National Institute for Health and Care Excellence

Draft for consultation

RRT and conservative management

Evidence review for sequencing modalities of RRT

NICE guideline

Intervention evidence review

April 2018

Draft for Consultation

This evidence review was developed by the National Guideline Centre

1

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN:

Contents

1

1 Sequencing for RRT modalities

1.1 Review question: What is the clinical and cost effectiveness of different sequences of modalities of renal replacement therapy and conservative management for people progressing or who have progressed through the later stages of CKD?

1.2 Introduction

This review is designed to determine the clinical and cost effectiveness of different sequences of renal replacement therapy, for example haemodialysis, haemodiafiltration or peritoneal dialysis prior to transplantation.

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 CKD, who have received more than one modality of RRT sequentially, either because the earlier modality was considered to have failed, or because they received one modality while waiting for another (e.g. receiving dialysis prior to receiving a kidney transplant). Studies will be included where the majority meet one of these criteria. Studies will be downgraded for indirectness if >25% are RRT naïve. Definition of modality failure to be determined by studies. Stratified by: • Previously modality • Age (<2, 2 to <18, 18 to <70, ≥70) • DM vs no DM • BAME vs non-BAME • Unplanned starters vs planned starters
Interventions and Comparisons	Modalities • Haemodialysis (HD) – including home or in centre, 3 days a week or more frequently, haemodialysis or haemodiafiltration • Peritoneal dialysis (PD) – including CAPD, assisted PD or APD/CCPD • Transplant – including live donor or deceased, pre-emptive or reactive • Conservative management Any modality or sub-modality vs any other, including where the comparison is between the first modality in a sequence (e.g. HD vs PD before transplantation), the second modality in a sequence (e.g. HD vs PD after transplantation) or between two sequences (e.g. HD then PD vs PD then HD)
Outcomes	Critical • Patient, family/carer health-related quality of life (continuous) • Mortality (dichotomous and time to event) • Time to failure of RRT form (time to event)

	Important
	• Hospitalisation (rates or continuous)
	• Preferred place of death (dichotomous)
	• Symptom scores and functional measures (continuous)
	• 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)

Study design	RCTs will be prioritised. 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 • Health at baseline • Co-morbidities • Ethnicity

1.4 Clinical evidence

1.4.1 Included studies

Three studies were included in the review;[13, 30, 31] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

A search was conducted for randomised trials and non-randomised studies comparing one modality over another for CKD, where a person received more than one modality of RRT sequentially. The papers identified were all non-randomised. Two papers looked at RRT treatment prior to transplantation, both comparing HD and PD. One looked at RRT treatment following a transplant that is failing, comparing pre-emptive retransplantation with non-pre-emptive retransplantation.

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

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
CTS trial Schwenger 2011[30]	• Dialysis prior to transplant HD then transplant (n=45,651)	Recipient of a first kidney transplant, deceased-donor Aged 18 or over.	Mortality (post-transplant) Failure RRT modality	Collaborative Transplant Study trial is multicentre registry with participating centres in Europe, N. America, Australia

Study	Intervention and comparison	Population	Outcomes	Comments
	PD then transplant (n=11,664)	Mean age 50y Gender (M:F) 65:35 92% Caucasian	(transplant)	and New Zealand (85% from Europe) Data 1998-2007 Duration: 5 years post-**transplant** (outcome censored at five years for model)
Snyder 2002 [31]	• Dialysis prior to transplant HD then transplant (n=17,155) PD then transplant (n=5,621)	Recipient of dialysis and subsequent first kidney transplant Aged 18 or over, median age ~44y Gender (M:F) 53:47 ~50% Caucasian, ~30% African American	Mortality (post-transplant) Failure RRT modality (transplant)	Database connected to U.S. Medicare Data 1995-2000 Duration: Up to 5 years post-**dialysis** (transplant could take place from 90 days after dialysis)
USRDS (retransplant) Goldfarb-rumyantzev 2006 [13]	• Post-transplant failure Pre-emptive re-transplant (<7d between reported failure of transplant kidney and retransplant) (n=1,609) Non-pre-emptive re-transplant (n=10,105)	People who received retransplants (both kidney and kidney-pancreas) regardless of number of previous transplants Any age, mean ~39y Gender (M:F) 59:41 ~78% White, 18% African American	Mortality (post-retransplant) Failure RRT modality (retransplant)	United States Renal Data Service (USRDS) and United Network for Organ Sharing (UNOS) used throughout USA Data 1990-1999 Duration: Up to 10 years post-transplant

1 See appendix D for full evidence tables.

2

3

1.4.14 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Peritoneal dialysis (PD) prior to transplant vs Haemodialysis (HD) prior to a transplant

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Haemodialysis (HD) prior to a transplant	Risk difference with Peritoneal dialysis (PD) prior to transplant (95% CI)
Death after transplant (time to event)	57315 (1 study) 5 years	VERY LOW[a] due to risk of bias	HR 1.1 (1.02 to 1.18)	No adjusted control rate available	
Death after transplant (relative risk)	22776 (1 study) 0-5 years	VERY LOW[a] due to risk of bias	RR 0.95 (0.85 to 1.06)	No adjusted control rate available	
Graft failure (time to event)	57315 (1 study) 5 years	VERY LOW[a] due to risk of bias	HR 1.06 (1.01 to 1.12)	No adjusted control rate available	
Graft failure (relative risk)	22776 (1 study) 0-5 years	VERY LOW[a] due to risk of bias	RR 1.05 (0.97 to 1.13)	No adjusted control rate available	

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

Table 4: Pre-emptive transplant for failing transplant vs Dialysis then transplant for failing transplant

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Non-pre-emptive	Risk difference with Pre-emptive transplant for failing transplant (95% CI)
Mortality (time to event) post-retransplant	11714 (1 study) 0-10 years	VERY LOW[a] due to risk of bias	HR 1.02 (0.9 to 1.15)	No adjusted control rate available	
Graft failure (time to event) -	11714	VERY LOW[a,b]	HR 1.36	No adjusted control rate available	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Non-pre-emptive	Risk difference with Pre-emptive transplant for failing transplant (95% CI)
retransplant	(1 study) 0-10 years	due to risk of bias, imprecision	(1.21 to 1.53)		
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					

1

2 See appendix F for full GRADE tables.

3

1.5 Economic evidence

1.5.1 Included studies

1 health economic study with relevant comparisons has been included in this review: it compared switching from HD to PD and PD to HD with HD and PD alone[7]; See also the health economic study selection flow chart in appendix G.

No health economic studies were included that looked at transplant.

None of the included studies were in children.

Note that current UK RRT intervention costs are discussed in section 1.5.5.

1.5.2 Excluded studies

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

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

1.5.8 Summary of studies included in the economic evidence review

Table 5: Health economic evidence profile: sequencing of RRT

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Chui 2013[7] (Canada)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Cohort analysis with all cost models adjusted for age, sex, body mass index, race, comorbid conditions, cause of ESRD, and pre-dialysis care. • Comparative costing • Population: Adult patients who initiated long-term dialysis (PD or in-centre HD) for ESRD • Comparators: ○ HD ○ PD ○ HD then switched to PD in first year ○ PD then switched to HD in first year • Follow-up: 1 and 3 years	**Vs HD 1 year** PD: -£31,097 HD>PD: -£14,478 PD>HD: -£6,493 **Vs HD 3 years** PD: -£66,404 HD>PD: -£34,820 PD>HD: -£1,522	n/a	n/a	**95% CI - 1 year incremental cost vs HD:** PD: -£34,064 to -£28,130 HD > PD: -£18,692 to -£10,264 PD >HD: -£12,845 to -£140 **95% CI - 3 years incremental cost vs HD:** PD: -£45,117 to -£24,523 HD > PD: -£74,672 to -£58,136 PD >HD: -£16,008 to £12,964

Abbreviations: CI = confidence interval; HD = haemodialysis; ICER: incremental cost-effectiveness ratio; PD = peritoneal dialysis; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) 2010 Canadian costs based on resource use from 1999-2006 may not reflect current NHS context. Discounting not applied. Health outcomes not incorporated.

