y); HR 1.04 (95%CI 0.83 to 1.3) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for General population: HD subgroup: All-cause mortality at follow-up (ave 3.6y); Group 1: 50/171, Group 2: 59/191; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for General population: HD subgroup: All-cause mortality (HR) at follow-up (ave 3.6y); HR 0.97 (95%CI 0.66 to 1.41) Reported; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for General population: PD subgroup: All-cause mortality at follow-up (ave 3.6y); Group 1: 102/233, Group 2: 96/233; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for General population: PD subgroup: All-cause mortality (HR) at follow-up (ave 3.6y); HR 1.04 (95%CI 0.79 to 1.37) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Hospitalisation - length of stay - Actual outcome for General population: Hospitalisation days at follow-up (ave 3.6y); Group 1: mean 48 days (SD 64); n=307, Group 2: mean 40 days (SD 54); n=335; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Hospitalisation or other healthcare resource use - Actual outcome for General population: Hospitalisation count at follow-up (ave 3.6y); Group 1: mean 8 (SD 6); n=307, Group 2: mean 8 (SD 6); n=335; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for General population: Non-admitted hospital visits count at follow-up (ave 3.6y); Group 1: mean 15 (SD 19); n=307, Group 2: mean 15 (SD 16); n=335; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for General population: GP and allied HCP visits count at follow-up (ave 3.6y); Group 1: mean 29 (SD 36); n=307, Group 2: mean 29 (SD 36); n=335; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 5: AEs - infections - Actual outcome for General population: Infection events (death or hospitalisation) at follow-up (ave 3.6y); Group 1: 148/404, Group 2: 174/424; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for General population: HD subgroup: Infection events at follow-up (ave 3.6y); Group 1: 60/171, Group 2: 72/191; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for General population: PD subgroup: Infection events at follow-up (ave 3.6y); Group 1: 88/233, Group 2: 102/233; Risk of bias: High; Indirectness of outcome: No indirectness	

Study (subsidiary papers)	IDEAL trial: Cooper 2010[10] (Whalley 2013[28], Johnson 2012[16], Collins 2011[8], Harris 2011[13], Cooper 2004[9])
Protocol outcome 6: AEs - dialysis access issues - Actual outcome for General population: Need for access revision at follow-up (ave 3.6y); Group 1: 145/404, Group 2: 147/424; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for General population: HD subgroup: Need for access revision at follow-up (ave 3.6y); Group 1: 73/171, Group 2: 75/191; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for General population: PD subgroup: Need for access revision at follow-up (ave 3.6y); Group 1: 72/233, Group 2: 72/233; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Symptom scores/functional measures ; Time to failure of RRT form ; Psychological distress and mental wellbeing ; Cognitive impairment ; Patient/family/carer experience of care ; Growth ; Malignancy ; AEs - vascular access issues ; AEs - acute transplant rejection episodes

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Study	Akkina 2008[1]
Study type	Non-randomised cohort
Number of studies (number of participants)	1 (n=671)
Countries and setting	Conducted in USA; Setting: Two Minnesota medical centres
Line of therapy	1st line
Duration of study	Intervention + follow up: Likely 1 year but not explicitly stated
Method of assessment of guideline condition	Adequate method of assessment/diagnosis:
Stratum	General population
Subgroup analysis within study	Not applicable
Inclusion criteria	18 and older, first pre-emptive kidney only transplant between 1984 and 2006 at two centres in Minnesota
Exclusion criteria	Nil else
Age, gender and ethnicity	Age - --: Not specified. Gender (M:F): 60:40. Ethnicity: 94% white
Further population details	
Extra comments	85% living donor transplants, 166/671 graft failures during study period, 85/671 deaths
Indirectness of population	No indirectness

