Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Six major treatment modalities for patients with end stage renal disease (ESRD) were investigated: (1) home haemodialysis (HHD), the cleaning of the blood from waste products through an artificial kidney as performed by the patient at home; (2) limited care haemodialysis (LCHD), as performed in a dialysis centre or hospital with more active input of the patient in the treatment; (3) full care centre haemodialysis (CHD), as performed in a dialysis centre or hospital with less active input of the patient in the treatment; (4) kidney transplantation (TX) with non-related donor organs; (5) continuous ambulatory peritoneal dialysis (CAPD), the removal of waste products through a cleaning fluid in the abdominal cavity with manual exchange of dialysis fluid; (6) continuous cycling PD (CCPD), PD with automated exchange of dialysis fluid at night.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
Patients with end stage renal disease (ESRD). In the original NECOSAD study, new ESRD patients aged 18 years or over who were started on chronic haemodialysis or peritoneal dialysis were included. Inclusion criteria for participation in the quality of life interviews were: age above 18 years, written informed consent from the patient, the same treatment for at least 3 months, adequate eyesight to enable the completion of questionnaires and an adequate understanding of the Dutch language.

Setting
Primary care and hospital. The economic study was carried out in the Netherlands.

Dates to which data relate
Effectiveness (quality of life) and resource use data were gathered between October 1993 and December 1996. Furthermore, some unmeasured quality-of-life and other effectiveness data were obtained from the literature published between 1985 and 1997. The price year was 1996.

Source of effectiveness data
The evidence for the final outcomes was based on two interwoven quality of life studies, studies from the published literature, and assumptions/extrapolations based on linear regression analyses made by the authors.

Link between effectiveness and cost data
Costing was in part based on the same study sample used in the NECOSAD study (data on volumes of hospitalizations...
and use of medication) and in part on a sample of 165 interviewed dialysis patients, of whom 135 participated in the NECOSAD study (data on resource use outside the hospital and dialysis centre (primary care services)).

**Study sample**

Power calculations were not used to determine the sample size. In the original NECOSAD study, 250 ESRD patients were available for the study, of whom 226 (90.4%) completed the SF-36. There were 120 patients with a mean (SD) age of 59.3 (15.5) years in the haemodialysis group and 106 patients with a mean (SD) age of 52.3 (14) years in the peritoneal dialysis group. A general population sample of 1,063 with an age range of 18 to 89 years and mean age of 44 years was used as the reference group.

Quality of life interviews were performed on 165 dialysis patients, of whom 135 participated in the NECOSAD study. Because of the lack of sufficient numbers of CCPD patients in the NECOSAD study, 30 extra CCPD patients were recruited in the quality of life interviews. There were 46 patients in the CHD group with a mean (SD) age of 67 (9) years, 23 patients (including 5 HHD patients) in the LCHD group with a mean (SD) age of 47 (15) years, 59 in the CAPD group with a mean (SD) age of 56 (13) years, and 37 in the CCPD group with a mean (SD) age of 55 (13) years.

**Study design**

This was a multicentre prospective cohort study, carried out in 16 centres (13 centres participating (27% of all centres in the Netherlands) in the original NECOSAD study and 3 extra centres providing the CCPD patients for the quality of life interviews). The duration of the follow-up in the NECOSAD study was 3 months after the start of chronic dialysis treatment. Loss to follow-up in the NECOSAD study was 9.6% (those who did not complete the SF-36). Except for a lower proportion of males and a lower haemoglobin level, non-participants (drop-outs) were comparable to the participants.

**Analysis of effectiveness**

The principle used in the analysis of effectiveness appears to have been treatment completers only. In the original NECOSAD study, the health outcome measure was quality of life of the new ESRD patients, which was compared with the quality of life of a general population sample. The impact of demographic, clinical, renal function, and dialysis characteristics on patients' quality of life was studied using a multivariate regression analysis. Patients' self-assessment of quality of life was measured by the 36-item Short Form Health Survey Questionnaire (SF-36). This has eight dimensions: physical functioning (PF), social functioning (SF), role-functioning physical (RP), role-functioning emotional (RE), mental health (MH), vitality (VT), bodily pain (BP), and general health perceptions (GH). In the original NECOSAD study, the study groups were not comparable in terms of age, employment rate, prevalence of malignancy, erythropoietin, haemoglobin, dialysis related Kt/V (urea), and nPCR. In the quality of life interviews, quality of life of patients was assessed with EuroQol (EQ-5D) Instrument, Standard Gamble (SG), and Time Trade Off (TTO). The four treatment groups in the quality of life interviews were comparable in terms of sex, time on dialysis and number of comorbid diseases. The LCHD/HHD patients were younger on average than patients treated with other dialysis modalities.