(b) Within-trial analysis (cohort) so does not reflect the full body of evidence in this area (note: no parallel clinical study, costs only). It is unclear whether any transport costs are included.

(c) Cost components incorporated: dialysis costs, inpatient costs, medication costs, and physician fees.

1.5.4 Unit costs

See Evidence report B: modalities of RRT for current unit costs of RRT.

1.6 Resource impact

No recommendations were made based on this review (Section 1.8).

1.7 Evidence statements

1.7.1 Clinical evidence statements

No evidence for quality of life, mortality, time to failure of RRT form, hospitalisation, preferred place of death, symptom scores and functional measures, psychological distress and mental wellbeing, cognitive impairment, experience of care, growth, malignancy, infections, vascular access issues, dialysis access issues, acute transplant rejection episodes.

Adults aged 18 to 70

Transplant after PD vs transplant after HD, NRS

No evidence for quality of life, hospitalisation, preferred place of death, symptom scores and functional measures, psychological distress and mental wellbeing, cognitive impairment, experience of care, growth, malignancy, infections, vascular access issues, dialysis access issues, acute transplant rejection episodes.

No clinical difference was found for mortality in time to event (1 study, very low quality) or relative risk (1 study very low quality) or graft failure in time to event (1 study, very low quality) or relative risk (1 study very low quality).

Pre-emptive transplant after transplant vs post-dialysis re-transplant after transplant

No evidence for quality of life, hospitalisation, preferred place of death, symptom scores and functional measures, psychological distress and mental wellbeing, cognitive impairment, experience of care, growth, malignancy, infections, vascular access issues, dialysis access issues, acute transplant rejection episodes.

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

No clinical difference was found for mortality in time to event (1 study, very low quality) or graft failure in time to event (1 study, very low quality) or relative risk (1 study very low quality).

1.7.2 Health economic evidence statements

- One comparative cost analysis found that people who switched from HD to PD in the first year had lower costs at one year and three years than people who switched from PD to HD in the first year. This was assessed as partially applicable with potentially serious limitations.

1.8 Recommendations

No recommendations.

1.8.1 Research recommendations

RR4. What is the clinical and cost effectiveness of haemodialysis/haemodiafiltration before PD versus PD before haemodialysis/haemodiafiltration?

1.9 Rationale and impact

1.9.1 Why the committee did not make any recommendations

There was not enough evidence to recommend any particular sequence of RRT modalities. The committee agreed that decisions about sequence would mostly be guided by personal circumstances.

1.10 The committee's discussion of the evidence

1.10 Interpreting the evidence

1.10.1 The outcomes that matter most

The committee considered quality of life, mortality, and time to failure of RRT modalities to be critical outcomes and hospitalisation, preferred place of death, symptom scores and functional measures, psychological distress and mental wellbeing, cognitive impairment, experience of care, growth, malignancy, infections, vascular access issues, dialysis access issues and acute transplant rejection episodes to be important outcomes.

1.10.2 The quality of the evidence

No evidence was identified for children under the age of 18 or adults over the age of 70. No evidence was identified for the majority of possible sequences of treatment.

The only identified evidence was very low quality due to a combination of the non-randomised study design and other sources of risk of bias.

1.10.3 Benefits and harms

The comparison between transplanting after HD and transplanting after PD showed no clinically important difference for the two reported included outcomes (mortality and graft failure). The committee agreed that this was broadly consistent with their experience.

The comparison between pre-emptive transplant with a failing transplant and transplant after dialysis with a failing transplant showed no clinically important difference for mortality but a clinically important harm of pre-emptive transplant for graft failure. The committee noted that this somewhat contradicted the general benefits of pre-emptive first transplant. While the included study did adjust for the key confounders in the analysis, the committee agreed that there may still be residual confounding factors. There may be people in the pre-emptive group who, had they been given the time to require dialysis, may have accrued other reasons to make transplantation inappropriate. Overall the committee agreed that the evidence certainly did not support recommendations to aim for pre-emptive second transplants in people with failing transplants but it was not strong enough to warrant recommendations against pre-emptive second transplants.

1.10.4 Cost effectiveness and resource use

One economic evaluation was included that compared costs in people who switched from HD to PD and PD to HD in the first year. Costs were lower in the group that switched from

HD to PD however this was largely due to lower dialysis costs as PD costs were lower in this analysis. This study was judged partially applicable; in particular Canadian costs may not be applicable and the cost savings in dialysis costs with PD in this setting may not be seen in current UK practice based on current NHS reference costs.

No economic evidence was identified relating to other sequences.

1.11.5 Other factors the committee took into account

The committee discussed that if renal transplant is unsuitable or cannot be provided for the person with kidney disease in a timely fashion then the over-riding factor of choosing initial dialysis treatment and subsequent switches should be patient preference."

References

1. Albrechtsen D, Flatmark A, Lundgren G, Brynger H, Frodin L, Groth CG et al. Retransplantation of renal grafts: prognostic influence of previous transplantation. Transplantation Proceedings. 1987; 19(5):3619-21

2. Ardalan M, Etemadi J, Ghabili K, Ghojazadeh M, Ghafari A, Khosroshahi HT. Effect of dialysis modality on transplantation outcome in living-donor renal transplantation. Nephro-Urology Monthly. 2011; 3(4):202-207

3. Binaut R, Hazzan M, Pruvot FR, Dracon M, Lelievre G, Noel C. Comparative study of chronic ambulatory peritoneal dialysis versus hemodialysis patients after kidney transplantation: clinical and financial assessment. Transplantation Proceedings. 1997; 29(5):2428

4. Bray RA, Nolen JDL, Larsen C, Pearson T, Newell KA, Kokko K et al. Transplanting the highly sensitized patient: The emory algorithm. American Journal of Transplantation. 2006; 6(10):2307-2315

5. Cecka JM, Terasaki PI. The UNOS scientific renal transplant registry. United Network for Organ Sharing. Clinical Transplants. 1995:1-18

6. Chertow GM, Milford EL, Mackenzie HS, Brenner BM. Antigen-independent determinants of cadaveric kidney transplant failure. JAMA. 1996; 276(21):1732-1736

7. Chui BK, Manns B, Pannu N, Dong J, Wiebe N, Jindal K et al. Health care costs of peritoneal dialysis technique failure and dialysis modality switching. American Journal of Kidney Diseases. 2013; 61(1):104-11

8. Cosio FG, Alamir A, Yim S, Pesavento TE, Falkenhain ME, Henry ML et al. Patient survival after renal transplantation: I. The impact of dialysis pre-transplant. Kidney International. 1998; 53(3):767-72

9. de Jonge H, Bammens B, Lemahieu W, Maes BD, Vanrenterghem Y. Comparison of peritoneal dialysis and haemodialysis after renal transplant failure. Nephrology Dialysis Transplantation. 2006; 21(6):1669-74

10. Donnelly PK, Lennard TW, Proud G, Taylor RM, Henderson R, Fletcher K et al. Continuous ambulatory peritoneal dialysis and renal transplantation: a five year experience. BMJ. 1985; 291(6501):1001-4

11. Doxiadis II, De Meester J, Smits JM, Witvliet M, de Lange P, Persijn GG et al. The impact of special programs for kidney transplantation of highly sensitized patients in Eurotransplant. Clinical Transplants. 1998:115-120

12. Freier DT, Haines RF, Rosenzweig J, Neiderhuber J, Konnak J, Turcotte JG. Sequential renal transplants. Some surgical and immunological implications on management of the first homograft. Surgery. 1976; 79(3):262-267

13. Goldfarb-Rumyantzev AS, Hurdle JF, Baird BC, Stoddard G, Wang Z, Scandling JD et al. The role of pre-emptive re-transplant in graft and recipient outcome. Nephrology Dialysis Transplantation. 2006; 21(5):1355-64

14. Griveas I, Visvardis G, Fleva A, Papadopoulou D, Mitsopoulos E, Kyriklidou P et al. Comparative analysis of immunophenotypic abnormalities in cellular immunity of uremic patients undergoing either hemodialysis or continuous ambulatory peritoneal dialysis. Renal Failure. 2005; 27(3):279-282