Study	Akkina 2008[1]
Interventions	(n=130) Intervention 1: Initiating RRT based on eGFR - Initiating RRT at "early" eGFR. Transplant at eGFR >/= 15ml/min. Duration 1 year. Concurrent medication/care: Usual care. Indirectness: No indirectness (n=217) Intervention 2: Initiating RRT based on eGFR - Initiating RRT at "early" eGFR. Transplant at eGFR 10-14.9ml/min. Duration 1 year. Concurrent medication/care: Usual care. Indirectness: No indirectness (n=324) Intervention 3: Initiating RRT based on eGFR - Initiating RRT at "late" eGFR. Transplant at <10ml/min. Duration 1 year . Concurrent medication/care: Usual care. Indirectness: No indirectness
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSPLANT AT >/=15ML/MIN versus TRANSPLANT AT <10ML/MIN Protocol outcome 1: Mortality - Actual outcome for General population: Death at Unclear, ?1 year follow-up; HR; 1.35 (95%CI 0.89 to 2.05); Risk of bias: All domain - 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: ; Group 2 Number missing: Protocol outcome 2: Time to failure of RRT form - Actual outcome for General population: Death censored graft loss at Unclear, ?1 year follow-up; HR; 1.96 (95%CI 1.1 to 3.5); Risk of bias: All domain - 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: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSPLANT AT 10-14.9ML/MIN versus TRANSPLANT AT <10ML/MIN Protocol outcome 1: Mortality - Actual outcome for General population: Death at Unclear, ?1 year follow-up; HR; 0.99 (95%CI 0.69 to 1.44); Risk of bias: All domain - 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: ; Group 2 Number missing: Protocol outcome 2: Time to failure of RRT form - Actual outcome for General population: Death censored graft loss at Unclear, ?1 year follow-up; HR; 1.89 (95%CI 1.14 to 3.12); Risk of bias: All domain - 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: ; Group 2 Number missing:	
Protocol outcomes not reported by the	Quality of life ; Symptom scores/functional measures ; Hospitalisation or other healthcare resource use ;

Study	Akkina 2008[1]
study	Hospitalisation - length of stay ; Psychological distress and mental wellbeing ; Cognitive impairment ; Patient/family/carer experience of care ; Growth ; Malignancy ; AEs - infections ; AEs - vascular access issues ; AEs - dialysis access issues ; AEs - acute transplant rejection episodes

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Study	Ishani 2003[15]
Study type	Non-randomised cohort
Number of studies (number of participants)	1 (n=4046)
Countries and setting	Conducted in USA; Setting: US
Line of therapy	1st line
Duration of study	Intervention + follow up: ~3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	General population
Subgroup analysis within study	Not applicable
Inclusion criteria	18 or older, ESRD between '94 and '00, pre-emptive TPx,
Exclusion criteria	Nil
Recruitment/selection of patients	USRDS and UNOS database
Age, gender and ethnicity	Age - Mean (SD): 42 (12). Gender (M:F): 58:42. Ethnicity: 84% white, 12% black
Further population details	
Extra comments	443 graft failures (10.9%), 111 (25.1% of GF) due to death with function
Indirectness of population	No indirectness
Interventions	(n=424) Intervention 1: Initiating RRT based on eGFR - Initiating RRT at "early" eGFR. TPx done at eGFR >/= 15ml/min. Duration 2.5 years median follow-up . Concurrent medication/care: Usual care . Indirectness: No indirectness (n=3622) Intervention 2: Initiating RRT based on eGFR - Initiating RRT at "late" eGFR. TPx at eGFR <15. Duration 3 years median follow-up. Concurrent medication/care: Usual care . Indirectness: No indirectness
Funding	Funding not stated

Study	Ishani 2003[15]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TPX AT EGFR >15 versus TPX AT EGFR <15 Protocol outcome 1: Time to failure of RRT form - Actual outcome for General population: Graft failure (including death with function) at Average follow-up 3 years; HR; 0.95 (95%CI 0.69 to 1.3); 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: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Symptom scores/functional measures ; Mortality ; Hospitalisation or other healthcare resource use ; Hospitalisation - length of stay ; Psychological distress and mental wellbeing ; Cognitive impairment ; Patient/family/carer experience of care ; Growth ; Malignancy ; AEs - infections ; AEs - vascular access issues ; AEs - dialysis access issues ; AEs - acute transplant rejection episodes