**Effectiveness results**

In the original NECOSAD study, the following results were reported.

Quality of life of haemodialysis and peritoneal dialysis patients was substantially impaired in comparison to the general population sample (p<0.05), particularly with respect to RP and GH.

Mean RP and GH scores of the haemodialysis patients corresponded with the lowest scoring 8% and 12%, respectively, of the reference group.

Mean RP and GH scores of the peritoneal dialysis patients corresponded with the lowest scoring 10% and 12%, respectively, of the reference group.
Haemodialysis patients showed lower levels of quality of life than peritoneal dialysis patients on PF, RE, MH, and BP, (p<0.05).

However, on the multivariate level, the authors could only demonstrate an impact of dialysis modality on MH. A higher number of comorbid conditions, a lower haemoglobin level, and a lower residual renal function were independently related to poorer quality of life. The variability of the SF-36 scores explained by selected demographic, clinical, renal function, and dialysis characteristics was highest for PF (29.7%). Explained variability of the other SF-36 dimensions ranged from 6.9% for GH to 15.4% for VT. In the quality of life interviews, patients’ SG, TTO and EQ-5D Visual Analog Scale scores were not significantly different across the four treatment groups, indicating that quality of life of patients in the four treatment groups was comparable.

Clinical conclusions
The NECOSAD study concluded that quality of life of new ESRD patients is substantially impaired. Comorbid conditions, haemoglobin, and residual renal function could explain poor quality of life only to a limited extent. Further research exploring determinants and indices of quality of life in ESRD patients is warranted. From a clinical perspective, the authors suggested that quality of life should be considered in the monitoring of dialysis patients. In the quality of life interviews, it was observed that the ranking of the quality of life of patients in the four treatment groups appeared to differ depending on the perspective (patient/general population) and valuation method. For instance, CCPD patients’ TTO scores were equal to or higher than other groups’ TTO scores, while CCPD patients’ SG scores were lower than other groups’ SG scores.

Modelling
A Markov-chain model was used to assess the cost-effectiveness and cost-utility of the treatment modalities over a period of 5 years (1997-2001). The actual patient numbers in the Dutch ESRD programme as of 1 January 1997 (about 8,300 patients, equally divided between dialysis and transplantation) were used as a starting-point. The model had 36 different states encompassing combinations of six treatment modalities, three age-groups (0-44, 45-64 years, and 65 years and older) and two treatment stages (the first year versus the second years and later years). Two irreversible states, death and recovery of kidney functions were added to the model. Because of the somewhat conflicting results of quality of life measurements and because valuations derived from the general population are considered most appropriate in a cost-utility analysis, the authors decided to incorporate the general population valuations in the base-case scenario and to apply patient valuations in sensitivity analysis.

Outcomes assessed in the review
The review assessed the valuation of health states by a general population, transition probabilities, population prognoses between 1997 and 2001, the distribution of new patients over 6 treatment modalities, the distribution of patients over 5 dialysis modalities after rejection of graft, and the quality of life of transplanted patients.

Study designs and other criteria for inclusion in the review
The Renal Replacement Registry of the Netherlands (RENINE), Statistics Netherlands and valuations of health states by UK general population were used. No more information was provided.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.
Not reported.

Number of primary studies included
In total, 7 studies were referenced from the published literature.

Methods of combining primary studies
Most of the studies had separate inputs in the review.

Investigation of differences between primary studies
Not reported.