15. Iles-Smith H, Curwell J, Gokal R. Comparative evaluation of CAPD and PD-plus effectiveness. Edtna-Erca Journal. 1999; 25(3):27-9

16. Jimenez C, Manrique A, Morales JM, Andres A, Ortuno T, Abradelo M et al. Influence of dialysis modality on complications and patient and graft survival after pancreas-kidney transplantation. Transplantation Proceedings. 2008; 40(9):2999-3000

17. Johnston O, Rose CL, Gill JS. Risks and benefits of preemptive second kidney transplantation. Transplantation. 2013; 95(5):705-710

18. Koc Y, Unsal A, Basturk T, Sakaci T, Ahbap-Dal E, Sinangil A et al. Is there impact of mortality prior hemodialysis therapy in peritoneal dialysis patients? Nefrologia. 2012; 32(3):335-342

19. Kostro JZ, Hellmann A, Kobiela J, Skora I, Lichodziejewska-Niemierko M, Debska-Slizien A et al. Quality of life after kidney transplantation: A prospective study. Transplantation Proceedings. 2016; 48(1):50-4

20. Lorent M, Giral M, Pascual M, Koller MT, Steiger J, Trebern-Launay K et al. Mortality prediction after the first year of kidney transplantation: An observational study on two European cohorts. PloS One. 2016; 11(5):e0155278

21. Nadeau-Fredette AC, Bargman JM, Chan CT. Clinical outcome of home hemodialysis in patients with previous peritoneal dialysis exposure: evaluation of the integrated home dialysis model. Peritoneal Dialysis International. 2015; 35(3):316-23

22. National Institute for Health and Clinical Excellence. The guidelines manual. London. National Institute for Health and Clinical Excellence, 2012. Available from: http://www.nice.org.uk/article/pmg6/

23. Odor-Morales A, Castorena G, Jimeno C, Pena JC, Bordes J, de la Rosa C et al. Hemodialysis or continuous ambulatory peritoneal dialysis before transplantation: prospective comparison of clinical and hemodynamic outcome. Transplantation Proceedings. 1987; 19(1 Pt 3):2197-9

24. Opelz G. Success rate and impact of HLA matching on kidney graft survival in highly immunized recipients. Collaborative Transplant Study. Transplant International. 1992; 5(Suppl 1):S601-603

25. Organisation for Economic Co-operation and Development (OECD). Purchasing power parities (PPP). Available from: http://www.oecd.org/std/prices-ppp/ Last accessed: 13/12/2017.

26. Persijn GG, D'Amaro J, Rood JJ. Pretransplant blood transfusions and long-term renal allograft survival. Lancet. 1984; 2(8410):1043-4

27. Resende L, Guerra J, Santana A, Mil-Homens C, Abreu F, da Costa AG. Influence of dialysis duration and modality on kidney transplant outcomes. Transplantation Proceedings. 2009; 41(3):837-9

28. Rigo DH, Ziraldo L, Di Monte L, Jimenez MP, Giotto AP, Gutierrez L et al. Preemptive kidney transplantation: experience in two centers. Transplantation Proceedings. 2011; 43(9):3355-8

29. Schold JD, Meier-Kriesche HU. Which renal transplant candidates should accept marginal kidneys in exchange for a shorter waiting time on dialysis? Clinical Journal of the American Society of Nephrology. 2006; 1(3):532-538

30. Schwenger V, Dohler B, Morath C, Zeier M, Opelz G. The role of pretransplant dialysis modality on renal allograft outcome. Nephrology Dialysis Transplantation. 2011; 26(11):3761-6

31. Snyder JJ, Kasiske BL, Gilbertson DT, Collins AJ. A comparison of transplant outcomes in peritoneal and hemodialysis patients. Kidney International. 2002; 62(4):1423-1430

32. Traynor JP, Thomson PC, Simpson K, Ayansina DT, Prescott GJ, Mactier RA. Comparison of patient survival in non-diabetic transplant-listed patients initially treated with haemodialysis or peritoneal dialysis. Nephrology, Dialysis, Transplantation. 2011; 26(1):245-52

33. Van Den Berg-Loonen EM, Billen EVA, Voorter CEM, Van Heurn LWE, Claas FHJ, Van Hooff JP et al. Clinical relevance of pretransplant donor-directed antibodies detected by single antigen beads in highly sensitized renal transplant patients. Transplantation. 2008; 85(8):1086-1090

34. West JC, Bisordi JE, Squiers EC, Latsha R, Miller J, Kelley SE. Length of time on dialysis prior to renal transplantation is a critical factor affecting patient survival after allografting. Transplant International. 1992; 5(Suppl 1):S148-150

35. Zhou YC, Cecka JM. Sensitization in renal transplantation. Clinical Transplants. 1991:313-323

Appendices

Appendix A: Review protocols

Table 6: Review protocol: Sequences of modalities of RRT and conservative management

Field	Content
Review question	What is the clinical and cost effectiveness of different sequences of modalities of renal replacement therapy and conservative management for people who are progressing or have progressed through to later stages of CKD?
Type of review question	Intervention
Objective of the review	Comparing the clinical and cost effectiveness of various modalities of RRT after failing previous modalities.
Eligibility criteria – population / disease / condition / issue / domain	People requiring RRT for CKD, who have received more than one modality of RRT sequentially, either because the earlier modality was considered to have failed, or because they received one modality while waiting for another (e.g. receiving dialysis prior to receiving a kidney transplant). Studies will be included where the majority meet one of these criteria. Studies will be downgraded for indirectness if >25% are RRT naïve. Definition of modality failure to be determined by studies. Stratified by: • Previously modality • Age (<2, 2 to <18, 18 to <70, ≥70) • DM vs no DM • BAME vs non-BAME • Unplanned starters vs planned starters
Eligibility criteria – interventions	Two RRT modalities received sequentially. RRT modalities are: Haemodialysis (HD) – including home or in centre, 3 days a week or more frequently, haemodialysis or haemodiafiltration Peritoneal dialysis (PD) – including CAPD, assisted PD or APD/CCPD Transplant (TPx) – including live donor or deceased, pre-emptive or reactive Conservative management
Eligibility criteria – comparator(s) / control or reference (gold) standard	Any modality or sub-modality vs any other, including where the comparison is between the first modality in a sequence (e.g. HD vs PD before transplantation), the second modality in a sequence (e.g. HD vs PD after transplantation) or between two sequences (e.g. HD then PD vs PD then HD) Studies comparing multiple sequences of RRT will also be included (for example HD then PD vs PD then HD)
Outcomes and prioritisation	Critical • Patient, family/carer health-related quality of life (continuous) • Mortality (dichotomous and time to event) • Time to failure of RRT form (time to event)

	Important
	• Hospitalisation (rates or continuous)
	• Preferred place of death (dichotomous)
	• Symptom scores and functional measures (continuous)
	• 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. Mortality and hospitalisation must be reported after at least 6 months of the intervention under investigation. All other outcomes must be reported after at least 1 month of the intervention under investigation.
	
	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 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	RCTs will be prioritised. 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 • Health at baseline • Co-morbidities • Ethnicity
Other inclusion exclusion criteria	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 / subgroup analysis, or meta-regression	People with a BMI ≥30 vs BMI <30 Aged ≥80 vs aged <80

	T1DM vs T2DM Sub-modalities (for intermodality comparisons) Nocturnal vs diurnal HD
Selection process – duplicate screening / selection / analysis	A sample of at least 10% of the abstract lists were double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus could not be reached, 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 B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendices of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group 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 separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jan Dudley in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

1

2 **Table 7: 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 B.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.[22] 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: Literature search strategies

B.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 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 11 December 2017	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 11 December 2017	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2017 Issue 12 of12 CENTRAL to 2017 Issue 11 of12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

1. Line 81 (Medline) and line 75 (Embase) were added to the search strategy to reduce the number of items retrieved for observational studies as the overall results from the search were very large.

   This was checked to ensure that relevant studies were not excluded.