Appendix F: Economic evidence tables

Study	Harris 2011[13]			
Study details	**Population & interventions**	**Costs(b)**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design**: within-RCT (IDEAL study[10]) analysis **Approach to analysis**: Cost analysis was a mixture of costs collected during trial and resource use collected during trial with unit costs (e.g. HRG costs) applied. QALYs were calculated as the sum of	**Population:** Progressive CKD, GFR 10-15, initiating dialysis. **Cohort settings**: N: 642 (subset of the 828 randomised in IDEAL study) Mean age: 60 years (SD:) Male: 34% **Intervention 1**: Late dialysis start (GFR is 5.0-7.0 ml/min, starting above allowed if physician	**Total costs per patient (median per group, incremental mean difference)** Intervention 1: £88,942 Intervention 2: £94,763 Incremental (2−1): £8,235 (95% CI: -£1,391, £18,931; p=NR) Cost breakdown (incremental (2-1), mean per patient): • Dialysis: £4,742 (95% CI: £138, £10,033)	**QALYs (mean per patient):** Intervention 1: 2.07 Intervention 2: 1.97 Incremental (2−1): -0.09 (95% CI: -0.12, 0.31; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Late dialysis start was dominant (lower costs and lower QALYs) Probability Intervention 2 cost-effective (£20K/30K threshold): NR Later dialysis start was dominant in 72% of bootstrap replications. **Analysis of uncertainty:** Uncertainty around the ICER was quantified using bootstrapping (results above). Sensitivity analyses included removing cost outliers (reduced cost difference to

years of survival weighted by average utility (AQoL) score for each patient during each year with missing AQOL data imputed. **Perspective:** Australian health care costs (all healthcare costs irrespective of who incurred them were included) **Follow-up**: up to 8 years; median 4.15 years in both groups **Treatment effect duration:**(a) n/a **Discounting**: Costs: 5%; Outcomes: 5%	recommended; median time to dialysis initiation 7.3 months) **Intervention 2:** Early dialysis start (GFR was 10.0-14.0 ml/min; median time to dialysis initiation 1.9 months)	• Transportation for dialysis: £1,589 (95% CI: £489, £4,382) • Hospital admissions: £2,249 (95% CI: -£1,611, £5,829) • Non-admitted hospital treatment: -£57 (95% CI: -£508, £471) • Out-of-hospital visits to physicians and other health professionals: -£114 (95% CI: -£318, £106) • Investigations: £39 (95% CI: -£1,300, £1,388) • Pharmaceuticals: -£213 (95% CI: -£1,837, £1,483) **Currency & cost year:** 2008 Australian dollars (presented here as 2008 UK pounds(b)) **Cost components incorporated:** Dialysis, transportation for dialysis, hospital admissions, non-admitted hospital treatment, out-of-hospital visits to physicians and other health professionals, investigations, pharmaceuticals.		£6156), using different unit costs for dialysis (increased total cost difference to £9803), discounting at 3% and 0% (increased cost and QALY differences to £8427 and -0.10, and £8736 and -0.10 respectively), removing the censoring adjustment (reported that it 'did not substantially affect the mean difference in cost or QALYs), analysing cost data for only those patients who completed at least some information in the patient diary (increased cost difference to £15,032), and complete case analysis for AQOL (changed QALY difference to a main gain for early initiation of 0.01, ICER results not reported).
Data sources				
Health outcomes: within-RCT analysis (IDEAL[10] economic subgroup) of survival and quality of life to estimate QALYs. **Quality-of-life weights:** within-RCT (IDEAL[10] economic subgroup) analysis: AQOL 6D, Australian population time trade off-derived valuation tariff. **Cost sources:** within-RCT (IDEAL[10]				

economic subgroup) analysis of resource use, unit costs either collected during study from Australian and New Zealand centres or Australian national unit costs applied.

Comments

Source of funding: The IDEAL study was an investigator-initiated and conducted study, funded by the National Health and Medical Research Council of Australia; the Australian Health Ministers Advisory Council; the Royal Australasian College of Physicians/Australian and New Zealand Society of Nephrology and the National Heart Foundation (Australia) and National Heart Foundation (New Zealand). Unrestricted grants were provided by Baxter Healthcare Corp; Health funding Authority New Zealand; International Society of Peritoneal Dialysis; Amgen Australia Pty Ltd; Janssen Cilag Pty Ltd. Limitations: Australian/New Zealand resource use data (2000-2008) and Australian unit costs (2008) may not reflect current NHS context. Non-NICE reference case discount rate (5% in base case analysis, 3% and 0% in sensitivity analysis) and utility instrument used - AQOL 6D (administered to patients in trial, Australian population time trade off-derived valuation tariff). Within-trial analysis but reflects full body of evidence for this question as only one clinical study identified. It is unclear if the trial duration is sufficient to reflect important difference in costs and QALYs, however given the lack of difference in clinical outcomes in the RCT this is not judged to be a serious limitation. Some sources of funding are from industry however primary funding is not. **Other:** None.