Results of the review
The distribution of new patients over 6 treatment modalities reflected the actual Dutch experience between 1994 and 1996. The distribution of patients over 5 dialysis modalities after rejection of graft was based on the observed experience between 1994 and 1996. The matrix of transition probabilities was constructed based on the actual treatment histories of all patients in the RENINE between 1994 and 1996 (n=11,192). The population prognoses between 1997 and 2001 was based on estimates from Statistics Netherlands. The authors applied data from a UK population sample on the valuation of health states to the health status as described by ESRD patients in the main study. The actual mean (SD) values were as follows: 0.66 (0.29) in the CHD group, 0.81 (0.24) in the LCHD group, 0.71 (0.29) in the CAPD group, and 0.81 (0.19) in the CCPD group. The general population valuations of the patients' health states were significantly higher for CCPD and LCHD/HHD patients than for CAPD and CHD patients. It was reported that studies have shown that the quality of life of transplanted patients is close to the quality of life as found in the general population. A recent study found a 23% increase in Time Trade Off scores in dialysis patients who had received a successful kidney transplant.

Methods used to derive estimates of effectiveness
Assumptions were made by the authors based on published literature and extrapolation of linear regression analyses performed by the authors on data from the RENINE.

Estimates of effectiveness and key assumptions
The inflow of new patients in 3 age-groups was based on extrapolation of a linear trend over the period 1987-1996. The number of transplantations per million population was based on extrapolation of the linear trend observed over 1987-1996. It was reported that the assessment of quality of life of transplanted patients fell outside the scope of this study. Thus, based on the literature and in comparison with the valuations found for the study dialysis patients, it was assumed that the quality of life factor for transplanted patients was 0.90.

Measure of benefits used in the economic analysis
Life years gained and Quality Adjusted Life Years (QALYs) over the 5-year period were the benefit measures.

Direct costs
Costs were discounted. Some resource use quantities were reported separately from the costs. Cost items were reported separately. The cost analysis covered the total costs of care for dialysis-related, transplantation, and other health related costs. A distinction was made between the costs of the first year of treatment (including extra costs at start of treatment, such as hospitalisations, vascular access operations and training of patients) and costs in second and later years of treatment. The breakdown of the annual costs of treatment of five dialysis modalities encompassed hospitalisation, surgery at start of dialysis, housing adaptations, staff, materials, hospital infrastructure, laboratory services, other health care services, diagnostic services, drugs, and travel. The perspective adopted in the cost analysis was reported to be
societal. Data on volumes of resource use, including hospitalizations and use of medication, were obtained from the NECOSAD study. Data on resource use outside the hospital and dialysis centre (primary care services) were obtained directly from patients at the quality of life interviews. Cost data were obtained from different sources, including some of the study hospitals, published studies, or national institutions. It was reported that in general, resource use was valued using real costs, not charges. The price year was 1996.

Indirect Costs
Not considered.

Currency
Dutch guilders (Dfl). The conversion rates in September 1997 were Dfl 1 = 0.31, Dfl 1 = $0.50.

Sensitivity analysis
A set of one-way sensitivity analyses was performed to assess the stability of the conclusions derived from the base-case scenario. This was an aggregate, based on the current and anticipated distribution of patients over transplantation and dialysis treatments. The effect of change from the life valuations of general population to the patients’ valuation was assessed. The model was also used to explore several scenarios for cost reduction, such as changing patients to less expensive modalities.

Estimated benefits used in the economic analysis
The predicted number of life years gained for all ESRD treatments over the 5-year study period was 41,149 years. The corresponding values in terms of QALYs gained was 32,955 years. The values for each of the modalities were not reported separately. The discount rate for health benefits was 5%.

Cost results
The discount rate was 5%. Average annual costs ranged from Dfl 18,000 for transplantation to Dfl 9,5000 for CAPD to Dfl 146,000 for CHD. Annual costs of HHD, CCPD and LCHD varied from Dfl 115,000 to Dfl 128,000. This implies that the annual costs of the most expensive dialysis (CHD) were 50% higher than the annual costs of the least expensive dialysis therapy (CAPD). The predicted total discounted costs for all ESRD treatments over the 5-year study period was Dfl 3,240,312,000.