Medline (Ovid) search terms

1.	exp Renal Replacement Therapy/
2.	((renal or kidney) adj2 replace*).ti,ab.
3.	(hemodiafilt* or haemodiafilt* or (biofilt* adj1 acetate-free)).ti,ab.
4.	(hemodialys* or haemodialys*).ti,ab.

5.	((kidney* or renal) adj3 (transplant* or graft*)).ti,ab.
6.	capd.ti,ab.
7.	dialys*.ti,ab.
8.	(artificial adj1 kidney*).ti,ab.
9.	or/1-8
10.	limit 9 to English language
11.	letter/
12.	editorial/
13.	news/
14.	exp historical article/
15.	Anecdotes as Topic/
16.	comment/
17.	case report/
18.	(letter or comment*).ti.
19.	or/11-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animals/ not humans/
23.	Animals, Laboratory/
24.	exp animal experiment/
25.	exp animal model/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	10 not 28
30.	randomized controlled trial.pt.
31.	controlled clinical trial.pt.
32.	randomi#ed.ti,ab.
33.	placebo.ab.
34.	drug therapy.fs.
35.	randomly.ti,ab.
36.	trial.ab.
37.	groups.ab.
38.	or/30-37
39.	Clinical Trials as topic.sh.
40.	trial.ti.
41.	or/30-33,35,39-40
42.	Meta-Analysis/
43.	Meta-Analysis as Topic/
44.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
45.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
46.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
47.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
48.	(search* adj4 literature).ab.

49.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
50.	cochrane.jw.
51.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
52.	or/42-51
53.	29 and (41 or 52)
54.	exp Renal Replacement Therapy/
55.	((renal or kidney*) adj2 replace*).ti,ab.
56.	(hemodiafilt* or haemodiafilt* or haemofilt* or hemofilt*).ti,ab.
57.	(hemodialys* or haemodialys*).ti,ab.
58.	((kidney* or renal or pre-empt* or preempt*) adj3 (transplant* or graft*)).ti,ab.
59.	(capd or apd or ccpd or dialys*).ti,ab.
60.	or/54-59
61.	letter/
62.	editorial/
63.	news/
64.	exp historical article/
65.	Anecdotes as Topic/
66.	comment/
67.	case report/
68.	(letter or comment*).ti.
69.	or/61-68
70.	randomized controlled trial/ or random*.ti,ab.
71.	147 not 148
72.	animals/ not humans/
73.	Animals, Laboratory/
74.	exp Animal Experimentation/
75.	exp Models, Animal/
76.	exp Rodentia/
77.	(rat or rats or mouse or mice).ti.
78.	or/72-77
79.	60 not 78
80.	limit 79 to English language
81.	(mycophenolic acid or azathioprine or sirolimus or everolimus or tacrolimus or cyclosporin* or steroid or calcineurin inhibitor or anaemi* or anemi* or vitamin d or immunosuppres*).ti.[1]
82.	80 not 81
83.	Epidemiologic studies/
84.	Observational study/
85.	exp Cohort studies/
86.	(cohort adj (study or studies or analys* or data)).ti,ab.
87.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
88.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
89.	Controlled Before-After Studies/

90.	Historically Controlled Study/
91.	Interrupted Time Series Analysis/
92.	(before adj2 after adj2 (study or studies or data)).ti,ab.
93.	or/83-92
94.	Registries/
95.	Management Audit/ or Clinical Audit/ or Nursing Audit/ or Medical Audit/
96.	(registry or registries).ti,ab.
97.	(audit or audits or auditor or auditors or auditing or auditable).ti,ab.
98.	or/94-97
99.	93 or 98
100.	82 and 99
101.	100 not 53
102.	53 or 101

1 **Embase (Ovid) search terms**

1.	exp *renal replacement therapy/
2.	((renal or kidney) adj2 replace*).ti,ab.
3.	(hemodiafilt* or haemodiafilt* or (biofilt* adj1 acetate-free)).ti,ab.
4.	(hemodialys* or haemodialys*).ti,ab.
5.	((kidney* or renal) adj3 (transplant* or graft*)).ti,ab.
6.	capd.ti,ab.
7.	dialys*.ti,ab.
8.	(artificial adj1 kidney*).ti,ab.
9.	or/1-8
10.	limit 9 to English language
11.	letter.pt. or letter/
12.	note.pt.
13.	editorial.pt.
14.	case report/ or case study/
15.	(letter or comment*).ti.
16.	or/11-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animal/ not human/
20.	nonhuman/
21.	exp Animal Experiment/
22.	exp Experimental Animal/
23.	animal model/
24.	exp Rodent/
25.	(rat or rats or mouse or mice).ti.
26.	or/18-25
27.	10 not 26
28.	random*.ti,ab.
29.	factorial*.ti,ab.
30.	(crossover* or cross over*).ti,ab.
31.	((doubl* or singl*) adj blind*).ti,ab.

32.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
33.	crossover procedure/
34.	single blind procedure/
35.	randomized controlled trial/
36.	double blind procedure/
37.	or/28-36
38.	systematic review/
39.	meta-analysis/
40.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
41.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
42.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
43.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
44.	(search* adj4 literature).ab.
45.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
46.	cochrane.jw.
47.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
48.	or/38-47
49.	27 and (37 or 48)
50.	*renal replacement therapy/
51.	((renal or kidney*) adj2 replace*).ti,ab.
52.	(hemodiafilt* or haemodiafilt* or haemofilt* or hemofilt*).ti,ab.
53.	(hemodialys* or haemodialys*).ti,ab.
54.	((kidney* or renal or pre-empt* or preempt*) adj3 (transplant* or graft*)).ti,ab.
55.	(capd or apd or ccpd or dialys*).ti,ab.
56.	or/50-55
57.	letter.pt. or letter/
58.	note.pt.
59.	editorial.pt.
60.	case report/ or case study/
61.	(letter or comment*).ti.
62.	or/57-61
63.	randomized controlled trial/ or random*.ti,ab.
64.	62 not 63
65.	animal/ not human/
66.	nonhuman/
67.	exp Animal Experiment/
68.	exp Experimental Animal/
69.	animal model/
70.	exp Rodent/
71.	(rat or rats or mouse or mice).ti.
72.	or/64-71
73.	56 not 72
74.	limit 73 to English language

75.	(mycophenolic acid or azathioprine or sirolimus or everolimus or tacrolimus or cyclosporin* or steroid or calcineurin inhibitor or anaemi* or anemi* or vitamin d or immunosuppres*).ti.[1]
76.	74 not 75
77.	Clinical study/
78.	Observational study/
79.	family study/
80.	longitudinal study/
81.	retrospective study/
82.	prospective study/
83.	cohort analysis/
84.	follow-up/
85.	cohort*.ti,ab.
86.	84 and 85
87.	(cohort adj (study or studies or analys* or data)).ti,ab.
88.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
89.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
90.	(before adj2 after adj2 (study or studies or data)).ti,ab.
91.	or/77-83,86-90
92.	register/
93.	medical audit/
94.	(registry or registries).ti,ab.
95.	(audit or audits or auditor or auditors or auditing or auditable).ti,ab.
96.	or/92-95
97.	91 or 96
98.	76 and 97
99.	98 not 49
100.	49 or 99

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Renal Replacement Therapy] explode all trees
#2.	((renal or kidney*) near/2 replace*):ti,ab
#3.	(hemodiafilt* or haemodiafilt* or haemofilt* or hemofilt*):ti,ab
#4.	(hemodialys* or haemodialys*):ti,ab
#5.	((kidney* or renal or pre-empt* or preempt*) near/3 (transplant* or graft*)):ti,ab
#6.	(capd or apd or ccpd or dialys*):ti,ab
#7.	(biofilt* near/1 acetate-free):ti,ab
#8.	(artificial near/1 kidney*):ti,ab
#9.	(or #1-#8)

B.2 Health Economics literature search strategy

3 Health economic evidence was identified by conducting a broad search relating to renal
4 replacement therapy population in NHS Economic Evaluation Database (NHS EED – this
5 ceased to be updated after March 2015) and the Health Technology Assessment database
6 (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 9: 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