Overall applicability: Partly applicable(c) **Overall quality:**(d) Minor limitations / potentially serious limitations (TBC)

Abbreviations: CCA: cost-consequence analysis; CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2008 purchasing power parities[23]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix G: GRADE tables

Table 12: Clinical evidence profile: Early vs Late initiation based on eGFR (early = 10-14 ml/min, late = 5-7 ml/min)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late initiation based on eGFR (early=10-14 ml/min, late=5-7 ml/min)	Relative (95% CI)	Absolute		
Quality of life - HD or PD (follow-up mean 3.6 years; measured with: AQoL; range of scores: 0-1; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	307	335	-	MD 0 higher (0.03 lower to 0.03 higher)	LOW	CRITICAL
All-cause mortality (follow-up mean 3.6 years)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	152/404 (37.6%)	155/424 (36.6%)	RR 1.03 (0.86 to 1.23)	11 more per 1000 (from 51 fewer to 84 more)	MODERATE	CRITICAL
All-cause mortality - HD planned (follow-up mean 3.6 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	50/171 (29.2%)	59/191 (30.9%)	RR 0.95 (0.69 to 1.3)	15 fewer per 1000 (from 96 fewer to 93 more)	VERY LOW	CRITICAL
All-cause mortality - PD planned (follow-up mean 3.6 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	102/233 (43.8%)	96/233 (41.2%)	RR 1.06 (0.86 to 1.31)	25 more per 1000 (from 58 fewer to 128 more)	LOW	CRITICAL
All-cause mortality: time to event - HD or PD (follow-up mean 3.6 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	152/404 (37.6%)	155/424 (36.6%)	HR 1.04 (0.83 to 1.3)	11 more per 1000 (from 51 fewer to 81 more)	LOW	CRITICAL
All-cause mortality: time to event - HD planned (follow-up mean 3.6 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	50/171 (29.2%)	59/191 (30.9%)	HR 0.97 (0.66 to 1.43)	8 fewer per 1000 (from 93 fewer to 102 more)	VERY LOW	CRITICAL
All-cause mortality: time to event - PD planned (follow-up mean 3.6 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	102/233 (43.8%)	96/233 (41.2%)	HR 1.04 (0.79 to 1.37)	12 more per 1000 (from 69 fewer to 105 more)	LOW	CRITICAL
Hospitalisation: average days spent as inpatient (follow-up mean 3 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	307	335	-	MD 8 higher (1.2 lower to 17.2 higher)	MODERATE	CRITICAL
Hospitalisations (follow-up mean 3 years; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	307	335	-	MD 0 higher (0.93 lower to 0.93 higher)	LOW	CRITICAL
Non-admitted hospital visits (follow-up mean 3 years; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	307	335	-	MD 0 higher (2.73 lower to 2.73 higher)	LOW	CRITICAL
GP and allied HCP visits (follow-up mean 3 years; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	307	335	-	MD 0 higher (5.57 lower to 5.57 higher)	LOW	CRITICAL
Infection events (follow-up mean 3.6 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	148/404 (36.6%)	174/424 (41%)	RR 0.89 (0.75 to 1.06)	45 fewer per 1000 (from 103 fewer to 25 more)	LOW	IMPORTANT

Infection events - HD planned (follow-up mean 3.6 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	60/171 (35.1%)	72/191 (37.7%)	RR 0.93 (0.71 to 1.22)	26 fewer per 1000 (from 109 fewer to 83 more)	VERY LOW	IMPORTANT
Infection events - PD planned (follow-up mean 3.6 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	88/233 (37.8%)	102/233 (43.8%)	RR 0.86 (0.69 to 1.07)	61 fewer per 1000 (from 136 fewer to 31 more)	LOW	IMPORTANT
Need for access revision (follow-up mean 3.6 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	145/404 (35.9%)	147/424 (34.7%)	RR 1.04 (0.86 to 1.25)	14 more per 1000 (from 49 fewer to 87 more)	LOW	IMPORTANT
Need for access revision - HD planned (follow-up mean 3.6 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	73/171 (42.7%)	75/191 (39.3%)	RR 1.09 (0.85 to 1.39)	35 more per 1000 (from 59 fewer to 153 more)	VERY LOW	IMPORTANT
Need for access revision - PD planned (follow-up mean 3.6 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	72/233 (30.9%)	72/233 (30.9%)	RR 1 (0.76 to 1.31)	0 fewer per 1000 (from 74 fewer to 96 more)	VERY LOW	IMPORTANT