Synthesis of costs and benefits
The cost per life year gained and cost per QALY gained over the 5-year period were calculated as the measures of cost-effectiveness and cost-utility ratios. The predicted average cost per life year gained for all ESRD treatments (based on the current and anticipated distribution of patients over transplantation and dialysis treatments) over the 5-year study period was Dfl 78,700 and Dfl 98,300 for the predicted average cost per QALY. The average cost per life year gained for the 5 dialysis modalities was Dfl 133,100 versus Dfl 25,000 for transplantation. The corresponding values in terms of cost per QALY were Dfl 190,000 and Dfl 27,800, respectively. Among the different dialysis modalities, the ratio of costs to life years gained and costs to QALYs was most favourable for CAPD and least favourable for CHD, with intermediate positions for LCHD, HHD and CCPD. The influence of the substitutive policies (policies directed towards substitution of patients from the CHD treatment modality to one of CAPD, LCHD < CCPD, and HHD) considered in the sensitivity study was found to be modest in the Dutch context, where a high percentage of patients are already being treated with more cost-effective treatment modalities.

Authors' conclusions
Centre Haemodialysis was found to be the least cost-effective treatment, while transplantation and Continuous Ambulatory Peritoneal Dialysis (CAPD) were the most cost-effective treatments.
CRD COMMENTARY - Selection of comparators

No specific alternative appears to have been treated as the comparator. The authors stressed the fact that there are mutual dependencies (complementarities) between transplantation and dialysis, and among the dialysis modalities. Because of that, the cost-effectiveness analysis of ESRD treatments, they noted, should primarily be assessed at a more aggregate level, before considering the different therapeutic modalities. You, as a database user, should consider whether this applies to your own setting.

Validity of estimate of measure of effectiveness

It is difficult to assess the internal validity of the effectiveness results given the fact that they were based on different sources from two quality of data studies, a literature review (which was not comprehensive/systematic and lacked a critical appraisal of the primary studies included in the review), and assumptions made and regression analyses performed by the authors. The effects of confounding variables were assessed using a multivariate regression analysis to take into considerations the impact of non-comparability of the study groups in NECOSAD study in terms of a number of baseline characteristics. This may have enhanced the internal validity of the effectiveness results. The study sample appears to have been representative of the study population.

Validity of estimate of measure of benefit

The estimation of benefits was modelled. The quality values were based on SG, TTO and EQ-5D Visual Analog Scale scores, which represent the state of the art in quality evaluations and were obtained both from ESRD patients and a UK population sample. The Markov-chain model was used to estimate the final benefit measures, which appears to have been appropriate. It would have been helpful to have reported the benefits of each modality in the paper.

Validity of estimate of costs

The validity of the cost analysis was enhanced by the following features. Some quantities were reported separately from the costs, adequate details of methods of cost estimation were given, the price year, exchange rate, and perspective adopted in the cost analysis were reported, the cost analysis was based on true costs rather than on charges and sensitivity analyses were performed on some cost parameters. However, the following limitations may have weakened the validity. No statistical analysis was performed on resource use or cost data despite the costing mainly being based on the NECOSAD study and although the authors claimed to have adopted a societal perspective they did not consider the indirect costs (productivity loss) in the cost analysis.

Other issues

The authors' conclusions appear to be justified given uncertainties in the data, which were addressed by performing a set of sensitivity analyses. Regarding the issue of generalisability, it was noted that the study results and conclusions only apply to the ESRD treatment as found in the Netherlands, where there is equal access to all forms of dialysis. Nephrologists’ fees are independent of the treatment modality of a patient. Without medical contraindications, patients in general are allowed to choose a treatment modality that best suits them. Appropriate comparisons were made with other studies. The degree to which the study sample was representative of the study population was implicitly addressed in the authors’ comments. Selecting a single comparator and calculating the incremental cost-effectiveness and cost-utility ratios was not performed although this would have been methodologically appropriate. The authors suggested the following implications of this study:

Implications of the study

(1) The quality of life of ESRD patients should be interpreted with a degree of caution by policy makers as the quality of life exercise in this study was somewhat confusing (for example, CCPD ranked highest using the TTO instrument and lowest using the SG instrument), and the quality of life differences across treatment groups were not large.

(2) The study result supports the hypothesis that matching patient and treatment criteria is an efficient process, resulting in the best outcomes that are possible in individual patients;
(3) The implication of the study findings regarding the CAPD stimulating scenarios is that countries with a lower rate of diffusion of PD treatments and similar cost profiles might benefit more from PD stimulating policies. This situation applies to many European countries.

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Other publications of related interest


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