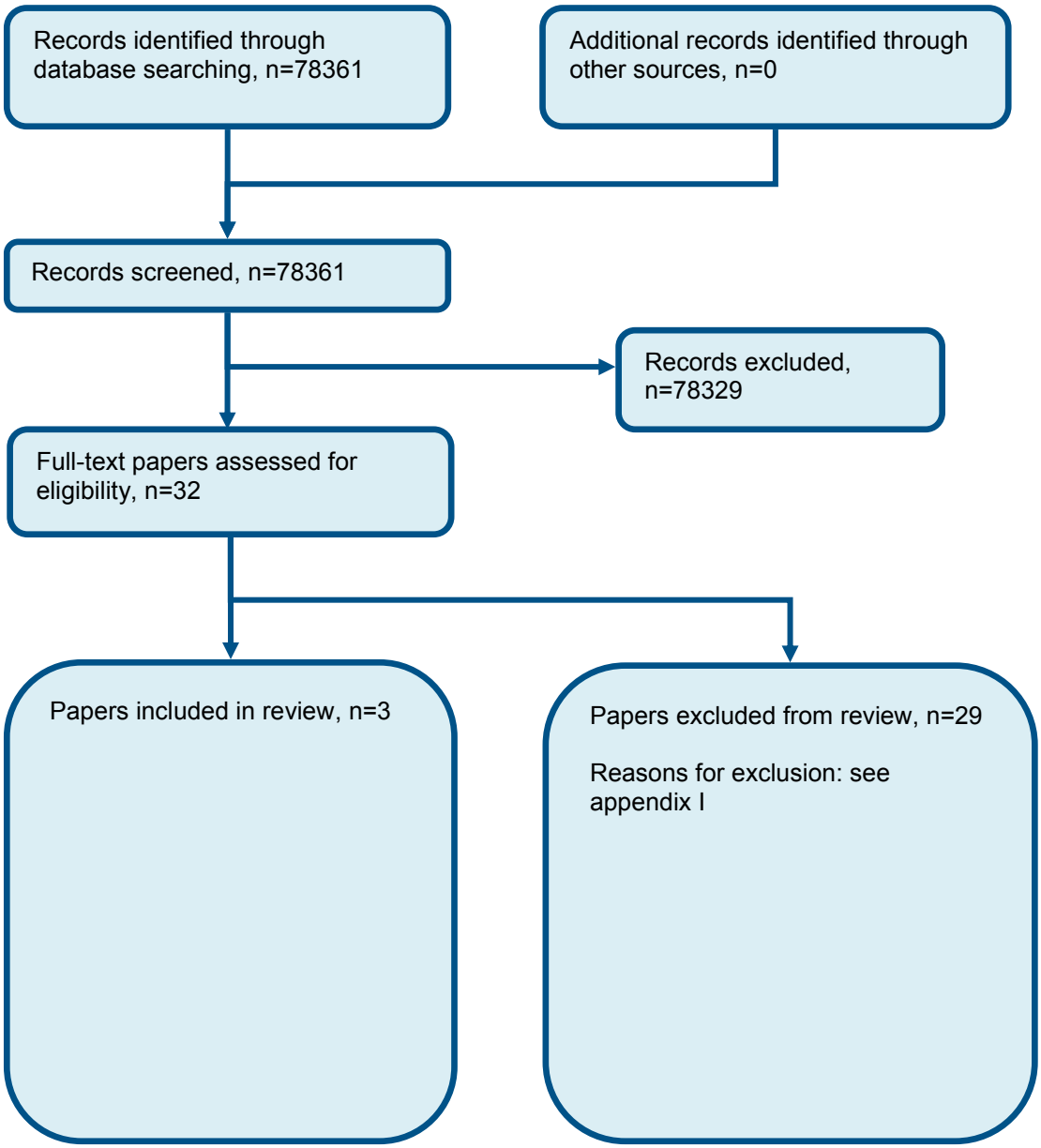
1 **NHS EED and HTA (CRD) search terms**

#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

2

Appendix C: Clinical evidence selection

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



Appendix D: Clinical evidence tables

Study	Collaborative Transplant Study trial: Schwenger 2011[30]
Study type	Non randomised study
Number of studies (number of participants)	1 (n=57315)
Countries and setting	Conducted in Multiple countries; Setting: CTS is a registry covering 400 transplant centres in 42 countries, covering kidney, heart, lung, liver and pancreas transplantation - coordinated by the University of Heidelberg
Line of therapy	2nd line
Duration of study	Not clear: Up to 5 post-transplant years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	General population: Dialysis then transplant sequence
Subgroup analysis within study	Not applicable
Inclusion criteria	Recipient of a deceased-donor kidney in a participating centre in Europe, North America, Australia and New Zealand. Aged 18 or over. First transplant
Exclusion criteria	Combined organ transplants
Recruitment/selection of patients	Data collected 1998-2007. Around 85% of cases identified were being treated in Europe
Age, gender and ethnicity	Age - Mean (SD): HD 50(13), PD 49(13). Gender (M:F): 65:35. Ethnicity: 92% Caucasian
Further population details	1. Age: 2. BMI: 3. DM: 4. Ethnicity:
Extra comments	Both standard and increased-risk recipients included. Both standard and expanded criteria donors included. Patients who received both HD and PD prior to transplant excluded.. Characteristics: Ave transplant year 2002 (+/- 2.7), diabetic cause 9.5, cardiovascular risk 15%, time on dialysis 4.1y (HD) 3.1y (PD)
Indirectness of population	No indirectness
Interventions	(n=45651) Intervention 1: HD then TPx. Pre-transplant dialysis modality HD only. Duration Up to five years post-transplant. Concurrent medication/care: Not defined, registry study (n=11664) Intervention 2: PD then TPx. Pre-transplant dialysis modality PD only. Duration Up to five years post-transplant. Concurrent medication/care: Not controlled, registry study

Funding	Other (No funding declared)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HD THEN TPX versus PD THEN TPX Protocol outcome 1: Mortality at >/= 6 months - Actual outcome for General population: Mortality (calculated as inverse of survival) at Up to five years post-transplant; HR 0.91 (95%CI 0.85 to 0.98) Reported; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Time to failure of RRT form - Actual outcome for General population: Graft failure (calculated as inverse of survival) at Up to five years post-transplant; HR 0.94 (95%CI 0.9 to 1) Reported; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Symptom scores/functional measures ; Hospitalisation or other healthcare resource use at >/= 6 months; Hospitalisation - length of stay at >/= 6 months; Psychological distress and mental wellbeing; Preferred location of death; 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

1

Study	**Snyder 2002[31]**
Study type	Non randomised study
Number of studies (number of participants)	1 (n=22,776)
Countries and setting	Conducted in USA; Setting: Data from US centres for Medicare and Medicaid Services (CMS)
Line of therapy	2nd line
Duration of study	Intervention + follow up: Unclear. At least 90 days on dialysis, up to 5 years after starting dialysis, no minimum time with transplant, median time likely to be around 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	General population: Patients selected on basis of sequence of RRT modalities
Subgroup analysis within study	Not applicable
Inclusion criteria	Medicare beneficiaries (in whole of USA) who (1) were 18 years old or older, (2) first started therapy for ESRD between 1995 and 1998, (3) had been on the same dialysis modality (hemodialysis or peritoneal dialysis) for at

	least 60 days on day 90 of ESRD therapy, and (4) had kidney transplantation occurring after day 90 of ESRD therapy, and before November 2000
Exclusion criteria	Any previous organ transplant
Recruitment/selection of patients	Identified 252,000 pts meeting dialysis criteria - 17% of pts receiving PD and 8% receiving HD have a kidney transplant in the window
Age, gender and ethnicity	Age - Other: age range 18-29y 3%, 30-44 52%, 45-64 34%, 65+ 11%. Gender (M:F): 53:47. Ethnicity: For PD/HD: Caucasian 65/52%, African American 21/32%, Hispanic 9/11%
Further population details	1. Age: 2. BMI: 3. DM: 4. Ethnicity:
Extra comments	. Baseline characteristics PD/HD: diabetic etiology 45/44%, obese 18/20%, GFR>8.7ml/min, ability to work 49/48%, cardio-vascular disease 32/41%, HTN 64/65%
Indirectness of population	No indirectness
Interventions	(n=5621) Intervention 1: PD then TPx. Receiving kidney-only transplant before the end of the trial and recorded as receiving peritoneal dialysis immediately prior to transplantation (as recorded on UNOS record or CMS if missing). Both living and deceased donor kidneys considered.. Duration Up to 5 years. Concurrent medication/care: Not controlled, registry study Comments: There is the possibility of switching from HD during follow-up (n=17155) Intervention 2: HD then TPx. Receiving kidney-only transplant before the end of the trial and recorded as receiving haemodialysis dialysis immediately prior to transplantation (as recorded on UNOS record or CMS if missing). Both living and deceased donor kidneys considered. Duration Up to 5 years. Concurrent medication/care: Not controlled
Funding	Study funded by industry (This work was supported by an unrestricted grant from Baxter International, Inc. and the Minneapolis Medical Research Foundation.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PD THEN TPX versus HD THEN TPX