[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] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 13: TPx at >15 vs TPx at <15

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TPx at >15 eGFR**	**TPx at <15 eGFR**	**Relative (95% CI)**	**Absolute**		
Graft failure (follow-up 3 years)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	424	3622	HR 0.95 (0.69 to 1.31)	-	⊕OOO VERY LOW	CRITICAL

[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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 14: TPx at >15 vs TPx at <10

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TPx at >15 eGFR	TPx at <10 eGFR	Relative (95% CI)	Absolute		
Mortality (follow-up 1 years)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	130	324	HR 1.35 (0.89 to 2.05)	-	⊕OOO VERY LOW	CRITICAL
Graft failure (follow-up 1 years)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	130	324	HR 1.96 (1.10 to 3.49)	-	⊕OOO VERY LOW	CRITICAL

[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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 15: TPx at 10-14.9 vs TPx at <10

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TPx at 10-14.9 eGFR	TPx at <10 eGFR	Relative (95% CI)	Absolute		
Mortality (follow-up 1 years)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	217	324	HR 0.99 (0.69 to 1.42)	-	⊕OOO VERY LOW	CRITICAL
Graft failure (follow-up 1 years)												

1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	217	324	HR 1.89 (1.14 to 3.12)	-	⊕OOO VERY LOW	CRITICAL

[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
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix H: Forest plots

H.1 Early vs Late dialysis initiation based on eGFR

(early=10-14 ml/min, late=5-7 ml/min)

Figure 3: Quality of Life (AQoL score, higher is better) – regression over the time of the trial

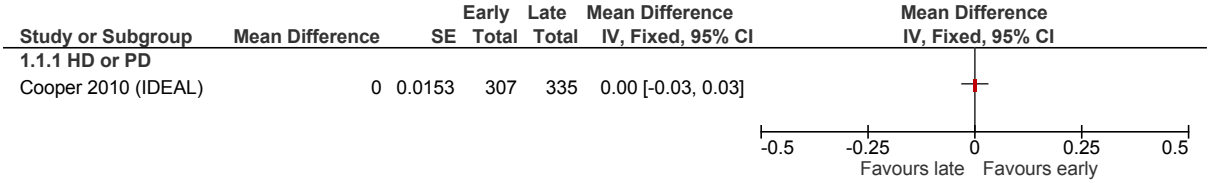


Figure 4: All-cause mortality (ave 3.6y)