Protocol outcome 1: Mortality at >/= 6 months
- Actual outcome for General population: Death at up to 5 years; RR 0.95 (95%CI 0.85 to 1.06); Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Time to failure of RRT form
- Actual outcome for General population: Graft failure at up to 5 years; RR 1.05 (95%CI 0.97 to 1.13); Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life ; Symptom scores/functional measures ; Hospitalisation or other healthcare resource use at >/= 6 months; Hospitalisation - length of stay at >/= 6 months; Psychological distress and mental wellbeing ; Preferred location of death ; 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

1

Study	**USRDS (retransplant) trial: Goldfarb-Rumyantzev 2006[13]**
Study type	Non randomised study
Number of studies (number of participants)	1 (n=11,714)
Countries and setting	Conducted in USA; Setting: United States Renal Data Service (USRDS) and United Network for Organ Sharing (UNOS) used throughout USA
Line of therapy	2nd line
Duration of study	Follow up (post intervention): Up to 10y
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Failed transplant: History of transplantation prior to study transplant. Includes paediatric and adults
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients recorded as having retransplant in the database, but kidney and kidney-pancreas transplants. Data presented for first retransplant and any retransplant
Exclusion criteria	Missing data on graft or patient survival
Recruitment/selection of patients	Between 1990 and end 1999, 92,844 received transplant, of which 11,714 were retransplants
Age, gender and ethnicity	Age - Mean (SD): 39(13), 34(14) in pre-emptive. Gender (M:F): 59:41. Ethnicity: 78% white (82% in pre-emptive), 18% African American (13% in pre-emptive), 2% Asian, 1% native American
Further population details	1. Age: Not applicable (All ages). 2. BMI: Not stated / Unclear (na). 3. DM: Not applicable (16%). 4. Ethnicity: Not applicable (78% white).
Extra comments	Donor characteristics: 81% deceased, age 33, number matched HLA antigens 1.9. Baseline data: Age at first transplant 32(13), HTN 39%, DM 16%, total duration ESRD 96 months, time since last graft failure and retransplant 22 months.
Indirectness of population	No indirectness

Interventions	(n=1609) Intervention 1: Transplant - Pre-emptive. Pre-emptive retransplant: patients with dialysis-free retransplant, or those who had <7 days between a graft failure and a retransplant. Duration Up to 10 years (average not given). Concurrent medication/care: Not controlled (registry study) Comments: Deceased donor 70% (HR corrected for this and multiple other confounders) (n=10105) Intervention 2: Transplant - Not pre-emptive. Not pre-emptive: defined as dialysis used prior to retransplant, or more than 7 days between recording of graft failure and retransplant. Duration Up to 10 years (average not given). Concurrent medication/care: Not controlled (registry study) Comments: Deceased donor 82%
Funding	Other (supported in part by the Dialysis Research Foundation (Ogden, UT) and the Department of Veterans Affairs)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRE-EMPTIVE versus NOT PRE-EMPTIVE Protocol outcome 1: Mortality at >/= 6 months - Actual outcome for Failed transplant: Recipient mortality at Up to 10 years; HR 1.02 (95%CI 0.9 to 1.15) Reported; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Time to failure of RRT form - Actual outcome for Failed transplant: Graft failure at Up to 10 years; HR 1.36 (95%CI 1.21 to 1.54) Reported; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Symptom scores/functional measures ; Hospitalisation or other healthcare resource use at >/= 6 months; Hospitalisation - length of stay at >/= 6 months; Psychological distress and mental wellbeing ; Preferred location of death ; 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

1

Appendix E: Forest plots

E.1 Peritoneal dialysis (PD) prior to transplant vs Haemodialysis (HD) prior to a transplant

Figure 2: Death after transplant (time to event) – follow-up 5y

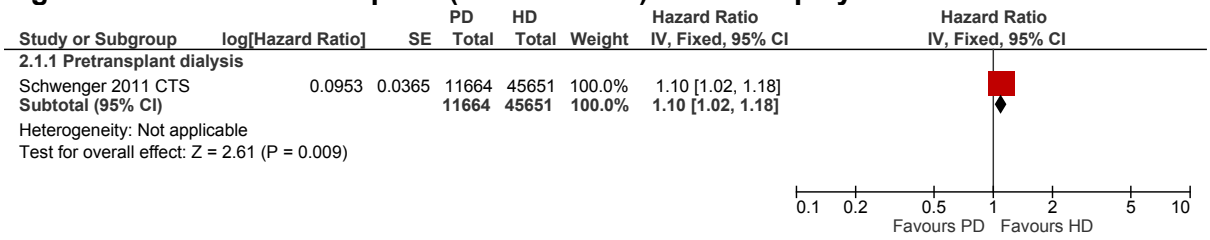


Figure 3: Death after transplant (risk) – follow-up up to 5y

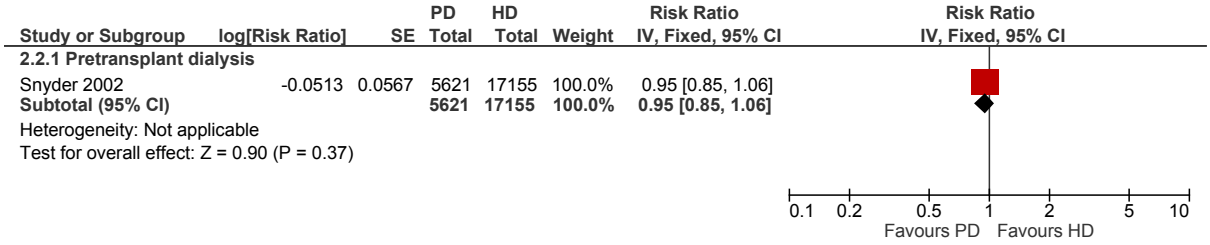


Figure 4: Graft failure (time to event) – follow-up 5y

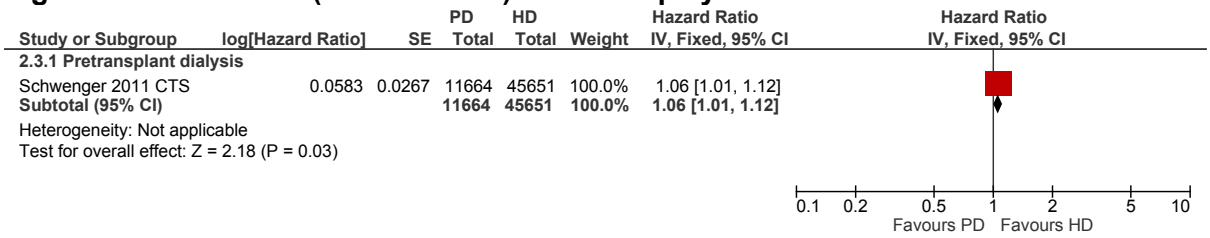
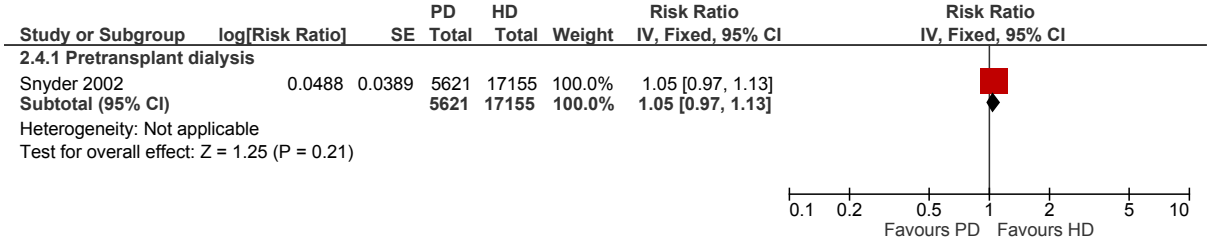