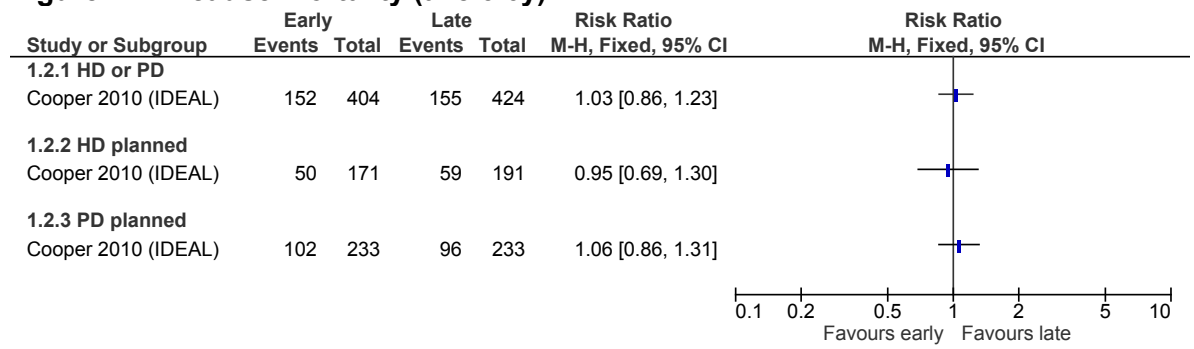


Figure 5: All-cause mortality: time to event

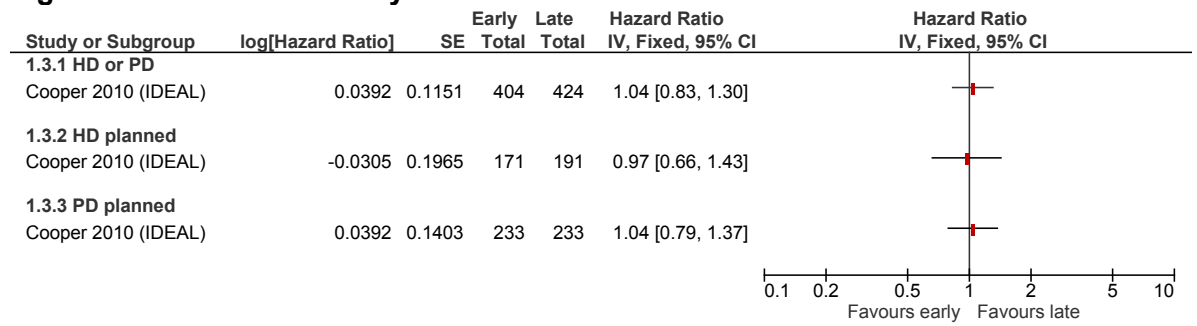


Figure 6: Hospitalisation: average days spent as inpatient over 3y

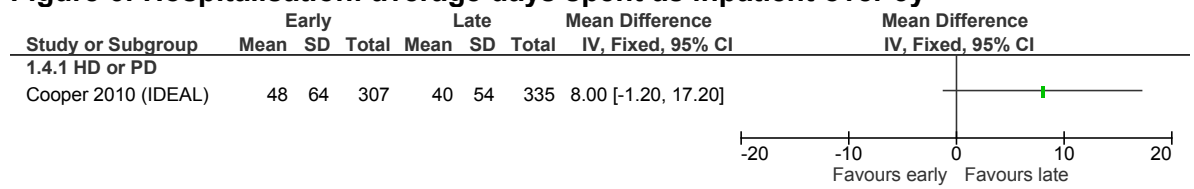


Figure 7: Healthcare resource use: average contacts over 3y

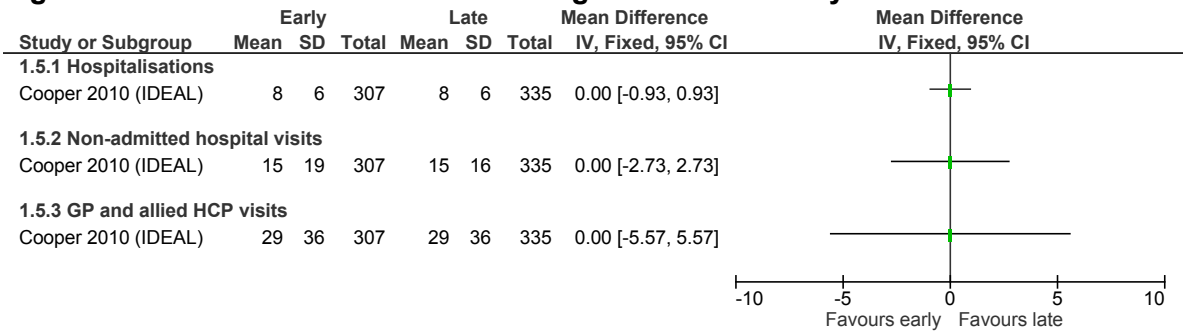


Figure 8: Adverse events - infection events (ave 3.6y).

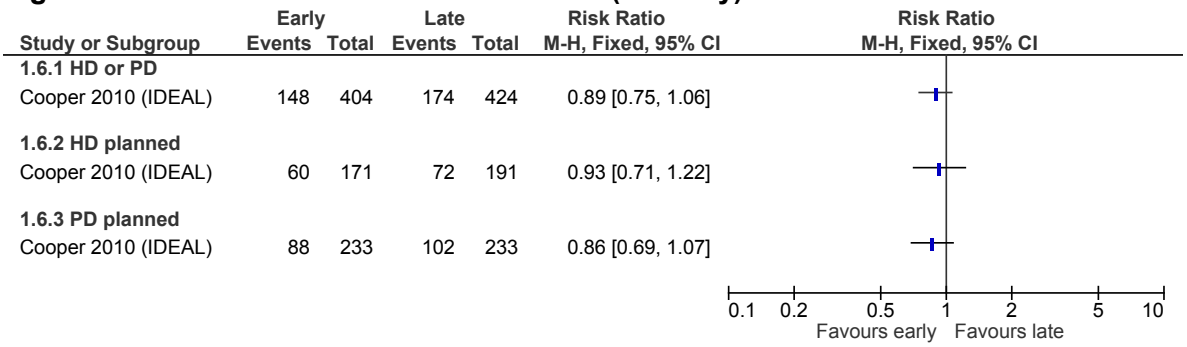
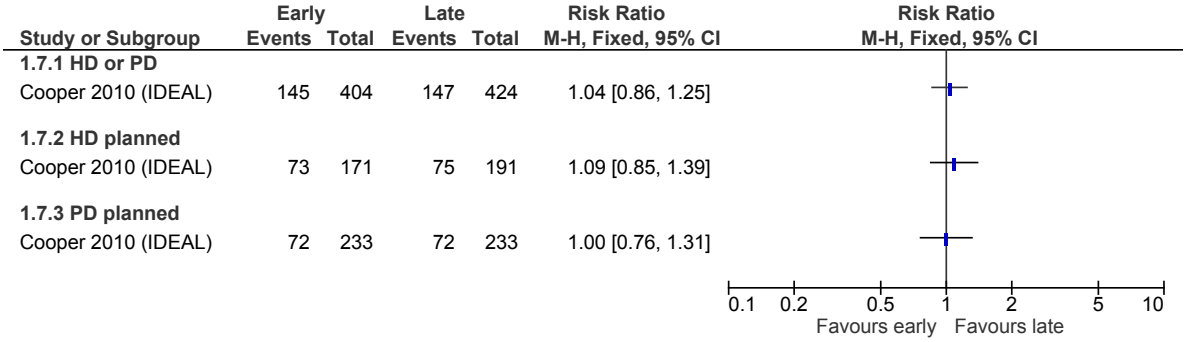
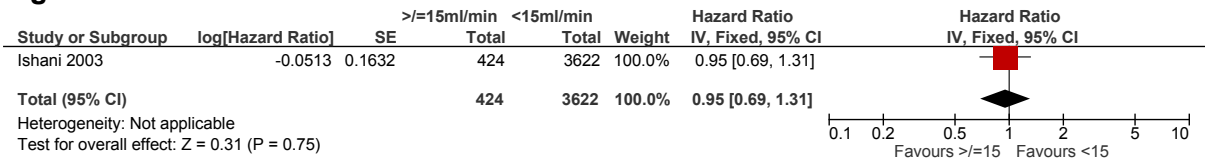


Figure 9: Adverse events - need for access revision (ave 3.6y)



H.2 Transplant at eGFR >/=15ml/min vs <15ml/min

Figure 10: Graft failure



H.3 Transplant at eGFR >/=15ml/min vs <10ml/min

Figure 11: Mortality

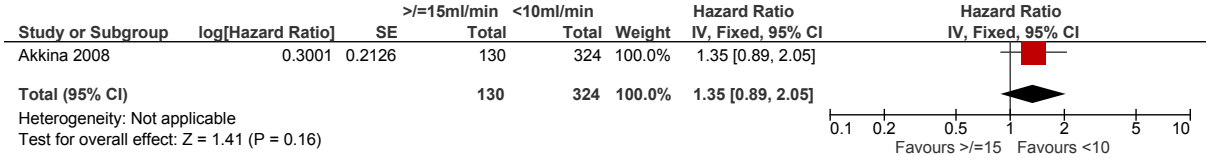
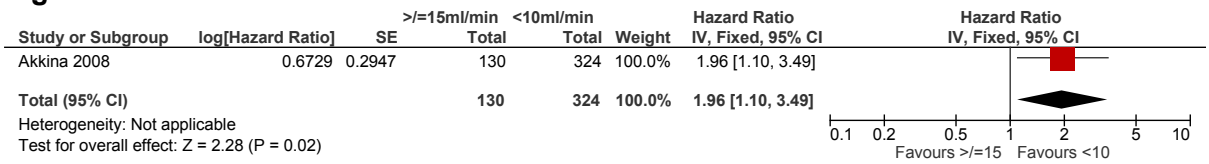