Figure 5: Graft failure (risk) – follow-up up to 5y



E.2 Pre-emptive transplant for failing transplant vs Dialysis then transplant for failing transplant

Figure 6: Death after retransplant (time to event) – up to 10y

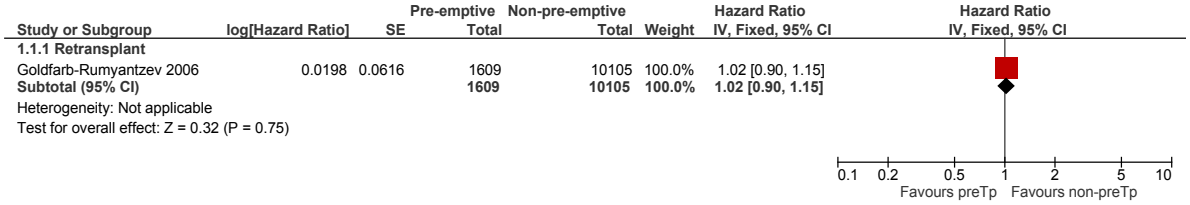
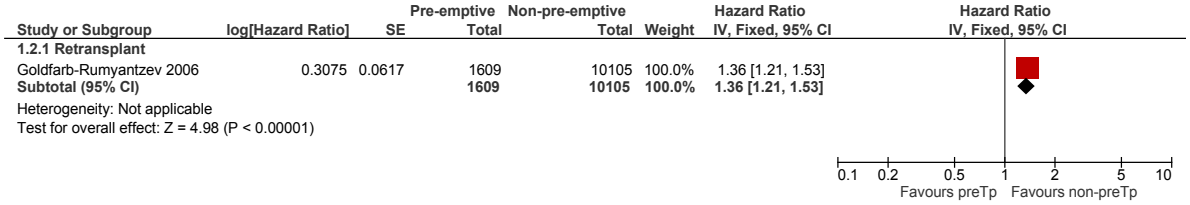


Figure 7: Graft failure (time to event) – up to 10y



Appendix F:GRADE tables

Table 10: Peritoneal dialysis (PD) prior to transplant vs Haemodialysis (HD) prior to a transplant

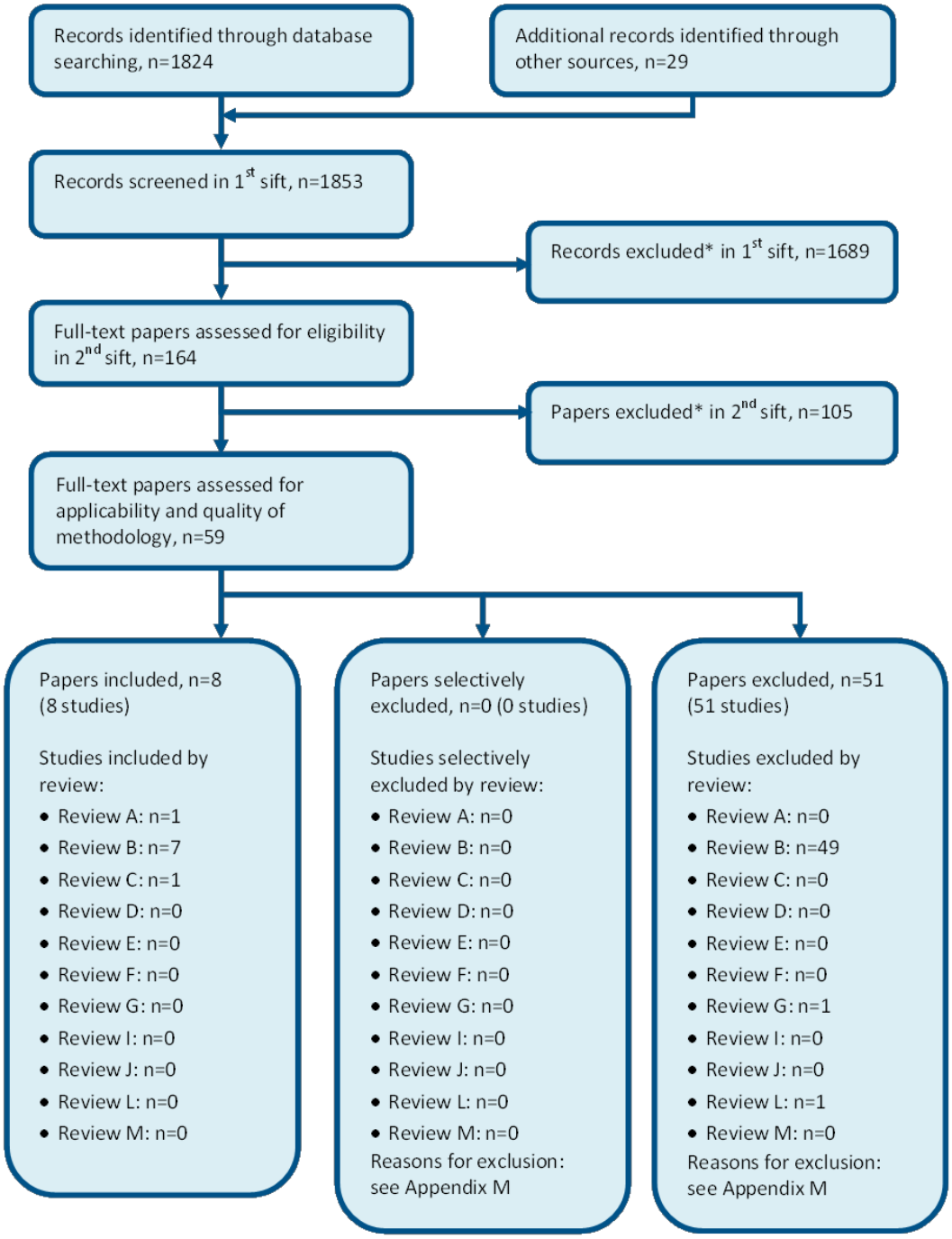
Quality assessment							No of patients		Effect PD vs HD		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peritoneal dialysis (PD) prior to transplant	Haemodialysis (HD) prior to a transplant	Relative (95% CI)	Absolute		
Death after transplant (time to event) (follow-up 0-5 years)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11,664	45,651	HR 1.1 (1.02 to 1.18)	-	VERY LOW	CRITICAL
Death after transplant (relative risk) (follow-up 0-5 years)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5,621	17,155	RR 0.95 (0.85 to 1.06)	-	VERY LOW	CRITICAL
Graft failure (time to event) (follow-up 0-5 years)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11,664	45,651	HR 1.06 (1.01 to 1.12)	-	VERY LOW	CRITICAL
Graft failure (relative risk) (follow-up 0-5 years)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5,621	17,155	RR 1.05 (0.97 to 1.13)	-	VERY LOW	CRITICAL

Table 11: Clinical evidence profile: Pre-emptive transplant for failing transplant vs Dialysis then transplant for failing transplant

Quality assessment							No of patients		Effect PreT vs Non-PreT		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-emptive transplant for failing transplant	Dialysis then transplant for failing transplant	Relative (95% CI)	Absolute		
Mortality (time to event) post-retransplant (follow-up 0-10 years)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1,609	10,105	HR 1.02 (0.9 to 1.15)	-	VERY LOW	CRITICAL
Graft failure (time to event) - retransplant (follow-up 0-10 years)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1,609	10,105	HR 1.36 (1.21 to 1.53)	-	VERY LOW	CRITICAL