Figure 12: Graft failure



H.4 Transplant at eGFR 10-14.9ml/min vs <10ml/min

Figure 13: Mortality

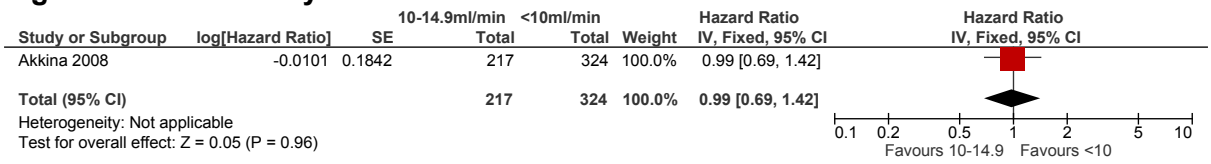
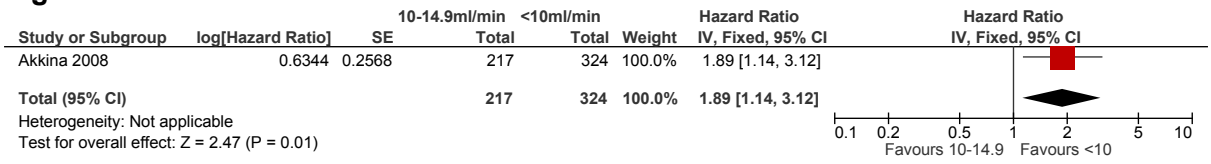


Figure 14: Graft failure



Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 16: Studies excluded from the clinical review

Study	Exclusion reason
Anonymous 1993[2]	Not relevant
Arici 2012[3]	Comment paper - references checked
Bayliss 2014[4]	Non-systematic review - references checked
Burkart 1998[5]	Non-systematic review - references checked
Chang 2012[6]	Observational trial
Churchill 1997[7]	Systematic review: study designs inappropriate
Crews 2014[11]	Observational trial

Study	Exclusion reason
Gursu 2011[12]	Review. Not in English
Ifudu 1998[14]	Observational trial
Korevaar 2005[17]	Non-systematic review - references checked
Lin 2015[18]	Non-systematic review - references checked
Maiorca 2000[19]	Incorrect interventions
Nacak 2016[20]	Systematic review: study designs inappropriate
O'hare 2015[22]	Incorrect study design
Pan 2012[24]	Systematic review: study designs inappropriate
Ranganathan 2010[25]	Inappropriate comparison. Regarding how soon can use access once the decision has been made to start dialysis, rather than how that decision is made
Sood 2014[26]	Full paper not available (review)
Susantitaphong 2012[27]	Systematic review: study designs inappropriate

I.2 Excluded health economic studies

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

Table 17: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Appendix J: Research recommendations

J.1 Optimal timing for pre-emptive transplant

Research question: What is the most clinical and cost effective strategy for timing of pre-emptive transplantation?

Why this is important: The evidence for the timing of transplants was very low quality with contradictory evidence. Further high quality evidence ideally including RCTs is needed to address this area and provide clinical and cost effective treatment.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People requiring RRT for deteriorating CKD, who are previously RRT naïve. Intervention/comparisons: 1. Performing pre-emptive transplant based on eGFR; Initiating pre-emptive transplant at "early" eGFR (e.g. 15-20 ml/min) 2. Performing pre-emptive transplant based on eGFR; Initiating pre-emptive transplant at "late" eGFR (e.g. 10-15 ml/min) Outcomes: Quality of life, symptom scores/functional measures, mortality, hospitalisation, other healthcare resource use, number requiring dialysis before transplant, time to failure of RRT form, psychological distress and mental wellbeing, patient/family/carer experience of care, growth (in children), malignancy, adverse events (infections, acute transplant

	rejection episodes)
Importance to patients or the population	While there is an RCT to inform the impacts on people of different eGFR based timepoints for initiating dialysis, there is currently little information to help people choose the optimum time to perform pre-emptive transplant, although evidence in general suggests a pre-emptive transplant (as opposed to after dialysis) has benefits
Relevance to NICE guidance	There is current uncertainty concerning the optimal time for performing a pre-emptive transplant.
Relevance to the NHS	Research in this area will inform NICE recommendations for service delivery and provide information about clinical and cost-effectiveness.
Current evidence base	The current evidence for pre-emptive transplant is limited due to lack of RCTs and consequently high quality evidence. It is important to have sufficient information on pre-emptive transplants so further evidence based information can be given.
Equality	Not applicable
Study design	RCT ideally, if not then a non-randomised cohort study with adequate adjustment for key confounders including age, ethnicity, co-morbidities and some measure of baseline health (e.g. quality of life)
Feasibility	No obvious feasibility issues
Other comments	Not applicable
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

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