Appendix G: Health economic evidence selection

Figure 8: 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

* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

Study	Chui 2013[7]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CC (health outcome: none) **Study design:** Cohort analysis with all cost models adjusted for age, sex, body mass index, race, comorbid conditions, cause of ESRD, and pre-dialysis care. **Approach to analysis:** multivariate regression **Perspective:** Canadian health care purchaser **Follow-up:** 3 years **Treatment effect duration:**[(a)] n/a **Discounting:** Costs: 0%; Outcomes: 0%	**Population:** Adult patients who initiated long-term dialysis (PD or in-centre HD) for ESRD. **Patient characteristics:** HD / PD / HD>PD/ PD>HD N=1005 / 208 / 120 / 45 Male: 59% / 57% / 51% / 56% Age: 61.9 / 54.6 / 52.5 / 55.7 years **Intervention 1:** HD **Intervention 2:** PD **Intervention 3:** HD then switched to PD in first year **Intervention 4:** PD then switched to HD in first year	**Total 1 year costs (mean per patient):** Intervention 1: £50,310 Intervention 2: £19,214 Intervention 3: £35,832 Intervention 4: £43,818 Incremental (2−1): -£31,097 (95% CI: -£34,064 to -£28,130; p=NR) Incremental (3−1): -£14,478 (95% CI: -£18,692 to -£10,264; p=NR) Incremental (4−1): -£6,493 (95% CI: -£12,845 to -£140; p=NR) **Total 3 year costs (mean per patient):** Intervention 1: £99,656 Intervention 2: £33,252 Intervention 3: £64,836 Intervention 4: £98,134 Incremental (2−1): -£66,404 (95% CI: -£74,672 to -£58,136; p=NR) Incremental (3−1):-£34,820 (95% CI: -£45,117 to -£24,523; p=NR) Incremental (4−1): -£1,522 (95% CI: -£16,008 to £12,964; p=NR) **Cost breakdowns:**	n/a	n/a **Analysis of uncertainty:** 95% CI determined through bootstrapping. Effects of non-censoring of cost data and logarithmic transformations of costs used in multivariate regression models were explored in sensitivity analysis. Results not reported but authors state results are similar.

		HD>PD vs HD (1 year / 3 years) Dialysis: -£16,220 (-£20,139 to -£12,301) / -£29,364 (-£37,120 to -£21,607) Inpatient: £333 (-£3,816 to £4,482) / £1,529 (-£6,738 to £9,795) Medication: -£13 (-£214 to £189) / -£31 (-£600 to £538) Physician fees: -£119 (-£655 to £417) / £488 (-£985 to £1,960) **PD>HD vs HD (1 year / 3 years)** Dialysis: -£7,667 (-£11,166 to -£4,067) / -£11,477 (-£21,253 to -£1,702) Inpatient: £2,283 (-£5,593 to £10,160) / £3,993 (-£6,119 to £14,104) Medication: £511 (-£3,425 to £4,448) / £1,259 (-£3,352 to £5,869) Physician fees: £993 (£37 to £1,949) / £2,652 (£493 to £4,811) **Currency & cost year:** 2010 Canadian dollars (presented here as 2010 UK pounds[(b)]) **Cost components incorporated:** Dialysis costs, inpatient costs, medication costs, and physician fees. It is unclear whether any transport costs are included.		

Data sources

Health outcomes: n/a **Quality-of-life weights:** n/a **Cost sources:** Resource use was based on an analysis of administrative records from the Northern and Southern Alberta Renal Programs. Unit costs for Alberta were applied.

Comments

Source of funding: Alberta Heritage Foundation for Medical Research, Alberta Health and Wellness and the Universities of Alberta and Calgary. **Limitations:** Does not include all RRT modalities of interest. 2010 Canadian costs based on resource use from 1999-2006 may not reflect current NHS context. Discounting not applied. Health outcomes not incorporated. Within-trial analysis (cohort) so does not reflect the full body of evidence in this area (note: no parallel clinical study, costs only). It is unclear whether any transport costs are included. **Other:** None.

Overall applicability:[c] Partially applicable	**Overall quality:**[d] Potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; NR: not reported; 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 2010 purchasing power parities[25]

(c) Directly applicable / Partially applicable / Not applicable

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

1 Appendix I: Excluded studies

I.1 Excluded clinical studies

3 **Table 12: Studies excluded from the clinical review**

Study	Exclusion reason
Albrechtsen 1987[1]	Wrong comparison
Ardalan 2011[2]	NRS without adequate adjustment
Binaut 1997[3]	NRS without adequate adjustment
Bray 2006[4]	Wrong intervention
Cecka 1995[5]	NRS without adequate adjustment
Chertow 1996[6]	Wrong comparison
Cosio 1998[8]	Inappropriate comparison
De Jonge 2006[9]	NRS without adequate adjustment
Donnelly 1985[10]	NRS without adequate adjustment
Doxiadis 1998[11]	Incorrect interventions
Freier 1976[12]	NRS without adequate adjustment
Griveas 2005[14]	NRS without adequate adjustment
Iles-Smith 1999[15]	Wrong comparison
Jimenez 2008[16]	NRS without adequate adjustment
Johnston 2013[17]	NRS without adequate adjustment
Koc 2012[18]	NRS without adequate adjustment
Kostro 2016[19]	NRS without adequate adjustment
Lorent 2016[20]	NRS without adequate adjustment
Nadeau-Fredette 2015[21]	Wrong comparison
Odor-Morales 1987[23]	NRS without adequate adjustment
Opelz 1992[24]	Incorrect interventions
Persijn 1984[26]	Wrong intervention
Resende 2009[27]	NRS without adequate adjustment

Rigo 2011[28]	NRS without adequate adjustment
Schold 2006[29]	Inappropriate comparison
Traynor 2011[32]	NRS without adequate adjustment
Van den Berg-Loonen 2008[33]	Wrong comparison
West 1992[34]	Inappropriate comparison
Zhou 1991[35]	Descriptive study

1

I.2 Excluded health economic studies

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

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

Reference	Reason for exclusion
None.	

7
8

Appendix J: Research recommendations

J.1 HD/HDF before PD vs PD before HD/HDF

Research question: What is the clinical and cost effectiveness of haemodialysis/haemodiafiltration before PD versus PD before haemodialysis/haemodiafiltration?

Why this is important:

In general this guideline concluded that the decision to use HD/HDF or PD was one guided by patient choice. However some people believe that the order of treatments may have an effect on overall efficacy, no high quality evidence was found in this area. If evidence was available this would allow people to make a more informed choice between HD/HDF and PD at the first point in the treatment pathway.

Criteria for selecting high-priority research recommendations:

PICO question	Population: people in the later stages of CKD who are not receiving a pre-emptive transplant Intervention(s): HD/HDF (at least 90 days) before PD Comparison: PD (at least 90 days) before HD/HDF Outcome(s): quality of life, mortality, time to failure of RRT modality, resource use/hospitalisation, symptom scores/functional measures, experience of care, adverse events (infections, access issues)
Importance to patients or the population	Improved evidence in this area could allow people to make a more informed choice with the long term consequences of choosing to start on either HD/HDF or PD
Relevance to NICE guidance	If one particularly strategy was found to be more clinically and cost effective than the other, this could feed into recommendations on which strategy may be optimal
Relevance to the NHS	If one strategy was more cost effective than the other, and supported by sufficient clinical benefit or lack of harm, recommendations promoting this strategy could be cost saving
National priorities	Not applicable
Current evidence base	There were no RCTs or non-randomised studies available in this area
Equality	Not applicable
Study design	Ideally this would be an RCT but given the likely long timeframe required for follow-up, non-randomised cohort studies with adequate adjustment for key confounders (including age, ethnicity, co-existing conditions and some estimate of baseline health (e.g. quality of life)) may be more feasible and appropriate
Feasibility	As above
Other comments	Not applicable
Importance	• Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.